MULTIDRUG-RESISTANT INFECTIONS

Two More Agents Bolster the Arsenal Against Gram-Negative Resistance
By Thomas P. Lodise, PharmD, PhD, and Monique Bidell, PharmD, BCPS

The World Health Organization (WHO) lists the emergence of antibiotic resistance as 1 of the top 10 threats to public health.1 Emergence of resistance is particularly problematic among patients with infections due to gram-negative bacteria (GNB). The terms multidrug resistant (MDR), extensively drug resistant, and pan-drug resistant are often used to characterize patterns of drug resistance exhibited by GNB.2 Strains that are resistant to antibiotics in multiple classes pose a substantial clinical challenge, often requiring use of novel or “last resort” agents.3

Fortunately, there has been impressive drug development in recent years in response to growing threats associated with antibiotic-resistant GNB that cause invasive infections in humans, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. Two recent additions to the armamentarium for the treatment of adult patients with GNB infections are imipenem/cilastatin/relebactam (IMI/REL) and cefiderocol. Below, we provide a general overview of each agent, describe its mechanism of action, detail the microbiologic activity against common highly resistant GNB, and highlight major clinical trial findings.

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#1 PRESCRIBED FOR ADULTS WITH HIV-1 STARTING AND SWITCHING ARV REGIMENS


INDICATION
BIKTARVY is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral (ARV) treatment history or to replace the current ARV regimen in those who are virologically suppressed (HIV-1 RNA <50 copies per mL) on a stable ARV regimen for ≥3 months with no history of treatment failure and no known resistance to any component of BIKTARVY.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted.

Contraindications
- Coadministration: Do not use BIKTARVY with dofetilide or rifampin.

Warnings and precautions
- Drug interactions: See Contraindications and Drug Interactions sections. Consider the potential for drug interactions prior to and during BIKTARVY therapy and monitor for adverse reactions.
- Immune reconstitution syndrome, including the occurrence of autoimmune disorders with variable time to onset, has been reported.
- New onset or worsening renal impairment: Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. In clinical trials of BIKTARVY, there have been no cases of Fanconi syndrome or proximal renal tubulopathy (PRT). Do not initiate BIKTARVY in patients with estimated creatinine clearance (CrCl) <30 mL/min. Patients with impaired renal function and/or taking nephrotoxic agents (including NSAIDs) are at increased risk of renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.
  
  Renal monitoring: Prior to or when initiating BIKTARVY and during therapy, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

Treatment-Naïve Study Designs1-5:

The efficacy and safety of BIKTARVY for treatment-naïve adults were evaluated in Study 1489 and Study 1490. In Study 1489, a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥50 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=314) or ABC/DTG/3TC (n=315) once daily. In Study 1490, a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥30 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=320) or FTC/TAF+DTG (n=325) once daily. The primary endpoint for both trials was the proportion of adults with HIV-1 RNA <50 copies/mL at Week 48. Secondary endpoints included efficacy, safety, and tolerability at Week 96.
**The Beauty of Possibilities**

BIKTARVY® combines the FTC/TAF® backbone with bictegravir, a novel and unboosted INSTI—for a powerful STR with a high barrier to resistance.1,6

No Treatment-Emergent Resistance Associated With BIKTARVY Through Week 96.1,4,5,7

In two large phase 3 clinical trials in treatment-naïve adults1,5,7

△ Among 634 treatment-naïve adults in Studies 1489 and 1490, 7 treatment-failure subjects were tested and no amino acid substitutions emerged that were associated with BIKTARVY resistance

**Powerful Efficacy in Treatment-Naïve Adults**1,5,7

Results noninferior to comparators at Week 481-3

Virologic Response

Results noninferior to comparators at Week 964,5,7

Virologic Response

Most common adverse reactions (incidence ≥5%; all grades) in treatment-naïve clinical studies through week 96 were diarrhea (6%), nausea (6%), and headache (5%).4,5

**IMPORTANT SAFETY INFORMATION (continued)**

**Warnings and precautions (continued)**

△ Lactic acidosis and severe hepatomegaly with steatosis: Fatal cases have been reported with the use of nucleoside analogs, including FTC and TDF. Discontinue BIKTARVY if clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity develop, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

Please see additional Important Safety Information for BIKTARVY, including BOXED WARNING, and Brief Summary of full Prescribing Information for BIKTARVY on following pages.

*emtricitabine 200 mg/tenofovir alafenamide 25 mg.
†95% confidence interval.
IMPORTANT SAFETY INFORMATION (continued)

Adverse reactions

- **Most common adverse reactions** (incidence ≥5%; all grades) in clinical studies through week 96 were diarrhea (6%), nausea (6%), and headache (5%).

Drug interactions

- **Prescribing information**: Consult the full prescribing information for BIKTARVY for more information on Contraindications, Warnings, and potentially significant drug interactions, including clinical comments.

- **Enzymes/transporters**: Drugs that induce P-gp or induce both CYP3A and UGT1A1 can substantially decrease the concentration of components of BIKTARVY. Drugs that inhibit P-gp, BCRP, or inhibit both CYP3A and UGT1A1 may significantly increase the concentrations of components of BIKTARVY. BIKTARVY can increase the concentration of drugs that are substrates of OCT2 or MATE1.

- **Drugs affecting renal function**: Coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC and tenofovir and the risk of adverse reactions.

Dosage and administration

- **Dosage**: 1 tablet taken once daily with or without food.

- **Renal impairment**: Not recommended in patients with CrCl <30 mL/min.

- **Hepatic impairment**: Not recommended in patients with severe hepatic impairment.

- **Prior to or when initiating**: Test patients for HBV infection.

- **Prior to or when initiating, and during treatment**: As clinically appropriate, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus.

Pregnancy and lactation

- **Pregnancy**: There is insufficient human data on the use of BIKTARVY during pregnancy. An Antiretroviral Pregnancy Registry (APR) has been established. Available data from the APR for FTC shows no difference in the rates of birth defects compared with a US reference population.

- **Lactation**: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

Please see Brief Summary of full Prescribing Information for BIKTARVY on following pages.

3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; STR, single-tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

BIKTARVY® (bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx only.

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B
Severe acute exacerbations of hepatitis B have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing emtricitabine (FTC) and/or tenofovir disoproxil fumarate (TDF), and may occur with discontinuation of BIKTARVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who are coinfected with HIV-1 and HBV and discontinue BIKTARVY. If appropriate, anti-hepatitis B therapy may be warranted [see Warnings and Precautions].

INDICATIONS AND USAGE
BIKTARVY is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of BIKTARVY.

DOSEAGE AND ADMINISTRATION
Also see Warnings and Precautions and Use in Specific Populations.

Testing Prior to or When Initiating: Test patients for HIV infection.

Testing Prior to or When Initiating, and During Treatment: As clinically appropriate, assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus.

Dosage: One tablet taken once daily with or without food.

Renal Impairment: BIKTARVY is not recommended in patients with CrCl <30 mL/min.

Hepatic Impairment: BIKTARVY is not recommended in patients with severe hepatic impairment.

CONTRAINDICATIONS
Also see Drug Interactions.

BIKTARVY is contraindicated to be co-administered with:

• doxefilide due to the potential for increased doxefilide plasma concentrations and associated serious and/or life-threatening events

• rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY

WARNINGS AND PRECAUTIONS
Also see BOXED WARNING, Contraindications, Adverse Reactions, and Drug Interactions.

Severe Acute Exacerbation of Hepatitis B in Patients Coinfected with HIV-1 and HBV: Patients with HIV-1 should be tested for the presence of chronic hepatitis B virus (HBV) before or when initiating ARV therapy. Severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing FTC and/or TDF, and may occur with discontinuation of BIKTARVY. Patients coinfected with HIV-1 and HBV who discontinue BIKTARVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis since post-treatment exacerbation of hepatitis may lead to hepatic decompensation and liver failure.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions: Coinadministration of BIKTARVY with certain other drugs may result in known or potentially significant drug interactions; this may lead to loss of efficacy and development of resistance to BIKTARVY or clinically significant adverse reactions from greater exposures of concomitant drugs. Consider the potential for drug interactions and review concomitant medications prior to and during therapy. Monitor for adverse reactions associated with concomitant drugs.

Immune Reconstitution Syndrome (IRS): IRS has been reported in patients treated with combination ARV therapy. During the initial phase of treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections, which may necessitate further evaluation and treatment. Autoimmune disorders have been reported to occur in the setting of immune reconstitution; the time to onset is variable, and can occur many months after initiation of treatment.

New Onset or Worsening Renal Impairment: Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs in animal studies and human trials. In clinical trials of BIKTARVY in subjects with no antiretroviral treatment history with eGFRs >30 mL/min, and in virologically suppressed subjects switched to BIKTARVY with eGFRs >50 mL/min, renal serious adverse events were encountered in less than 1% of subjects treated with BIKTARVY through Week 48. BIKTARVY is not recommended in patients with CrCl <30 mL/min. Patients taking tenofovir prodrugs who have renal impairment and/or are taking nephrotoxic agents including NSAIDs are at increased risk of developing renal-related adverse reactions. Discontinue BIKTARVY in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Renal Monitoring: Prior to or when initiating BIKTARVY, and during treatment with BIKTARVY, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients as clinically appropriate. In patients with chronic kidney disease, also assess serum phosphorus.

Lactic Acidosis/Severe Hepatomegaly with Steatosis:
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs, including FTC and TDF. Treatment with BIKTARVY should be suspended in any individual who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, including hepatomegaly and steatosis in the absence of marked transaminase elevations.

ADVERSE REACTIONS
Also see BOXED WARNING and Warnings and Precautions.

In Adults with No ARV Treatment History:
The safety assessment of BIKTARVY is based on Week 48 data from two randomized, double-blind, active-controlled trials: 1489 (n=314) and 1490 (n=320), in HIV-1 infected, ARV treatment-naive adults. Through Week 48, 1% of subjects discontinued BIKTARVY due to adverse events, regardless of severity.

Adverse Reactions: Adverse reactions (all Grades) reported in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 and 1490, respectively were: diarrhea (6%, 3%), nausea (5%, 3%), headache (5%, 4%), fatigue (3%, 2%), abnormal dreams (3%, <1%), dizziness (2%, 2%), and insomnia (2%, 2%). Additional adverse reactions (all Grades) occurring in less than 2% of subjects administered BIKTARVY in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression. Suicidal ideation, suicide attempt, and depression suicidal occurred in <1% of subjects administered BIKTARVY; all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

Laboratory Abnormalities: Laboratory abnormalities (Grades 3–4) occurring in ≥2% of subjects receiving BIKTARVY through Week 48 in Trials 1489 or 1490, respectively were: amylase ≥2.0 x ULN (2%, 2%), ALT ≥5.0 x ULN (1%, 2%), AST ≥5.0 x ULN (2%, 1%), Creatine Kinase ≥10.0 x ULN (4%, 4%), Neutrophils ≥7.5 x 10^3 /μL (2%, 2%), and fasted LDL-cholesterol >190 mg/dL (2%, 3%).

Changes in Serum Creatinine: Increases in serum creatinine occurred by Week 4 of treatment and remained stable through Week 48. In Trials 1489 and 1490, median serum creatinine increased by 0.10 mg/dL from baseline to Week 48 in the BIKTARVY group and was similar to the comparator groups.

Continued on next page.
Changes in Bilirubin: Continued from previous page.

In Virologically Suppressed Adults: The safety of BIKTARVY in HIV-1 infected, virologically suppressed adults is based on Week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial in which virologically suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to BIKTARVY; and Week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to BIKTARVY.

Adverse Reactions: Overall, the safety profile in virologically suppressed adult subjects was similar to that in subjects with no antiretroviral treatment history.

DRUG INTERACTIONS

Also see Indications and Usage, Contraindications, and Warnings and Precautions.

Other Antiretroviral Medications: BIKTARVY is a complete regimen for the treatment of HIV-1 infection, BIKTARVY coadministration with other ARV medications for treatment of HIV-1 infection is not recommended. Complete information regarding potential drug interactions with other ARV medications is not provided.

Potential for BIKTARVY to Affect Other Drugs: BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) in vitro. Coadministration of BIKTARVY with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations.

Potential Effect of Other Drugs to Affect BIKTARVY: BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of efficacy and development of resistance. The use of BIKTARVY with a drug that is a strong inhibitor of CYP3A and also an inhibitor of UGT1A1 may significantly increase the plasma concentrations of BIC. TAF is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Co-administration of drugs that inhibit P-gp and BCRP may increase the absorption and plasma concentrations of TAF. Co-administration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of efficacy and development of resistance.

Drugs Affecting Renal Function: Because FTC and tenofovir are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs, which may increase the risk of adverse reactions.

Established and Potentially Significant Drug Interactions: The listing of established or potentially clinically significant drug interactions with recommended prevention or management strategies described are based on studies conducted with either BIKTARVY, the components of BIKTARVY (BIC, FTC, and TAF) as individual agents, or are drug interactions that may occur with BIKTARVY. An alteration in regimen may be recommended.

• Antiarrhythmics: dofetilide. Coadministration is contraindicated due to potential for serious and/or life-threatening events.
• Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin. Coadministration with alternative anticonvulsants should be considered.
• Antimycobacterials: rifampin. Coadministration is contraindicated due to the effect on BIKTARVY. Rifabutin, rifapentine. Coadministration is not recommended.
• Herbal Products: St. John’s wort. Coadministration is not recommended.
• Medications/oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Antacids containing Al/Mg or Calcium; BIKTARVY can be taken under fasting conditions 2 hours before antacids containing Al/Mg or calcium. Routine administration of BIKTARVY simultaneously with, or 2 hours after, antacids containing Al/Mg or calcium is not recommended. Supplements containing Calcium or Iron; BIKTARVY and supplements containing calcium or iron can be taken together with food. Routine administration of BIKTARVY under fasting conditions simultaneously with, or 2 hours after, supplements containing calcium or iron is not recommended.
• Metformin: Refer to the prescribing information of metformin for assessing the benefit and risk of concomitant use of BIKTARVY and metformin.

Consult the full Prescribing Information prior to and during treatment with BIKTARVY for important drug interactions; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS

Also see Dosage and Administration, Warnings and Precautions, and Adverse Reactions.

Pregnancy: Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIKTARVY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263. Risk Summary: There are insufficient human data on the use of BIKTARVY during pregnancy to inform a drug-associated risk of birth defects and miscarriage. BIC and TAF use in women during pregnancy has not been evaluated; however, FTC use during pregnancy has been evaluated in a limited number of women as reported to the APR. Available data from the APR show no difference in the overall risk of major birth defects for FTC compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR.

Lactation: The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV. Based on published data, FTC has been detected in human milk; it is not known whether BIKTARVY or all of the components of BIKTARVY are present in human breast milk, affects human milk production, or has effects on the breastfed infant. BIC was detected in the plasma of nursing rat pups likely due to the presence of BIC in milk, and tenofovir has been shown to be present in the milk of lactating rats and rhesus monkeys after administration of TDF. It is unknown if TAF is present in animal milk. Because of the potential for HIV transmission in HIV-negative infants, developing viral resistance in HIV-positive infants, and adverse reactions in nursing infants, mothers should be instructed not to breastfeed.

Pediatric Use: Safety and effectiveness of BIKTARVY in pediatric patients less than 18 years of age have not been established.

Geriatric Use: Clinical studies of BIKTARVY did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Renal Impairment: BIKTARVY is not recommended in patients with severe renal impairment (CrCl <30mL/min). No dosage adjustment of BIKTARVY is recommended in patients with CrCl >=30mL/min.

Hepatic Impairment: No dosage adjustment of BIKTARVY is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. BIKTARVY is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) as BIKTARVY has not been studied in these patients.

OVERDOSAGE:

If overdose occurs, monitor the patient for evidence of toxicity. Treatment consists of general supportive measures including monitoring of vital signs as well as observation of the clinical status of the patient.

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Two More Agents Bolster the Arsenal Against Gram-Negative Resistance

As the antibiotic pipeline produces new therapies, clinicians must understand each agent’s specific role in management of patients infected by multidrug-resistant pathogens.

BY THOMAS P. LODISE, PHARMD, PHD, AND MONIQUE BIDELL, PHARMD, BCPS
THE YEAR ENDS WITH A BIG STEP IN PREP AND PEP

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omething novel in infectious diseases practice has occurred and, like many big changes, it is not without controversy. In October, Gov Gavin Newsom of California signed SB 159 into law. This legislation allows pharmacists to dispense up to a 60-day supply of antiretrovirals for either pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) without a prescription, provided certain conditions are met. The law goes into effect in July.

Some conditions include limiting the supply of the drug to 60 days, requiring dispensing pharmacists to complete an approved education program, documenting a negative HIV test or negative in-pharmacy HIV test at the time of dispensing (waived for PEP), and notifying the patient’s primary care physician. It also requires the state Medicaid program, Medi-Cal, to cover the cost of the medication and forbids commercial insurance from requiring pre-authorization for dispensing.

