Multidrug-Resistant Infections
Cefiderocol's Role in Managing Carbapenem-Resistant Acinetobacter baumannii Infections

This agent is likely best utilized as part of a combination when treating this bacterium but data regarding appropriate combinations are scarce.

by Caleb C. McLeod, PharmD; Jacinda C. Abdul-Mutakabbir, PharmD, MPH, AAHIVP; and Karen Tan, PharmD, BCIDP

Carbapenem-resistant Acinetobacter species (spp) have emerged as important health care-associated pathogens due to their array of intrinsic resistance mechanisms and propensity to acquire additional resistance mechanisms.1 Although carbapenems have been readily used to overcome multidrug-resistant Acinetobacter spp infections, the Centers for Disease Control and Prevention antimicrobial resistance threat report identified carbapenem-resistant Acinetobacter spp as an urgent threat.2 Carbapenem-resistant Acinetobacter baumannii (CRAB) is an especially difficult pathogen to manage, often requiring combination therapy.

Acute Infections
Rickettsial Infections Heat Up in the US
by Madeline King, PharmD, BCIDP

The bacteria that cause rickettsial infections are gram-negative, obligate intracellular organisms.1 Spotted fever rickettsial (SFR) diseases constitute the majority of rickettsial infections in the United States, and all rickettsial infections are notifiable diseases in the US. This means all

Emerging & Re-Emerging Infections
A Day in the Life of a Public Health Professional
by SASKIA POPESCU, PHD, MPH, MA, CIC

The phrase "a day in the life" of a public health professional seems almost darkly comical. First, it begs the question, "What life?" for an infectious disease epidemiologist and infection preventionist during the third year of the COVID-19 pandemic. In addition, every day is

HIV/AIDS
PrEP State of the Union: Adherence, Access, Uptake Issues
by Kaitlyn Jarrell, PharmD, BCPS, AAHIVP

In 2012, the Food and Drug Administration (FDA) approved the first oral HIV preexposure prophylaxis (PrEP) medication. PrEP, consisting of 1 or 2 antiretroviral medications, helps prevent individuals at risk of exposure to HIV from acquiring the virus. There are 3 PrEP products in

(continued on page 16)
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We Are Living in Interesting Times With Infectious Diseases

“May you live in interesting times.” This is an English interpretation of what is believed to be a traditional Chinese curse. Although it seems to be a blessing bestowed upon someone, the saying is often used ironically. Life in uninteresting times may be peaceful, and life in interesting times may be marked with turmoil.

The expression certainly can be applied to today’s infectious disease environment. Despite the fact that COVID-19 incidence rates have been dropping, questions remain about when the next resurgence will happen and what form of new variant it will take.

There also has been talk of when—not if—the next infectious disease outbreak will occur. At the moment there is an international outbreak of monkeypox, and although there are very few cases in the United States, the outbreak is not completely under control. The origins of the outbreak remain a mystery.

As of this writing, smallpox vaccines have been deployed to close contacts of patients with confirmed monkeypox infections to serve as postexposure prophylaxis. The United States has a stockpile of 2 smallpox vaccines (ACAM200 and Jynneos’, also known as Imvanex or Imvaneq) that can be distributed to manage monkeypox outbreaks if needed.

In these interesting times, the work of infectious disease professionals goes on, and in this month’s issue, there are a number of stories that are not related to COVID-19. For example, Caleb C. McLeod, PharmD; Jacinda C. Abdul-Mutakabbir, PharmD, MPH, AAHIVP; and Karen Tan, PharmD, BCIDP, write about the role of cefiderocol in combination therapy for the treatment of carbapenem-resistant Acinetobacter baumannii infections. And Madeline King, PharmD, writes about rickettsial infections.

As always, thank you for reading and please feel free to reach out to us with any feedback.

Mike Hennessy Jr
President and CEO
MJH Life Sciences®
Oral Carbapenems Are Failing to Break Through

Developing antibiotics is a tricky business. Although all new drug products in the United States have to go through the rigorous process of obtaining FDA approval, only anti-infectives face targets that change as the approval process is being completed. Antibiotics are the only class of medications of which use in one person affects the utility in another and that have generally declining utility across their life span.

The 10 by ‘20 Initiative spearheaded by the Infectious Diseases Society of America, which aimed to produce 10 new antibiotics during the 21st century’s second decade, was successful, much to my amazement.1 In fact, 14 systemically active microbials were approved from 2010 to 2019: ceftaroline, dalbavancin, tedizolid, oritavancin, ceftolozane-tazobactam, ceftazidime-avibactam, delafloxacin, meropenem-vaborbactam, plazomicin, eravacycline, omadacycline, imipenem-clastatin-relebactam, lefamulin, and tebipenem. It was an impressive success, particularly against multidrug-resistant (MDR) gram-negative rod (GNR) infections previously treated with polymyxins or aminoglycosides.

However, look at that list and you will see a key omission: oral medications active against resistant GNRs. Although delafloxacin is active against many GNRs (including Pseudomonas aeruginosa), its activity against these organisms is not appreciably better than other fluoroquinolones.2 Omadacycline has activity against some resistant GNRs but is inactive against others. It has pharmacokinetics that make it problematic (and unevaluated) for urinary tract infections (UTIs).3 Thus, although the 2010s saw antibiotic development that we had not seen for many years, it left a major need unmet: the outpatient treatment of resistant GNR infections caused by high rates of resistance to fluoroquinolones, trimethoprim-sulfamethoxazole, and highly bioavailable β-lactams coupled with the limited utility of nitrofurantoin outside of uncomplicated cystitis. This leaves patients with UTIs with limited options, which oral carbapenems could address.

In the past 2 years, 2 oral agents completed phase 3 trials that could have addressed this need, specifically for UTIs. On page 8 of Contagion®, you will find a “News and Breakthroughs” piece I coauthored describing the bumpy road that these drugs, sulopenem and tebipenem, have faced. Unfortunately, the ending has not been a happy one because the US Food and Drug Administration (FDA) did not approve their new drug applications as submitted, sulopenem in 2021 and tebipenem in 2022.4

I do not take issue with this, but I do find the FDA decisions disheartening for 2 reasons. First is the obvious concern for a continued lack of options to treat our patients with resistant infections without using intravenous agents (and the challenges they involve). The second is the chorus of concerned clinicians who vocalized umbrage over the prospect of oral carbapenem availability. Conceptually, it is easy to see why: Carbapenems have been the most broad-spectrum and reliable agents for resistant GNR in hospitals since the approval of imipenem-clastatin in 1985.5 Widespread use of carbapenems in outpatient settings could have major effects on the utility of these drugs for serious infections. However, the need for better outpatient options is real.

This is a challenge that we will need to address. Either or both agents could still be further studied and approved one day, but if they are not, then other oral agents with activity against MDR GNRs will be needed to take their place. The effort to develop and promote antimicrobial stewardship in outpatient settings is still nascent.6 Hopefully those who expressed fear at the concept of an oral carbapenem can help to champion outpatient stewardship as a solution to both the known problems of today and the unknown resistance issues of tomorrow. ▲

References are available at ContagionLive.com.

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

Active member of the Society of Infectious Diseases Pharmacists

Editor-in-Chief

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Bioaccumulation of Drugs by Human Gut Bacteria Can Affect Drug Availability

by DESTINY O. OKPOMO, PHARMD CANDIDATE; and KIRK E. HEVENER, PHARMD, PHD

It is well known that orally administered drugs can affect the gut microbiome, resulting in dysbiosis-mediated adverse effects. A common example is antibiotic-associated diarrhea. Less understood is the effect that gut bacteria can have on therapeutic drugs, primarily their systemic availability and subsequent drug levels. Although microbial biotransformation of drugs has been previously documented in a small number of cases, such as the conversion of sulfasalazine by gut bacteria into its active moieties, results from a recent study showed that gut organisms can alter drug availability by biotransformation on a significantly broader scale than previously expected. These findings and those of other related studies have played a significant role in the emergence of a new field of personalized medicine known as pharmacomicrobiomics, which has a strong potential to complement pharmacogenomics, metabolomics, and other personalized medicine disciplines.

In a recent publication, Klünemann and colleagues demonstrated that in addition to the biotransformation of therapeutic drugs, gut bacteria can bioaccumulate therapeutic drugs without chemically altering them. The authors showed that the sequestering of therapeutic drugs by gut bacteria had the primary effect of reducing drug availability and, interestingly, a secondary effect of changing bacterial metabolite production. The secondary effect can lead to changes in the gut bacteria composition and potentially result in altered drug adverse effects and drug mode of action. The authors investigated bacteria-drug interactions using 15 structurally diverse drugs and 25 unique strains of gut bacteria totaling 375 bacteria-drug pairs. The depletion of drug from the culture media was measured by ultraperformance liquid chromatography with ultraviolet detection after 48 hours of anaerobic growth. Postgrowth drug concentrations from the culture supernatant were compared with drug concentrations from total culture extracts, which included the bacterial cells, to track the fate of the depleted drugs. The investigators identified 70 bacteria-drug interactions, of which 29 were previously unknown. Approximately half the newly identified interactions involved intracellular storage of the drug without chemical modification. Nuclear magnetic resonance and liquid chromatography–mass spectrometry studies were used to confirm these results. The authors also tested for bacterial growth alterations by the studied drugs and identified 30 inhibitory drug-bacteria interactions, but only 3 also involved altered drug concentrations. The authors concluded that bacteria-drug and drug-bacteria interactions, although prevalent, appear to be largely independent.

To investigate the mechanism by which bacteria were able to bioaccumulate the drugs, the authors performed a series of follow-up studies using the drug duloxetine, which several bacterial species were shown to have accumulated. Using a chemically activated duloxetine analogue, the investigators performed a “click chemistry” pull-down assay to identify several metabolic bacterial enzymes that bound to the drug. Thermal proteome profiling studies with nonmodified drug were used to confirm these results, demonstrating that intracellular protein binding, in this case to metabolic enzymes, was the mechanism for bacterial accumulation of duloxetine. The authors went on to show that duloxetine bioaccumulation in gut bacteria shifted the overall gut bacterial community composition by altering the bacterial metabolite secretion and inducing metabolic cross-feeding, which was consistent with duloxetine binding to metabolic enzymes. These results are important because they demonstrate that human-targeted drugs can alter microbial gut communities by inhibiting direct bacterial growth and by creating bacterial cross-feeding opportunities. Lastly, the authors showed that drug bioaccumulation by bacteria can affect host response by studying duloxetine bioaccumulation using Caenorhabditis elegans as a model system. They followed animal movement as a behavioral readout for duloxetine in the presence and absence of bioaccumulating bacterial species and showed that the duloxetine-bioaccumulating strains attenuated the effect of the drug on the host.

These results further demonstrate the critical role that the gut microbiome can potentially play in altering human drug therapeutic response. The ability of drugs to alter the microbiome directly by antibacterial activity and indirectly via altered metabolic cross-feeding, and the ability of bacteria to alter drug availability by both biotransformation and bioaccumulation, highlight the need for and the importance of pharmacomicrobiomics in therapeutic approaches to personalized medicine. The findings of this study, although demonstrative, are limited by the small sample sizes of both drugs and gut bacteria in the study. Further, the mechanism of bioaccumulation of other drugs by gut bacteria may differ from that identified here for duloxetine. Overall, the results suggest that a broader scale mapping of the interactions between drugs and human gut bacteria is needed along with studies of gut bacteria interactions with drugs in the broader context of the microbiome versus the individual gut-bacteria pairs studied here.

“Human-targeted drugs can alter microbial gut communities by inhibiting direct bacterial growth and by creating bacterial cross-feeding opportunities.”

References are available at ContagionLive.com.

