Bacteriophage-Antibiotic Combinations: A Promising Alternative for Refractory Infections?

Despite the initial abandonment of bacteriophages in most areas of the world, the era of antibiotic resistance has led to a resurgence of phage therapy in clinical practice.

Taylor Morrisette, PharmD; Razieh Kebriaei, PhD; Sandra Morales, PhD; and Michael J. Rybak, PharmD, MPH, PhD

The constant increase of multidrug-resistant (MDR) organisms has led to an unavoidable decline of effective antimicrobials. Despite a resurgence of the antibiotic pipeline in recent years, the discovery of novel therapeutic targets remains limited. Obligately lytic bacteriophages (phages) are viruses that target, infect, and kill bacterial cells. As multiple reports have shown that phages used in combination with antibiotics could lead to improved efficacy (eg, phage-antibiotic synergy, resensitization of antibiotic therapy, etc), this therapeutic strategy could be a rational method to battle the antibiotic resistance currently facing clinicians.
FOR YOUR PATIENTS AT RISK OF HIV
UPDATE THEIR PrEP WITH DESCOVY®

IMPORTANT SAFETY INFORMATION
BOXED WARNING: RISK OF DRUG RESISTANCE WITH USE OF DESCOVY FOR PrEP IN UNDIAGNOSED EARLY HIV-1 INFECTION and POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

- DESCOVY FOR PrEP must be prescribed only to patients confirmed to be HIV negative immediately prior to initiation and at least every 3 months during use. Drug-resistant HIV-1 variants have been identified with use of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for HIV-1 PrEP following undetected acute HIV-1 infection. Do not initiate if signs or symptoms of acute HIV-1 infection are present unless HIV-negative status is confirmed.
- Severe acute exacerbations of hepatitis B have been reported in patients infected with hepatitis B virus (HBV) who discontinued products containing FTC and/or TDF and may occur with discontinuation of DESCOVY. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients with HBV who discontinue DESCOVY. If appropriate, anti-hepatitis B therapy may be warranted.

Contraindication
- DESCOVY FOR PrEP is contraindicated in patients with unknown or positive HIV status.

Warnings and precautions
- Comprehensive management to reduce risks:
  - Use DESCOVY FOR PrEP to reduce the risk of HIV-1 infection as part of a comprehensive strategy that includes adherence to daily dosing and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs)
  - HIV-1 risk factors: Behavioral, biological, or epidemiologic HIV-1 risk factors may include, but are not limited to: condomless sex, past or current STIs, self-identified HIV risk, having sexual partners of unknown HIV-1 viremic status, or sexual activity in a high-prevalence area or network
  - Reduce STI risk: Counsel on the use of STI prevention measures (e.g., consistent and correct condom use, knowledge of partner's HIV-1 viremic status, regular testing for STIs)
  - Reduce potential for drug resistance: Only prescribe DESCOVY FOR PrEP to patients confirmed to be HIV negative immediately prior to initiation, at least every 3 months while taking DESCOVY, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in patients with undetected HIV-1 infection who are taking only DESCOVY because DESCOVY alone is not a complete regimen for treating HIV-1.

BMD=bone mineral density; eGFR=estimated glomerular filtration rate; MSM=men who have sex with men; PY=person-years; TGW=transgender women (who have sex with men).
**INDICATION**

DESCOVY for HIV-1 pre-exposure prophylaxis (PrEP) is indicated in at-risk adults and adolescents (≥35 kg) to reduce the risk of sexually acquired HIV-1 infection, excluding individuals at risk from receptive vaginal sex. HIV-1–negative status must be confirmed immediately prior to initiation.