Some controversy followed SB 159 as it made its way through the legislature, which led to some of those conditions. I first learned of the proposed law in March, when I attended a conference of the Infectious Diseases Association of California. During an open forum about the bill, pharmacist attendees expressed concerns about patients falling into and out of care without follow-up and the potential for busy pharmacists in community settings to assume responsibilities for which they are not ready.

I was shocked by that response, which I believe missed the bigger picture: the need to expand access to therapies that lower the number of patients who contract HIV. It can help unburden emergency departments, where patients typically seek out PEP.

That response also ignores the fact that pharmacists are a generally conservative group and, as a profession, reluctant to become involved in areas in which they are uncomfortable. One of the great untapped resources of clinical expertise in 21st-century medicine is the training of doctors of pharmacy, in which curricula long ago moved from focusing on the basic sciences of pharmacology to clinical sciences of pharmacotherapy. Taking advantage of the broad accessibility of community pharmacists to expand the reach of therapies proven to prevent HIV infection is a no-brainer.

This law has enormous potential beyond California. Uptake of PrEP increased by a year-over-year average of 73% from 2012 to 2016 but is still used by less than 10% of people who are at high risk of HIV infection. The changes made to California’s pharmacy practice act are clear-cut and straightforward. These can be easily replicated by other states where access to PrEP is even more essential.

Use of and access to PrEP is already uneven. In 2016, just 5 states accounted for nearly half of all PrEP use: California, New York, Florida, Texas, and Illinois. Although each of these states has room for improved PrEP use, the biggest need is probably in the South, where over half of new HIV diagnoses occurred in 2016. Further, uptake of PrEP is unsurprisingly related to access to health care, because it is more commonly used in states that expanded Medicaid under the Affordable Care Act.

The United States has set a goal of reducing HIV by 90% by 2030, and the plan relies heavily on prophylaxis. Improved access to PrEP is key to realizing this aim, and California found a way to open to door to preventive therapy a little bit wider.

Our feature article this month—by Thomas P. Lodise, PharmD, PhD, and Monique Bidell, PharmD—discusses 2 new agents for the treatment of adult patients with highly resistant gram-negative infections: imipenem/cilastatin/relabactam and ceftiderocol.

As always, enjoy this issue, and keep up with us at ContagionLive.com.
Enter the Ring: Oral Vancomycin Versus Metronidazole for *C. difficile* Infection and the Risk of Vancomycin-Resistant Enterococcus

BY RACHEL BRITT, PHARMD

Clostridoides difficile infection (CDI) continues to be a tough arena among healthcare-associated infections and is classified as a major health threat by the US Centers for Disease Control and Prevention. Traditionally, to combat CDI, oral metronidazole was a top contender, recommended as first-line therapy for mild to moderate cases (now known as nonsevere), reserving oral vancomycin for severe CDI.1 In 2017, however, a guideline update stripped metronidazole of its first-line therapy designation and crowned oral vancomycin as initial therapy for all CDI cases.2

Some providers already regarded oral vancomycin as the champion treatment, but others had concerns about increased individual and health care costs and emergence of vancomycin-resistant Enterococcus (VRE) from routine use of oral vancomycin. In literature, a link between vancomycin exposure and an increased risk of VRE has been suggested, but these studies have many limitations, such as small populations, heterogeneity, and little to no oral vancomycin representation.3-5 Oral metronidazole has also been associated with VRE growth and colonization, further clouding predictions of the effect of a widespread practice change.3,4

To address the concern of increased clinically relevant VRE infection risk with routine oral vancomycin use, Stevens and colleagues generated a direct matchup between oral metronidazole and vancomycin. The retrospective, multicenter, propensity-matched cohort study included inpatients, long-term care residents, and outpatients of the US Department of Veterans Affairs (VA) Health System who received a diagnosis of CDI from January 2006 to December 2015. Patients who tested positive for CDI toxin and were treated with oral vancomycin or intravenous or oral metronidazole within 14 days after diagnosis were included. Patients who did not receive treatment and had a history of VRE in the past year were excluded.

CDI episodes were categorized by location of symptom onset, episode type, and year of diagnosis. Maximum white blood cell count (WBC) and maximum and average serum creatinine (SCR) values were used as markers of CDI severity. Multiple imputation was used to estimate missing values, and 50 imputed data sets were generated, with propensity score matching of 1 vancomycin-treated patient to up to 2 metronidazole-treated patients in each set. The primary outcome was presence of positive VRE clinical cultures at 3 and 6 months after CDI treatment initiation. Isolation of VRE from blood and surveillance cultures at 3 months after treatment initiation was also evaluated.

A total of 82,405 patients met inclusion criteria, and 15,776 were included in the propensity score–matched final analysis, with 5,266 patients receiving oral vancomycin and 10,510 receiving metronidazole. Patients were primarily male (95%), with a median age at diagnosis of 69 years. A majority of CDI cases were initial episodes (99%) with a community onset (70%). The median maximum WBC, maximum SCR, and average baseline SCR were ~11 10^3 cells/mL, 1.20 mg/dL, and 1.10 mg/dL, respectively. Baseline characteristics in the matched cohort, including receipt of fluoroquinolones, cephloporsins, and proton pump inhibitors in the previous 3 months, were similar between groups.

Compared with metronidazole, oral vancomycin was not associated with an increased risk of VRE in clinical cultures at 3 months (adjusted relative risk [aRR], 0.96; 95% CI, 0.77-1.20; absolute risk difference [RD], 0.11%; 95% CI, –0.68 to 0.47) or 6 months (aRR, 1.05; 95% CI, 0.85-1.28; RD, 0.14%; 95% CI, –0.5 to 0.78) (Table). Similarly, there was no increased risk of VRE bloodstream infection with oral vancomycin treatment (aRR, 0.56; 95% CI, 0.3-1.05; RD, –0.22%; 95% CI, –0.45 to 0.00) or isolation of VRE from surveillance cultures (aRR, 0.98; 95% CI, 0.79-1.21; RD, –0.07%; 95% CI, –0.69 to 0.55) at 3 months. These findings were consistent across predefined sensitivity analyses, excluding the top 10 surveillance facilities and including only incident cases.

The retrospective, observational design is a limitation of this study, but the authors attempted to adjust for confounders with propensity score matching. Additionally, data collection was limited by imperfect provider documentation over time. Given the predominantly male, comorbidity-heavy VA population, generalizability to other patient groups is limited. VRE colonization status was also unable to be collected due to variability in facility surveillance practices, and this study was not designed to evaluate oral vancomycin treatment effects on VRE transmission. CDI was defined using laboratory measures only and did not evaluate symptomatic presentation; however, authors adjusted for this factor by excluding patients who did not receive CDI treatment. Lastly, this study focused on vancomycin treatment and not vancomycin prophylaxis, which is often dosed less frequently. Whether vancomycin prophylaxis against CDI perpetuates VRE acquisition is unknown.

Infectious diseases providers and antimicrobial stewards are growing increasingly nervous as antimicrobial resistance increases. This study offers some reassurance that the newly recommended practice of first-line treatment of all cases of CDI with broader-spectrum oral vancomycin may not have negative individual and ecologic effects on VRE risk. Although concerns over the optimal agent for treatment are valid, a focus on diagnostic stewardship and efforts to discontinue therapy in patients without true CDI should be prioritized minimize the risk of multidrug-resistant organism development. ▲

**REFERENCES**

References are available at ContagionLive.com.
Differences in *C difficile* Diagnostics Blunt the Benefits of Bezlotoxumab

BY TIFFANY LEE, PHARMD

Bezlotoxumab, a human monoclonal antibody directed against *Clostridioides difficile* toxin B, is currently indicated for the prevention of recurrent *C difficile* infection (rCDI). Its US Food and Drug Administration approval follows the results of 2 phase 3 trials, MODIFY I and MODIFY II, which have shown significantly lower rates of rCDI at 12 weeks with the use of bezlotoxumab compared with placebo.1

In these trials, a number of different laboratory tests were used to diagnose *C difficile* infection (CDI), as summarized in the Table. In brief, these tests detect either the organism with the capacity to produce harmful toxin (ie, toxigenic culture [TC], polymerase chain reaction [PCR]) or the presence of major toxins directly in the stool (ie, enzyme immunoassay [EIA], cell cytotoxicity assay [CCA]).

Having a heterogeneous mix of diagnostic tests presents an issue with interpreting results of MODIFY I/II. Recent evidence suggests that although detecting the presence of toxigenic *C difficile* is highly sensitive, these tests on their own have poor positive predictive value of true clinical disease.2,3 As a result, bezlotoxumab’s effect may have been diminished due to inclusion of false-positive CDI cases in these trials. Through post hoc analysis of MODIFY I/II, Wilcox and colleagues sought to further differentiate the clinical impact of bezlotoxumab between cases diagnosed through the presence of toxigenic *C difficile* versus direct toxin detection.4

The primary end points of interest were the rates of initial clinical cure and rCDI. Out of concern for bezlotoxumab causing a false negative in subsequent toxin testing because of its toxin-neutralizing effect, an assay interference experiment was performed to control for any confounding.

From the pooled MODIFY I/II population, 781 patients who received bezlotoxumab and 773 who received placebo were included for analysis. Within each group, there was a near-even split number of patients whose disease was diagnosed through either PCR/TC or EIA/CCA. Baseline demographics were mostly well balanced across all 4 study arms and were notable for a population aged 60 to 70 years, with a slight female predominance. Apparent differences between the 2 diagnostic arms included a higher rate of inpatient diagnosis and severe CDI in cases diagnosed via EIA/CCA. Notably, there was a consistent majority (range, 70.9%-80.1%) of patients across all arms with at least 1 predefined risk factor for rCDI, which includes CDI history in the past 6 months, severe CDI per the Zar score, age >65 years, infection with a hypervirulent strain, and immunosuppression.

Overall, initial clinical cure rates were similar between the bezlotoxumab (82.3%) and placebo (78.1%) groups. Comparing by diagnostic methods, however, showed a higher rate of initial cure in cases diagnosed using EIA/CCA (bezlotoxumab, 81.7% vs placebo, 82.9%) compared with PCR/TC (bezlotoxumab, 78.4% vs placebo, 77.7%). Bezlotoxumab reduced rCDI rates regardless of diagnostic method, as shown in the Figure. Although the therapeutic differences in both diagnostic groups were statistically significant, the relative rCDI reduction with bezlotoxumab was more pronounced in those tested via EIA/CCA compared with PCR/TC (46.6% vs 29.1%). In the assay interference experiment, bezlotoxumab did not appear to affect diagnostic EIA results but may result in false positives for samples tested by CCA.

Findings from this post hoc analysis add further credence to acknowledging the differences in CDI diagnostic modalities. The clinical impact of bezlotoxumab becomes more evident in patients whose disease was diagnosed via EIA/CCA, suggesting that a proportion of recipients whose disease was diagnosed using PCR/TC may not have been truly infected. Although the current iteration of CDI guidelines still does not give strong recommendations regarding the optimal diagnostic method,5 this study sheds additional light on the limitations of detecting the presence of toxigenic *C difficile* on its own, with additional stewardship implications to suggest that poorer predictive value can lead to unnecessary treatment and use of bezlotoxumab. ▲

**TABLE.** Comparison of Diagnostic Methods

<table>
<thead>
<tr>
<th>TEST</th>
<th>SENSITIVITY</th>
<th>SPECIFICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxigenic culture</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
<td>High</td>
<td>Low/ moderate</td>
</tr>
<tr>
<td>Cell cytotoxicity assay</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Toxin A/B enzyme immunoassay</td>
<td>Low</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Patients from MODIFY I/II were included for analysis if they received bezlotoxumab or placebo as study drug. Each treatment group was subdivided into those whose disease was diagnosed via PCR or TC (PCR/TC) and those with disease diagnosed via EIA or CCA (EIA/CCA). Although patients in the EIA/CCA group included only toxin-positive patients, those in the PCR/TC group notably included both toxin-positive and toxin-negative patients because of differences in diagnostic algorithms.

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

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**HIGHLIGHTED STUDY**

**Influence of diagnostic method on outcomes in phase 3 clinical trials of bezlotoxumab for the prevention of recurrent *Clostridioides difficile* infection: a post hoc analysis of MODIFY I/II.**

Keith Kaye, MD, MPH, on the Approval of Imipenem/Cilastatin + Relebactam

In July, the US Food and Drug Administration announced the approval of Merck’s imipenem/cilastatin plus relebactam (Recarbrio) for the treatment of complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAIs) in adult patients with limited or no available treatment options.

Following the approval, Contagion® spoke with Keith Kaye, MD, MPH, professor of internal medicine and director of research in the Division of Infectious Diseases at Michigan Medicine at the University of Michigan in Ann Arbor.

Kaye is also a principal investigator in Merck’s clinical program on imipenem/cilastatin plus relebactam and a member of Contagion®’s editorial advisory board.

Contagion®: Can you describe the makeup of imipenem/cilastatin plus relebactam?

Kaye: This novel agent combines an old, broad-spectrum, trusted agent, which is imipenem/cilastatin, with a novel β-lactamase inhibitor, relebactam, which is very effective and active against carbapenemases and also different types of extended spectrum β-lactamases [ESBLs] and cephalosporinases like AmpC. So, essentially, it takes an old, trusted, very effective carbapenem β-lactam and combines it with a novel β-lactamase inhibitor, which can restore the activity of imipenem in the presence of emerging and disseminating resistance mechanisms.

Apart from determining noninferiority to colistin plus imipenem in RESTORE-IMI 1, were there any significant advantages observed in patients treated with imipenem/cilastatin plus relebactam?

The bottom line is, from an efficacy perspective, in terms of clinical outcomes, there is significant advantage in using imipenem/cilastatin plus relebactam over imipenem plus colistin. Also, importantly, from a safety perspective [eg, looking at nephrotoxicity], there are notable safety advantages with imipenem/cilastatin plus relebactam. This points to the fact that, although colistin is an important antimicrobial that we have historically leaned on for the treatment of resistant pathogens such as carbapenem resistant Enterobacteriaceae [CRE], newer agents such as imipenem/cilastatin plus relebactam offer a safety advantage with regard to nephrotoxicity and a pharmacokinetic/pharmacodynamic advantage in terms of safety attainable, effective levels in the serum and sites of active infections. Imipenem-relebactam performed very impressively from efficacy and safety perspectives, including in studies of resistant infections in the RESTORE-IMI 1 trial.

What does imipenem/cilastatin plus relebactam bring to the armamentarium for clinicians treating cUTIs and cIAIs with limited treatment options?

As recently as 4 years ago, we had 1 tool to treat CRE and highly resistant Pseudomonas, and that was the polymyxin class. We now have a tool kit of therapeautic options that are safe and effective. Imipenem/cilastatin plus relebactam offers a unique option that is part of a newer class of advanced β-lactam/β-lactamase inhibitor combinations. It couples an old school carbapenem, imipenem, which we know and love, with a relatively broad-spectrum β-lactamase inhibitor. It is an inhibitor that can not only inhibit carbapenemases like KPCs but also cephalosporinases like AmpC. In doing so, it not only provides enhanced activity against ESBLs and many strains of CRE but also restores susceptibility in some Pseudomonas. Imipenem/cilastatin plus relebactam offers enhanced CRE and ESBL coverage and also provides, in many scenarios, enhanced Pseudomonas coverage.

I think also, due to it being coupled with cilastatin, there are potential nephroprotective effects. If imipenem/cilastatin plus relebactam is used in combination with nephrotoxic agents, such as the polymyxins, it might offer some nephroprotective advantages over combinations that do not include cilastatin. This is hypothetical but deserves consideration.

Yoav Golan, MD, on the Recent Approval of Ceftolozane/Tazobactam for HABP/VABP

In June, the US Food and Drug Administration (FDA) approved a new indication for Merck’s ceftolozane/tazobactam (Zerbaxa). The approval now allows the drug to be used to treat hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP).

Following the approval, Contagion® spoke with Yoav Golan, MD, attending physician and associate professor of medicine at Tufts University School of Medicine in Boston, Massachusetts, to discuss the implications of the approval.

Contagion®: What evidence supports the efficacy of ceftolozane/tazobactam for treating HABP/VABP?

Golan: Ceftolozane/tazobactam, when it comes to pneumonia, is a good starting point because, when you look at its in vitro activity, it is uniquely positioned to cover the type of bacteria that cause HABP/VABP.

The next step was the proof of efficacy for ceftolozane/tazobactam in complicated intra-abdominal infections and complicated urinary tract infections, which are often caused by some types of pathogens that you see in pneumonia.

The third and most important facet of evidence has been the clinical trial itself, the ASPECT-NP study…a noninferiority study versus meropenem, which represents the standard of care. Ceftolozane/tazobactam was found to be noninferior to meropenem in terms of mortality at 28 days, as well as cure at test-of-cure visit.

What does the approval bring to clinicians treating patients with HABP/VABP?

The approval of ceftolozane/tazobactam for hospital- and ventilator-associated pneumonia is important news for clinicians who care for these types of patients. This is for 2 main reasons: The activity of ceftolozane/tazobactam against multidrug-resistant pathogens that cause pneumonia such as multidrug-resistant Pseudomonas. The other reason is the activity of ceftolozane/tazobactam against both resistant Pseudomonas, as well as extended-spectrum β-lactamase producers.