Highlighted Study
**IV Push Administration for Outpatient Parenteral Antimicrobial Therapy**

**TANNER JOHNSON, PHARMD, AAHIVP**

Intravenous (IV) antimicrobials administered in the outpatient setting, such as outpatient parenteral antimicrobial therapy (OPAT), offer the advantages of shorter hospital length of stay (LOS), prevention of hospital-associated complications, and significant cost savings. They also allow patients to return to activities of daily living with less interruption in their lives compared with prolonged hospitalization to receive IV antimicrobials. In OPAT, IV antimicrobials are typically administered via intermittent IV infusion, which is the generally accepted standard. In contrast, certain medications with a low risk of infusion-related reactions may be given more rapidly via IV push (IVP). Daptomycin, etrapenem, and several cephalosporin antibiotics are commonly administered as IVP in the outpatient setting because of convenience, patient preference, and demonstrated safety profile. Although IVP is a common administration method for these selected antimicrobials, there are limited effectiveness data regarding how this translates to OPAT patient-related clinical outcomes.

As a response to the nationwide IV fluid shortage associated with Hurricane Maria, Yagnik and colleagues from Parkland Health in Dallas, Texas, reported on an institutional protocol to transition select medications from IV drip infusion to IVP administration. Their paper details protocol execution and patient outcomes for self-administered IV antibiotics. Parkland Health pharmacists evaluated all self-administered antimicrobials in the outpatient setting for feasibility of IV drip infusion to IVP administration therapeutic interchange for cefazolin, ceftriaxone, cepfipime, and daptomycin based on published safety, efficacy, and syringe stability data.

To evaluate OPAT-related outcomes with their IVP administration therapeutic interchange protocol, Yagnik et al designed a quasi-experimental pre- and postintervention analysis comparing a preintervention cohort receiving IV drip antibiotic infusion (November 2016-June 2017) with a postintervention cohort receiving IVP administration (November 2017-June 2018). Included patients had osteoarticular infections and were treated with daptomycin, cefazolin, ceftriaxone, or cefepime. Data were retrospectively extracted from the electronic medical record, including patient demographics and antibiotic treatment regimen. Evaluated clinical outcomes included hospital LOS, all-cause 30-day and 1-year readmission, 30-day and 1-year emergency department (ED) visits, central line–associated bloodstream infection (CLABSI), and mortality. Additional outcomes evaluated cost comparison data, predischarge medication administration competency assessments, and nurse and patient satisfaction.

The authors evaluated 200 patients, including 95 in the preintervention cohort (IV drip) and 105 in the postintervention cohort (IVP). Patient baseline characteristics were similar between groups, which mostly comprised Hispanic men. The only statistical baseline difference between the groups was patient age (47 ± 13 years in the IV drip cohort vs 51 ± 12 years in the IVP cohort; \( P = .01 \)). The predominant antimicrobials used were ceftriaxone and daptomycin.

Evaluated clinical outcomes demonstrated a significant reduction in median hospital LOS in the IVP cohort compared with the IV drip cohort (11 vs 12 days; \( P = .03 \)). No differences were seen in 30-day or 1-year all-cause readmission, 30-day or 1-year ED visits, or mortality. No cases of CLABSI were reported in either cohort. Using the predischarge teach-back competency ratio—the number of times administration technique was taught before the patient demonstrated proficiency—the authors showed that IVP administration was easier and faster for patients to learn. They hypothesized that easier administration may explain the modest reduction in hospital LOS. Among 30 patients who took the patient satisfaction survey, 22 completed the interview, with 21 (95%) preferring IVP administration over IV drip. Cited reasons for IVP preference were reduced administration times, convenience, and clear instructions for administration. In addition to nurse and patient preference, the transition to IVP saved more than 500 L of normal saline and reduced infusion supplies and drug costs, resulting in nearly $45,000 in savings for the institution over the 6-month intervention period. Combined with decreased nursing education time and reduced hospital LOS for IVP patients, an additional $550,000 in costs was avoided.

The study had several limitations introduced by its quasi-experimental design. First, changes in medication and infusion supply–related costs likely decreased over time, which may have artificially inflated cost-savings findings. Additionally, a significantly higher proportion of patients in the IV drip cohort received daptomycin, which carries a higher average wholesale price than the cephalosporin antibiotics used more frequently in the IVP cohort. Second, although the IVP cohort demonstrated proficiency at medication administration more quickly than the IV drip cohort, it seems improbable that an additional teaching session would delay discharge by a full calendar day. It is likely that increased efficiencies in other steps of the discharge process, likely unrelated to the teaching and unaccounted for in this study, also contributed to a timelier discharge.

This study is one of the first to date examining the clinical, financial, and patient impact of IVP administration of antibiotics in the OPAT setting. With comparable clinical outcomes, the results demonstrate that IVP antibiotics are a reasonable alternative to IV drip administration in times of fluid shortages. In addition, documented patient preference and obvious financial incentives demonstrate a clear role for IVP administration in everyday OPAT practice.

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

**Highlighted Study**


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*Active member of the Society of Infectious Diseases Pharmacists*

*Active member of MAD-ID (Making a Difference in Infectious Diseases)*
Thromboembolism is a known complication of COVID-19 infection, although to date almost all data have focused on hospitalized patients with the disease. A team of scientists conducted a study examining the number of thrombosis cases in individuals with a COVID-19 diagnosis but who were not hospitalized, then compared the findings with data on people who were hospitalized with COVID-19. The study findings were published in the Lancet.

The research team accessed health records from the Netherlands, Italy, Spain, the United Kingdom, and Germany, including 909,473 individuals with COVID-19 who were not hospitalized and 32,329 patients in Spain who were hospitalized. They followed individuals' health journeys for a period of 90 days from COVID-19 diagnosis, noting the incidence of venous and arterial thromboembolism during that time. The mortality rate among each cohort during that time also was calculated.

Over a 90-day period beginning with a COVID-19 diagnosis or positive polymerase chain reaction (PCR) test, patients who were not hospitalized experienced venous thromboembolism at rates ranging from 0.21% (95% CI, 0.16%-0.27%) in the Netherlands to 0.80% (95% CI, 0.77%-0.83%) in Spain. Italian patients with COVID-19 experienced venous thromboembolism at a rate of 0.27% (95% CI, 0.21%-0.25%), UK patients at a rate of 0.27% (95% CI, 0.26%-0.29%), and German patients at 0.44% (95% CI, 0.36%-0.53%). For hospitalized patients in Spain, the 90-day incidence of venous thromboembolism was 4.52% (95% CI, 4.37%-4.68%).

Rates of arterial embolism in nonhospitalized individuals ranged from 0.06% (95% CI, 0.05%-0.07%) in the UK and Italy (95% CI, 0.04%-0.11%) to 0.79% (95% CI, 0.77%-0.82%) in Spain. In nonhospitalized patients in the Netherlands the arterial embolism rate was 0.10% (95% CI, 0.07%-0.15%), whereas in Germany it was 0.18% (95% CI, 0.12%-0.23%). In Spain, the rate rose to 3.08% (95% CI, 2.96%-3.21%) in hospitalized patients with COVID-19.

The authors noted that the higher rates of embolism seen in the cohort of Spanish patients, even in nonhospitalized individuals, were likely due to the data from Spain being particularly comprehensive (covering 80% of the population of Catalonia) and linked to hospital databases. This “probably indicates underreporting in data sets based solely on primary care records,” they wrote.

The death rate for individuals who were COVID-19 positive but not hospitalized in the 90-day period after diagnosis or positive PCR test ranged from 1.08% (95% CI, 0.96%-1.20%) in the Netherlands to 1.99% (95% CI, 1.95%-2.03%) in Spain, whereas the death rate for hospitalized patients was 14.61% (95% CI, 14.22%-15.00%). Venous and arterial thromboembolism that occurred after COVID-19 infection but before hospitalization was associated with higher rates of hospitalization and death. Venous and arterial thromboembolisms occurring after hospitalization also corresponded with higher mortality rates.

The investigators found that being male was associated with a higher risk of arterial thromboembolism and death; venous thromboembolism risk was higher in men in all locations except Germany and Italy. The authors reported that venous and arterial thromboembolism and death rates among nonhospitalized individuals with COVID-19 generally were higher for people 65 years and older. In the hospitalized cohort, the 65-plus age group had a higher risk of arterial thromboembolism and death, but not venous thromboembolism, which seemed to peak at approximately age 70 and then level off or decline. “This is probably largely explained by the substantial competing risk of death for those with COVID-19, which is much increased with older age,” they wrote.
Treatment With Direct-Acting Antivirals Improves Outcomes for Patients With Hepatitis C

by JEFF BENDIX and LOGAN LUTTON

Direct-acting antiviral (DAA) medicines show great promise as a way of improving the overall health of patients with chronic hepatitis C, according to results of a recent study.

As part of a national hepatitis C collaborative, investigators at Henry Ford Health System analyzed data from 6100 patients with hepatitis C, half of whom were treated with DAA. They found that patients treated with DAA had lower rates of hospitalization and shorter stays for both liver- and non–liver-related health issues than those not receiving DAA, and fewer emergency department visits for issues related to liver disease.

The study is believed to be the first examining health care utilization among patients who have hepatitis C with and without advanced liver disease and treated with DAA, according to a Henry Ford news release. The results were published online in *Clinical Infectious Diseases*.

“The findings of our study show that curing hepatitis C not only gets rid of the virus, it also improves the overall health of patients,” Stuart Gordon, MD, director of Henry Ford’s Hepatology Division and lead study author, said in the release.

The results, he added, are “consistent with our earlier studies that showed effective treatment of hepatitis C also reduces the risk of patients developing other health conditions like diabetes, kidney disease, stroke, and heart attacks.” DAA have been shown to cure hepatitis C in 98% of patients who take them, according to the release.

The release cites federal data showing that rates of new liver cancer cases rose by 38% from 2003 to 2012, and that at least 2.4 million Americans have hepatitis C, many without knowing it.

Although investigators did not quantify the potential cost savings resulting from DAA treatment, Gordon said they would be substantial. “If you're cured of the virus, your overall health will get better and you're less likely to be hospitalized for some other health condition,” he said.

The study, known as the Chronic Hepatitis Cohort Study, was conducted in collaboration with investigators from Geisinger Health System, Kaiser Permanente in Hawaii and Oregon, and the Centers for Disease Control and Prevention, who have been collecting and analyzing data drawn from the 4 health systems to assess the impact of hepatitis C and B on the US population.

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HIV Infection Increases Odds of Severe COVID-19 Disease

by RACHEL LUTZ

People living with HIV are at increased risk for severe COVID-19 at hospital admission and in-hospital mortality compared with those without HIV, according to a paper published in the *Lancet*.

Investigators from Switzerland used World Health Organization data from January 2020 to July 2021 to determine whether individuals with HIV and COVID-19 had increased odds of severe symptoms and in-hospital mortality compared with HIV-negative patients. The study authors noted that patients with HIV have underlying immune issues that put them at risk for severe disease.

The authors identified 19,655 individuals living with HIV and 180,524 who were HIV-negative whose information was submitted to the WHO Global COVID-19 Clinical Platform during their study period. The study population included patients from 38 countries.

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AFTER HOURS™: SENDING MEDICAL SUPPLIES TO UKRAINE

Taras Mahalay, MD, joins After Hours™ to discuss how he has been collecting and shipping medical supplies to Ukraine.

WELLBEING CHECKUP™: STAYING UP-TO-DATE ON VACCINATIONS

Iriny Salib, PharmD, shares tips for clinicians to get their patients up-to-date on vaccinations missed during the pandemic, with hopes of boosting immunization rates even higher than they were prepandemic.

BEHIND THE SCIENCE™: BEHIND THE IMPACT OF PREP IN HIV PREVENTION

Experts including Christina M. Madison, PharmD, FCCP, AAHIVP; Brenna Veres, PharmD, CSP; Jennifer Cocohoba, PharmD, MAS; and Cassandra Esperant, PharmD, AAHIVP, discuss the history and role of preexposure prophylaxis and the opportunities it presents for HIV care and prevention.