Limitation of Use: DESCOVY FOR PrEP is not indicated in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

---

**IMPORTANT SAFETY INFORMATION** (cont'd)

**Warnings and precautions** (cont’d)

- **Comprehensive management to reduce risks** (cont’d):
  - Some HIV tests may not detect acute HIV infection. Prior to initiating DESCOVY FOR PrEP, ask patients about potential recent exposure events. If recent (<1 month) exposures are reported or suspected, or symptoms of acute HIV infection (e.g., fever, fatigue, myalgia, skin rash) are present, confirm HIV-negative status with a test approved by the FDA for use in the diagnosis of acute HIV infection.
  - If HIV-1 infection is suspected or if symptoms of acute infection are present while taking DESCOVY FOR PrEP, convert the DESCOVY FOR PrEP regimen to a complete HIV treatment regimen until HIV-negative status is confirmed by a test approved by the FDA for use in the diagnosis of acute HIV infection.
  - **Counsel on adherence:** Counsel patients to strictly adhere to daily dosing, as efficacy is strongly correlated with adherence. Some patients, such as adolescents, may benefit from more frequent visits and counseling.

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**The DISCOVER Trial design**

The efficacy and safety of DESCOVY to reduce the risk of acquiring HIV-1 infection were evaluated in the randomized, double-blind DISCOVER Trial comparing DESCOVY (n=2670 for efficacy; n=2694 for safety) with TRUVADA (n=2665 for efficacy; n=2693 for safety). HIV-seronegative men and transgender women who have sex with men, who were at risk of HIV-1 infection and reported condomless anal sex with ≥2 partners in the prior 12 weeks; or who had syphilis or rectal gonorrhea or chlamydia in the prior 24 weeks, were randomized 1:1 to receive once-daily, blinded, active tablets of DESCOVY or TRUVADA with matching placebos. The primary endpoint was the incidence of documented HIV-1 infection per 100 PY (primary analysis occurred with a minimum follow-up of 48 weeks and at least 50% of patients having 96 weeks of follow-up). In the study population, a subset of 17% of patients (n=905) were using TRUVADA at baseline. Of these patients, 465 were randomized to DESCOVY and 440 were randomized to continue using TRUVADA.

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**The same robust protection as TRUVADA®, with less impact on markers of renal function and BMD**

Data from a randomized, active-controlled, double-blind study of MSM and TGW using DESCOVY FOR PrEP™ (n=2694) vs TRUVADA (n=2693):

<table>
<thead>
<tr>
<th>At primary analysis*</th>
<th>At Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninferior efficacy</strong> (HIV incidence rate) 0.16/100 PY vs 0.34/100 PY [IRR=0.47; CI: 0.19–1.15]).</td>
<td><strong>Less impact on eGFR and BMD.</strong></td>
</tr>
<tr>
<td>99.7% vs 99.4% of patients remained HIV-free.</td>
<td><strong>The long-term clinical significance of these changes is not known.</strong></td>
</tr>
</tbody>
</table>

*When 100% of patients reached Week 48 and ≥50% reached Week 96.
Immediate coverage across major plans

Eligible patients may pay as little as a $0 co-pay*

*For eligible, commercially insured patients only. See full terms and conditions at gileadadvancingaccess.com/hcp. This is not health insurance. Only accepted at participating pharmacies.

The Gilead Advancing Access® program is committed to helping eligible patients afford their Gilead medication whether they are insured, uninsured, or underinsured.

The co-pay coupon card covers up to $7200 per year for DESCovy®, with no monthly limit for eligible patients.

IMPORTANT SAFETY INFORMATION (cont’d)

Warnings and precautions (cont’d)

• New onset or worsening renal impairment: Cases of acute renal failure and Fanconi syndrome have been reported with the use of tenofovir prodrugs. Do not initiate DESCovy 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 DESCovy in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome. Monitor renal function in all patients (see Dosage and Administration section)

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

Adverse reactions

• Most common adverse reactions (≥2%) in the DESCovy FOR PrEP™ clinical trial were diarrhea, nausea, headache, fatigue, and abdominal pain

Drug interactions (cont’d)

• Drugs affecting renal function: Coadministration of DESCovy 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: One tablet taken once daily with or without food

• HIV screening: Test for HIV-1 infection immediately prior to initiating, at least every 3 months during use, and upon diagnosis of an STI (see Warnings and Precautions section)

• HBV screening: Test for HBV infection prior to or when initiating DESCovy

• Renal impairment and monitoring: Not recommended in patients with creatinine clearance (CrCl) <30 mL/min. Prior to or when initiating DESCovy, and during use on a clinically appropriate schedule, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the following pages.