When initiating empiric therapy for patients with [HABP], we often need to choose between better coverage of 1 or the other. Ceftolozane/tazobactam offers the possibility to cover both types of bacteria. This is useful when treating very ill patients who cannot tolerate any delays in the initiation of adequate empiric antibiotic therapy.
Karam Mounzer, MD, on the Approval of Dolutegravir/Lamivudine

In addition, several post hoc analyses revealed the rate and magnitude of viral decline to be identical between the 2-D and 3-D regimens, even in people with pretreatment viral loads up to 500,000 copies. Some of these studies have suggested that the level of residual viremia measured by an ultrasensitive assay and the frequency of viral blips post suppression were similar between a 2-D and a 3-D regimen.

What benefits can a 2-drug regimen offer?

Since the advent of ART, clinicians, patients, patient advocates, scientists, researchers, and other stakeholders have been striving to develop the ideal regimen for patients living with HIV. This is the simplest, most potent, best tolerated, least toxic regimen that has no drug-drug or drug-comorbidities interactions and a regimen that is extremely forgiving.

By definition, a 2-D regimen eliminates a full drug from the equation; that is, a full exposure, which over a life span can translate to a significantly lower cumulative toxicity. In the case of the TDF-sparing 2-drug regimen, nephrotoxicity and bone mineral density demise will be significantly lower. Both of these favorable outcomes are attractive in our aging patient population, which is at higher risk of developing renal insufficiency and fragility fractures. This benefit is somewhat flattened by the favorable lipid profile associated with a TDF-based regimen. Another advantage of a 2-drug regimen is reducing the likelihood of drug-drug interactions and the subsequent clinical implications.

Finally, the favorable cost-effectiveness of a 2-D regimen such as DGV/3TC may lead to substantial savings that can be channeled to scale up treatment to more individuals living with HIV worldwide and support preventive measures [pre-exposure prophylaxis, test, and treat] that will help curtail the HIV epidemic.

Robert Poirier Jr, MD, on the Approval of Lefamulin for CABP

In August, the US Food and Drug Administration approved lefamulin (Xenleta) for the treatment of community-acquired bacterial pneumonia (CABP) after results from 2 phase 3 studies showed that the novel antibiotic was noninferior to existing treatment options.

Contagion® spoke with Robert Poirier Jr, MD, clinical chief of emergency medicine at Washington University School of Medicine in St Louis, Missouri, and an investigator on the LEAP 2 trial, to learn more about the antibiotic and what it will bring to clinicians.

Contagion®: Can you discuss the phase 3 LEAP trials that evaluated lefamulin?

Poirier: I’ll begin with the LEAP 1 trial, which enrolled 551 patients with a PORT [Pneumonia Patient Outcomes Research Team] class score of 3 to 4 and looked at the study drug lefamulin first, moxifloxacin plus or minus linezolid. So if the clinician had suspicion that MRSA, or methicillin resistant Staphylococcus aureus, was a potential cause with the pneumonia, they could add in the drug linezolid. The good thing with lefamulin is that it is broad spectrum. It has activity against the gram-positive bacteria that commonly cause pneumonia, and most of the gram-negative bacteria that cause pneumonia out there are covered. It looks like it works against S aureus, as well.

The participants received IV [intravenous] lefamulin or IV moxifloxacin plus/minus linezolid for 6 doses and then could switch over to the oral formulation of those drugs, so it was either lefamulin or moxifloxacin. It was a double-blind and noninferiority trial. The results showed similar outcomes in both groups of patients tested with the 2 medications.

In LEAP 1, the rates of study discontinuation—stopping the drugs midtreatment due to AEs—were 2.9% for the lefamulin group and 4.4% for the moxifloxacin, so there was, at least by percentage, an increased rate of discontinuation seen in the moxifloxacin group.

I was involved in the LEAP 2 trial and enrolled patients here in the United States. Now, the LEAP 2 trial looked at just the oral formulation of lefamulin; the comparator was again moxifloxacin, and 738 patients were enrolled. It included patients with pneumonia that had a PORT class score of 2, 3, or 4. The patients were treated with 5 days of lefamulin versus 7 days of moxifloxacin.

And so, of course, all patients enrolled in the trial received 7 days of medication—the investigators and the patients were blinded to which antibiotic they were receiving, so all patients received 7 days of treatment. Again, the clinical response rate and adverse effect [AE] profile were similar, and lefamulin was shown to be noninferior to moxifloxacin.

What does lefamulin overall bring to the armamentarium for clinicians who are treating CABP?

As physicians, we welcome a new antibiotic as long as it’s accessible to patients when we prescribe it to treat CABP, especially an antibiotic that can be prescribed much like we have done with the fluoroquinolones. So you can prescribe it as IV initially when needed, and it can be quickly converted to the oral formulation, or you could just prescribe the oral formulation, as well. So that reduces—in our very hectic and busy clinician role—our cognitive load a little bit. It also leads to more patient [adherence].

I see this class of drugs fitting very seamlessly into our workflow. In fact, it’ll be integrated similarly to how we integrated the fluoroquinolones and why that became a top choice or one of our primary go-to medications, at least before all the AEs were published and became known.
Teaching Old Dogs New Tricks: Make the Most of Twitter to Boost ID Education, Engagement, and Advocacy

Infectious diseases clinicians turn to Twitter as a tool for education and collaboration.

BY DEBRA GOFF, PHARMD; PAUL SAX, MD; AND CARLOS DEL RIO, MD

“Tell me and I forget. Teach me and I remember. Involve me and I learn.” These time-honored words of wisdom from Benjamin Franklin hold true today in medical and pharmacy education as the field advances into social media. Twitter represents a significant evolution in how information is developed and shared, including between people who otherwise would not have been able to connect. Twitter flattens the existent hierarchy, is immediate, and allows timely dissemination of relevant infectious diseases (ID) information beyond the reach of traditional education methods. Twitter can be an appropriate pedagogical tool to foster collaborative learning, engagement, and advocacy.

The way students and residents learn is rapidly changing. Currently, most medical and pharmacy students, residents, and early career physicians and pharmacists belong to the millenial generation, consisting of individuals born between 1980 and 1999. Millennials prefer a broad spectrum of learning strategies, with fewer lectures and more collaboration with peers.1 Millennials grew up with social media as an integral part of life. Facebook, Twitter, Instagram, and Snapchat were founded between 2004 and 2011. Most ID mentors and educators are from the baby boomer generation, born from 1946 to 1964. An “old dog” mentor must be willing to learn “new tricks” to educate the next generation of health care providers. Our purpose is to review how we use Twitter to educate, advocate, and engage others in various ID topics. Take a look at our list of popular accounts (Table 1) and a list of handles for the accounts of relevant and influential clinicians and advocates in the space (Table 2).

**Table 1. Selected List of Infectious Diseases Twitter Accounts**

<table>
<thead>
<tr>
<th>HANDLE</th>
<th>ACCOUNT OWNER</th>
<th>NO. OF FOLLOWERS</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>@dpharmd</td>
<td>Debra Goff, PharmD</td>
<td>6310</td>
<td>Promotes global antibiotic stewardship</td>
</tr>
<tr>
<td>@KhalidJa</td>
<td>Khalid Jaafy, PharmD, MS, BCPS</td>
<td>12,600</td>
<td>Posts links to recent ID studies</td>
</tr>
<tr>
<td>@ABSteward</td>
<td>Bassam Ghanem, PharmD, MS, BCPS</td>
<td>11,100</td>
<td>Posts monthly top ID stewardship papers</td>
</tr>
<tr>
<td>@IDStewardship</td>
<td>Tim Gauthier, PharmD (Bug Pharmacist)</td>
<td>9,262</td>
<td>Posts recent ID studies with links to Instagram for commentary, podcasts, and more</td>
</tr>
<tr>
<td>@JGPharmD</td>
<td>Jason Gallagher, PharmD</td>
<td>5,228</td>
<td>Posts about ID pharmacy education</td>
</tr>
<tr>
<td>@CarlosdR</td>
<td>Carlos del Rio, MD</td>
<td>8,839</td>
<td>Promotes health equity and HIV education</td>
</tr>
<tr>
<td>@PaulSaxMD</td>
<td>Paul Sax, MD</td>
<td>10,700</td>
<td>Shares clinical ID studies and blog posts</td>
</tr>
<tr>
<td>@PeggyFund</td>
<td>Peggy Lillis Foundation</td>
<td>1,714</td>
<td>Promotes Clostridoides difficile awareness</td>
</tr>
<tr>
<td>@FaceSA</td>
<td>Vanessa Carter</td>
<td>5,393</td>
<td>Posts from e-patient scholar on antibiotic resistance</td>
</tr>
<tr>
<td>@IDSAinfo</td>
<td>IDSA (Infectious Diseases Society of America)</td>
<td>24,000</td>
<td>Provides news and information from IDSA</td>
</tr>
<tr>
<td>@SIDPharm</td>
<td>SIDP (Society of Infectious Diseases Pharmacists)</td>
<td>9,522</td>
<td>Provides news and information from SIDP</td>
</tr>
<tr>
<td>@CIDRAP-ASP</td>
<td>CIDRAP-ASP (Center for Infectious Disease Research and Policy’s Antimicrobial Stewardship Project)</td>
<td>3,770</td>
<td>Provides current, comprehensive information on antimicrobial resistance and stewardship</td>
</tr>
<tr>
<td>@PewHealth</td>
<td>The Pew Charitable Trusts</td>
<td>8,697</td>
<td>Provides health news, research, and policy</td>
</tr>
</tbody>
</table>

*As of November 21, 2019.

I proposed a study: I wanted to find out if Twitter could engage surgeons in topics related to antibiotic resistance and stewardship. We did surgical grand rounds on Twitter for Antibiotic Stewardship and recruited surgeons for our study. We found that Twitter indeed engage surgeons in ID topics relevant to surgeons.2 Our most retweeted tweet was on the University of California, Los Angeles outbreak of carbapenem-resistant Klebsiella pneumoniae transmitted by contaminated duodenoscopes during endoscopic retrograde cholangiopancreatography procedures.3 My tweet was linked to a PubMed abstract that described treatment options for carbapenem-resistant K pneumoniae. Over 3000 people viewed the tweet. That was the start of my journey on Twitter for ID.

I tweet about research papers from ID journals; however, my tweets are targeted to specific audiences. For example, for a study on postoperative infections, my tweet will include several surgeons. For a study on joint implant infections, I will tweet a link to the PubMed abstract or the open access paper to orthopedic surgeons. Live tweeting from conferences such as IDWeek offers a way to increase the event’s reach to people who are not in attendance. I frequently tweet and add photos from global travel related to my work in antibiotic stewardship.

Twitter helps me engage with a large, diverse group of people from around the world on a variety of topics related to antibiotic stewardship. With the growing number of new antibiotic resistance reports, I find people posting abstracts, papers, and presentations on related cutting-edge data. My time on Twitter has led to many positive experiences, such as research with Twitter contacts, invitations to speak at national and international conferences, an invitation to the new social media committee at OSUWMC, and coauthoring this paper with Twitter friends.
I have always been a bit of a gadget nut and follow quite closely the writing of David Pogue, a tech writer for multiple venues—most famously, The New York Times. When he first described how Twitter could provide a crowdsourced answer to problems very quickly, it seemed like magic, and I instantly signed up. Surely this would have an application in medicine, where we frequently strive to find expert opinion to help our patients.

However, like most people who initially join, I didn’t really get it, and my account lay dormant for years. I also confess that certain horror stories about people being fools on Twitter kept me away. Why would anyone care about some stranger’s trite observations? Or Twitter could provide a crowdsourced answer to problems very quickly, it seemed like magic, and I instantly signed up. Surely this would have been as useful as or probably more than I teach on social media. List your degree or certification (eg, MD, PharmD, RN). Check with health care providers are held to higher standards on social media. List your degree or certification (eg, MD, PharmD, RN). Check with your hospital or place of employment to see if you are allowed to list your employer. Many will add the statement “Tweets represent my own opinion.”

Two things changed: First, some of my colleagues mentioned how they learned about important ID papers or conference presentations on Twitter, and I wanted to share that immediacy. Second, one of my editors at NEJM Journal Watch said it would be a great way to engage further with the people who read my writing. When I became editor in chief of Open Forum Infectious Diseases, I saw how commonly content posted on Twitter generated discussion and comment, usually for the better. That it did so from every level of medical training and from all health professionals only added to the value. Some of the very best ID content on Twitter is emphatically from ID pharmacists.

Here’s a simple example of how Twitter can be useful to all of us practicing clinical ID: When the OVIVA study of oral therapy for osteomyelitis was first presented at the 2017 European Congress of Clinical Microbiology & Infectious Disease—a conference I’ve never been to—I was able to see the presented slides years before the study was (finally) published and without traveling to Europe. The authors of that trial have been great on Twitter, engaging with people who had questions about the study after it was published. Their input was critical for a review of OVIVA I wrote for NEJM Journal Watch, and I thank them for that.

Most of what I post is related to ID and my particular focus within it, which is HIV. However, I am a rabid baseball fan, love good writing of any sort, and think dogs are a great gift to humankind. As a result, I follow not only ID and other interesting medical experts but also really talented baseball analysts, writers, and journalists in many diverse fields, as well as the requisite cute dog accounts. If you’re not following Thoughts of Dog (@dog_feelings) or WeRateDogs (@dog_rates), what are you waiting for?

I work in global health, and Twitter provides an amazing way to connect with colleagues around the globe. Although 66% of my followers are in the United States, the other 34% are in 117 countries, from Mexico to South Sudan, which allows me to be part of a community interested in sharing information and improving health globally.

Finally, I go back to where I started: advocacy. In times of injustice and where the most vulnerable don’t have a voice, I continue to rely on Twitter to fight for that which I believe in. From ending gun violence with the hashtag #ThisIsOurLane to fighting for gender equity and ending sexual harassment in medicine with the hashtag #MeForshe, Twitter allows me to increasingly engage in the public debate and, hopefully, contribute to transforming society for the better.

References are available at ContagionLive.com.

Activity of MAD-ID (Making a Difference in Infectious Diseases)
The focus of this article continues with the number of scoring systems that have been used in bacteremia and sepsis, in particular. Table 1 (see online) offers an overview of the clinical and laboratory criteria for select, commonly encountered scoring systems for acute severity of illness. Each scoring system brings certain advantages and disadvantages for clinical decision making (Table 2). The evolution of these scores has been observed in peer-reviewed literature and national guidelines, most recently with the advent of the quick Sequential Organ Failure Assessment (qSOFA) score supported in the 2016 Surviving Sepsis Campaign. Although this is a simple bedside scoring system with no laboratory values required, there is a lack of universal support for this score among leading experts in the field. We will describe the development of a simplified bedside scoring tool derived from the original Pitt bacteremia score (PBS), also referred to as the quick PBS or qPitt.

EVOLUTION OF THE PITT BACTEREMIA SCORE
Since its inception in 1989, the PBS has been used in numerous pivotal studies of bloodstream infections (BSIs). It has outperformed more complex scores of acute severity of illness in predicting mortality in various clinical settings. Among its other advantages, the PBS is solely based on clinical variables and lacks any laboratory criteria. This means it may be applied immediately at the bedside without the need to wait for blood collection or laboratory results.

During the first decade of the PBS usage, point allocation for temperature underwent several revisions. This is conceivable because fever represents a natural response to systemic infections, including BSI, and is not a consistent predictor of mortality. On the other hand, hypothermia (temperature <36°C) constitutes a dysregulated host response to infection and has been associated with high risk of mortality in patients with BSI.

DERIVATION OF THE QUICK PITT BACTEREMIA SCORE
Despite its relative simplicity, the PBS may still require some reference of the score’s criteria and take some thought to calculate. A quick form of the PBS (qPitt) was developed to further simplify the score by using only binary variables and allocating 1 point for each variable. This was achieved by either merging categorical into binary variables or eliminating variables that did not predict mortality. This also provided an opportunity to reexamine fever and allowed earlier detection of respiratory failure prior to mechanical ventilation.

In the derivation study of the qPitt, Battle and colleagues examined clinical risk factors for 14-day mortality in patients with gram-negative BSI. This retrospective cohort study included 832 patients hospitalized with gram-negative BSI at Prisma Health–Midlands hospitals in South Carolina over a 4-year period. All variables in the PBS were independently associated with 14-day mortality except fever (temperature >39°C). In addition, respiratory rate (>25 breaths/minute) was associated with 14-day mortality.

The quick Pitt Bacteremia Score offers accuracy comparable to the original version’s across multiple infections, and maintains ease of use.