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Oral Carbapenems: Promise, Peril, and Pushbacks

By KATELYN KENNEDY, PHARMD; AND JASON GALLAGHER, PHARMD, FCCP, FIDP, FIDSA, BCPS

Gram-negative bacterial resistance in the United States continues to increase. As it has spread to the community setting, common infections such as urinary tract infections (UTIs) have become increasingly difficult to manage using oral medications and may necessitate the use of intravenous antibiotics. For complicated UTIs, 1 in 5 patients will have an infection caused by an extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, which limits options when they also are resistant to fluoroquinolones and trimethoprim-sulfamethoxazole.

Tebipenem and sulopenem are carbapenems with oral formulations that have been studied in phase 3 trials.3,4 Each typically has a broad spectrum of activity, including streptococci, methicillin-susceptible strains of staphylococci, Enterobacterales (including ESBL-producing strains), and many anaerobes. Notable exceptions to their useful activity include Enterococcus faecium, Clostridoides difficile, and many nonfermenting gram-negative bacilli such as Pseudomonas aeruginosa and Acinetobacter baumannii.3,6

TEBIPENEM PIVOXIL HYDROBROMIDE (TEBIPENEM HBR)

Tebipenem pivoxil is a formulation of tebipenem marketed in Japan as Orapenem for the management of otitis media, sinusitis, and pneumonia in pediatric patients with difficult to treat infections. Tebipenem pivoxil is used to manage infections caused by penicillin-resistant Streptococcus pneumoniae and Haemophilus influenzae.7 The drug has been reformulated as tebipenem HBr to improve stability and oral absorption. The oral bioavailability of tebipenem HBr is estimated to be 60%. It is rapidly converted to the active moiety, tebipenem, by carboxylesterases located in the intestinal epithelial cells.8 Tebipenem HBr is not metabolized by the liver or kidneys, but tebipenem undergoes renal elimination with 80% of the active metabolites excreted through the kidneys.9

The clinical efficacy and safety of tebipenem HBr for complicated urinary tract infections (cUTIs) were evaluated in a published double-blind, phase III, randomized clinical trial (NCT03788967) conducted at 101 sites in 15 different countries within central and eastern Europe, South Africa, and the United States. Patients were randomly assigned to either receive tebipenem HBr 600 mg by mouth every 8 hours or ertapenem (Invanz) 1 g intravenously every 24 hours for 7 to 10 days. The primary end point was a composite of clinical cure and microbiologic response, typical of trials for cUTIs. The median patient age was 58.1 years, and 50.8% of patients had a cUTI, with the remainder having acute pyelonephritis. Bacteremia was found in 11.5% of patients, and 19.7% of patients met criteria for systemic inflammatory response syndrome. Of the infecting pathogens, 90% were Enterobacterales, primarily Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, and Proteus mirabilis. ESBL production was detected in 23.4% of infecting pathogens, 39% of pathogens were fluoroquinolone nonsusceptible, and 43% of pathogens were resistant to trimethoprim-sulfamethoxazole. Tebipenem HBr was shown to be noninferior to intravenous ertapenem with respect to the primary end point (58.8% and 61.6%, weighted difference, –3.3%; 95% CI, –9.7 to 3.2). Tebipenem HBr was effective against common gram-negative pathogens, but the clinical response for ESBL-producing pathogens trended lower, with 83.9% response compared with 93.3% for ertapenem (difference, –9.50%; 95% CI, –21.62 to 2.10).2

In January 2022, the FDA granted a priority review of a new drug application (NDA) for tebipenem HBr. The FDA then conducted an analysis of the microbiological intent-to-treat (micro-ITT) population separate from what was outlined in the original statistical analysis plan. From this analysis, the FDA concluded that the prespecified noninferiority margin of –12.5% was not met and halted the approval of the medication. Spero Therapeutics, the manufacturer of tebipenem HBr, released a statement shifting the company focus to other...
TABLE. Comparison of Agents\(^2,5,17-19\)

<table>
<thead>
<tr>
<th></th>
<th>Tebipenem HBr</th>
<th>Sulopenem</th>
<th>Sulopenem etzadroxil/probenecid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Tebipenem, sulopenem: Each binds to penicillin binding proteins on the bacterial cell wall, inhibiting cell wall synthesis, leading to cell lysis.</td>
<td>Probenecid: blocks tubular secretion of β-lactams, decreasing renal elimination of drug and increasing systemic concentrations</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>600 mg by mouth every 8 hours</td>
<td>1000 mg intravenously daily</td>
<td>500 mg / 500 mg by mouth every 12 hours</td>
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<tr>
<td><strong>Dose adjustment</strong></td>
<td>May require renal adjustment</td>
<td>No data for hepatic or renal adjustment</td>
<td></td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>Significant reduction in valproic acid concentrations</td>
<td>Combination should be avoided</td>
<td></td>
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<tr>
<td><strong>Adverse effects</strong></td>
<td>Diarrhea, Headache, Nausea</td>
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Sulopenem is another carbapenem being developed for cUTIs. It is available in both an intravenous formulation as sulopenem and oral formulation as sulopenem etzadroxil with probenecid.\(^12\) The pharmacokinetics and pharmacodynamics of sulopenem are similar to that of other intravenous carbapenems. Sulopenem etzadroxil is an esterified prodrug designed for oral administration. The oral bioavailability is estimated to be 20% to 34% under fasted conditions but can be increased when administered with food or probenecid. Food consumption increases the area under the curve (AUC) by 23.6%, and 500 mg of probenecid increases the AUC by 62%.\(^11,12\) The oral formulation is being paired with probenecid.

The clinical efficacy and safety of sulopenem etzadroxil/probenecid were first studied for the treatment of uncomplicated UTIs in adult women. Patients were randomly assigned to receive either sulopenem etzadroxil/probenecid (500 mg/500 mg) by mouth twice daily for 5 days with 3 days of placebo or ciprofloxacin 250 mg by mouth twice daily for 3 days with 5 days of placebo. The primary outcome was overall success, which was a composite outcome of clinical and microbiologic success. The data analysis in this trial included both a microbiologic modified ITT resistant (micro-MITT R) and microbiologic modified ITT susceptible (micro-MITT S) population. These populations included all randomly assigned patients who received at least 1 dose of study drug and had a baseline uropathogen that was either nonsusceptible or susceptible to ciprofloxacin, respectively. As expected, sulopenem etzadroxil/probenecid was superior to ciprofloxacin in the micro-MITT R population with an overall success rate of 62.2% with sulopenem etzadroxil/probenecid and 36.0% with ciprofloxacin (difference, 26.2%; 95% CI, 15.1-37.4). For the micro-MITT S population, sulopenem etzadroxil/probenecid was not noninferior to ciprofloxacin with overall success rates of 66.8% and 78.6%, respectively (difference, −11.8%; 95% CI, −18.0 to −5.6).\(^3\)

Following the oral-only study, a study focusing on an intravenous to oral strategy of sulopenem formulation was conducted to assess the clinical efficacy and safety of intravenous sulopenem etzadroxil/probenecid for complicated UTIs. Patients were randomly assigned to receive either sulopenem 1000 mg intravenously for 5 days followed by sulopenem etzadroxil/probenecid (500 mg/500 mg) by mouth twice daily for 7 to 10 days of total treatment or ertapenem 1 g intravenously for 5 days followed by ciprofloxacin 500 mg by mouth twice daily (or amoxicillin-clavulanate if patient was ciprofloxacin resistant) for 7 to 10 total days of treatment. The primary outcome was the same as the previous trial. The intravenous and oral combination of sulopenem was not found to be noninferior to the combination of ertapenem and ciprofloxacin (67.8% vs 73.0%; difference, −6.1%; 95% CI, −12.0 to −0.1).\(^3\) This trial did not investigate complicated UTIs caused by multidrug resistant pathogens.\(^4\) In the previous 2 trials, the failure was hypothesized to be due to lower rates of asymptomatic bacteriuria, resulting in microbiologic failure in the patients treated with ciprofloxacin. The combination of intravenous and oral sulopenem also was investigated in complicated intra-abdominal infections and did not meet noninferiority criteria compared to the combination of ertapenem with step down to ciprofloxacin and metronidazole.\(^7\) Three clinical trials were completed and unfortunately all 3 missed their end points. The manufacturing company, Iterum Therapeutics, applied for an NDA based on results from the trial (NCT03354598) completed in uncomplicated UTIs that showed sulopenem etzadroxil/probenecid could be used for infections caused by fluoroquinolone-resistant pathogens. The FDA denied this request and required more supporting evidence to approve the medication. The manufacturing company, Iterum Therapeutics, is working with external vendors to design a clinical trial to provide additional evidence for the FDA.\(^14\)

**SUMMARY**

The approval of an effective oral carbapenem could change the way complicated UTIs caused by multidrug resistant organisms are managed. It could help reduce health care–related costs associated with the need for intravenous therapy by either preventing hospital admission or reducing hospital length of stay. However, the prospect of an oral carbapenem raises concern among health care professionals with regard to misuse further leading to antimicrobial resistance. Currently, tebipenem pivoxil, marketed in Japan as Orapenem for pediatric infections, is not recommended in first-line use but can be used after other antibiotics fail.\(^10\) The potential availability of oral carbapenems may worry infectious diseases clinicians, but they would increase options for oral therapy of infections currently treated parenterally. However, it seems these agents are not likely to be available as soon as once anticipated. ▲

References are available at ContagionLive.com.
Rickettsial Infections Heat Up in the US

With the warmer months in full swing, here are clinical considerations and strategies for tick-borne infections.


(continued from cover page)
documented cases must be reported to the local health department.

SFR infections in the US are commonly caused by Rickettsia rickettsii, transmitted by the dog tick (Dermacentor variabilis); Rickettsia parkeri, transmitted by the Gulf Coast tick (Amblyomma maculatum); or Rickettsia akari, transmitted by the bite of an infected mouse mite (Liponyssoides sanguineus). All rickettsial infections are most prevalent in the warmer summer months (May-August). In the US, Rocky Mountain spotted fever (RMSF), caused by R. rickettsii, is the most dangerous of the rickettsial infections. There were more than 5000 cases of RMSF in the US in 2019, slightly lower than the peak in 2017 of more than 6000 cases. However, rates of all rickettsial diseases have steadily increased from 2000 to 2017. Individuals older than 40 years and younger than 10 years have the highest risk for acquiring and dying from RMSF, respectively. In 2019, the highest number of SFR cases was seen in individuals 60 years and older. Fortunately, the fatality rate for RMSF is much lower than in the previous century, before tetracycline antibiotics (the agent of choice) were discovered, but it remains as high as 30% in untreated individuals. 

Other rickettsial infections in the US include anaplasmosis, ehrlichiosis, and typhus. Anaplasmosis is more commonly found in the midwestern and northeast US, and cases have been rising over the past 20 years. Anaplasma phagocytophilum is also transmitted by Ixodes scapularis ticks. The mortality rate for these infections is less than 1%. There are 3 ehrlichial infections common in the US: Ehrlichia chaffeensis and Ehrlichia ewingii transmitted by the lone star tick (Amblyomma americanum) found in the southeast US from Texas to Delaware, and E. muris, more commonly transmitted by the I scapularis tick, with cases being discovered in Wisconsin in 2009. The highest prevalence of ehrlichia is in the Oklahoma, Kansas, Arkansas, and Missouri region, with cases extending east from there. Ehrlichia cases do not seem to be fatal; no cases have been reported to the Centers for Disease Control and Prevention (CDC). Lastly, typhus is caused by Rickettsia typhi (mouse flea), and Rickettsia prowazekii (lice) in the US, although R prowazekii is relatively uncommon. Typhus caused by R typhi is most commonly found in California, Hawaii, and Texas and the incubation period is 5 to 14 days. It can lead to hospitalizations but has low mortality.

PATHOPHYSIOLOGY AND TRANSMISSION

Rickettsial infections are transmitted by the bite of an infected vector (eg, lice, ticks, or fleas). In individuals bitten by a tick with one of the SFR species, the disease starts a couple of days after the bite and rapidly progresses. It potentially lead to necrosis of the digits or limbs and the need for amputation.