NSAIDs=nonsteroidal anti-inflammatory drugs.

**INDICATIONS AND USAGE** [See Dosage and Administration]:
DESCOVY for HIV-1 pre-exposure prophylaxis (PrEP) is indicated in at-risk adults and adolescents (≥35 kg) to reduce the risk of sexually acquired HIV-1 infection, excluding individuals at risk from receptive vaginal sex. HIV-1–negative status must be confirmed immediately prior to initiation.

Limitation of Use: DESCOVY FOR PrEP is not indicated in individuals at risk of HIV-1 from receptive vaginal sex because effectiveness in this population has not been evaluated.

**DOSE AND ADMINISTRATION** [See Indications and Usage, Contraindications, Warnings and Precautions, and Use in Specific Populations]:

**HIV-1 Screening:** Screen all patients for HIV-1 infection before initiating DESCOVY FOR PrEP and at least once every 3 months during use.

**Testing Prior to Initiation and During Use:** Prior to or when initiating DESCOVY, test patients for hepatitis B infection. Assess serum creatinine, estimated creatinine clearance (CrCl), urine glucose, and urine protein in all patients on a clinically appropriate schedule. In patients with chronic kidney disease, also assess serum phosphorus. DESCOVY is not recommended in individuals with a CrCl <30 mL/min.

**Dosage for PrEP Use:** One tablet once daily with or without food

**CONTRAINDICATIONS:**
DESCOVY FOR PrEP is contraindicated in individuals with unknown or positive HIV-1 status.

**WARNINGS AND PRECAUTIONS** [See Dosage and Administration]:

**Severe Acute Exacerbation of Hepatitis B in Individuals with HBV Infection:** All individuals should be tested for chronic HBV before or when initiating DESCOVY. Severe acute exacerbations of hepatitis B have been reported in HBV-infected patients who discontinued products containing FTC and/or TDF. Patients infected with HBV who discontinue DESCOVY should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. If appropriate, initiation of anti-hepatitis B therapy may be warranted, especially in patients with advanced liver disease or cirrhosis, since post-treatment exacerbation of HBV may lead to hepatic decompensation and liver failure. HBV-uninfected individuals should be offered vaccination.

**Comprehensive Management to Reduce the Risk of Sexually Transmitted Infections, Including HIV-1, and Development of HIV-1 Resistance:**
Use DESCOVY FOR PrEP to reduce the risk of HIV-1 infection as part of a comprehensive prevention strategy, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually transmitted infections (STIs). The time from initiation of DESCOVY FOR PrEP to maximal protection against HIV-1 infection is unknown.

HIV-1 Risk Factors: Behavioral, biological, or epidemiological HIV-1 risk factors may include, but are not limited to: condomless sex, past or current sexually transmitted infections (STIs), self-identified HIV risk, having sexual partners of unknown HIV-1 virome status, and/or sexual activity in a high-prevalence area or network.

Reduce STI Risk: Counsel on reducing sexual risk behaviors and on the use of STI prevention measures.

Reduce Potential For Drug Resistance: Only prescribe DESCOVY FOR PrEP to individuals confirmed to be HIV-negative immediately prior to initiation, at least every 3 months while taking DESCOVY, and upon an STI diagnosis. HIV-1 resistance substitutions may emerge in individuals with undetected HIV-1 infection who are taking only DESCOVY because DESCOVY alone is not a complete regimen for treating HIV-1.

• Some HIV tests may not detect acute HIV infection. Prior to initiating DESCOVY FOR PrEP, ask individuals about potential recent exposure events. If recent (<1 month) exposures to HIV are reported or suspected or symptoms of acute HIV infection (e.g., fever, fatigue, myalgia, skin rash) are present, confirm HIV-negative status with a test approved by the FDA for use in the diagnosis of acute HIV infection

• If an HIV monitoring test indicates HIV-1 infection or if symptoms of acute infection are present while taking DESCOVY FOR PrEP, convert the DESCOVY FOR PrEP regimen to a complete HIV treatment regimen until HIV-negative status is confirmed by a test approved by the FDA for use in the diagnosis of acute HIV infection

**Counsel On Adherence [See Use in Specific Populations]:** Counsel individuals to strictly adhere to their dosing schedule, as efficacy is strongly correlated with adherence. Some individuals, such as adolescents, may benefit from more frequent visits and counseling.