BY AUSTIN WILLIAMS, PHARM D CANDIDATE; P. BRANDON BOOKSTAYER, PHARM D; SARAH BATTLE, MD; JULIE ANN JUSTO, PHARM D, MS; JOSEPH KOHN, PHARM D; AND MAJDI AL-HASAN, MBBS

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P. BRANDON BOOKSTAYER, PHARM D
Bookstayer is an associate professor and director of residency and fellowship training in the Department of Clinical Pharmacy and Outcomes Sciences at USC College of Pharmacy. He also maintains a practice site in infectious diseases at Prisma Health Richland, where he serves as director of the infectious diseases PGY-2 residency program and clinical fellowship program.

Get Off the SOFA! Introducing the Quick Pitt Bacteremia Score

The quick Pitt Bacteremia Score offers accuracy comparable to the original version’s across multiple infections, and maintains ease of use.
After adjustment in a multivariate model, hypothermia, systolic blood pressure of <90 mm Hg or vasopressor use, respiratory rate of ≥25 breaths/minute or mechanical ventilation, cardiac arrest, and altered mental status were independently associated with 14-day mortality and were included in the qPitt. The worst (highest or lowest) variables collected 24 hours prior and 24 hours following the collection of index blood culture were used. The qPitt had good discrimination (area under the receiver operating characteristic curve [AUROC], 0.85) and performed better than both qSOFA (0.77) and systemic inflammatory response syndrome (SIRS) score (0.63) in predicting 14-day mortality following gram-negative BSI. A score of 2 was found to be the best cutoff value in the qPitt. A qPitt ≥2 was clinically useful in identifying critically ill patients in whom appropriate empirical antibiotic therapy was associated with improved survival.14

THE ROLE OF QPITT IN STAPHYLOCOCCUS AUREUS BACTEREMIA

In a more recent study presented at IDWeek 2019, Battle and colleagues evaluated the qPitt’s performance in patients with Staphylococcus aureus BSI.15 The retrospective cohort study included 398 hospitalized patients with S aureus BSI at Prisma Health–Midlands hospitals from 2015 through 2017. After adjustment for age, clinical, and microbiological characteristics in the multivariate model, all 5 qPitt components were independently associated with 28-day mortality. Each point increase in the qPitt was associated with a 3-fold increase in 28-day mortality (OR, 3.1; 95% CI, 2.4–4.0). In agreement with the previous study of gram-negative BSI, the qPitt had an AUROC of 0.82 for predicting 28-day mortality. A score of 2 was also the best cutoff value. Mortality was 8.7% in patients with a qPitt <2 and 57.5% in those with a score ≥2. As in the previous analysis, the qPitt in this study had a better predictive utility for mortality compared with qSOFA (AUROC, 0.82 vs 0.77, respectively).15

THE ROLE OF QPITT IN NONBACTEREMIC PATIENTS

A multicenter cohort study published in Clinical Infections Diseases by Henderson and colleagues prospectively evaluated the predictive capabilities of the PBS and qPitt in patients with carbapenem-resistant Enterobacteriaceae (CRE) infections, with or without BSI.16 Patients were included from the Consortium on Resistance Against Carbenpemems in Klebsiella and Other Enterobacteriaceae (CRACKLE-1) study, for which the PBS and qPitt were calculated at baseline to predict 14-day mortality. Among patients with nonbacteremic CRE infections, the discrimination was similar between the PBS and qPitt scores (C-statistic for both, 0.85). A qPitt <2 and ≥2 represented the best cutoff values in the score similar to the 2 previous cohorts. The study validates both the PBS and qPitt in infected patients without BSI. It demonstrates that, like the PBS, the qPitt can be used at the bedside to predict mortality in patients with nonbacteremic infections using simple binary variables.16

APPLICATION AND FUTURE DIRECTIONS

The qPitt may be used at the bedside to determine acute severity of illness and predict mortality in patients with gram-negative or gram-positive BSI, as well as other infections. The qPitt combines the best of both the PBS and the qSOFA. The PBS predicts mortality with high precision solely based on clinical criteria. Lack of laboratory variables makes it immediately applicable at the bedside, with no need to wait for laboratory results. This is a major advantage over comparator scores. However, it requires some effort to calculate, given various point allocations for categorical variables.

On the other hand, the qSOFA is the simplest clinical score out there; however, it lacks the high discrimination of the PBS based on several studies in various clinical settings. Despite the endorsement in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3),17 many clinicians, scientific societies, and health care organizations remain reluctant to implement the qSOFA. The qPitt predicts mortality with an accuracy comparable to the PBS, while maintaining the simplicity and ease of use of the qSOFA. The qPitt offers an alternative clinical score to the qSOFA that is as simple but more precise in identifying patients at high risk of mortality. The qPitt shows notably higher discrimination than the qSOFA in predicting mortality following gram-negative and S aureus BSI, justifying its use in future investigations. Because the qPitt also performs well in other infections, it would be interesting to evaluate its ability to identify patients with life-threatening infections, such as sepsis, among those admitted to the hospital or intensive care units with suspected infections. ▲

References and full author bios are available at ContagionLive.com.
Twenty-five years ago, large community outbreaks were driven by infections among children, most of whom are asymptomatic when infected with HAV. Initial vaccine recommendations focused on children in high-prevalence counties but in 2006 were expanded to recommend that all children be vaccinated with 2 doses of vaccine starting at 12 months of age. As a result, the epidemiology of hepatitis A has shifted, reflecting a higher proportion of adults susceptible to infection compared with children, particularly adults reporting certain risk behaviors and exposures. This article describes the changing epidemiology of hepatitis A and the community-wide person-to-person outbreaks of hepatitis A infections occurring among adults in the United States.

HEPATITIS A IN THE PREVACCINE ERA (1966-1995)

HAV is a single-stranded RNA virus in the picornavirus family that replicates in the liver and is then excreted as bile into the stool. Illness is typically acute and self-limited. Clinical symptoms are indistinguishable from other infectious and noninfectious causes of hepatitis. The average incubation time after exposure to HAV is 28 days but can range from 15 to 50 days. Children under the age of 6 years are typically asymptomatic, and an infected person can excrete virus in stool for up to 2 weeks prior to experiencing symptoms, making identification of exposures and early detection of outbreaks particularly difficult.

Hepatitis A epidemiology varies worldwide. In endemic regions, up to 90% of children have been infected by 10 years of age. Outbreaks among older children and adults are rare in HAV-endemic countries because the majority of infections occur in early childhood, which confers lifelong immunity. As countries transition to lower endemcity through improved sanitation and hygiene and access to clean water, the overall susceptibility of the older populations increases. Because susceptible adults are more likely to present with symptoms when infected with HAV, outbreaks are more commonly observed in low-endemicity countries.

The United States transitioned to a low-endemicity country during the last century. Prior to the licensing of single-antigen hepatitis A vaccine in the United States in 1995, the highest hepatitis A incidence rates were among children, and most cases occurred in the context of community-wide epidemics in which the virus was transmitted from person to person. Community-wide epidemics lasted 6 to 18 months and exhibited bimodal age-specific attack rates (ages 5-9 years and 20-24 years). The cyclic nature of these outbreaks resulted from the periodic increase in sufficient numbers of susceptible children to sustain transmission. The bimodal age distribution among hepatitis A cases in the prevaccine era was likely due to infections among children and infections among adults at risk—namely, persons who use drugs (PWUDs) and men who have sex with men (MSM). Illicit drug use was reported in many community-wide hepatitis A outbreaks prior to the availability and widespread use of the vaccine. During the prevaccine era, outbreaks of hepatitis A occurred relatively frequently among MSM. Behaviors associated with infection included high-risk sexual practices (eg, >1 anonymous sex partner, group sex, oral-anal sex). Seroprevalence studies showed that a greater number of sex partners, longer
duration of sexual activity, and serological evidence of other sexually transmitted infections were also associated with HAV infection. As an important source of HAV transmission during previously reported outbreaks, improving vaccine coverage among PWUDs and MSM is critical to reducing the frequency and duration of community-wide outbreaks. The main challenge was and remains amassing the resources early enough in an outbreak response to maximize their impact.

In 1996, after the vaccine was licensed, in an effort to control ongoing outbreaks, the Advisory Committee on Immunization Practices (ACIP) recommended vaccinating children in communities with high rates of hepatitis A, PWUDs, and MSM. In 1999, it was recommended that children living in regions with double the national incidence rate of 10 per 100,000 be vaccinated.

**Hepatitis A During the Vaccine Era (1996-Present)**

During 1987-1997, the national average HAV incidence rate was 10.8 cases per 100,000 population, with a total of 11 states, mostly in the West, having an average annual rate of ≥20 cases per 100,000 population. After the recommendations to vaccinate adults at risk and routine vaccination for children living in states that had consistently elevated hepatitis A incidence rates, incidence rates declined 78% during 1990-2003, with 90% of that decline occurring after 1997. Although most vaccinations went to children, incidence rates declined in all age groups. The observed decline in hepatitis A incidence could not be solely attributed to vaccination, given the historical cyclic pattern of the disease and the absence of vaccination coverage data in at-risk adults. During this time, large-community outbreaks that had accounted for the majority of reported cases virtually disappeared. Although vaccination of children resulted in fewer adult cases, those that occurred were commonly associated with contact with children. Transmission among at-risk adults continued, likely due to low vaccination coverage. Although overall case counts were decreasing, the cases that were identified were increasingly identified among adults, in particular those in high-risk groups.

The main challenge to control HAV transmission among at-risk adults involves providing outreach and vaccination due to societal marginalization. Vaccinations provided through drug treatment facilities, HIV counseling and testing sites, homeless shelters, syringe exchange programs, and correctional facilities have proved to be successful interventions in containing outbreaks within these groups.

There was also a shift in the reported potential sources of infection, with a declining proportion of adults reporting exposure to infected children and an increasing proportion reporting exposure to contaminated food.

**Food-Associated Hepatitis A Outbreaks (2000-2016)**

The epidemiologic shift from community-wide outbreaks driven by infected children to an increasing number of outbreaks associated with contaminated food occurred around the year 2000. In general, food-associated hepatitis A outbreaks are difficult to detect because of the many factors involved, including the long incubation period, difficulty recalling food histories during the exposure period, challenges in identifying focal contamination of a food product, varying immunity among exposed individuals, geographically scattered cases, and inability to determine if case-patients were infected through person-to-person transmission. Although HAV contamination of food can occur at any point during harvesting, processing, distribution, or preparation, HAV infections among food handlers decreased, mirroring the overall decline observed nationally after widespread adoption of childhood hepatitis A vaccination recommendations.

After the year 2000, all the major (n >100 cases) food-associated outbreaks of HAV that occurred in the United States were associated with food items that were imported from endemic countries and were likely contaminated prior to distribution. In 2003, over 600 individuals were infected by hepatitis A-contaminated green onions imported from Mexico and served in multiple dishes at a single restaurant.

The next large HAV food-associated outbreak occurred 10 years later. In 2013, the CDC identified 165 individuals from 10 states infected by consuming HAV-contaminated pomegranate arils imported from Turkey. The arils were sold in a frozen berry mix from a single retailer. The retailer maintained information systems that included itemized sales data, purchase dates, and customer information, which aided the ability to identify the contaminated product and offer postexposure prophylaxis.

Just 3 years later, the CDC investigated 2 large food-associated HAV outbreaks: HAV-contaminated frozen scallops imported from the Philippines served in Hawaii (n = 292) and HAV-contaminated frozen strawberries imported from Egypt and served in multiple states along the East Coast (n = 144). In both outbreaks, the contaminated food items were served uncooked from multiple locations of implicated restaurant chains.

None of these outbreak investigations could determine at what point in harvesting or processing the contamination occurred. Shellfish may be contaminated because of harvesting near known sources of sewage or discharge of sewage near shellfish beds.

**Return of Person-to-Person Hepatitis A Outbreaks (2016-Present)**

A large population of susceptible, unvaccinated adults remains vulnerable to infection, and certain groups remain at particularly high risk because of behaviors that increase risk of person-to-person transmission. HAV transmission among people who report drug use, people experiencing homelessness, and MSM can result from inadequate sanitary conditions or specific sexual contact or practices or through sharing drug paraphernalia. Despite the long-standing recommendations that PWUDs and MSM receive hepatitis A vaccination, vaccination coverage rates are estimated to be low.

Since 2016, the United States has experienced unprecedented person-to-person outbreaks of hepatitis A infections, primarily involving adults reporting drug use or homelessness and MSM. These outbreaks started in California, Utah, and Kentucky but have affected at least 30 states, with more than 26,000 reported outbreak cases. Hospitalization rates have been high (60%), and novel vaccination strategies requiring substantial public health resources have been required to stop transmission.

Vaccination is the cornerstone of outbreak control. Identifying and targeting groups at risk early in outbreaks can be logistically difficult and costly; therefore, public health officials recommend proactive vaccination of groups at highest risk because this is the most effective strategy for preventing outbreaks. Transient housing, economic instability, anonymous sexual contact that impedes contact tracing, limited access to health care, and distrust of government services make outbreaks among these at-risk populations more difficult to control, requiring tailored comprehensive public health interventions that address their specific circumstances and needs.

**Conclusions**

Although the United States transitioned from high hepatitis A endemicity to low endemicity over the past century, the most at-risk populations continue to evolve. Introduction and widespread use of a safe and effective hepatitis A vaccine decreased overall incidence of hepatitis A infections, but community-wide outbreaks continue to occur, particularly among adults at risk. Continued efforts to increase hepatitis A vaccination coverage among the ACIP-identified at-risk groups is vital to halting the current ongoing hepatitis A outbreaks, preventing large community outbreaks in the future, and reducing overall hepatitis A incidence in the United States. References are available at ContagionLive.com.

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the CDC.
Alternative Antiretroviral Medication Delivery Systems Emerge to Treat, Prevent HIV Infection

Novel modes of delivery are imperative to improve HIV suppression and prevent transmission.

BY NEHA SHETH PANDIT, PHARMD, BCP, AAHIVP • NIMISH PATEL, PHARMD, PHD, AAHIVP • DANIEL B. CHASTAIN, PHARMD, BCIDP, AAHIVP

Most chronic disease states are treated with daily oral administration of medications, which are often ideal because of ease of administration. However, real-life adherence to oral medications can be approximately 50%. Improved adherence has been seen with novel formulations of medications in disease states such as schizophrenia. Currently, all recommended initial HIV treatment/prevention regimens include daily oral administration. Novel formulations are necessary to provide options for patients who have difficulty swallowing, a history of medication nonadherence, or concerns about HIV disclosure or even those learning to cope with their HIV diagnosis.

Emerging alternative antiretroviral (ARV) delivery systems for HIV treatment and prevention include injectables, topicals, and implants. These delivery systems may give patients the ability to administer daily medication less frequently and allow in-clinic administration for those who have not disclosed their status and do not want to bring medication bottles home. However, each system has advantages and disadvantages (Table 1).

INJECTABLE DRUGS: POPULAR BUT CHALLENGING

Injectable medications have the potential of rapid onset of action, improved medication adherence, and minimized concerns regarding absorption and dosing frequency. A few injectable ARVs are available, such as enfuvirtide (T20), ibalizumab (IBA), and zidovudine (ZDV). T20 requires twice-daily subcutaneous administration and can lead to injection site reactions (ISRs), limiting its use. Intravenous (IV) IBA is used for patients with multidrug-resistant HIV in combination with optimized background oral ARV therapy (ART). IV ZDV is primarily used for intrapartum care to prevent perinatal HIV transmission. Otherwise, because of toxicity concerns, ZDV is no longer routinely recommended for HIV treatment. Although no long-acting injectables (LAIs) are currently available, those in development include non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and fusion inhibitors.

Coformulated cabotegravir/rilpivirine (CAB/RPV), an INSTI and NNRTI combination, is the most-studied LAI for HIV treatment and prevention. The ATLAS and FLAIR studies assessed intramuscular CAB/RPV in virologically suppressed patients. ATLAS included patients who were virologically suppressed for 6 months on any oral 3-drug ART, whereas FLAIR included patients who were virologically suppressed at least 20 weeks on abacavir/lamivudine/dolutegravir. Both studies required an oral CAB plus oral RPV lead-in period for 4 weeks prior to LAI CAB/RPV initiation. Both studies found that CAB/RPV administered every 4 weeks was noninferior to oral therapy at 48 weeks. Over 97% of patients in both studies who completed a satisfaction survey preferred CAB/RPV over oral ART. CAB/RPV was submitted to the US Food and Drug Administration for approval for HIV treatment simplification in early 2019.

A phase 3 study assessing the use of intramuscular CAB/RPV given every 8 weeks is also under way. In addition, a phase 2/3 study is comparing LAI CAB and emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for pre-exposure prophylaxis (PrEP).

Despite the promise that LAI CAB/RPV has shown in patient satisfaction and clinical outcomes, using this medication in real-world settings poses many challenges. LAI CAB/RPV would require patients to be seen by a health care professional at least every 4 to 8 weeks for injection rather than every 3 to 6 months for routine follow-up. In addition, due to the long half-lives, prolonged toxicities may occur with unclear risk of resistance. Little is known about the potential harm and appropriate management of missed doses. As described in the studies, a 4-week lead-in period of oral CAB and RPV is required, and even though patient satisfaction was high in the studies, real-world adherence and satisfaction results are imperative to identify the appropriate population for this regimen.