R prowazekii is transmitted person-to-person via body lice, but other rickettsial infections have rodents as the natural reservoirs. Rickettsia akari and Orientia tsutsugamushi (found only in Southeast Asia) can recur years after the primary infection, despite antibiotic therapy.

When an individual is bitten by an infected vector, the bacteria travel through the lymphatic system and invade host cells to replicate by fission. They move cell to cell without damaging host cells, but cells are damaged via free radical injury, and there is enzymatic damage to cells that line blood vessels, which leads to leaky vessels. Increased permeability of membrane causes loss of protein, and the inflammatory response (vasculitis) leads to vasodilation, which also increases vascular permeability. This will cause edema and hypovolemia. If the brain or lungs are involved, there is no way to drain the fluid. Death is due to organ failure, often of the liver or kidneys.

For individuals with RMSF, within 2 weeks most will experience a spotted rash that starts on the wrists and ankles, which can then spread to palms, soles, and trunk. The rash will become raised,
and it may be possible to see petechiae in the center. Without treatment, the mortality rate is approximately 25% but could be as high as 85%. Rates are closer to 5% in those receiving treatment, but delayed treatment can increase the risk of mortality. RMSF disproportionally affects individuals with darker skin, at least in part because providers find it difficult to evaluate rashes on dark-pigmented skin.15

DIAGNOSIS
The key to diagnosing a rickettsial infection is knowing the patient’s exposure risks. Patients typically present with vague symptoms such as a headache, fever, and/or gastrointestinal upset. These are symptoms that could be mistaken for a variety of other infections if exposure isn’t known. Since the average incubation period for rickettsial infections is approximately 2 to 4 days, individuals who were infected while traveling may not develop symptoms until returning home, adding to the diagnostic challenge.16

Diagnostic tests may include immuno-fluorescence assays (IFAs), which detect IgG and IgM. These are very sensitive and specific for detection of antibodies early in the course of the disease (> 7 days after exposure) but are expensive and require training to perform. IFAs may not be available in areas with less access to health care technology. The same is true for the enzyme-linked immunosorbent assay (ELISA), although this method does allow for screening of many samples at once. Both IFA and ELISA can have cross-reactivity among rickettsial species.16 In addition, E. chaffeensis and E. ewingii cannot be distinguished from each other with serologic testing.17 Molecular testing in the form of polymerase chain reaction is another promising diagnostic tool that can provide more rapid results than serology or culture.17

The future of diagnosis may include whole-genome sequencing, which is highly sensitive and specific and can detect more species than current technology allows.17

PREVENTION
Individuals and pets should be checked for ticks after being outside. No vaccine is currently available for any rickettsial infections. A vaccine was attempted in the 1920s, however, it was time-consuming to create and only led to a milder disease in those exposed, rather than preventing disease. A subsequent vaccine produced in chicken egg embryos also was ineffective at preventing disease, but it did result in a less severe illness in those who did become infected. A live attenuated vaccine using human R. prowazekii was developed during World War II but 14% of those vaccinated developed the disease despite the vaccine showing long-lasting immunity.18

At this time, avoiding vectors—ticks, fleas, and lice—is the most important method of prevention. To avoid typhus, individuals should not reside in crowded areas, when possible. Maintaining distance from animal reservoirs is also important. Awareness of the risk of specific infections in a region can help travelers or immigrants to that region prepare properly.

TREATMENT
Because rickettsiae are obligate intracellular organisms, antibiotics that achieve intracellular concentrations are needed for effective treatment. Tetracycline-type antibiotics are the most effective and preferred treatment agents for rickettsial diseases. There have been historical concerns about using tetracyclines in children younger than 8 years for fear of staining the teeth or weakening the tooth enamel.19 Tetracyclines are lifesaving drugs in the case of SFR and are recommended even for children. More recent research into the adverse effects has shown that short courses of the drugs are unlikely to cause any harm to children.19

FUTURE OF RICKETTSIAL INFECTIONS
Increasing temperatures as a result of climate change can increase the survival and active periods for ticks that transmit rickettsial infections. This may increase the prevalence of ticks in areas where they are already established, as well as increase their habitable environments and allow for increased activity. Climate changes also affect ticks’ reproduction rates and the reservoirs for these organisms (often rodents). Prolonged warm seasons may lead to human hosts being in the outdoors for longer portions of the year as well.20,21 Mass migration, due to changes in climate that affect agriculture and livability of certain regions, also can have an impact on the spread of infectious diseases.22 Overcrowding, which is seen in some refugee camps, can lead to the spread of louse-borne typhus, which travels person to person.

As climate changes, we will see shifts in the distribution of these pathogens, as they expand into currently uninhabitable regions. For example, it is proposed that anaplasmosis, babesiosis, and ehrlichiosis will expand northward from their current endemic regions in the northeast into and beyond Rhode Island.23 Lyme disease has already spread from the Northeast US into Canada, and increasing temperatures are cited as the main influence. Lyme disease is proposed to spread farther northward as the climate changes and northern latitudes become increasingly warmer. In addition, as warmer temperatures begin earlier in the year, people may be more likely to encounter ticks because they will be able to be outdoors for an extended period of time.24

Lastly, R. prowazekii also is considered a suitable agent for biowarfare. It was developed into an aerosolized version as a biologic weapon in the 1930s by the Soviet Union and was tested as a biowarfare agent.18 Although categorized as a category B biologic agent by the CDC, to date it has not been used in biowarfare.25 Although rickettsial infections usually are limited to specific regions, it is important for all health care providers to be aware of the presenting signs and symptoms, as well as the risk factors a patient may have. Luckily, the treatment for all rickettsial infections is simple with a tetracycline antibiotic. ▲

References are available at ContagionLive.com.
A Day in the Life of a Public Health Professional

As the pandemic enters its third year, fatigue and frustration grow, but there is hope for the future.

by Saskia Popescu, PhD, MPH, MA, CIC

(continued from cover page)

so utterly unique that each brings its own hurdles.

Working in public health has never been for the faint of heart. Our work isn’t glamorous, and it is mostly filled with long hours, lower pay, and often few thanks. Add in the pandemic and that amplifies the worst of days. That being said, I’ve never worked with a more passionate, dedicated, and optimistic group of professionals. Trying to explain a day in the life of a public health professional involves an ever-changing dynamic of pandemic response, but it also entails trying to build a sustainable approach to COVID-19 while managing the day-to-day health threats that haven’t gone away during the pandemic.

It’s critical to note that my experiences in public health are unique and that no single epidemiologist or infection preventionist shares the same daily experiences. My path has been different, sometimes winding off the normal pathway and into perilous journeys, so my experiences are not always indicative of what others’ may be. Mistakes have been and will continue to be made, each with its own lesson and goal of avoiding such frustrations moving forward. This is especially painful and obvious during a pandemic, when your mistakes in this field have that much more impact and attention. In short, my journey is uniquely my own, but I hope this shares insight into what a day in public health is like during a pandemic.

RESPONSE

The COVID-19 response hasn’t stopped. In fact, for most public health workers I know (including myself) this period in response and life has become more complicated, more nuanced, and, frankly, more frustrating. We’re tired. I realize that everyone is exhausted, and COVID-19 has done untold damage to the collective world psyche. Working in public health during a pandemic, especially if you focus on infectious disease, is especially difficult. It’s an odd thing, training and studying your entire life to prevent and respond to a pandemic and then have it happen in your lifetime. Even now, friends often say, “Ah, this is like your Super Bowl!”

I understand that sentiment, I do. But let’s be frank about what it feels like to be in year 3 of a pandemic. Sure, those exercises, policies, lessons, and trainings we've done throughout our careers do have a place and are helpful. But imagine watching a disaster that you’ve dedicated your life to preventing happen, slowly and over and over—and you’re powerless. You work more hours than ever to try to slow the disastrous burn and prevent the disease from reaching every corner of the globe—and it doesn’t matter. Is this a scenario that we’ve trained our whole lives for? Yes. But we’re not happy about it. We’re not celebrating being here, and there is no winner. People are dying and will continue to die from the disease. Death rates will likely increase if people consider COVID-19 “over with” and ignore the need for boosters and...
continued public intervention efforts such as masks and testing.

Right now, the response to the pandemic looks different than it did in 2020. My days are spent dealing with outbreaks and clusters, navigating the complexities of at-home testing, and helping identify interventions that are sustainable despite declining public interest. I work with public health departments reporting clusters or other communicable diseases. I identify ways to build a sustainable COVID-19 approach that is more long term. Lately I’ve spent a lot of time doing risk-matched approaches to COVID-19 that are more nuanced and situational. I often discuss the local public health requirements vs how employers may want to navigate opaque public health guidance. Should we quarantine an individual if it’s not required? What about masks? Should we still wear masks if the numbers aren’t that bad and they’re no longer required? These are the questions we face. This often requires explaining that the way the Centers for Disease Control and Prevention (CDC) has changed community risk levels is no longer ideal. It means describing that we’re only seeing the tip of the iceberg in the number of cases because at-home antigen tests aren’t being reported consistently. Now more than ever, my work in COVID-19 response for hospitals and businesses is much more nuanced and a balancing act. It’s like explaining the risks of a choose-your-own adventure when it comes to recommendations such as shortened isolation.

Much of my infectious disease epidemiology work now focuses on reviewing public health guidance, designing and implementing policies, and exploring the social dynamics of 3 exhaustive years of COVID-19. Moreover, this work must happen in the face of individuals and businesses that want to be done with COVID-19 and no longer want to invest time and resources into dealing with it. What probably feels like a complex time for the public is amplified for us in public health. Michael Bazaco, PhD, a infectious disease epidemiologist, and I were recently chatting when I asked him—“if you could say anything about us and the work we do, what would it be?” He replied, “We aren’t perfect but we try our best and we work our butts off trying our best to protect as many people as we can, particularly the most vulnerable among us.”

Oh, and did I mention monkeypox?

TEACHING
Many of my public health colleagues also are academics. I continue to teach, which is often a good break from the emergent, rapid response nature of COVID-19 public health work. Academic work allows us to do research and also share some of our lessons learned. More recently, my courses on health care readiness and epidemiology and policy have included lessons from COVID-19 response. They also included how pandemics affect our ability to respond to other health threats. This has been a great time to discuss the impact of a pandemic on our day-to-day health threats such as antimicrobial resistance, vaccine-preventable diseases, food safety, emerging infectious diseases (aahem, monkeypox), etc.

One thing that many of my colleagues and I have noticed is the effect the pandemic has had on students, including their engagement, quality of work, and more. So many have lost family members, or are dealing with personal issues in the midst of school and COVID-19. We have voiced the need for empathy right now. I routinely tell my students that we’re going to talk about non-COVID-19 issues (because we all need that break) and to let me know if they need an extra few days because of, well, life. I also remind students that going to graduate school during a pandemic, especially if they’re working and/or caring for family, is a lot to handle and I’m here to support them. Now more than ever we can all use a moment to catch up or embrace empathy from our professors, bosses, and colleagues.

SCIENCE COMMUNICATIONS AND MEDIA
Perhaps one of the more unexpected facets of working in public health right now is the media attention. I’ve been fortunate to speak with journalists about COVID-19 response and its impact on health care and public health. Since 2020 so many of us in public health have found ourselves unintentional voices for infectious disease and global health issues. I’m eternally grateful for the amazing journalists who have asked for my insights and their continued work to bring truth and science to this novel situation.

Navigating the world of science communications (scimm) and media has been harrowing. It comes with good and bad. Seeing so many wonderful and brilliant professionals share their expertise and insights is awe-inspiring. But with that come not only the armchair experts but also the vitriol. As we work in social media and various forms of journalism, we are learning how best to communicate nuanced and often complicated topics. We have also learned about the often-abusive nature of social media and how to communicate frustrations or a critique of government response and CDC guidance. Developing public health guidance is not easy and often we’re making recommendations based off preliminary data because we know the public needs something to help navigate life in a pandemic. It’s difficult, though, to see a policy change or data reporting shift that you disagree with but you don’t want to disparage publicly so as not to diminish trust in our national public health agencies or leaders.