**New Onset or Worsening Renal Impairment** [See Adverse Reactions]: Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with the use of tenofovir prodrugs. DESCOVY is not recommended in individuals with a CrCl <30 mL/min. Individuals taking tenofovir prodrugs who have impaired renal function and those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions. Prior to initiation and during use, on a clinically appropriate schedule, assess serum creatinine, estimated CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, also assess serum phosphorus. Discontinue DESCOVY in individuals who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

**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 DESCOVY 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** [See Warnings and Precautions]:

**Clinical Trials in HIV-1 Uninfected Adult Subjects:** The safety and effectiveness of DESCOVY FOR PrEP was evaluated in a double-blind, randomized, active-controlled trial (DISCOVER) in which a total of 5387 HIV-1 uninfected men and transgender women who have sex with men received DESCOVY (N=2694) or TRUVADA (N=2693)
once daily for HIV-1 PrEP. The median duration of exposure was 86 and 87 weeks, respectively. The most common adverse reactions (≥2%) in participants who received DESCovy FOR PrEP were diarrhea (5%), nausea (4%), headache (2%), abdominal pain (2%), and fatigue (2%).

Renal Laboratory Tests: In the DISCOVER trial, mean serum creatinine decreased by 0.01 mg/dL from baseline in the DESCovy group and increased by 0.01 mg/dL in the TRUVADA group; median eGFR increased by 1.8 mL/min in the DESCovy group and decreased by 2.3 mL/min in the TRUVADA group.

Bone Mineral Density Effects: In the DISCOVER trial, mean increases from baseline to Week 48 of 0.5% at the lumbar spine (N=159) and 0.2% at the total hip (N=158) were observed in participants receiving DESCovy, compared to mean decreases of 1.1% at the lumbar spine (N=160) and 1.0% at the total hip (N=158) in participants receiving TRUVADA. BMD declines of 5% or greater at the lumbar spine and 7% or greater at the total hip were experienced by 4% and 1% of participants, respectively, in both treatment groups at Week 48.

The long-term clinical significance of these renal laboratory and BMD changes is not known.

Consult the full Prescribing Information for DESCovy for additional information regarding adverse reactions, laboratory abnormalities, and postmarketing events when used for another indication.

DRUG INTERACTIONS [See Warnings and Precautions]:

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

USE IN SPECIFIC POPULATIONS [See Dosage and Administration, Warnings and Precautions, and Adverse Reactions]:

Pediatric Use: The safety and effectiveness of DESCovy FOR PrEP in at-risk adolescents weighing at least 35 kg is supported by data from an adequate and well-controlled trial of DESCovy FOR PrEP in adults with additional data from safety and pharmacokinetic studies in previously conducted trials with the individual drug products, FTC and TAF, with cobicistat plus elvitegravir, in HIV-1 infected adults and pediatric subjects. While using DESCovy FOR PrEP, HIV-1 testing should be repeated at least every 3 months, and upon diagnosis of any other STIs. Adolescents may benefit from more frequent visits and counseling.

Renal Impairment: DESCovy is not recommended in HIV-1 uninfected individuals with severe renal impairment (CrCl below 30 mL/min).

OVERDOSAGE:

If overdose occurs, the patient must be monitored for evidence of toxicity and treated with general supportive measures as necessary.
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BY TAYLOR MORRISETTE, PHARMD; RAZIEH KEBRIAEI, PHD; SANDRA MORALES, PHD; AND MICHAEL J. RYBAK, PHARMD, MPH, PHD

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*Active member of the Society of Infectious Diseases Pharmacists*

*Active member of MAD-ID (Making a Difference in Infectious Diseases)*

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Oseltamivir on the Move, but Where Should It Go?