Oral elsalevirine, a prodrug of VM-1500, is a long-acting NNRTI with a half-life of about 8 days. Elsalevirine with 2 nucleoside reverse transcriptase inhibitors was found to be noninferior to an efavirenz-based regimen, with fewer adverse drug reactions. Given

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Data are needed on how to transition patients from oral to new antiretroviral delivery systems, such as injectables or rings.
its long half-life, VM-1500A, an aqueous nanosuspension formulation, was developed to be administered intramuscularly monthly or quarterly. VM-1500A is in a phase 1b study to assess the safety and pharmacokinetics of various dosing regimens.14 Albuvirtide inhibits HIV attachment to CD4 cells by adhering to gp41 and has the potential for extended interval infusions with its half-life of 11 days. IV albuvirtide administered every 2 to 4 weeks in combination with an investigational IV monoclonal antibody (3BNC117) is being evaluated to assess its efficacy to maintain viral suppression.9 UB-421, an IV CD4 attachment inhibitor, was found to maintain viral suppression as monotherapy in patients who underwent oral ART interruption.10 UB-421 monotherapy is in phase 2/3 studies evaluating its use in patients previously stable on ART and those currently failing oral ART.11,12

The novel fusion inhibitors leneronlimab and combexitin are being evaluated as subcutaneous injections for HIV treatment. Leneronlimab, a CC chemokine receptor type 5 (CCR5) monoclonal antibody, and combexitin, an antibody with multiple HIV entry inhibition methods, have the potential for weekly administration. Because adnectins are such small proteins, combexitin could potentially be a self-administered subcutaneous LAI.13 Leneronlimab monotherapy is being evaluated to assess efficacy in patients suppressed on oral ART and those failing on oral ART.14,15 Combexitin is currently in a phase 1 trial to assess the safety, tolerability, and pharmacokinetics in healthy study participants.16 GS-CA compounds, part of a new class called HIV capsid inhibitors, are involved in multiple steps of the HIV replication cycle.17 Two of them, GS-CA1 and GS-6207, are being evaluated for HIV treatment and have been found to have high in vitro potency compared with dolutegravir.18 GS-6207, as a single subcutaneous injection, led to a sustained concentration in patients who were HIV negative, showing potential for quarterly administration.19 Phase 1 studies in people living with HIV are under way.20

**TOPICAL DRUGS: A DISCREET OPTION**

A unique and convenient option for HIV prevention, topical agents are particularly useful for individuals who fear stigma or seek a discreet prevention modality that their sexual partners do not need to know about. An ideal topical microbicidal is easy to administer, confers immediate protection, provides a long duration of protection, is durable in multiple sites (vaginally and rectally), and is unaffected by the presence of other products (examples: intravaginal device, menstrual cup/sponge, recent rectal enema). The main topical ARVs include tenofovir 1% gel, TDF intravaginal ring, and dapivirine intravaginal ring/film. Most clinical data are from the CAPRISA 004 trial, which assessed use of tenofovir gel in South African women aged 18 to 40 years who were sexually active and HIV negative. Adherence was highly variable. Among high adherers (>80%), HIV incidence was reduced by 54%.21 In a subsequent phase 1 pharmacokinetic study, a TDF intravaginal ring was assessed but discontinued early because of 8 of 12 women developed vaginal ulceration.22 Rectal TDF gel was well tolerated in men who have sex with men/transgender women, but gel adherence was less than that of oral FTC/TDF.23

There appears to be a growing amount of data regarding the dapivirine intravaginal ring, which was associated with high adherence/acceptability and achieves similar plasma/vaginal fluid concentrations between pre- and postmenopausal women that exceed the 99% inhibitory concentration over 4000 times.24–26 The film formulation, which releases dapivirine in <10 minutes, results in genital/plasma concentrations similar to those of the intravaginal ring.27

**IMPLANTABLE DRUGS: IN THE WORKS**

Because of physiochemical properties and potency, most ARVs cannot be formulated as an LAI, like CAB/RPV.28 To overcome these barriers, long-acting (LA) implantable formulations are placed subcutaneously and use a variety of implants, including polymeric matrices, semipermeable membranes, nonerodable silicone, and drug-eluting implants, to deliver ARVs for an extended period. Although most require surgical removal, biodegradable ARV implants are being developed.29,30 LA implantable ARVs are not yet in clinical trials but are under development, primarily for HIV prevention, with results that inspire optimism. Multiple LA tenofovir alafenamide implants have been found to provide tenofovir concentrations higher than that required for effective pre-exposure prophylaxis (PrEP) for at least 3 months.31,32 Already under investigation as an LA ARV, a nano-channel delivery implant provided CAB concentrations for 3 months that inhibited viral replication.33,34 Islatravir (MK-8591; EfDA) has a long plasma half-life that may allow once-weekly dosing when formulated for oral administration or potentially annual implantation as a drug-eluting implant for PrEP.35–37 A dolutegravir injectable solution that solidifies after subcutaneous administration is also under investigation.38

Similar to when using LAs for treatment, an oral lead-in period would be required for LA implantable ARVs. Partner ARVs with similar physiochemical and pharmacokinetic properties would need to be identified to formulate into a single implant to avoid inserting multiple implants for treatment purposes. Alternatively, LA implantable ARVs could be combined with LAI ARVs or oral formulations. Although multiple studies evaluating the LA implantable ARVs have found concentrations higher than that required for PrEP or virologic suppression, efficacy data are lacking.

**PROMISE DESPITE PROBLEMS TO OVERCOME**

Significant improvements have been made in ARV efficacy, safety, convenience, and accessibility. However, ARV efficacy for HIV treatment and prevention are directly associated with adherence, so in select patients, ARV administration with currently available oral options may not be feasible or ideal. A variety of ART delivery systems is critically needed to improve adherence for the treatment and prevention of HIV infection, because each modality comes with particular considerations.

Although initial results for these new delivery systems seem promising, clinical and regulatory barriers exist. In addition, data are needed on how to transition patients between oral to new ARV delivery systems, address missed doses, manage toxicities, and minimize drug-drug interactions, as well as use in special populations. Despite this, these emerging delivery systems hold great promise as additional tools to improve virologic suppression and prevent transmission. ▲

References and tables are available at ContagionLive.com.
Two More Agents Bolster the Arsenal Against Gram-Negative Resistance

As the antibiotic pipeline produces new therapies, clinicians must understand each agent’s specific role in management of patients infected by multidrug-resistant pathogens.

BY THOMAS P. LODISE, PHARMD, PHD, AND MONIQUE BIDELL, PHARMD, BCPS

(continued from cover page)

**IMIPENEM/CILASTATIN/RELEBACTAM**

Indication and Dosing

IMI/REL is a combination of imipenem, a carbapenem antibacterial; cilastatin, a renal dehydropeptidase inhibitor; and relebactam, a non-β-lactam β-lactamase inhibitor. In July 2019, the US Food and Drug Administration (FDA) approved IMI/REL (Recarbrio) to treat complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs), including pyelonephritis, caused by susceptible GNB in adult patients who have limited or no alternative treatment options. It is dosed at 1.25 g (imipenem 500 mg, cilastatin 500 mg, relebactam 250 mg) every 6 hours in patients with creatinine clearances 90 mL/min or greater, and dosage adjustments are required in patients with renal impairment.4

**Microbiologic Activity**

Although imipenem is active against many GNB, its activity is markedly enhanced with the addition of relebactam, a bicyclic diazabicyclooctane that is structurally similar to avibactam. Relebactam exhibits a positively charged piperidine ring added to the carbonyl group, which reduces efflux of relebactam from certain GNB.5 It inhibits Ambler class A (eg, extended-spectrum β-lactamases, carbapenemases), and class C cephalosporinases, effectively restoring imipenem activity against resistant *K pneumoniae* carbapenemase (KPC)– and AmpC-producing Enterobacteriaceae.

Like avibactam, relebactam does not inhibit metallo-β-lactamases (MBLs) or most carbapenem-destructive OXA-β-lactamases. Furthermore, porin deficiency in *K pneumoniae* appears to play a significant role in its susceptibility, as in vitro resistance has been reported with OmpK36 porin mutations in *K pneumoniae*.6 The activity of IMI/REL against non-MBL carbapenemase-producing *K pneumoniae* isolates was best highlighted in an analysis of 314 consecutive clinical strains collected across 18 hospitals in Greece between November 2014 and December 2016. Overall, IMI/REL inhibited 98.0% of KPC-producing isolates at concentrations of ≤2 mg/L. Reduced activity of IMI/REL was rarely detected (2%) and was associated with chromosomal factors (OmpK35 disruption and/or mutated OmpK36). Against KPC-producing *K pneumoniae*, relebactam lowered the imipenem minimum inhibitory concentration 90th percentile (MIC90) from >64 to 1 mg/L. However, relebactam provided only weak potentiation of imipenem activity against *K pneumoniae* with class D OXA-48-like enzymes.7

IMI/REL also has potent in vitro activity against MDR *P aeruginosa*. Unlike vaborbactam, which has a limited propensity to improve meropenem susceptibility for *P aeruginosa*, relebactam appears to substantially potentiate imipenem activity against imipenem-resistant *P aeruginosa* isolates.8 Neither imipenem nor relebactam appears to be a substrate for the efflux pumps present in *P aeruginosa*, and relebactam preserves imipenem activity in the setting of AmpC hyperproduction.9 The IMI/REL combination reduces imipenem MICs by approximately 8-fold in imipenem-nonsusceptible *P aeruginosa* isolates. When relebactam was added to clinical isolates from the SMART global surveillance program (n = 993, 2009; n = 1702, 2011; n = 5953, 2015; n = 6165, 2016), imipenem susceptibilities increased to 87.6, 86.0, 91.7, and 89.8%, respectively, compared with 68.4, 67.7, 70.4, and 67.3%, respectively, for imipenem alone.10

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Thomas P. Lodise, PharmD, PhD

Lodise is a professor at Albany College of Pharmacy and Health Sciences in New York. He is also an infectious diseases clinical pharmacy specialist at Albany Stratton VA Medical Center.
Clinical Experience
Two phase 2 clinical trials—one for cUTI and 1 for cIAI—compared IMI/REL with imipenem/cilastatin. Both studies evaluated 2 dosing regimens for IMI/REL (imipenem 500 mg/cilastatin 500 mg/relebactam 250 mg and imipenem 500 mg/cilastatin 500 mg/relebactam 125 mg). The cUTI trial included 298 adult patients, with 99 treated with the now FDA-approved dose of IMI/REL; the cIAI trial included 347 patients, with 117 treated with the FDA-approved dose. In both trials, clinical and microbiologic efficacy was >95% for all treatment groups, demonstrating noninferiority for IMI/REL versus imipenem/cilastatin. The most common treatment-associated adverse events (AEs) across groups were gastrointestinal related and headache.

To generate clinically applicable data with IMI/REL for the treatment of adult patients with imipenem-nonsusceptible GNB infections, a randomized, controlled, double-blind trial, RESTORE-IMI 1, was conducted. This noninferential, descriptive study compared IMI/REL with colistin-based therapy (colistin plus imipenem/cilastatin) for patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VAP), cUTIs, or cIAIs caused by imipenem-nonsusceptible (but colistin- and IMI/REL-susceptible) pathogens.

Among the 31 patients (n = 21, IMI/REL; n = 10, colistin-based therapy) in the modified microbiologic intent-to-treat population (qualifying baseline pathogen and ≥1 dose study treatment), there were 11 HABP/VAP, 16 cUTI, and 4 cIAI cases, and the predominating pathogen was P aeruginosa. Overall, a favorable response was observed in ~70% of patients in each treatment group. Day 28 favorable clinical response was higher among patients who received IMI/REL versus colistin-based therapy (71% and 40%, respectively; 90% CI, 1.3-51.5), and 28-day mortality was lower among patients in the IMI/REL group relative to the colistin-based therapy group (10% and 30%, respectively; 90% CI, –46.4 to 6.7).

Notably, there were no instances of treatment-emergent IMI/REL nonsusceptibility. Treatment-emergent nephrotoxicity was significantly less frequent with IMI/REL than with colistin-based therapy (10% and 56%, respectively [95% CI, –69.1% to –18.4%]). Although statistical inferences could not be drawn because of the trial’s descriptive nature, the results showed that IMI/REL was effective for treating imipenem-nonsusceptible GNB infections without the nephrotoxicity associated with colistin.

IMI/REL was compared with piperacillin/tazobactam in RESTORE-IMI 2, a global, multicenter, randomized, noninferiority trial of adult patients with HABP/VAP. In a press release, Merck indicated that IMI/REL met both the primary end point (day 28 all-cause mortality) and key secondary end points (eg, clinical response at early follow-up) of statistical noninferiority compared with piperacillin/tazobactam in the modified intent-to-treat population. Rates of AEs observed in the trial were also reported to be similar in both groups. Merck plans to present the full data at a scientific congress in 2020.14

Cefiderocol
Indication and Dosing
Cefiderocol (Fetroja), a first-in-class siderophore cephalosporin, is currently FDA approved for the treatment of adult patients with cUTIs, including pyelonephritis, caused by susceptible GNB who have limited or no alternative treatment options. The dosing regimen of cefiderocol is 2 g administered every 8 hours by intravenous infusion over 3 hours. Adjustments to the dosage and/or frequency of administration are recommended for patients with renal impairment or augmented renal clearance.

Microbiologic Activity
Like all β-lactams, cefiderocol exerts a bactericidal effect by binding to penicillin-binding proteins (PBPs) and inhibiting cell wall synthesis. Cefiderocol also has a distinctive mechanism for efficiently penetrating the outer membrane of GNB. As a siderophore cephalosporin, it binds to ferric iron, an essential nutrient for bacterial growth and virulence, and is actively transported across the outer membrane common to all GNB into the periplasmic space. This results in high concentrations of cefiderocol in the periplasmic space, where it can then bind to PBPs and inhibit cell wall synthesis. It is also stable against both serine and MBL carbapenemases.

Data from global surveillance studies for cefiderocol demonstrated potent in vitro activity against a wide spectrum of MDR-GNB, including carbapenem-resistant A baumannii, P aeruginosa, Enterobacteriaceae, and Stenotrophomonas maltophilia. Of the approximately 30,000 isolates collected in the SIDERO-WT surveillance studies (2014-2017), just 161 had a cefiderocol MIC >4 mg/L. Of the 11,168 isolates from the United States, 99.7% demonstrated a MIC of ≤4 mg/L; 19 showed a cefiderocol MIC >4 mg/L (9 A baumannii, 6 Enterobacteriaceae, 3 Burkholderia cepacia complex, 1 P aeruginosa). Among the 1272 meropenem-nonsusceptible isolates of Enterobacteriaceae, P aeruginosa, and A baumannii collected as part of the 2014 surveillance study, MIC values for cefiderocol were ≤4 mg/L against 97.7% of tested isolates. Notably, susceptibility was demonstrated for 100% of IMP, OXA-58, KPC, VIM, and OXA-48-like-producing isolates; 99.3% of carbapenemase-negative isolates; 97.2% of OXA-23-positive isolates; 95.2% of OXA-24-positive isolates; 91.7% of GES-positive isolates; and 64.3% of NDM-positive isolates. Cefiderocol MICs were ≤4 mg/L against 99.3% of 136 colistin-resistant Enterobacteriaceae, including isolates carrying mcr-1.

Clinical Experience
To date, cefiderocol has been evaluated in 3 clinical trials (1 phase 2, cUTI; 1 phase 3, HABP/VAP; 1 open-label, carbapenem-resistant isolates). The phase 2 cUTI trial was a randomized, double-blind, multicenter, noninferiority trial involving adult patients with cUTIs at risk of MDR gram-negative infection. Patients were randomly assigned 2:1 to cefiderocol 2 g infused over 1 hour 3 times daily (n = 303) or imipenem-cilastatin 1 g infused over 1 hour 3 times daily (n = 149) for 7 to 4 days. Of note, the currently recommended cefiderocol infusion duration is 3 hours.

Among the 371 patients (n = 252, cefiderocol group; n = 119, imipenem-cilastatin group) that had qualifying infection, the primary efficacy end point, a composite of clinical and microbiological response, at test of cure (TOC) was observed more frequently in the cefiderocol group than in the imipenem-cilastatin group (73% vs 55%; adjusted treatment difference, 18.58%; 95% CI, 8.23-28.92; P = .0004). The difference in the primary composite end point at TOC was due to greater microbiologic eradication in the...
Multidrug-Resistant Infections

cefiderocol arm. Both drugs were well tolerated, and the AE profile of cefiderocol was similar to that of imipenem/cilastatin, with the most commonly reported effects being gastrointestinal.

The CREDIBLE-CR study, a descriptive, open-label trial, investigated the efficacy and safety of cefiderocol versus best available therapy (BAT) in patients with evidence of gram-negative, carbapenem-resistant (CR) pathogens. Patients were randomized 2:1 to cefiderocol or BAT. Selection of BAT in the control arm was at the discretion of the treating clinician; most patients received colistin-based therapy. Cefiderocol was dosed at 2 g every 8 hours administered as a 3-hour infusion. In total, 150 patients were enrolled. The primary end point population (CR microbiologic intent-to-treat [MITT]) included 80 patients who received cefiderocol and 38 patients who received BAT.