It’s a quiet week if you don’t receive creepy private messages or abusive comments telling you how stupid you are or what you could have done differently in the COVID-19 response. This part of working in public health is exhausting and there have been periods in the past 3 years when I simply have not had the energy to engage. I don’t get paid for social media posts or interviews. In fact, these often require finding time in our day for conversations or securing a spot for a Skype interview. The amount of times I’ve had to find a quiet corner in a hospital parking lot, empty conference room, or airport corner is comical. Finding innovative ways to prop up an iPad or laptop is a skill we all now have. Although I am grateful for these platforms, it is difficult knowing that no matter what you say, it will incur the wrath of those online who want to argue. Even other investigators find ways to continue scientific debates across specialties that do us a disservice when done on Twitter and not in good faith.

In addition to our daily work duties and scimm, many of us still serve on boards or panels. From science associations to organizations, we work to bring our fields forward. This increasingly comes with conferences that again are being held in person. Professional conferences and meetings are important in the field of infectious disease and help us identify research gaps, possible collaborations, and achievements our peers have made. Even masked, getting to see our peers after 3 years, or meet some for the first time in person, is very welcome.

FATIGUE AND OPTIMISM
Each day is different. Sometimes I spend my whole day just dealing with a single cluster of COVID-19 issues, discussing quarantine across multiple public health jurisdictions, learning about monkeypox protocols, developing lesson plans, or running from meeting to meeting. Some days involve doing interviews on current COVID-19 topics, such as gaps in data due to at-home testing; sharing the latest pandemic information on social media; or working on research collaborations with colleagues.

What is consistent is the fatigue. The exhaustion that we in public health feel in our bones. The people we have lost. The personal battles we’ve faced while working in a pandemic. Some days are more difficult than others, but in all days I try to end with a sense of optimism. The world of public health and infectious disease is filled with so many brilliant, kind, supportive, hard-working, and humorous individuals. Each day, I’m grateful for my peers, colleagues, and role models who inspire me to not only continue this work but also bring about innovation and pragmatism into the future of public health.
PrEP State of the Union: Adherence, Access, Uptake Issues

Although this form of prophylaxis is highly protective, there are situations in which breakthrough infections occur.

By Kaitlyn Jarrell, PharmD, BCPS, AAHIVP

(continued from cover page)

the US: 2 oral pills and 1 long-acting injectable (TABLE 1).1–13

Since PrEP became available, its uptake has steadily increased over the years. Unfortunately, disparities and underutilization remain. The Centers for Disease Control and Prevention (CDC) esti mates 1.2 million individuals would benefit from PrEP. However, in 2020, only 25% of eligible individuals received a prescription for it. Although this is a significant increase from previous years (eg, 3% received a prescription in 2015), there is room for growth, particularly within groups disproportionately affected by HIV.1

HOW EFFECTIVE IS PREP?

PrEP reduces the risk of acquiring HIV infection through intercourse by 99% when it is taken as prescribed:1 There are not as much data on those at risk for HIV acquisition through injection drug use. However, clinical trials have shown oral PrEP to reduce the risk of acquiring HIV by at least 74%. This figure is based on PrEP with tenofovir disoproxil fumarate (TDF) monotherapy with less-than-perfect adherence.3 Knowing this, it can be inferred that protection is likely greater using the 2-drug regimen (F/TDF) daily. Regardless, in order for PrEP to be effective, adherence is key.

Although injectable cabotegravir (CAB-LA) is newer to the scene it was approved by the FDA in December 2021, data from the initial safety and efficacy trials, HPTN 083 (NCT02720994) and HPTN 084 (NCT03164564), have demonstrated its superiority compared with daily oral F/TDF. These results likely can be attributed to eliminating the need for daily adherence: CAB-LA is administered every 2 months.

It is important to note that PrEP is not immediately effective. It takes time for the drug to accumulate in tissues to provide maximum protection. For receptive anal intercourse, oral PrEP is maximally protective after 7 days of daily use. For receptive vaginal intercourse and injection drug use, oral PrEP is maximally protective after 21 days of daily use. To date, there are no data showing how long it takes to achieve maximum protection for insertive anal and insertive vaginal intercourse. It also is unknown how long it takes for injectable PrEP to reach maximum protection.1

WHAT ABOUT THE OTHER 1%?

Most of the cases in which PrEP fails are due to less-than-optimal adherence, which results in inadequate drug levels that do not offer protection against HIV. These cases are different from breakthrough infections or true PrEP failures. Breakthrough infections are rare but they still are possible. As more individuals are prescribed oral PrEP, clinicians are slowly starting to see more individuals with optimal adherence who still contract HIV while on PrEP. So far, there have been fewer than 20 documented breakthrough infections despite more than 2 million PrEP initiations worldwide.7,9

Twelve case reports have been published describing cases of seroconversion while on oral PrEP despite adherence confirmed by detectable drug levels. Among these cases, 9 had HIV with mutations to 1 or both components of oral PrEP with or without additional mutations. Three of the 12 cases had no HIV resistance. Of the 12, 9 were receiving PrEP consisting of F/TDF (8 daily, 1 on demand). The remaining 3 were receiving daily TDF.10

The initial trial for CAB-LA included both cisgender men who have sex with men and transgender women who have sex with men. During the trial, there were 7 breakthrough infections among participants who received their injections on time. In 2 of the 7 cases, drug levels unexpectedly decreased after the first injection.3 It may be that it takes longer for drug levels to reach adequate concentrations to provide protection. Despite these breakthrough infections, CAB-LA was shown to be highly effective, with a 66% reduction in incident HIV infections in study participants who received CAB-LA compared with F/TDF.6 A trial evaluating CAB-LA in women is ongoing, but there have been no breakthrough infections to date.

WHY DOES PREP FAIL?

There is no consensus definition for PrEP failure. Some have defined PrEP failure as any HIV infection that occurs at any point along the PrEP continuum of care.11 These infections can occur due to several reasons (TABLE 2).11,12

WHAT HAPPENS WHEN PREP FAILS?

When PrEP fails, there may be a delay in detection of HIV infection due to
Most of the cases in which PrEP fails are due to less-than-optimal adherence, which results in inadequate drug levels that do not offer protection against HIV.
Cefiderocol’s Role in Managing Carbapenem-Resistant *Acinetobacter baumannii* Infections

This agent is likely best utilized as part of a combination when treating this bacterium, but data regarding appropriate combinations are scarce.
pathogen to manage, often requiring combination therapy with polymyxins or tigecycline. Cefiderocol, a siderophore cephalosporin, has emerged as an attractive therapeutic option for multidrug-resistant gram-negative pathogens, including CRAB, due to its relative stability in the presence of a wide array of β-lactamases and its novel mechanism of entry into the periplasmic space of gram-negative pathogens. Although cefiderocol retains excellent in vitro activity against gram-negative isolates, its role in the management of infections caused by CRAB remains uncertain. A key gap in our understanding of cefiderocol is whether it is an appropriate agent for monotherapy or is best reserved as a component of combination regimens against CRAB infections.

CEFIDEROCOL PHARMACOLOGY

As a siderophore cephalosporin, cefiderocol contains a conjugated catechol moiety at the 3-position side chain, which allows it to chelate soluble ferric iron and subsequently undergo active transport across the outer cell membrane of gram-negative pathogens. This ability to utilize active transport allows cefiderocol to achieve higher concentrations at the site of action, resulting in a relative decrease in the minimum inhibitory concentration. Cefiderocol is stable in the presence of a wide array of clinically relevant β-lactamases, including extended-spectrum β-lactamases, serine carbapenemases, and metallo-β-lactamases. These features contribute to the potent in vitro activity of cefiderocol, making it an important therapeutic agent to manage extensively drug-resistant infections.

CEFIDEROCOL IN VITRO DATA

Overall rates of cefiderocol resistance are low, although resistance has been reported following exposure to cefiderocol or other β-lactams among both Enterobacteriales and nonfermenters. Cefiderocol heteroresistance also has been reported among surveillance of carbapenem-resistant gram-negative organisms, including Acinetobacter spp, and may complicate its use in clinical practice because heteroresistance screening is not readily integrated into routine susceptibility testing. Heteroresistance is a phenomenon in which a susceptible population develops resistance when exposed to an antimicrobial but susceptibility is restored after cessation of antimicrobial exposure and is not detected by routine susceptibility testing. Heteroresistance is thought to be caused by the presence of resistant subpopulations that thrive under the selective pressure of antimicrobial exposure. Although the clinical relevance of cefiderocol heteroresistance is unclear at this time, colistin heteroresistance has been associated with antimicrobial failure in in vivo models of Enterobacter cloacae and Klebsiella pneumoniae infections. A surveillance study of carbapenem-resistant pathogens reported similarly low rates of resistance to cefiderocol compared with results from the CREDIBLE-CR trial (NCT02714595) (8% vs 3%), but population analysis profiling indicated that cefiderocol heteroresistance was much higher and more closely aligned with all-cause mortality results from CREDIBLE-CR (59% and 49%). Although this surveillance study represents in vitro data and is not directly correlated with clinical outcomes, high rates of cefiderocol heteroresistance support avoiding cefiderocol as monotherapy for serious CRAB infections because an adjunctive agent may provide antimicrobial activity against cefiderocol-resistant subpopulations.

An in vitro study of cefiderocol activity alone or as part of a combination against multidrug-resistant Acinetobacter baumannii reported synergy with multiple other agents. Synergy was most consistently observed when combined with amikacin or meropenem, despite resistance to both of these agents in all isolates tested.

CEFIDEROCOL COMBINATION THERAPY CLINICAL DATA

Despite in vitro activity, clinical data supporting use of cefiderocol remain sparse. Results from APEKS-cUTI (NCT02321800), a phase 2 clinical trial in patients (n=371) with complicated urinary tract infections and pyelonephritis, established the clinical utility of cefiderocol for genitourinary infections but failed to establish its role in the management of carbapenem-resistant pathogens. As expected, none of the patients with microbiological data in this study had CRAB isolated.
in their cultures. Subsequent studies evaluated cefiderocol use for infections outside the urinary tract.

APEKS-NP (NCT03032380), a phase 3 trial evaluating cefiderocol use in nosocomial pneumonia (n=292), was not designed to study carbapenem-resistant pathogens but did include a small number (n=53) of meropenem-resistant isolates, including *Acinetobacter* spp. Among patients with meropenem-resistant *Acinetobacter* spp respiratory isolates, no differences in 14- and 28-day all-cause mortality were seen between the 26 patients who received cefiderocol and the 27 patients who received meropenem. The results from the APEKS-NP trial suggest that cefiderocol monotherapy is no better than meropenem monotherapy for CRAB.15

The role of cefiderocol for the management of carbapenem-resistant pathogens from a range of clinical syndromes was further explored in the CREDIBLE-CR trial (n=150). Patients with bloodstream, pulmonary, or genitourinary infections caused by carbapenem-resistant gram-negative pathogens were assigned to receive either cefiderocol or best available therapy. Combination therapy was permitted in the trial with a maximum of 3 agents in the best available therapy arm and up to 1 adjunctive antibiotic, excluding polymyxins or β-lactams, for patients who received cefiderocol. All-cause mortality rates among 42 patients who received cefiderocol and 17 patients who received alternative therapy with infections caused by CRAB were 50% (n=21) and 18% (n=3) respectively. Excess mortality was also compounded by lower frequency of combination therapy in the cefiderocol arm (18%) than the alternative therapy arm (71%) and more patients in the cefiderocol arm in the intensive care unit at randomization (56% vs 43%) or in septic shock (19% vs 12%).16 The exact cause of this excess mortality is not entirely clear. However, mortality did appear elevated in patients with *Acinetobacter* spp isolates.16

A recent observational, retrospective cohort study compared outcomes of 47 patients who received cefiderocol-based regimens and 77 patients who received colistin-based regimens for the management of infections caused by CRAB.17 The study population was critically ill, with 89% of patients in the intensive care unit and 56% of patients on mechanical ventilation. Most patients had bloodstream infections (62%) or ventilator-associated pneumonia (28%).