JUST AS INFLUENZA season started ramping up in the Northern Hemisphere, news hit that Sanofi had secured over-the-counter rights for oseltamivir. The news caused a flurry of interest among the infectious disease community about the implications this change would have on patient care.

A lot of questions are difficult to answer, but a few have data. Patients are not good at self-diagnosing influenza, as they both overdiagnose and underrecognize the condition.\(^1\) In fact, the confusion is understandable, as the spectrum of symptoms is more variable than commonly thought.\(^2\) Oseltamivir resistance in influenza viruses varies annually and has been detected in both patients treated with oseltamivir and antiviral-naïve populations, particularly children.\(^3\)

The remaining questions are less clear. However, potential solution splits the difference between prescription-only and over-the-counter status, offering the benefits of expanded access while retaining a level of professional assessment: a third medication category, namely pharmacist prescription. Over the past 20 years the shift in pharmacy education to pharmacist prescription has been on the radar of clinicians working in infectious diseases.\(^4\)

In order to work toward mitigating this threat, we must acknowledge that it is not a threat that is simply on the horizon. Antimicrobial resistance is occurring now, across the globe, and in the United States. And in order to work toward mitigating this threat, we all have a role to play.

On page 16 of this issue, a team of communications experts and clinicians from the CDC provide a summary of the new report and present 5 ways that infectious diseases clinicians can combat the threat of resistance.

In 2020, Contagion® will continue to provide clinicians with timely news to improve the diagnosis, treatment, and prevention of infectious diseases. Make sure you visit our website and keep up with us on Facebook (@ContagionLive), Twitter (@Contagion_Live), and LinkedIn (@Contagion_Live).

Please reach out to Senior Editor Michaela Fleming at mfl3@contagionlive.com if you have any questions or comments.

Stay informed and thanks for reading.

Mike Hennessy Sr Chairman and Founder

Confronting Antimicrobial Resistance: We All Play a Role

IN EARLY 2019, the World Health Organization released a list of the top 10 threats to global health.\(^1\) The list featured a broad range of challenges from noncommunicable diseases to vaccine hesitancy. However, it caught the eye of Contagion\(^®\) that 6 of the 10 issues identified fell into the realm of infectious diseases.

One of the most pressing issues on the list, antimicrobial resistance, has been on the radar of clinicians working in infectious diseases for years. Ever since the discovery of penicillin by Alexander Fleming in 1928, it has been acknowledged that bacteria will continue to evolve, even as new antibiotics are discovered and introduced.\(^2\)

To address this urgent global health threat, the US Centers for Disease Control and Prevention (CDC) recently released a report titled *Antibiotic Resistance Threats in the United States, 2019*. The document is an update to a report issued in 2013 and provides updated data on 18 pathogens that have been classified as threats to human health.\(^3\)

One of the main points addressed in the foreword, written by Robert Redfield, MD, director of the CDC, is that in order to fight antimicrobial resistance, we must acknowledge that it is not a threat that is simply on the horizon. Antimicrobial resistance is occurring now, across the globe, and in the United States. And in order to work toward mitigating this threat, we all have a role to play.

References are available at ContagionLive.com.
The Early Bird Gets to Stay Home: Early OPAT Follow-Up Reduces 30-Day Readmissions

BY MEAGAN ADAMSICK, PHARM.D, AND MONIQUE R. BIDELL, PHARM.D, BCPS

Inpatient parenteral antimicrobial therapy (OPAT) programs offer support for patients who require prolonged intravenous antibiotic therapy outside of an acute care setting. These programs aim to reduce hospital readmissions and allow patients to safely complete antibiotic therapy at home or in a skilled nursing facility. The 2004 Infectious Diseases Society of America OPAT guidelines recommend weekly follow-up with an infectious diseases (ID) provider as best practice. Despite this recommendation, most programs report less frequent patient follow-up. Readmission rates for patients receiving OPAT are reported to be as high as 20%, mostly due to catheter-related problems, adverse drug reactions, or worsening of the primary infection.