The 3 most commonly reported pathogens in this study were CR A baumannii, CR K pneumoniae, and CR P aeruginosa. Most patients had HABP, VABP, or health care–associated pneumonia (HCAP) (45%), followed by bloodstream infections (BSIs) and/or sepsis (31%) and cUTIs (24%). Of note, there were several baseline imbalances between the cefiderocol and BAT groups. For example, the cefiderocol group had a greater proportion of patients ≥65 years old, and all 5 patients with S maltophilia were randomized to cefiderocol. In contrast, although the rate was high in both groups, a higher percentage of patients in the BAT group had prior antibiotic therapy in the 2 weeks before randomization than in the cefiderocol group (100% vs 92.1%, respectively).

In the CR MITT population, clinical cure rates for all infection sites combined in patients treated with cefiderocol compared with those treated with BAT at TOC were 52.5% versus 50.0%, respectively, and clinical failure rates at TOC were 33.8% versus 36.8%, respectively. Likewise, microbiologic eradication rates for cefiderocol versus BAT at TOC were 31.3% and 23.7%, respectively, and microbiologic failure rates at TOC were 20.0% and 26.3%, respectively.

There was a higher all-cause mortality rate in cefiderocol-treated patients compared with BAT-treated patients at days 14 and 28 and at end of study (18.8% vs 12.2%, 24.8% vs 18.4%, and 33.7% vs 18.4%, respectively). At day 14, day 28, and end of study, all-cause mortality was higher in patients with baseline HAP/VAP/HCAP and BSI/sepsis and lower in patients with baseline cUTI in the cefiderocol group compared with those in the BAT group. A higher mortality rate in the cefiderocol compared with the BAT group at day 49 was also observed among patients with A baumannii or P aeruginosa as a baseline pathogen and those with an acute physiology and chronic health evaluation (APACHE) II score ≥16. Although there were numerical differences in death at different time points between cefiderocol- and BAT-treated patients, confidence intervals for mortality differences did not provide nominally statistically significant evidence of a mortality increase at any time point.

An independent adjudication committee determined that a greater percentage of patients in the cefiderocol group than in the BAT group had infection-related death with treatment failure (15.8% vs 8.2%) but also noted an imbalance in death due to underlying comorbidities (9.9% vs 4.1%). Based on the findings from this trial, the following warning is included in its package insert: "Increase in All-Cause Mortality in Patients With Carbapenem-Resistant Gram-Negative Bacterial Infections: An increase in all-cause mortality was observed in Fetroja-treated patients compared to those treated with best available therapy (BAT). Reserve Fetroja for use in patients who have limited or no alternative treatment options for the treatment of cUTI. Closely monitor the clinical response to therapy in patients with cUTI."

APEKS-NP® (A baumannii, P aeruginosa, Escherichia coli, K pneumoniae, and S maltophilia in Nosocomial Pneumonia) was a phase 3 global, double-blind, randomized, active-controlled, noninferiority study of 300 adult patients with documented nosocomial pneumonia caused by GNB who received either cefiderocol (2 g every 8 hours over 3 hours) or meropenem (2 g every 8 hours over 3 hours). The primary end point was all-cause mortality at day 14 for the MITT population, defined as all treated patients except those that had gram-positive pathogens identified only at baseline. In the ITT population, 148 patients were randomized to cefiderocol and 150 to high-dose meropenem.

With regard to the population at baseline, many patients (59.7%) were ventilated, prior antibiotic failure was commonplace (32.6%), and the median APACHE II score was 15. In contrast to the CREDIBLE-CR study, no difference in mortality was observed between cefiderocol and meropenem in the ITT population at days 14 and 28, as well as at the end of study (12.8% vs 11.4%, 21.2% vs 20.1%, and 26.9% vs 22.8%, respectively). At day 14, all-cause mortality in the MITT population was 12.4% for cefiderocol and 11.6% for high-dose meropenem. In the microbiologically evaluable population, all-cause mortality was 12.4% for cefiderocol and 13% for high-dose meropenem. Mortality at day 14 was also comparable between cefiderocol and high-dose meropenem among patients that had P aeruginosa at baseline (2 of 24 [8.3%] vs 3 of 24 [12.5%]); A baumannii at baseline (5 of 23 [21.7%] vs 4 of 24 [16.7%]), and an APACHE-II score ≥16 (12 of 71 [16.9%] vs 12 of 71 [16.9%]).

Clinical and microbiological outcomes were also comparable between groups at TOC. Notably, in the MITT population, 22.2% of patients in the meropenem arm were infected by GNB resistant to meropenem (MIC >8 µg/mL) compared with 1.7% of patients treated with cefiderocol who were infected by GNB potentially resistant to cefiderocol (MIC > 4 µg/mL). No unexpected safety signals were observed in the study, and the incidence of treatment-emergent adverse events was similar between treatment arms.

CONCLUSIONS

There is an urgent need for novel antimicrobial agents to address the emergence of MDR pathogens, an increasing cause of morbidity and mortality worldwide. Antibiotic development initiatives over the past several years have introduced new therapies with novel mechanisms that may show promise in the treatment of patients with infections due to highly resistant GNB. Based on the available data, IMI/REL and cefiderocol appear to be 2 promising treatments for these patients. Additional data are essential to further elucidate the safety and efficacy of these agents in real-world settings, especially among patients with highly resistant gram-negative infections. ▲

References are available at ContagionLive.com.
Single-dose ORBACTIV® (oritavancin) is an alternative to multi-dose vancomycin course of therapy for ABSSSI.1,2

**Efficacy profile for single-dose ORBACTIV® (oritavancin) established in 978 patients.1,2**

<table>
<thead>
<tr>
<th>Clinical response at 48–72 hours (primary endpoint)§</th>
<th>ORBACTIV® % (n)</th>
<th>VANCOMYCIN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>81.2% (794)</td>
<td>80.9% (794)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical success at 14–24 days (secondary endpoint)¶</th>
<th>ORBACTIV® % (n)</th>
<th>VANCOMYCIN % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>81.2% (794)</td>
<td>80.2% (787)</td>
<td></td>
</tr>
</tbody>
</table>

§ Early clinical response defined as a composite of the cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibacterial drug at 48–72 hours.

¶ Clinical success was defined if the patient experienced a complete or nearly complete resolution of baseline signs and symptoms at post-therapy evaluation at day 14–24 and no further treatment with antibiotics was needed.

**mITT population; SOLO I and SOLO II were two identical, randomized, double-blind, non-inferiority Phase 3 trials comparing ORBACTIV® 1200 mg to vancomycin 1 g or 15 mg/kg twice daily for 7 to 10 days for the treatment of ABSSSI in 1959 patients.**

### To learn more about single-dose ORBACTIV®, please visit:
www.ORBACTIV.com

### Real Patient Case Study

**John F — Diabetic with Cellulitis**

This case study is an actual ABSSSI patient who was treated with a single 1200-mg dose of ORBACTIV®.

No additional treatments were given to the patient for this infection. Individual results may vary.

The treating physician is a paid consultant of Melinta Therapeutics, Inc.

### Resolution of John's cellulitis following single-dose ORBACTIV®

<table>
<thead>
<tr>
<th>Prior to single-dose ORBACTIV® 1200-mg infusion</th>
<th>12 hours after ORBACTIV® infusion</th>
<th>48 hours after ORBACTIV® infusion</th>
</tr>
</thead>
</table>

### References:

Please see Brief Summary of ORBACTIV® Prescribing Information on following pages.
4.1 Intravenous Unfractionated Heparin Sodium

Use of intravenous unfractionated heparin sodium is contraindicated for 120 hours (5 days) after ORBACTIV® administration because the activated partial thromboplastin time (aPTT) test results may remain falsely elevated for up to 120 hours (5 days) after ORBACTIV® administration [see Warnings and Precautions (5.1) and Drug Interactions (7.2)].

ORBACTIV® has been shown to artificially prolong prothrombin time (PT) and international normalized ratio (INR) for up to 12 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 12 hours after an ORBACTIV® dose [see Warnings and Precautions (5.1)]. Patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin [see Drug Interactions (7.9)].

4.2 Hypersensitivity

ORBACTIV® is contraindicated in patients with known hypersensitivity to ORBACTIV®.

4.3 Infusion Related Reactions

ORBACTIV® has been shown to artificially prolong aPTT for up to 120 hours, PT and INR for up to 12 hours, and activated clotting time (ACT) for up to 24 hours following administration of a single 1200 mg dose by binding to and preventing action of the phospholipid reagents commonly used in laboratory coagulation tests. ORBACTIV® has also been shown to elevate D-dimer concentrations up to 72 hours after ORBACTIV® administration.

5.2 Hypersensitivity

Serious hypersensitivity reactions have been reported with the use of ORBACTIV®. If an acute hypersensitivity reaction occurs during ORBACTIV® infusion, discontinue ORBACTIV® immediately and institute appropriate supportive care. Before using ORBACTIV®, inquire carefully about previous hypersensitivity reactions to glycopeptides. Due to the possibility of cross-sensitivity, carefully monitor for signs of hypersensitivity during ORBACTIV® infusion in patients with a history of glycopeptide allergy. In the Phase 3 ABSSSI clinical trials, the median onset of hypersensitivity reactions in ORBACTIV®-treated patients was 1.2 days and the median duration of these reactions was 2.4 days [see Adverse Reactions (6.1)].

5.3. Infusion Related Reactions

ORBACTIV® is administered via intravenous infusion, using a total infusion time of 3 hours to minimize the risk of infusion-related reactions. Infusion related reactions have been reported with the glycopeptide class of antimicrobial agents, including ORBACTIV®, that resemble “Redman Syndrome,” including flushing of the upper body, urtica, pruritus and/or rash. Stopping or slowing the infusion may result in cessation of these reactions [see Adverse Reactions (6.1)].

5.4 Clostridium difficile-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial drugs, including ORBACTIV®, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

5.5 Potential Risk of Bleeding with Concomitant Use of Warfarin

ORBACTIV® has been shown to artificially prolong prothrombin time (PT) and international normalized ratio (INR) for up to 12 hours, making the monitoring of the anticoagulation effect of warfarin unreliable up to 12 hours after an ORBACTIV® dose [see Warnings and Precautions (5.1)]. Patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin [see Drug Interactions (7.9)].

5.6 Osteomyelitis

In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the ORBACTIV® treated arm than in the vancomycin-treated arm. Monitor patients for signs and symptoms of osteomyelitis. If osteomyelitis is suspected or diagnosed, institute appropriate alternate antibacterial therapy [see Adverse Reactions (6.1)].

5.7 Development of Drug Resistant Bacteria

Prescribing ORBACTIV® in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Patient Counseling Information (17)].

6. ADVERSE REACTIONS

The following adverse reactions are also discussed in the Warnings and Precautions section of labeling:

• Hypersensitivity Reactions [see Warnings and Precautions (5.2)]
• Infusion Related Reactions [see Warnings and Precautions (5.3)]
• Clostridium difficile-associated Diarrhea [see Warnings and Precautions (5.4)]
• Osteomyelitis [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of ORBACTIV® cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

ORBACTIV® has been evaluated in two, double-blind, controlled ABSSSI clinical trials, which included 976 adult patients treated with a single 1200 mg intravenous dose of ORBACTIV® and 983 patients treated with intravenous vancomycin for 7 to 10 days. The median age of patients treated with ORBACTIV® was 45.6 years, ranging between 18 and 89 years of age with 8.8% ≥ 65 years of age. Patients treated with ORBACTIV® were predominantly male (65.4%), 64.4% were Caucasian, 5.8% were African American, and 28.1% were Asian. Safety was evaluated for up to 60 days after dosing. In the pooled ABSSSI clinical trials, serious adverse reactions were reported in 57/976 (5.8%) patients treated with ORBACTIV® and 58/983 (5.9%) treated with vancomycin. The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/976 (1.1%) in ORBACTIV® and 12/983 (1.2%) in the vancomycin arms, respectively.

The most commonly reported adverse reactions (≥3%) in patients receiving a single 1200 mg dose of ORBACTIV® in the pooled ABSSSI clinical trials were: headache, nausea, vomiting, limb and subcutaneous abscesses, and diarrhea.

In the pooled ABSSSI clinical trials, ORBACTIV® was discontinued due to adverse reactions in 36/976 (3.7%) of patients; the most common reported reactions leading to discontinuation were cellulitis (4/976, 0.4%) and osteomyelitis (3/976, 0.3%).

Table 1 provides selected adverse reactions occurring in ≥1% of patients receiving ORBACTIV® in the pooled ABSSSI clinical trials. There were 540 (55.3%) patients in the ORBACTIV® arm and 559 (56.9%) patients in the vancomycin arm, who reported ≥1 adverse reaction.

Table 1: Incidence of Selected Adverse Reactions Occurring in ≥1% of Patients Receiving ORBACTIV® in the Pooled ABSSSI Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>ORBACTIV N=976 (%)</th>
<th>Vancomycin N=983 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (3.7)</td>
<td>32 (3.4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>97 (9.9)</td>
<td>103 (10.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45 (4.6)</td>
<td>46 (4.7)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>26 (2.7)</td>
<td>26 (2.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>69 (7.1)</td>
<td>66 (6.7)</td>
</tr>
<tr>
<td>General disorders and administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion site phlebitis</td>
<td>24 (2.5)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>19 (1.9)</td>
<td>34 (3.5)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess (limb and subcutaneous)</td>
<td>37 (3.8)</td>
<td>23 (2.3)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>27 (2.8)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>18 (1.8)</td>
<td>15 (1.5)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>24 (2.5)</td>
<td>11 (1.1)</td>
</tr>
</tbody>
</table>
6.1 Clinical Trials Experience (continued)
The following selected adverse reactions were reported in ORBACTIV®-treated patients at a rate of less than 15%:
- **Blood and lymphatic system disorders**: anemia, eosinophilia
- **General Disorders and administration site conditions**: infusion site erythema, extravasation, induration, pruritus, rash, edema peripheral
- **Immune system disorders**: hypersensitivity
- **Infections and infestations**: osteomyelitis
- **Investigations**: total bilirubin increased, hyperuricemia
- **Metabolism and nutrition disorders**: hypoglycemia
- **Musculoskeletal and connective tissue disorders**: tenosynovitis, myalgia
- **Respiratory, thoracic and mediastinal disorders**: bronchospasm, wheezing
- **Skin and Subcutaneous Tissue Disorders**: urticaria, angioedema, erythema multiforme, pruritis, leucocytoclastic vasculitis, rash.

7. DRUG INTERACTIONS
7.1 Effect of ORBACTIV® on CYP Substrates
A screening drug-drug interactions study indicated that ORBACTIV® is a nonspecific, weak inhibitor (CYP2C9 and CYP2C19) or inducer (CYP3A4 and CYP2D6) of several CYP isoforms [see Clinical Pharmacology (12.3)]. A drug-drug interaction study that assessed the interaction potential of a single 1200 mg dose of ORBACTIV® on the pharmacokinetics of S-warfarin (CYP2C9 probe substrate) showed no effect of ORBACTIV® on S-warfarin Cmax or AUC. Avoid administering ORBACTIV® concomitantly with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes, as co-administration may increase or decrease concentrations of the narrow therapeutic range drug. Patients should be closely monitored for signs of toxicity or lack of efficacy if they have been given ORBACTIV® while on a potentially affected compound (e.g. patients should be monitored for bleeding if concomitantly receiving ORBACTIV® and warfarin).

7.2 Drug-Laboratory Test Interactions
ORBACTIV® may artificially prolong certain laboratory coagulation tests (see Table 2) by binding to and preventing the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests [see Contraindications (4.1) and Warnings and Precautions (5.1, 5.3)]. For patients who require monitoring of anticoagulation effect within the indicated time after ORBACTIV® dosing, a non phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered. ORBACTIV® does not interfere with coagulation in vivo. In addition, ORBACTIV® does not affect tests that are used for diagnosis of Heparin Induced Thrombocytopenia (HIT).

### Table 2: Coagulation Tests Affected and Unaffected by ORBACTIV®

<table>
<thead>
<tr>
<th>Affected by ORBACTIV®</th>
<th>Unaffected by ORBACTIV®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time (PT) up to 12 hours</td>
<td>Chromogenic Factor Xa Assay</td>
</tr>
<tr>
<td>International normalized ratio (INR) up to 12 hours</td>
<td>Thrombin Time (TT)</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (aPTT) up to 120 hours</td>
<td></td>
</tr>
<tr>
<td>Activated clotting time (ACT) up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Silica clot time (SCT) up to 18 hours</td>
<td></td>
</tr>
<tr>
<td>Dilute Russell's viper venom time (DRVVT) up to 72 hours</td>
<td></td>
</tr>
<tr>
<td>D-dimer up to 72 hours</td>
<td></td>
</tr>
</tbody>
</table>

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C
Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to oritavancin at the highest concentrations administered, 30 mg/kg/day and 15 mg/kg/day, respectively. Those daily doses would be equivalent to a human dose of 300 mg, or 25% of the single clinical dose of 1200 mg. Higher doses were not evaluated in nonclinical developmental and reproductive toxicology studies. There are no adequate and well-controlled trials in pregnant women. ORBACTIV® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers
It is unknown whether oritavancin is excreted in human milk. Following a single intravenous infusion in lactating rats, radio-labeled [14C]-oritavancin was excreted in milk and absorbed by nursing pups. Caution should be exercised when ORBACTIV® is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness of ORBACTIV® in pediatric patients (younger than 18 years of age) has not been studied.