In contrast to cefiderocol use in CREDIBLE-CR, 68% of patients in this study received cefiderocol as part of a combination regimen, most commonly with tigecycline (n=21), followed by fosfomycin (n=8).17 Cefiderocol-based therapy was associated with a decrease in 30-day mortality compared with colistin-based regimens, 34% and 55.8% respectively.17 Improved 30-day mortality in the cefiderocol arm was largely driven by bloodstream infections (25.9% vs 57.5%), but there was no significant difference for patients treated for ventilator-associated pneumonia (58.3% vs 56.5%).17 Monotherapy with either cefiderocol or colistin therapy was associated with microbiological failure (42.9% vs 6.3%), and mortality was lower among patients who received a cefiderocol-based combination compared with cefiderocol monotherapy (6.3% vs 40%).17

The results of this study suggest that cefiderocol combination therapy for severe CRAB infections may be appropriate.

**PRACTICAL APPLICATIONS**

Current recommendations for the management of severe infections caused by CRAB suggest combination therapy with at least 2 agents, with in vitro activity preferred when possible.3 Cefiderocol is currently only recommended as combination therapy for CRAB in refractory infections or situations where tolerability precludes the use of other agents. Available clinical trial data report inconsistent success with cefiderocol use with outcomes possibly improved when used in combination with other agents.

Although in vitro data suggest synergy when combined with meropenem or amikacin, clinical data on these combinations are lacking. A small number of published cases of cefiderocol use for CRAB infections are available, with use reported as both monotherapy and combination therapy. Cefiderocol frequently has been combined with fosfomycin, tigecycline, or polymyxins in available published cases, similar to prospective and retrospective studies including cefiderocol as combination therapy.4,16-20 When used for infections caused by CRAB, cefiderocol should be used in combination with another in vitro active agent if possible, or with meropenem or amikacin if no other active agents are available or a third agent is used.

**CONCLUSION**

CRAB is a difficult-to-manage nosocomial pathogen with limited treatment options. Current expert recommendations prefer combination therapy, often relying on high-dose ampicillin/sulbactam or an intolerable, highly toxic agent such as a polymyxin.3 The arrival of cefiderocol initially offered hope for a single-agent regimen for the management of CRAB infections. However, available data do not support its use as monotherapy. In clinical practice, cefiderocol may be an option as a component of combination therapy, but data regarding the use of cefiderocol as a component of combination therapy are scarce and no preferred combination has been identified. ▲

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Antimicrobial Stewardship: More Is Better

A robust stewardship program requires a comprehensive investment in technology and staff.

by Meghan N. Jeffres, PharmD, BCIDP; and Lauren R. Biehle, PharmD, BCPS, BCIDP

The original antimicrobial steward was Alexander Fleming. After discovering the antimicrobial properties of Penicillium notatum in 1928, he spent the next 20 years identifying the active component, determining the spectrum of activity, and establishing that penicillin would be safe for human consumption because it did not destroy leukocytes in human blood as did so many compounds he had tested before. This work earned Fleming the Nobel Prize in Physiology or Medicine in 1945, which he shared with Ernest B. Chain and Howard Florey. In his acceptance speech, Fleming told the inspiring story of penicillin. However, the mood changed in his closing paragraph: “But I would like to sound 1 note of warning. Penicillin is to all intents and purposes nonpoisonous, so there is no need to worry about giving an overdose and poisoning the patient. There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant. Here is a hypothetical illustration: Mr X has a sore throat. He buys some penicillin to give himself, not enough to kill the streptococci but enough to educate them to resist penicillin. He then infects his wife. Mrs X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin, the treatment fails. Mrs X dies. Who is primarily responsible for Mrs X’s death? Why, Mr X, whose negligent use of penicillin changed the nature of the microbe. Moral: If you use penicillin, use enough.”

Although “the danger of the ignorant man” is a tempting tag line, clearer heads have identified antimicrobial stewardship as the more palatable description for those who have heeded Fleming’s warning.

Nearly 100 years after the discovery of penicillin and 77 years after Fleming’s warning of the ignorant man, antimicrobial stewardship programs are mandatory for acute and long-term care facilities that participate in Centers for Medicare & Medicaid Services (CMS) and that are accredited by The Joint Commission. In 2016, CMS requirements included policies and procedures to identify, report, investigate, and control infections and communicable diseases among residents, staff, and visitors. In 2017, the requirements added the presence of an antibiotic stewardship program. Medical centers that have invested in staff and technology can lead to robust stewardship programs that are more likely to slow the progress of microbial resistance and improve patient outcomes.
program as a subset or partner of an infection prevention program. The stewardship program must have antibiotic use protocols and a method of monitoring antibiotic use. An update in 2019 added some requirements (eg, naming a leader of the stewardship program and distinctly separating the program from infection control and prevention) but also relaxed other requirements and clarified several areas of confusion.²

For instance, the 2019 update allowed hospitals within a single health system to have a unified stewardship program as well as a single quality assessment and performance improvement content for infection prevention and the antimicrobial stewardship program.

Although CMS regulations do not dictate how hospitals complete all aspects of a stewardship program, they do require that all hospitals comply with a specific guideline or set of guidelines. One of the most commonly used is the Core Elements of Hospital Antibiotic Stewardship Programs created by the Centers for Disease Control and Prevention.³ The Core Elements guidelines initially were available in 2014 and served as a guide for implementation. The 7 core elements are hospital leadership, accountability, pharmacy expertise, action, tracking, reporting, and education. In 2014, 41% of hospitals reported that all Core Elements were in place at their institution. Self-reported adherence increased to 91% by 2020, likely due in part to the change in requirements in the 2019 update.⁴

Because the Core Elements were written with enough ambiguity and flexibility to allow for innovation and tailoring to the needs of each facility, this can result in varying degrees of effort and/or scope. Facilities that have not hired stewardship experts can check the boxes of Core Elements with relatively rudimentary practices. The practice of box checking by a stewardship program is often not the fault of program members but the outcome of limited resources. Limitations may include a lack of facility infrastructure for antimicrobial data extraction and communication, lack of stewardship expertise or specialized training, and/or inconsistent communication with an outside microbiology laboratory.⁵ The concern with box checking is that these efforts may not actually prevent the emergence of resistant pathogens and infections, the foremost goals of stewardship programs. Conversely, facilities that have invested in staff and technology can lead robust stewardship programs that are more likely to slow the progress of microbial resistance and improve patient outcomes.

A robust stewardship program requires investment in health information technology (HIT) such as electronic health record (EHR) systems, add-on clinical decision support systems (CDSS), clinical dosing tools, application-based technology, and learning management systems. EHR systems such as Cerner, EPIC, and Meditech allow all stewardship interventions to be performed within a single system. Add-on CDSS can collate data from multiple sources, produce intervention alerts, and allow intervention documentation separate from the EHR.⁶ Mobile applications containing facility-specific treatment pathways and antimicrobial use guidance have increasingly replaced printed booklets. A systematic review of 13 studies assessing the efficacy of stewardship smartphone applications found that guidelines were more frequently accessed and compliance with treatment guidelines increased after app implementation.⁷ Learning management systems are needed to deliver and track educational programs. The Core Elements note that education is most effective when paired with interventions and outcomes. A learning management system can track who has engaged in or completed educational initiatives and allows for comparative analysis both before and after the education and between participants and those who have not engaged in the education initiative. Many of these HIT support systems require capital investment but allow clinicians to make more stewardship interventions as well as assess the efficacy of these initiatives.

The other key area of investment when developing a robust stewardship program is staff.⁸ The CMS regulations do not address staffing requirements or ratios to accomplish their requirements. The Veterans Health Administration, the Antibiotic Stewardship Task Force, and the Clinical Pharmacy Practice Office collaborated to create a staffing calculator based on time-in-motion tracking studies from 12 facilities that assessed clinical interventions and program management activities.⁹ The calculated result was 1 full-time employee (FTE) per 100 occupied hospital beds. After excluding outliers, the group proposed 1 pharmacist FTE and 0.25 physician FTE per 100 occupied beds. They concluded that a minimum of 0.25 physician FTE and 0.5 pharmacist FTE should be allotted for hospitals with fewer than 100 beds. The accompanying TABLE includes options for external resources such as telestewardship and online training for programs without on-site staff.

CMS is likely to both increase requirements in the acute care setting and expand antimicrobial stewardship requirements to all other health care settings, including rehabilitation facilities, ambulatory surgery centers, dialysis and wound care centers, and out-patient clinics. It would be helpful if they also included criteria on the technology and staffing required to meet these regulations. These criteria should make the days of a single pharmacist running a stewardship program for a 600-bed hospital a thing of the past. And stories from these days will be added to the list of campfire stories of calculating vancomycin kinetics by hand and carrying a pager.¹⁰

References are available at ContagionLive.com.

—Alexander Fleming

<table>
<thead>
<tr>
<th>Lauren R. Biehle, PharmD, BCPS, BCIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauren R. Biehle, PharmD, BCPS, BCIDP, is a clinical associate professor of pharmacy practice at the University of Wyoming School of Pharmacy. Her practice involves daily rounds with an inpatient family medicine team and her research interests include hospital-acquired infections, antimicrobial stewardship, and active learning.</td>
</tr>
</tbody>
</table>

Go to page 22 to see the differences between rudimentary and robust stewardship programs. >>
### TABLE. Comparison of Stewardship Programs by Resources and Development