Recently, Saini et al aimed to determine the impact of early outpatient ID follow-up on all-cause 30-day hospital readmission rates for patients enrolled in the PennState Health OPAT program. Patients were included if they were enrolled in the OPAT program between January 2012 and December 2014, then pair-matched in a case-control manner relative to 30-day readmission. Patients were excluded from the study if the OPAT course was never started, if OPAT was managed primarily by providers at the patient’s facility, or if the OPAT course included only oral agents. Case (ie, readmission occurred)–control (ie, readmission did not occur) pairs were matched based on age, sex, discharge year, and discharge diagnosis category. Both bivariable and multivariable conditional logistic regression analyses were performed. Patients were followed weekly, with laboratory tests dependent on the antimicrobial regimen.

During the study period, 1102 patients were enrolled in the OPAT program and 201 (18%) were readmitted within 30 days of discharge. A total of 388 patients (194 case–control pairs) were included in the study. The Table shows patient demographics and indications for OPAT. The average age was 59.6 years; past medical histories of diabetes, renal failure, and immune compromise were present in 32.2%, 10%, and 12.1%, respectively. The most commonly administered antibiotic was vancomycin (36% of the case group and 29% of the control group). Antifungal use (9% vs 2%), fluoroquinolone use (17% vs 10%), and metronidazole use (13% vs 6%) were more common in the case compared with the control group, respectively. More case patients received 3 or more antimicrobials relative to their control counterparts (21% vs 7%).

Approximately 40% of the readmissions occurred within 7 days of discharge and 97 of 201 (46%) of readmissions were attributed to OPAT-related issues, including worsening infection and acute kidney injury. Of the patients who were readmitted, 13% were seen by an ID provider within 14 days of discharge, compared with 33% of patients in the control group (P = .0001). This finding suggests that early outpatient ID follow-up may reduce the risk of 30-day readmission. On multivariable analysis, immunosuppression was significantly more common in the case group (17% vs 6%; P = .0015; OR, 2.79; 95% CI, 1.17-6.64). Ceftriaxone use, however, was more common in the control group (11% vs 20%; P = .02; OR, 0.49; 95% CI, 0.26-0.92). This study has some notable limitations, including that microbiologic data were not assessed. Specific pathogens, such as Staphylococcus aureus, may have further stratified complex patients who may have benefited from early ID follow-up. Additionally, a limited number of patient comorbidities were characterized, preventing identification of any other patient-specific factors that may be associated with readmission.

Although not the central focus of the study, these findings reinforce the challenges surrounding early OPAT follow-up. Patients in this study were intended to be assessed weekly, which was not achieved in many cases. Delays in care seemingly increased risk of hospital readmission. OPAT programs can use these findings to identify potentially high-risk patients, such as those on 3 or more agents or with immune compromise, to prioritize them for early ID follow-up to help prevent readmission. However, patients on well-tolerated antibiotics, like ceftriaxone, may not require early follow-up. Additional research on risk factors associated with readmission in patients on OPAT is necessary to further stratify which individuals would most benefit from early ID follow-up. Furthermore, programs with an interdisciplinary approach (eg, inclusion of nurses, pharmacists) may be able to optimize safe OPAT based on the reasons for readmission in this study.

References are available at ContagionLive.com.

**HIGHLIGHTED STUDY**

Early infectious disease outpatient follow-up of outpatient parenteral antimicrobial therapy patients reduces 30-day readmission.


**TABLE. Baseline Characteristics and Indication for OPAT Enrollment**

<table>
<thead>
<tr>
<th></th>
<th>CASES: N (%)</th>
<th>CONTROLS: N (%)</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>102 (53)</td>
<td>102 (53)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>65 (33)</td>
<td>60 (31)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>19 (10)</td>
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<tr>
<td>Imunosuppression</td>
<td>34 (17)</td>
<td>13 (6)</td>
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<tr>
<td>Orthopedic infections</td>
<td>93 (48)</td>
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<tr>
<td>Bacteremia</td>
<td>21 (11)</td>
<td>14 (7)</td>
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<tr>
<td>Abscess</td>
<td>17 (9)</td>
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<tr>
<td>Cellulitis/wound infections</td>
<td>9 (5)</td>
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<tr>
<td>Endocarditis (native)</td>
<td>13 (7)</td>
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<tr>
<td>Device infections</td>
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<tr>
<td>Endocarditis (prosthetic)</td>
<td>7 (4)</td>
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<td>Meningitis</td>
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<td>Pneumonia</td>
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<tr>
<td>Other</td>
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<td>22 (11)</td>
</tr>
</tbody>
</table>