8.5 Geriatric Use
The pooled Phase 3 ABSSSI clinical trials of ORBACTIV® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate renal impairment [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)]. The pharmacokinetics of ORBACTIV® in severe renal impairment have not been evaluated. ORBACTIV® is not removed from blood by hemodialysis.

8.7 Hepatic Impairment
No dosage adjustment of ORBACTIV® is needed in patients with mild or moderate hepatic impairment. The pharmacokinetics of ORBACTIV® in patients with severe hepatic insufficiency has not been studied [see Dosage and Administration (2.1), Clinical Pharmacology (12.3)].

10. OVERDOSE
In the ORBACTIV® clinical program there was no incidence of accidental overdose of ORBACTIV®. Based on in vitro hemodialysis study, ORBACTIV® is unlikely to be removed from blood by hemodialysis. In the event of overdose, supportive measures should be taken.

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long term studies in animals have not been conducted to determine the carcinogenic potential of oritavancin. No mutagenic or clastogenic potential of oritavancin was found in a battery of tests, including an Ames assay, in vitro chromosome aberration assay in Chinese hamster ovary cells, in vitro forward mutation assay in mouse lymphoma cells and an in vivo mouse micronucleus assay.

Oritavancin did not affect the fertility or reproductive performance of male rats (exposed to daily doses up to 30 mg/kg for at least 4 weeks) and female rats (exposed to daily doses up to 30 mg/kg for at least 2 weeks prior to mating). Those daily doses would be equivalent to a human dose of 300 mg, or 25% of clinical dose. Higher doses were not evaluated in nonclinical fertility studies.

This Brief Summary is based on the ORBACTIV® Prescribing Information, Rev. 03/2018
Rx only
Marketed by: Melinta Therapeutics, Inc. Lincolnshire, IL 60069 USA
Institutions have invested resources to ensure that their programs meet the minimum requirements to comply with the standard, but what if cost wasn’t an issue?

Beyond the antimicrobial stewardship requirements described in the Joint Commission standard, various enhancements have the potential to dramatically boost the impact of an ASP. If resources and funds were unlimited, what would the ideal stewardship program look like?

The following wish list includes the perspectives of two community-teaching hospital stewardship pharmacists on items that would be “nice to have” and those they “dream to have.”

**NICE TO HAVE**

**Information Technology (IT) Specialist**

As with all quality improvement initiatives, regular evaluation of pertinent metrics is essential in the evaluation of ASP successes and opportunities. Many programs rely on staff to compile and assess metrics, which may be time-consuming and can displace patient care activities. Incorporating an IT specialist with dedicated responsibility for ASP metrics can alleviate this issue, with the added benefit of expertise for higher-level data generation. Dedicated IT resources can also help navigate the requirements for reporting to the National Healthcare Safety Network Antimicrobial Use and Resistance (AUR) Module, allowing for robust interhospital benchmarking.

Various studies have demonstrated the benefits of leveraging behavioral interventions, such as peer comparison, to positively influence antibiotic prescribing. Peer comparisons typically involve a report or dashboard of various metrics detailing prescriber-level practices and outcomes. An IT specialist’s expertise is critical in the development of such dashboards, and consistent involvement of the IT specialist for regular maintenance of these metrics is likely necessary for sustained impact on prescribing practices.

Passive stewardship interventions, such as developing guidelines and provider education, may have some immediate impact but lack sustainability. However, incorporating such guidelines and education at the point of prescribing through the electronic medical record (EMR) may overcome these issues. As use of the EMR becomes a mainstay of health care, it is clear that IT specialists can be valuable members of health care teams. In the past 5 years, nearly 100 publications indexed by PubMed have described EMR enhancements that optimize antimicrobial prescribing. The IT specialist can assist an ASP in building several clinical decision support tools within the EMR, such as order sets, clinical pathways, and best practice alerts.

**What’s on Your Antimicrobial Stewardship “Wish List”?**

If resources and funds were unlimited, what would the ideal stewardship program look like?

BY DIMPLE PATEL, PHARMD, BCPS-AQ ID, AND ESTHER KING, PHARMD

(continued from cover page)
Outpatient Collaboration with Dedicated Outpatient Stewardship Personnel

Structured antimicrobial stewardship programs have been advocated in the inpatient setting for many years to reduce the emergence of resistant pathogens and *Clostridium difficile*. However, similar efforts are not yet as widespread outside the acute care setting. Collaboration with providers in outpatient and skilled nursing facility (SNF) settings can be beneficial in recognizing the burden of resistance and *C difficile* across the entire health care continuum. A dedicated outpatient stewardship human resource can oversee the development of local outpatient and SNF antibiograms, clinical pathways/guidelines, and metrics.

Microbiology Resources

The benefits of a strong collaboration with the microbiology laboratory department cannot be overstated. Purposeful modifications of the culture and antibiotic susceptibility reports can have significant effects on definitive antibiotic selection. Cascade reporting is the practice of reporting the results of broad-spectrum antibiotics only in response to resistance to narrow-spectrum antibiotics in an effort to guide de-escalation. Several studies have demonstrated improvements in appropriate selection of narrow-spectrum definitive therapy. In addition, including interpretive comments within antibiotic susceptibility reports may improve the utility of these results by embedding therapy recommendations to guide appropriate antibiotic selection. For example, one study evaluated the impact of including a “nudge” comment within respiratory culture results demonstrating isolation of normal flora. The comment specifically addressed lack of substantial growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa*, resulting in higher rates of de-escalation/discontinuation and lower rates of acute kidney injury, with no adverse outcomes observed. Initial implementation of these microbiology enhancements may be resource intensive, but sustained benefit can be seen without the need for long-term dedicated resources.

In addition, the widespread availability of various rapid diagnostic tests (RDTs) has introduced exciting opportunities for optimization of antimicrobial stewardship. These methods include multiplex polymerase chain reaction (PCR) panels, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, peptide nucleic acid fluorescent in situ hybridization, morphokinetic cellular analysis, nanoparticle probe technology, and magnetic resonance technology. These methods differ in ability to detect various organisms and/or resistance mechanisms but generally offer a faster turnaround compared with traditional culture-based methods, resulting in improved time to appropriate therapy. Although RDTs are attractive wish list items for ASPs, additional stewardship personnel may be needed to respond to results with appropriate interventions in a timely manner. For the full benefit to be realized, RDTs should be coupled with active ASP engagement, as demonstrated in previous studies.

Many technological platforms have a variety of products to address different infectious disease syndromes. Unfortunately, due to cost and space constraints, laboratories are generally unable to purchase several platforms to use the most robust products for each syndrome. For example, a facility that uses a platform that performs multiplex PCR testing for respiratory illness may have the option to purchase panels for rapid blood culture identification that could be run on the same platform as discounted pricing. At this time, these panels are unable to provide robust resistance markers or rapid susceptibility information. Morphokinetic cellular analysis can offer rapid organism identification and phenotypic susceptibility but would require the purchase of an additional testing platform. The ability to use several testing platforms could provide new opportunities to enhance ASPs.

DREAM TO HAVE

**Stewardship Transitions-of-Care (TOC) Pharmacist**

Antibiotic duration of therapy continues to be a topic of discussion, with more data becoming available for various disease states to suggest shorter durations of therapy. Despite several randomized controlled trials demonstrating similar outcomes and guideline endorsement for shorter durations of therapy, a recent study demonstrated that more than two-thirds of patients treated for pneumonia were prescribed excessive antibiotic treatment durations, predominantly at discharge. Although TOC has generally focused on chronic disease states (eg, chronic obstructive pulmonary disease, heart failure), antibiotic review at the time of discharge, including antibiotic selection and duration of therapy, has surfaced as an unmet need. Adding a dedicated TOC pharmacist to focus on antimicrobial stewardship could decrease overall antibiotic use and, in turn, reduce antibiotic-associated adverse events and possibly *C difficile*.

**Infectious Diseases/Stewardship Data Abstractor**

After implementing all the incredible stewardship initiatives that take place day to day, stewards may find that lack of time and resources keep them from evaluating and fully scrutinizing data to determine the initiatives’ impact on patient outcomes. Performing in-depth chart reviews for each intervention in an institution that has 1 dedicated antimicrobial steward generally takes time away from the daily activities required to sustain a stewardship program. Having a dedicated data abstractor for infectious diseases and antimicrobial stewardship would allow data to be collected (with possible publication) without compromising daily stewardship activities.

**Hospitalist/Stewardship Collaboration**

IDWeek 2019 had several sessions describing the impact of including a hospitalist as part of the ASP team. Tejal Gandhi, MD, of the University of Michigan presented data on a large ASP/hospitalist collaborative that showed a significant increase in appropriate duration of antibiotic therapy for community-acquired pneumonia that, in turn, decreased antibiotic-associated adverse events. Part of the collaborative included financial incentives for prescribing appropriate duration of therapy, which was described by Valerie Vaughn, MD, during the IDweek session “Collaboration with Hospitalists.” Having sufficient funds to give a hospitalist champion dedicated time for stewardship efforts and offer hospitalists antimicrobial stewardship financial incentives could potentially affect a large portion of inpatient and outpatient antibiotic use.

Although many of the ideal human resources described above are considered wish list items, business models are being proposed in the literature to help support these resources as standard of care. References are available at ContagionLive.com.

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**References are available at ContagionLive.com.**
A lthough first-line treatment of HIV infection has improved in recent years, the complexity of treatment regimens can create barriers to adherence and has prompted research into long-acting agents that reduce treatment burden. In a recent Contagion® Peer Exchange panel, experts discussed reasons for virological failure, clinical significance of low-level viremia, long-acting drugs in development, and recommendations for managing HIV infection in the community practice setting.

VIROLOGICAL FAILURE AND INCOMPLETE RESPONSE
Rates of virological failure dropped in recent years with the improvement in first-line treatments for HIV, according to Eric S. Daar, MD. When he does see viral load go up, he ensures patients are taking their medications correctly before he performs resistance testing, because drug-drug and drug-food interactions can affect absorption of some commonly used drugs. “The resistance testing will usually answer the question, because if they have no resistance, then there’s probably something going on with the way they’re taking their meds,” he said. “If they have resistance, then we design a new regimen.”

Daar noted that although no randomized trial data identify the optimal treatment regimen, protease inhibitors boosted with a nucleoside reverse transcriptase inhibitor or an integrase inhibitor are usually effective after first-line failure on integrase inhibitors alone. “The most important thing we need to do is figure out what went wrong, because it’s so unusual to see [virological failure] actually happen,” Daar said.

Similarly, W. David Hardy, MD, said that a lapse in adherence, perhaps because of loss of interest, a chaotic life event, or issues with insurance coverage, is usually behind virological failure with current therapies. “It’s not the medication failing,” he said. “The medication is failing to get inside the patient.”

Although an imperfect method, checking the pharmacy fill dates is considered a valid way to keep tabs on adherence, according to the panelists. Ian Frank, MD, added that he has a case manager talk with patients to identify obstacles to taking their medications correctly.

The panelists also noted that external resources, such as co-pay cards from drug manufacturing companies and pharmacies that organize a patient’s pills by day of the week, can improve adherence. However, Daar cautioned, the occasional patient will have resistant virus even after 20 years of adherence to treatment. “Occasionally, we get to fall back to the lessons learned over a decade ago about how to manage people with truly multidrug-resistant virus,” he said.
SIGNIFICANCE OF LOW-LEVEL VIREMIA INDICATION

Frank said that he has a small group of patients who have low but measurable levels of viral loads of less than 200 copies/mL, likely stemming from a virus released from a latent reservoir rather than perpetuating ongoing infection. Although data show that these individuals are not failing treatment. Although data show that although these are not failing therapy, “it just makes me nervous to see this at every visit,” he said.

Paul Sax, MD, pointed out that studies of preventative treatment used thresholds higher than 200 copies/mL as the cutoff for virological control, below which no case reports have shown transmission of HIV with a measurable value. Noting that low-level viremia does bother his patients, session moderator Joseph Eron, MD, said that treatment decisions (such as switching regimens or intensifying the current one) should not be made based on a single testing value between 50 and 200 copies/mL.

HIV LONG-ACTING INJECTABLE THERAPIES IN THE PIPELINE

Long-acting injectable drugs for treatment of HIV infection are in development, with cabotegravir and rilpivirine farthest along in the pipeline. Frank said. He identified studies showing that switching to these injectable drugs, administered every 4 to 8 weeks as maintenance therapy, was as effective at maintaining virological suppression as continuing oral regimens. Injection site reactions occurred but were rarely the reason for discontinuing treatment, and patients tended to tolerate the injections better as they continued in the study.

Frank pointed out that, although a key goal of long-acting injectable therapies is to improve adherence by eliminating the need for daily oral medications, repeated injections create a different set of challenges, which may increase risk of drug resistance because of missed doses. “They’ll need to be administered by a friend or a family member, or people will need to come into the office to receive the injection, or the office is going to need to go to them to administer the injection,” he said.

The panelists also debated just how many virologically stable patients might switch from oral antiretroviral treatment to injectable therapy every 4 weeks. Although Eron guessed that a very small proportion of patients would consider the injections, Daar presumed that more might be interested if shots could be administered every 8 weeks. “My fantasy is that I’ll be able to tell those newly diagnosed people that...they’ll have to think about their HIV [just] 6 days a year, when they’re going to show up at their local pharmacy for an injection,” he said.

Other advantages of injectable therapy include fewer pills and the potential availability of the injectable drug in pharmacies, which may help patients who are traveling or have a change in living situation. Eron added that the switch to injectable therapy need not be permanent: “Someone could go on injectables for a year and then go back to oral therapy.”

Daar and Eron noted that the tolerability data from the phase 2b trial were promising, with some patients on their third or fourth year of receiving the injections as part of the LATTE-2 study. “It will definitely have a following, I’m quite sure, and it will be interesting to see if it increases over time,” Eron said.

HIV NONINJECTABLE LONG-ACTING THERAPIES IN DEVELOPMENT

The panelists discussed the efficacy of another long-acting injectable therapy, ibalizumab, and the long-acting noninjectable drugs fostemsavir and MK-8591 for patients with HIV infection. Ibalizumab, a nonimmunosuppressive humanized monoclonal antibody, may be an option for patients with multidrug-resistant infection. However, Hardy pointed out that requiring intravenous infusion increases the regimen’s complexity, and Daar added that the high cost of ibalizumab and need for infusions every 2 weeks limits its uptake among patients. Nevertheless, Daar noted that ibalizumab may represent a shift toward using monoclonal antibodies as HIV therapeutics and modifying them to increase the half-life of the drugs (and thereby reduce the frequency of injections).

Fostemsavir, an orally available HIV attachment inhibitor taken twice a day, is being studied in a small population of patients with multidrug-resistant HIV infection who have no other treatment options, Sax said. “One thing that I keep having to clarify to people who don’t know this field as well as we do is that there are a lot of people with multidrug-resistant HIV out there. But most of them are suppressed. It’s only for people who are failing, so it’s a very tiny patient population.”

The panelists shifted their discussion to MK-8591 (EfDA or islatravir), a potent nucleoside reverse transcriptase translocation inhibitor being studied as a daily oral drug or in a slow-release implant. Hardy noted that the slightly different mechanism of action reduces the likelihood of drug resistance, and Eron pointed out that MK-8591’s long half-life introduces the potential for less frequent dosing—such as a single pill once a week—but more research is needed to determine the feasibility of this approach and need for a partner drug.

References are available at ContagionLive.com.
Antibiotic Prophylaxis Prior to Dental Procedures Proves Risky and Largely Unnecessary

BY ALEXANDRA WARD, MA

Dental visits have been identified as ripe opportunities for implementing antibiotic stewardship to cut down on the rising rate of unnecessary prescriptions.

Previous studies have shown that in the United States, dentists prescribe 10% of outpatient antibiotics, a significant portion of which includes prophylaxis prior to dental visits. What’s more, 80% of these prophylactic prescriptions have been found to be unnecessary.

A group of investigators from the University of Illinois at Urbana-Champaign set out to assess the risks of unnecessary antibiotic prophylaxis, according to a national health claims database. The study was presented at IDWeek 2019 and chosen by the Society for Healthcare Epidemiology of America as the featured oral abstract.