<table>
<thead>
<tr>
<th>MINIMAL RESOURCES—RUDIMENTARY PROGRAM</th>
<th>SUBSTANTIAL RESOURCES—ROBUST PROGRAM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Policies/ procedures</strong></td>
<td>Institution-specific multidisciplinary antimicrobial policies/procedures†</td>
</tr>
<tr>
<td>Design policy describing stewardship program that contains the core elements* and reflects the scope/level of acuity of the institution†</td>
<td>Describe resistance patterns and identify pathogens of interest</td>
</tr>
<tr>
<td>Design policy describing stewardship program that contain the core elements* and reflect the scope/level of acuity of the institution†</td>
<td>Design policies describing stewardship program that contain the core elements* and reflect the scope/level of acuity of the institution†</td>
</tr>
<tr>
<td>Integrate stewardship into existing quality improvement/patient safety initiatives</td>
<td>Provide stewardship leadership dedicated time for initiatives</td>
</tr>
<tr>
<td>Support online or in-person training for personnel involved in stewardship</td>
<td>Provide technical support and training to stewardship leadership</td>
</tr>
<tr>
<td>Make formal statement of support of stewardship efforts a priority†</td>
<td>Make formal statement of support of stewardship efforts a priority†</td>
</tr>
<tr>
<td>Consider telestewardship or other external resources and include training in stewardship in job description</td>
<td>Incorporate expectations of stewardship into job descriptions and annual reviews</td>
</tr>
<tr>
<td>Demonstrate coordination between those involved in antibiotic use and resistance on a multidisciplinary team, including (when available): infection prevention, quality improvement, medical staff (and infectious diseases physicians), nursing, and pharmacy†</td>
<td>Design multidisciplinary stewardship team to coordinate interventions including, clinicians, infectious diseases physicians†, infection prevention, patient safety/quality improvement, microbiologists, information technology, nursing, and others†</td>
</tr>
<tr>
<td>Appoint leader who is qualified through “education, training, or experience” in infectious diseases/stewardship†</td>
<td>Appoint experienced leaders or coleaders, often physician and pharmacist experienced in antimicrobial stewardship†</td>
</tr>
<tr>
<td><strong>Accountability</strong></td>
<td>Select senior executive as leader (“champion”)</td>
</tr>
<tr>
<td>Identify physician at executive level or an individual who reports outcomes to executive level</td>
<td>Routinely schedule meetings with institution leadership</td>
</tr>
<tr>
<td>Routinely schedule reporting of outcomes with institution leadership</td>
<td>Stewardship leader responsible for documentation, communication, and education regarding stewardship initiatives†</td>
</tr>
<tr>
<td>Stewardship leader responsible for documentation, communication, and education regarding stewardship initiatives†</td>
<td>Designate pharmacist trained in infectious diseases/stewardship as a leader of stewardship initiatives</td>
</tr>
<tr>
<td><strong>Pharmacy expertise</strong></td>
<td>Designate diagnostic stewardship as component of antimicrobial stewardship</td>
</tr>
<tr>
<td>Designate part-time or full-time pharmacist leader</td>
<td>Have microbiology laboratory design cascade/selective reporting of results based on facility-specific treatment guidelines</td>
</tr>
<tr>
<td>Train in stewardship</td>
<td>Collaborate with microbiology laboratory and infection control to incorporate appropriate ordering of urine cultures that represent infection instead of colonization, purulent vs nonpurulent skin infections, blood culture and line infection vs contamination, etc</td>
</tr>
<tr>
<td>Participate in systemwide stewardship initiatives</td>
<td>Incorporate prospective audit and feedback as well as preauthorization as foundation of stewardship interventions</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Incorporate institution-specific treatment guidelines into order sets and clinical decision support</td>
</tr>
<tr>
<td>Consider adopting antibiotic treatment recommendations from other institutions within system or nearby facilities that align with national guidelines and best practices†</td>
<td>Design institution-specific treatment guidelines that align with national guidelines and best practices; base them on evidence-based empiric recommendations, patterns of resistance, formulary, and antimicrobial data†</td>
</tr>
<tr>
<td>Target broad-spectrum antibiotics for streamlining/discontinuation such as those active against methicillin-resistant Staphylococcus aureus (MRSA) or Pseudomonas</td>
<td>Incorporate prospective audit and feedback as well as preauthorization as foundation of stewardship interventions</td>
</tr>
<tr>
<td>Focus on common infections for intervention†: community-acquired pneumonia, skin and soft tissue infections, and urinary tract infections</td>
<td>Design institution-specific treatment guidelines that align with national guidelines and best practices; base them on evidence-based empiric recommendations, patterns of resistance, formulary, and antimicrobial data†</td>
</tr>
<tr>
<td>Review antibiotic orders for appropriate duration of therapy</td>
<td>Review antibiotic orders for appropriate duration of therapy, consider automatic stop orders</td>
</tr>
<tr>
<td>Review antibiotic orders for duplicate therapy</td>
<td>Review antibiotic orders for duplicate therapy</td>
</tr>
<tr>
<td>Review antibiotic orders for opportunities to convert from intravenous to oral therapy†</td>
<td>Design policies for automatic conversion from intravenous to oral therapy for appropriate antimicrobials†</td>
</tr>
<tr>
<td>Consider antibiotic time-outs with assistance from nursing, pharmacy, and/or clinicians</td>
<td>Consider provider-led antibiotic time-outs</td>
</tr>
<tr>
<td>Update electronic medical record with reaction to β-lactams and provide antimicrobial recommendations based on level of risk</td>
<td>Assess patients with reported β-lactam allergy for risk stratification and appropriateness of antibiotics</td>
</tr>
<tr>
<td>Review antimicrobial dosing for renal/hepatic dysfunction</td>
<td>Require indication for antibiotic orders</td>
</tr>
<tr>
<td><strong>Tracking</strong></td>
<td>Review antimicrobial dosing for renal/hepatic dysfunction and dose optimization</td>
</tr>
<tr>
<td>Submit antibiotic use data to National Healthcare Safety Network Antimicrobial Use Option, if available</td>
<td>Incorporate infection-specific interventions for disease states such as sepsis, Clostridioidesdifficile, bloodstream infections, outpatient parenteral therapy, etc</td>
</tr>
<tr>
<td>Monitor guideline adherence for common disease states such as community-acquired pneumonia, skin and soft tissue infections, and urinary tract infections</td>
<td>Incorporate infection-specific interventions for disease states such as sepsis, Clostridioides difficile, bloodstream infections, outpatient parenteral therapy, etc</td>
</tr>
<tr>
<td>Conduct medication use evaluation for broad-spectrum antibiotics such as those active against MRSA or Pseudomonas</td>
<td>Incorporate infection-specific interventions for disease states such as sepsis, Clostridioides difficile, bloodstream infections, outpatient parenteral therapy, etc</td>
</tr>
<tr>
<td>Document evidence-based antibiotic use†</td>
<td>Document evidence-based antibiotic use†</td>
</tr>
<tr>
<td><strong>Reporting</strong></td>
<td>Review interventions and missed opportunities for each action listed above, including duration of therapy, duplicate therapy, intravenous to oral conversions, and dosing optimization</td>
</tr>
<tr>
<td>Collect, analyze, and report on stewardship interventions and antibiotic use†</td>
<td>Assess appropriateness of antibiotics on discharge, including antibiotic choice and duration</td>
</tr>
<tr>
<td>Report stewardship efforts through staff messaging and newsletters</td>
<td>Create standardized audits/reports for antimicrobial medication use evaluations to be performed routinely</td>
</tr>
<tr>
<td>Demonstrate (sustained) improvement in antibiotic use*</td>
<td>Create standardized audits/reports for antimicrobial medication use evaluations to be performed routinely</td>
</tr>
<tr>
<td>Report action taken on areas identified for improvement†</td>
<td>Document evidence-based antibiotic use†</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>Review interventions and missed opportunities for each action listed above, including duration of therapy, duplicate therapy, intravenous to oral conversions, and dosing optimization</td>
</tr>
<tr>
<td>Provide stewardship updates in facilitywide communication</td>
<td>Create antibiogram annually and distribute it to all professions involved in antimicrobial stewardship team</td>
</tr>
<tr>
<td>Educate key stakeholders periodically†</td>
<td>Collect, analyze, and report on facility and potentially provider-level antibiotic use with prescribers†</td>
</tr>
<tr>
<td>Include stewardship in new staff orientation†</td>
<td>Report adherence to facility-specific treatment guidelines</td>
</tr>
<tr>
<td>Provide information on antibiotics in patient education documents for patients and their families†</td>
<td>Demonstrate (sustained) improvement(s) in antibiotic use*</td>
</tr>
<tr>
<td><strong>Comparison of Stewardship Programs by Resources and Development</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Centers for Medicare & Medicaid Services requirement as of 2020
†Joint Commission requirement as of 2017
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COVID-19 vaccine boosters are beneficial for reducing risk for transmission, hospitalization, and severe disease, particularly among older individuals and frontline workers, but increasing uptake of COVID-19 vaccines among vaccine-hesitant individuals and those without access to the vaccines should remain a priority moving forward, according to infectious disease experts who participated in a recent Contagion® Peer Exchange. The program was moderated by Peter Salgo, MD, professor of medicine and anesthesiology at Columbia University Vagelos College of Physicians and Surgeons in New York, New York. The panelists also discussed the background behind the misinformation related to the rapid development of the COVID-19 vaccines and recent data on the safety and efficacy of mixing and matching of different vaccines.

EXPANSION OF COVID-19 BOOSTER SHOT USAGE

With the high level of immune-evasive mutations in the Omicron variant of SARS-CoV-2, increasing titers of neutralizing antibodies with a COVID-19 booster is likely justified, said Angela Rasmussen, PhD, a research scientist at the Vaccine and Infectious Disease Organization in Saskatchewan, Canada. However, she added that the expansion of eligibility for COVID-19 boosters does not address the individuals who are vaccine hesitant or do not have access to vaccines.

Donald Alcendor, PhD, added that many of the individuals currently seeking vaccines are those who have already received their first 2 primary doses and that vaccinating individuals who have not received any vaccines (whether it was due to hesitancy or lack of access) should be a priority.

“To avoid the unvaccinated in light of a booster is an overall mistake in judgment going forward,” said Alcendor, an associate professor of microbiology and immunology at Meharry Medical College and adjunct associate professor of pathology, microbiology, and immunology at Vanderbilt University School of Medicine in Nashville, Tennessee. “People who want boosters, they’re already convinced that the vaccine is for them. There’s no [need] to push them toward getting that booster. They sit down and get that booster right away. They think it’s going to work for them, and they’re excited about it.”

Alcendor added that the mRNA vaccine platform, first developed 2 decades ago and tested in SARS-CoV-1 and Ebola virus but only recently reaching the public eye in the form of the COVID-19 vaccines, is likely to be groundbreaking for changing the general concepts of vaccines. For example, a combination vaccine with influenza and COVID-19 on the same mRNA cassette is undergoing development.

“Because these vaccines are modular, you can adapt them relatively quickly to variants as well,” Alcendor said. “You can change the mRNA sequence and now you have a targeted vaccine that can deal with a specific variant.”

COVID-19 BOOSTER SHOT ELIGIBILITY

Alcendor noted that there is a prevailing misperception that the mRNA COVID-19 vaccines are new experimental vaccines that have not been adequately tested. Jason Gallagher, PharmD, BCPS, FIDP, FIDSA, added that this may be because most of the general public is unaware of research conducted in the years leading up to the pandemic and only know about the seemingly rapid development and approval of the vaccine. Gallagher, who is a professor and clinical specialist, infectious diseases, and director of the PGY2 Residency in Infectious Diseases Pharmacy at the Temple University School of Pharmacy in Philadelphia, Pennsylvania, also noted that demonstrating vaccine efficacy during the COVID-19 pandemic could have been done relatively quickly because infection rates were high.

“To get [the COVID-19 vaccine] from clinical trials to authorization in a fairly short time is incredible,” Gallagher said. “They didn’t see all the development that went on over those years. The only part people have seen is that last part: disease detected, being described, and then a vaccine developed in the space of roughly a year by the time it got to people.”

The populations with the strongest need for a COVID-19 booster are older individuals, particularly...
those in congregate living situations, because they have a less robust immune response to the vaccine, said Jeff Goad, PharmD, MPH, associate dean of academic affairs, professor, and chair of the Department of Pharmacy Practice at Chapman University School of Pharmacy in Irvine, California. Individuals who received their original series of vaccines early also should receive a booster to reduce risks for transmission, hospitalization, and severe disease. Alcendor and Goad added that frontline workers, including those who work in health care or daycare centers, teachers, firefighters, and police officers, should be prioritized for boosters because their public presence makes them a key link in the transmission chain.

MIXING AND MATCHING COVID-19 VACCINES

Gallagher said that heterologous boosters (different from the primary vaccine) were shown to be safe and immunogenic in the phase 1/2 MixNMatch study (NCT04889209) funded by the National Institute of Allergy and Infectious Diseases.1 Results of the study, which included healthy adults who received a full COVID-19 vaccine regimen available under emergency use authorization, showed that neutralizing antibody titers increased with heterologous boosters as well as homologous boosters (same as the primary vaccine), and spike protein–specific T-cell responses increased with all combinations except for the homologous Ad26.COV2.S (Johnson & Johnson-Janssen) group.1 Rasmussen added that heterologous vaccination has been done in several European countries and Canada because of supply issues and that the National Advisory Committee on Immunization (Canada’s immunization advisory board) stated that heterologous vaccination is ideal because individuals who received an adenovirus vector vaccine as the initial dose followed by an mRNA vaccine tended to have higher antibody responses. However, whether this higher antibody response translates to increased protection against the effects of COVID-19 remains to be seen, Rasmussen said.

“We’ve been doing heterologous vaccinations for a long time for many other vaccine platforms. In general, it’s not something that is a huge mystery,” she said. “I think it’s only a mystery to people now because they are paying more and more attention to different types of vaccines. Before this pandemic, I certainly wouldn’t think of anybody coming in and saying, ‘I got whatever the flu vaccine I got is and you got something else. I got recombinant, you got egg based.’ I’ve never heard of people doing that. I think that’s just because people probably haven’t put a lot of thought into vaccine brand names.”