OPAT indicates outpatient parenteral antimicrobial therapy.
Consider the MIC: Treating Respiratory Infections Caused by *Pseudomonas aeruginosa* With Ceftolozane/Tazobactam

BY CATHERINE LI, PHARMD

Ceftolozane/tazobactam (Zerbaxa) is a β-lactam/β-lactamase inhibitor combination that first entered the market after receiving US Food and Drug Administration approval on December 19, 2014, for the treatment of complicated intra-abdominal and urinary tract infections. The labeled dose for these infections is 1.5 g every 8 hours intravenously, with an infusion time of 1 hour. Dose adjustments are recommended for patients with renal dysfunction. With increasing concern for antibiotic-resistant bacteria, ceftolozane/tazobactam is a potential treatment option for β-lactamase–producing organisms including *Pseudomonas aeruginosa* with derepressed class C cephalosporinase production.1

As a time-dependent agent, the activity of ceftolozane/tazobactam is best predicted by the time of antibiotic concentration greater than the minimum inhibitory concentration (MIC). Pharmacokinetic models have demonstrated that for *P aeruginosa* strains with MICs up to 8 mg/L, a higher ceftolozane/tazobactam dose of 3 grams every 8 hours achieves more than 90% probability of attaining a 50% time >MIC in the lung epithelial lining fluid.2 This higher dose was employed in the ASPECT-NP phase 3 trial of ceftolozane/tazobactam versus meropenem for nosocomial pneumonia, which led to the FDA approval for ceftolozane/tazobactam for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia on June 3, 2019.3

Prior to the publication of the ASPECT-NP trial, Rodriguez-Núñez et al conducted this retrospective, observational study in 90 patients who received treatment with ceftolozane/tazobactam for a lower respiratory tract infection with susceptible *P aeruginosa* isolated from at least 1 respiratory or blood culture.4 The study enrolled patients across 13 hospitals in the United States, the United Kingdom, Spain, and France from 2016 to 2018. Susceptibility to ceftolozane/tazobactam was defined as an MIC ≤4 mg/L by Epsilonometer test, in concordance with the breakpoints established by the Clinical and Laboratory Standards Institute and the European Committee on Antimicrobial Susceptibility Testing. Patients who received <72 hours of ceftolozane/tazobactam were excluded from the analysis. Standard ceftolozane/tazobactam dose was defined as the labeled dose for intra-abdominal/urinary tract infections (1.5 g every 8 hours for normal renal function), whereas high dose was defined as at least twice the standard dose (Table).5 The primary outcome was 30-day mortality after ceftolozane/tazobactam therapy was initiated. Univariate and multivariate analyses were conducted to identify risk factors associated with mortality.

The study enrolled 90 patients with a median age of 65 years; their comorbidities included chronic lung disease (43.3%), vascular disease (28.9%), diabetes (16.7%), receipt of a solid organ transplant (8.9%) including lung transplant (5.6%), and cystic fibrosis (6.7%). Pneumonia was the most common lower respiratory tract infection. In terms of illness severity, the cohort had a median Charlson Comorbidity Index score of 5. Of all infections, 36.7% were ventilator associated; 34.4% of patients presented with septic shock, and 12.2% required continuous renal replacement therapy. As for *P aeruginosa* MIC distribution, 24.4% of patients had isolates with an MIC ≤1 mg/L, 51.1% had isolates with an MIC 1-2 mg/L, and 24.4% had isolates with an MIC of 4 mg/L.