The retrospective cohort study included data from patients who visited the dentist between 2011 and 2015 and were linked to a medical and/or prescription claim. The research team defined unnecessary antibiotic prophylaxis as “antibiotic prophylaxis in patients who both did not undergo a procedure that manipulated the gingiva/tooth periapex and did not have an appropriate cardiac diagnosis.” Patients deemed to meet the unnecessary antibiotic prophylaxis criteria were included in the study and assessed for antibiotic-related adverse effects (AAEs).

Investigators also considered patients with commercial dental insurance without a hospitalization or extraoral infection 14 days prior to antibiotic prophylaxis (≤2 days supply dispensed within 7 days before a dental visit) for inclusion.

The primary end point was the cumulative incidence of any AAE within 14 days post prescription (composite of allergy, anaphylaxis, Clostridioides difficile infection, or emergency department [ED] visit), with secondary end points including cumulative incidence of each individual AAE and the risk difference of the primary end point between amoxicillin and clindamycin.

A total of 168,420 dental visits included antibiotic prophylaxis, 136,177 (80%) of which were judged unnecessary and included for analysis in the study. Unnecessary prescriptions were associated with AAEs in 3.8% of cases, with ED visits (1.2%) and new allergies (2.9%) the most frequent. Clindamycin was associated with more AAEs than amoxicillin (risk difference, 322.1 per 1000 person-years; 95% CI, 238.5-405.8).

“Even though antibiotic prophylaxis is prescribed for a short duration (≤2 days), it is not without risk. Since most [AAEs] are diagnosed in medical settings, dentists may not be aware of these adverse effects,” investigators concluded. “These data provide further impetus to decrease unnecessary prescribing of antibiotic prophylaxis prior to dental procedures.”

The study, Serious Antibiotic-Related Adverse Effects Following Unnecessary Dental Prophylaxis in the United States, was presented in an oral abstract session Friday, October 4, at IDWeek 2019 in Washington, DC.

Investigators Conclude That Cefiderocol Works as Well as Meropenem in Nosocomial Pneumonia

BY MICHAELA FLEMING

Cefiderocol, an experimental novel siderophore cephalosporin, has activity against a broad range of gram-negative bacteria. In a new study, investigators assessed rates of all-cause mortality at day 14 for cefiderocol and meropenem in patients with nosocomial gram-negative pneumonia.

The study team’s findings were presented in a late-breaking oral abstract session at IDWeek 2019. The phase 3, international, double-blind, noninferiority study enrolled patients with ventilator-associated, hospital-acquired, or health care–associated pneumonia caused by gram-negative bacteria.

Participants were randomized to receive 2 g of either cefiderocol or meropenem every 8 hours; both drugs were infused for 3 hours for 7 to 14 days. In both treatment arms, adjunctive linezolid (600 mg every 12 hours ≤5 days) was given to cover gram-positive bacteria.

The primary end point was noninferiority of cefiderocol to meropenem for all-cause mortality at day 14 in the modified intent-to-treat population. Secondary end points included clinical and microbiological outcomes at test of cure and day 28 mortality. The study team also assessed safety up to 28 days following the termination of treatment.

In the intent-to-treat population, 148 patients were randomized to receive cefiderocol and 150 participants to meropenem. In this population, 59.7% of participants were ventilated, 32.6% had documented failure of prior therapy, the median Acute Physiology and Chronic Health Evaluation II score was 15, and 6.0% of participants had concomitant gram-negative bacteremia at baseline.

In the modified intent-to-treat population, noninferiority of cefiderocol to meropenem was demonstrated for day 14 all-cause mortality (cefiderocol, 12.4% [18 of 145 participants], vs meropenem, 11.6% [17 of 146 participants]; treatment difference, 0.8; 95% CI, –6.6 to 8.2).

“Comparable day 28 all-cause mortality (cefiderocol, 21.0%, vs meropenem, 20.5%), clinical cure (cefiderocol, 64.8%, vs meropenem, 66.7%), and microbiological eradication (cefiderocol, 47.6% vs meropenem, 48.0%) rates were demonstrated in the modified intent-to-treat population at test of cure,” the investigators wrote in their abstract.

The study team also reported that clinical cure rates for target pathogens at test of cure were similar between the cefiderocol and meropenem arms. Additionally, the rates of adverse events (AEs), including treatment-emergent, drug-related, and serious AEs, as well as deaths, were similar between the 2 arms.

“This study demonstrated the noninferiority of cefiderocol to high-dose meropenem for the prespecified end point of day 14 all-cause mortality,” the investigators concluded. “No unexpected safety signals were observed in the study.”

The abstract, Efficacy and Safety of Cefiderocol Versus High-Dose Meropenem in Patients With Nosocomial Pneumonia—Results of a Phase 3 Randomized, Multicenter, Double-Blind, Noninferiority Study, was presented at a late-breaking session Thursday, October 3, in Washington, DC.
ACX-362E Holds Promise as Potential Treatment for *C difficile*, First-in-Human Phase 1 Trial Demonstrates

A first-in-human trial evaluating the pharmacokinetics, safety, and fecal microbiome effects of a novel DNA polymerase IIIC inhibitor demonstrated the antibacterial’s promise as an alternative to vancomycin for the treatment of *Clostridioides difficile*.

In a late-breaking presentation at IDWeek 2019, a team of investigators detailed the 3-part phase 1, double-blind, randomized healthy volunteer trial of the narrow-spectrum antibacterial ACX-362E.

The trial evaluated the safety profile, food effect, and systemic/stool pharmacokinetics of escalating single (150, 300, 600, and 900 mg) and multiple (300 and 450 mg) doses of oral ACX-362E compared with placebo. An oversight committee reviewed the safety and pharmacokinetic data prior to dose escalation within each cohort. Investigators compared the fecal microbiome effects of multiple doses of ACX-362E with 6 participants receiving concomitant open-label vancomycin 125 mg 4 times daily.

A total of 44 individuals received ACX-362E—24 got single doses, 12 received multiple doses, and 8 were in the food effect group. Twelve participants received placebo.

Investigators observed no moderate, severe, cumulative, or dose-limiting adverse events leading to discontinuation, and ACX-362E was generally well tolerated at all dose levels. The mean plasma half-life was approximately 2 hours, with no further accumulation with repeat dosing.

"Systemic exposure was less than 1 µg/mL and decreased with food. Fecal concentrations during multiple dosing exceeded the C [minimum inhibitory concentration (MIC90) = 4 µg/mL] by multiples of up to ~2500," investigators reported. "ACX-362E had minimal effect on Bacteroides phylum and caused significantly less dysbiosis than vancomycin."

The favorable safety profile, low systemic and high fecal concentrations, and favorable gut microbiome changes demonstrated by this first-in-human trial, compared with vancomycin, make ACX-362E a promising candidate for future clinical development for the treatment of *C difficile*, investigators concluded.

The study, A Randomized, Blinded, Placebo- and Vancomycin-Controlled, First-In-Human (FIH) Study of the Safety, Pharmacokinetics (PK), and Fecal Microbiome Effects of ACX-362E, a Novel Anti-Clostridial DNA Polymerase IIIC (polIIIC) Inhibitor, was presented as a late-breaking oral abstract Thursday, October 3, at IDWeek 2019 in Washington, DC. ▲

Microarray Patches May Offer Discreet Delivery of Long-Acting PrEP and Contraceptives

**BY CONTAGION® EDITORIAL STAFF**

Now in clinical development, microarray patches (MAPs) offer an alternative to intradermal delivery of vaccines and pharmaceuticals. MAPs are applied to the skin like bandages and consist of a number of micron-scale projections (~1 mm high) amassed on a baseplate.

As bringing long-acting injectables to the continuum of care for HIV becomes more realistic, investigators are looking to develop a related MAP, also known as a microneedle patch. MAPs could be key to providing a self-delivery system that could discreetly administer HIV prevention and contraception to women in low-resource settings.

At IDWeek 2019, a team of investigators from PATH presented research on the development of a MAP to deliver long-acting cabotegravir (CAB LA) for HIV pre-exposure prophylaxis (PrEP) along with codelivery of a hormonal contraceptive to evaluate multipurpose prevention technology.

In a late-breaking oral abstract session, the investigators presented preclinical pharmacokinetic results from a 3-year project funded by the United States Agency for International Development. The team aims to develop a MAP for CAB LA through phase 1 clinical readiness. The investigators created a target product profile that identified the patch’s key attributes, including a size of 20 to 140 cm², similar to commercially available transdermal patches; an ideal wear time of 20 minutes; weekly or monthly administration to achieve therapeutic efficacy; and simple instructions that promote self-administration.

"We successfully formulated and optimized MAP projection geometry to accommodate high drug-loading requirements of CAB LA (5.86 mg CAB LA per 1 cm² MAP), a hydrophobic drug," the authors wrote in their abstract. "The MAPs are stable for 6 months under accelerated aging conditions in foil packaging, readily pierce the skin, and rapidly dissolve."

When evaluated in rats, plasma concentration levels of CAB LA were maintained above therapeutic targets of 4 times the protein-adjusted IC90 (4xPA-IC90) for 28 days; however, bioavailability was lower than intramuscular or intradermal injections.

The authors note that further development is needed. Future research should focus on optimizing bioavailability and evaluating MAPs as a maintenance dose in vivo. Additionally, future research is warranted on the cost of both manufacturing and delivery analyses and an assessment on the potential end-user acceptability.

The abstract, Microarray Patch Delivery of Long-Acting HIV PrEP and Contraception, was presented in a late-breaking session Friday, October 4, at IDWeek 2019 in Washington, DC. ▲
An Unknown Contagious Rash: Case Report and Literature Review of Norwegian Crusted Scabies

A patient with HIV and skin lesions should trigger a broad differential.

BY MOLLY WEINBERG, MD (RESIDENT); TASHNIA TAHSIN, DO (RESIDENT); LAUREN MUSSER, MD (RESIDENT); AND NAITIK PATEL, MD

**FINAL DIAGNOSIS**
Norwegian crusted scabies

**HISTORY OF PRESENT ILLNESS**
A 29-year-old African American man presented to Hahnemann University Hospital in Philadelphia, Pennsylvania, with odynophagia, visible thrush, and a diffuse body rash that was worse on his lower extremities. The patient reported receiving an HIV diagnosis in 2015; however, he started antiretroviral therapy just 1 month prior at an outside hospital, where he was found to have pneumonia and neurosyphilis. He left the outside hospital against medical advice (AMA) and was since off antiretroviral therapy. On admission, he reported odynophagia leading to a 30-pound weight loss over the past 4 months. He reported having a diffuse body rash of unclear onset, which was nonpruritic. On review of systems, he reported 2 episodes of watery diarrhea.

**MEDICAL HISTORY**
The patient received an HIV diagnosis in 2015 and was not engaged in care or on treatment. He took antiretroviral treatment for a short period 1 month earlier. Records obtained from an outside hospital noted neurosyphilis, which was inadequately treated when the patient left AMA.

**KEY MEDICATIONS**
He was not taking any medications. Records showed that during the prior hospital admission he was started on bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy).

**EPIDEMIOLOGICAL HISTORY**
The patient said he believed he had contracted HIV through sex. He stated that he is in a relationship with a male partner but not sexually active. He denied tobacco use, alcohol use, or intravenous drug use. He had no recent travel history. He lives in New Jersey with his mother, who brought him to Philadelphia for admission to Hahnemann, and has no pets. He does not work.

**PHYSICAL EXAMINATION**
On admission, his vital signs were within normal limits. He was alert and lying comfortably, in no acute distress. On oropharyngeal examination, he had a thick, white exudate over his tongue, posterior pharynx, and throat. On auscultation of his lungs, he had decreased breath sounds at the bilateral bases. His heart sounds were regular, with no murmurs, rubs, or gallops. His abdomen was thin, soft, and nontender to palpation and had positive bowel sounds. On skin inspection, there were hyperkeratotic plaques diffusely on his legs (Figure 1a/b) with scattered, less hyperkeratotic lesions on the hands (Figure 1c) and chest and abdomen (Figure 1d). These plaques were scaling, crusting, and sloughing in areas.

**STUDIES**
Initial laboratory tests showed a white blood cell count of 6000/μL with 6% bands; hemoglobin, 10.4 g/dL; platelets, 106,000/μL. Chemistry panel was remarkable for a creatinine of 1.72 mg/dL; serum urea nitrogen, 87 mg/dL; alkaline phosphatase, 2546 U/L; alanine aminotransferase, 212 U/L;
and aspartate aminotransferase, 399 U/L. His troponin was elevated at 0.132 ng/mL. His CD4 cell count was 11/µL, with a viral load of 151,245 copies. Rapid plasma reagin and treponemal antibody were positive. Records from his prior hospital admission showed positive Venereal Disease Research Laboratory (VDRL) testing of his cerebrospinal fluid (CSF). Electrocardiogram showed normal sinus rhythm with no signs of ischemia. Chest x-ray showed cystic luencies in the right and left midlung. Follow-up computed tomography (CT) of the chest showed bilateral upper-lobe cavitary lesions and ground-glass attenuation in the bilateral lungs. Echocardiogram showed a reduced left ventricular ejection fraction of 10% to 15%.

**DISCUSSION**

When first described, Norwegian crusted scabies was associated with patients who had a decreased itch response, such as those with leprosy or various cognitive impairments. Its first description in conjunction with immunosuppressive therapy was in 1973. Since that time, much more has been learned about the host immune response to the *Sarcoptes scabiei* mite infection.

The rash and itch that follow a scabies infection have features of both type I and IV hypersensitivity reactions, and the initial inflammatory response toward the mite consists primarily of Langerhans cells and eosinophils. The host immune response to scabetic infection is complex and involves aspects of both innate and adaptive immunity. In the humoral response, immunoglobulin (Ig) E antibodies are released in large numbers in response to parasitic infections. Hosts infected with crusty scabies have shown to possess higher levels of scabies-specific IgE and IgG antibody levels compared with those of ordinary scabies. However, instead of providing protective immunity to reinfection, as with other parasitic infections, these elevated levels of antibodies do not lower reinfection rates of crusted scabies.

The cell-mediated immune response is initiated with T lymphocytes. In traditional scabies, isolated skin lesions demonstrate high levels of CD4+ T lymphocytes. However, crusted scabies skin lesions demonstrate high levels of CD8+ T lymphocytes with almost no CD4+ T lymphocytes. This could explain why crusted scabies is seen more often in HIV/AIDS patients, given their lack of CD4+ T cells.

In immunocompromised individuals, such as patients with AIDS, the immune system is unable to control the mites, which allows them to reproduce at an overpowering rate, with parasitic burden in the thousands to millions. This causes the body to generate an inflammatory response and a buildup of hyperkeratotic lesions. These lesions are typically found on the extremities, back, face, and scalp and around the nails. Norwegian scabies is very contagious and is transmitted by direct contact with the individual and by sharing infested items. The scabies mite can persist for 48 to 72 hours at room temperature on a contaminated surface.

Misdiagnosis is frequent in patients with Norwegian crusted scabies because of the infection’s similarity to other dermatologic conditions. The lesions can also be masked by a secondary bacterial infection, excoriation, or existing skin disease. The differential diagnosis encompasses psoriasis, eczema, contact dermatitis, insect bites, seborrheic dermatitis, lichen planus, systemic infection, palmoplantar keratoderma, and cutaneous lymphoma. The standard diagnostic technique is to take a skin scraping using a scalpel on the lesion, particularly in areas of burrowing or skin breakdown. The sample is placed on a slide with a drop of silicone oil and examined under the microscope, which can reveal the scabies mite and its eggs and feces. Other methods for diagnosis include the tape test, dermoscopy, skin biopsy, and the ink test.

The US Centers for Disease Control and Prevention recommends that treatment for Norwegian crusted scabies consist of both topical and oral medications. The antiparasitic agent ivermectin is shown to be safe and effective for treatment; however, it is not US Food and Drug Administration-approved for this indication. Dosing for oral ivermectin is 200 µg/kg on specific days, depending on severity. For severe infections, ivermectin 200 µg/kg should be given on days 1, 2, 8, 9, 15, 22, and 29. At the same time, topical permethrin cream 5% or benzyl benzoate 5% should be used on the entire body daily for 7 days, then twice a week until the infection has cleared. It is also recommended to use a keratolytic agent, such as 5% to 10% salicylic acid in petrolatum or 40% urea, to help remove the hyperkeratotic covering and aid infiltration of the topical permethrin or benzyl benzoate.
This global Outbreak Monitor allows users to visualize occurrences of infectious diseases, such as *E. coli* and *Hepatitis A* on a local, regional, national, and international level. The monitor also tracks trends and details on confirmed cases and deaths, matched with recent coverage related to each outbreak. Use the *Contagion® Outbreak Monitor* to learn about infectious disease outbreaks in your geographical region, and manipulate the map to find out the latest information on global outbreaks.

- Use the new **Map Key** to easily find the outbreak that you’re looking for and hone in on the details specific to that outbreak.
- Review outbreaks that are no longer active by clicking on the new **Resolved Outbreaks** tab.

The *Contagion® Outbreak Monitor* is regularly updated with information from trusted global reporting organizations, such as the Centers for Disease Control and Prevention, the World Health Organization, and local and public health departments.