Alcendor added that when the booster shots initially became available, some individuals chose the Moderna vaccine because it appeared to have better efficacy when it was mixed and matched with other vaccines. However, Gallagher noted that the dose of the Moderna vaccine used in the MixNMatch trial (100 μg) was higher than the dose used in the Moderna booster available to the public (50 μg), whereas the doses of the Pfizer and J&J vaccines used in the study were the same as those given to adults (30 μg and 5 × 1010 virus particles, respectively). Gallagher and Salgo both noted that keeping track of the dose received at each booster is particularly important with the availability of pediatric vaccines.

“Some people, when they get their children vaccinated, refuse to go and get their booster on the same day,” Salgo said. “They don’t want there to be any question on that table with these syringes about which one is the adult dose and which one is the pediatric dose.”

The pediatric vaccine formulation has been altered slightly to contain a small amount of Tris buffer that acts to improve the shelf life of the vaccine, which will be important when vaccination moves from large centers to pediatricians’ offices, Gallagher said. However, this change in formulation has garnered additional media attention and a misperception of Tris buffer as a potentially injurious agent. Addressing these and future misperceptions remains a continued priority, Alcendor said.

“I had to explain to people that the Tris buffer is there in an amount that wouldn’t affect anybody,” he said. “The Tris buffer is there to improve the shelf life of the vaccine. [The media sources] have misinformation saying that this Tris buffer is there to cause all sorts of injury to children who would receive the childhood vaccine.”

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.
Monoclonal Antibody ADG20 Neutralizes COVID-19 Variants

Monoclonal antibodies became 2 of the biggest buzzwords of the COVID-19 pandemic. Although proven less effective at neutralizing the Omicron variant, monoclonal antibodies are still an exciting treatment option with untapped potential for past and future variants.

One study, “ADG20, a Half-life–Extended Monoclonal Antibody in Development for the Prevention and Treatment of COVID-19, Demonstrates Potent Neutralization Against SARS-CoV-2 Variants,” examined the investigational fully human immunoglobulin 1 monoclonal antibody ADG20 for the treatment of COVID-19. The study was accepted as an abstract for the Making a Difference in Infectious Diseases (MAD-ID) 2022 Annual Meeting, held in May.

The investigators assessed the in vitro neutralizing activity of ADG20 against circulating COVID-19 variants. The study included the COVID-19 variants and variants of concern as of November 18, 2021. Utilizing a lentiviral pseudovirus assay, the investigators tested ADG20 against circulating variants. For the variants associated with reduced susceptibility to some or all currently authorized monoclonal antibodies, the investigators used a nonreplicative vesicular stomatitis virus pseudovirus system to test ADG20’s efficacy.

In an exploratory analysis of ADG20 administration in healthy adults, investigators determined serum viral neutralizing antibody (sVNA) titers with a plaque reduction assay for authentic SARS-CoV-2 BavPat (D614G) and variants of concern. These were compared with antibody titers in a second adult cohort 7 to 30 days after participants received their second dose of an authorized COVID-19 vaccine.

The investigators found that ADG20 successfully neutralized all COVID-19 variants tested, with 50% inhibitory concentrations within 0.4-fold to 5.1-fold of the reference D614G strain. ADG20 also demonstrated potent in vitro activity against COVID-19 variants that had shown resistance to some authorized monoclonal antibodies.

At 6 months after administration, ADG20 sVNA titers were comparable to peak antibody responses after Moderna messenger RNA COVID-19 vaccination. sVNA titers from the phase 1 study suggest the potential of a single 300-mg intramuscular injection of ADG20 to protect against symptomatic or severe COVID-19 disease for at least 6 months.

Highlights From Our MAD-ID Interviews

Challenging Gram-Negative Pathogens and Oral Carbapenems

Jason Pogue, PharmD, BCPS, BCIDP, shares key takeaways from his 2 presentations at Making a Difference in Infectious Diseases (MAD-ID) 2022 Annual Meeting, including a new alternative to the SPACE acronym (Serratia, Pseudomonas, Acinetobacter, Citrobacter, Enterobacter) and how to navigate anxieties around oral carbapenems.

Rapid Diagnostic Testing’s Impact on Timing to Optimal Therapy

Alexander Aucoin, PharmD, BCPS, of Saint Francis Hospital in Tulsa, Oklahoma, provides insights into the concept of utilizing new technology for diagnostic stewardship.

How the COVID-19 Pandemic Affected Antimicrobial Stewardship

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Case Study: Pulmonary Coinfection With \( C \) neoformans and \( C \) immitis: A Novel Fungal Cohabitation

**by** MEAGAN MAYO, DO; ANNEKA HUTTON, MD; and GABRIEL SANDKOVSKY, MD

A 47-year-old man was brought to the emergency department by police due to erratic behavior and suspected intoxication. He had been found shouting in the street and had lost control of his bowels. He was initially unable to provide additional pertinent history due to his altered mental status.

**MEDICAL HISTORY**

The patient was hemodynamically stable on presentation. Physical examination was notable for slurred speech, confusion with the patient oriented only to self, agitation, and choreoathetoid movements including lip smacking and repetitive jerking of the upper and lower extremities. He had no focal neurological deficits. His reflexes and muscle strength were equal across the extremities.

**STUDIES**

Initial studies revealed leukocytosis of 14.1 cells/\( \mu \)L, mixed cell lines without neutrophil predominance, and elevated creatinine of 3.4 mg/dL. His HIV viral load was 323,000 copies/mL and CD4+ count was 278 cells/\( \mu \)L. His urine drug screen was positive for methamphetamine. The other results of his complete blood cell count, comprehensive metabolic panel, and toxicology panel were unremarkable. Based on his neurologic symptoms, a central nervous system infection was suspected, and a lumbar puncture was immediately performed. opening pressure was within normal limits. Cell count, Gram stain, and cerebral spinal fluid protein levels all were within normal limits. Aerobic, anaerobic, and fungal cultures were negative. A brain CT showed global cerebral atrophy. An MRI revealed global and caudate atrophy consistent with possible Huntington disease.

**TREATMENT AND FOLLOW-UP**

Throughout the hospitalization, the patient's chorea and speech improved. Underlying Huntington disease exacerbated by amphetamine use was suspected, although the patient refused genetic testing. He was started on oral fluconazole at a dose of 400 mg daily, which was to be continued for a minimum of 3 months. Additionally, cortisol was added to help control his bowels.

**FINAL DIAGNOSIS**

Cryptococcus neoformans and Coccidioides immitis coinfection

**HISTORY OF PRESENT ILLNESS**

A 47-year-old man was brought to the emergency department by police due to erratic behavior and suspected intoxication. He had been found shouting in the street and had lost control of his bowels. He was initially unable to provide additional pertinent history due to his altered mental status.

**MEDICAL HISTORY**

The patient was not taking any prescription medications. He previously was prescribed antiretroviral therapy but had not taken it for more than 1 year.

**EPIDEMIOLOGICAL HISTORY**

The patient later reported a history of uncontrolled HIV and a history of poly-substance use, including inhaled methamphetamine and intravenous heroin.

**KEY MEDICATIONS**

The patient was not taking any prescription medications. He previously was prescribed antiretroviral therapy but had not taken it for more than 1 year.

**STUDIES**

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**REFERENCES**


**IMAGES**

Figure 1A and 1B. Transverse slice of chest CT with a well-defined pleural based mass measuring 2.4 cm × 2.2 cm

**DIAGNOSTIC PROCEDURES**

The patient underwent a CT-guided lung biopsy, which revealed benign pulmonary parenchyma with extensive necrosis (Figure 2). Grocott methenamine silver and mucicarmine stains (Figure 3) were consistent with 2 morphologically distinct fungal species. Coinfection of Cryptococcus neoformans and Coccidioides immitis was confirmed by fungal culture.

**CLINICAL COURSE**

On hospital day 2, he was febrile (102.7 °F) with associated nonproductive cough. He was started on broad-spectrum antibiotics vancomycin, piperaicillin-tazobactam, and azithromycin. Chest x-ray revealed a pneumatic consolidation in the left lower lobe and a well-defined right lower lobe nodule. Chest CT confirmed a pleural based mass measuring 2.4 cm × 2.2 cm (Figures 1A, 1B).
antiretroviral therapy was initiated. The patient wished to return home to California to continue medical treatment.

DISCUSSION

*C. neoformans* and *C. immitis* are independently rare opportunistic mycoses, with coinfection representing an exceptionally uncommon entity. As our literature review returned no prior reports of such a coinfection, we report the first case of coinfection with these specific organisms. We hypothesize that such a coinfection occurred in this patient due to severely impaired host immune function coupled with geographic prevalence of these fungal species.

Pulmonary coinfection with other fungal species has rarely been documented in isolated case-reports; these fungal coinfections include *Histoplasma* and *Cryptococcus*, as well as *Cryptococcus* and *Aspergillus*. In those cases, the majority of patients had evidence of significant immune compromise. It also has been postulated that existing pulmonary cavitary lesions may provide optimal breeding grounds for fungi, resulting in coinfection.

*C. neoformans* is an encapsulated yeast found in soil and bird droppings worldwide. Despite its wide distribution, it accounts for only approximately 20% of pulmonary fungal infections. Pulmonary cryptococcosis may have an indolent presentation or may cause cough, increased sputum production, and chest pain. In individuals with altered immune function, it may establish latent infection through persistence within granulomas or may cause disseminated disease such as meningitis. Radiographically, *C. neoformans* may present as a pulmonary consolidation, reticulonodular opacity, or lung mass that mimics malignancy.

In contrast, *C. immitis* grows as a mold below the soil surface and is endemic to the southwestern United States. The mold releases spores that remain airborne for long periods of time. These spores may enter the lungs where they further divide into endospores that propagate infection. The risk of infection for those living in endemic areas is approximately 3% per year. *C. immitis* typically causes severe pneumonia with cough and fever but may present as disseminated disease in immunocompromised hosts. Radiographic findings may include nodules, cavitary lesions, or peribronchial thickening with intrathoracic adenopathy.

Treatment for *C. neoformans* infection requires 200 mg/day to 400 mg/day of oral fluconazole for a minimum of 3 to 6 months in an immunocompetent host as well as in an immunocompromised host without central nervous system involvement. Treatment for *C. immitis* is required in patients with disseminated disease such as meningitis or diffuse pulmonary disease, or those who are immunocompromised with CD4 cell counts of less than 250/mL. Fluconazole is the agent of choice for *C. immitis* treatment although amphotericin may be considered if respiratory compromise is present. Treatment duration varies, but a minimum of 3 months is typically recommended.

Fungal infections represent an important differential diagnosis for pulmonary nodules that may initially be suspected to represent malignancy. Furthermore, both *C. neoformans* and *C. immitis* may be positive on 18F-Fluorodeoxyglucose-PET imaging due to increased metabolic activity and therefore be further mischaracterized as malignancy. A comprehensive patient history should be undertaken to rule out risk factors for pulmonary fungal infections, including immunocompromised state, area of residence, and lifestyle risk factors.

“*C. neoformans* and *C. immitis* are independently rare opportunistic mycoses, with coinfection representing an exceptionally uncommon entity.”

As fungal coinfections are exceedingly rare, identification of 1 organism may result in failure to fully investigate superimposed pathogens. In patients with more than 1 fungal pathogen, identification of each organism is essential for optimal management as eradication of multiple fungal species may necessitate changes to routine treatment regimens. With a trend toward high levels of steroid and antibiotic use in clinical practice, fungal coinfections may become more prevalent.
THE CONSEQUENCES OF RECURRENCE ARE SIGNIFICANT, POTENTIALLY DEADLY.2

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

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

A VICIOUS CYCLE WITH SIGNIFICANT BURDEN

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

Learn why it requires aggressive action


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