The overall 30-day mortality rate was 27.8%. In the univariate analysis, 2 factors were identified to be associated with increased mortality: a higher Charlson Comorbidity Index score (OR, 1.2; *P* = .029) and septic shock (OR, 5.9; *P* < .001). Decreased mortality was observed in patients who received high-dose ceftolozane/tazobactam with a corresponding MIC ≤2 mg/L (OR, 0.3; *P* = .033). A mortality benefit was not seen with standard ceftolozane/tazobactam dosing for MIC ≤2 mg/L (OR, 1.1; *P* = .847). Although the use of high-dose ceftolozane/tazobactam trended toward decreased mortality for MIC ≤1 mg/L, MIC 1-2 mg/L, and MIC 3-4 mg/L, the differences were not statistically significant. The multivariate analysis demonstrated similar results as the univariate analysis: a higher Charlson Comorbidity Index score (OR, 1.27; *P* = .019), septic shock (OR, 7.96; *P* < .0001), and a ceftolozane/tazobactam MIC >2 mg/L (OR, 3.33; *P* = .045) were independently associated with 30-day mortality. Four adverse events attributable to ceftolozane/tazobactam occurred: leukopenia, encephalopathy with myoclonus, renal failure, and hepatitis.

Although this study was retrospective and observational in nature, the cohort included patients with multidrug-resistant and extensively drug-resistant *P aeruginosa* respiratory tract infections with significant comorbidities and severity-of-illness indicators. The mortality benefit of high-dose ceftolozane/tazobactam in patients with MICs ≤2 mg/L strengthens the case for the higher dose of ceftolozane/tazobactam for respiratory tract infections, now FDA approved. In this study, MIC >2 mg/L was a stronger predictor for increased mortality than was the ceftolozane/tazobactam dosing strategy, reinforcing the difficulty of treating patients who have these resistant organisms. The association of increased MIC with risk of clinical failure has been described in other studies as well.6 Further research on strategies to optimize the pharmacokinetic and pharmacodynamic parameters of these novel agents in the age of antimicrobial resistance is needed to improve outcomes. When using ceftolozane/tazobactam to treat patients with *P aeruginosa* respiratory tract infections, the use of extended or continuous antibiotic infusion and/or combination therapy with other active antibiotic agents should be considered, particularly if targeting higher MIC values.7-9

**TABLE.** Ceftolozane/Tazobactam Dosing Based on Renal Function

<table>
<thead>
<tr>
<th>ESTIMATED CREATININE CLEARANCE</th>
<th>STANDARD DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50 mL/min</td>
<td>1.5 g Q8H</td>
<td>3 g Q8H</td>
</tr>
<tr>
<td>30-50 mL/min</td>
<td>750 mg Q8H</td>
<td>1.5 g Q8H</td>
</tr>
<tr>
<td>15-29 mL/min</td>
<td>375 mg Q8H</td>
<td>750 mg Q8H</td>
</tr>
<tr>
<td>&lt;15 mL/min or intermittent hemodialysis</td>
<td>750 mg x 1, then 150 mg Q8H</td>
<td>2.25 g x 1, then 450 mg Q8H</td>
</tr>
</tbody>
</table>

Q8H indicates every 8 hours.

*Dosing in continuous renal replacement therapy is not provided in the ceftolozane/tazobactam (Zerbaxa) package insert. Rodriguez-Núñez et al used 1.5 g Q8H for standard dose and 3 g Q8H for high dose in these patients.*

References are available at ContagionLive.com.

**HIGHLIGHTED STUDY**

**Higher MICs (>2 mg/L) predict 30-day mortality in patients with lower respiratory tract infections caused by *Pseudomonas aeruginosa* treated with ceftolozane/tazobactam.**

Clinical Characteristics of Initial Novel Coronavirus Cases

BY MICHAELA FLEMING

The recent outbreaks of a novel coronavirus (2019-nCoV) in Wuhan, China, have prompted increased concern and speculation about the virus and the implications for global health. A team of investigators from Wuhan released an article detailing the clinical characteristics of the first 41 patients infected with 2019-nCoV. Their article, featuring information on epidemiology, laboratory, and radiology elements of the initial cases confirmed in Wuhan, was published in The Lancet.

The article notes that 73% of the infected patients were men and the median age of patients was 49 years (interquartile range [IQR]: 41.0-58.0). In total, 32% of patients had underlying diseases, which included diabetes (8%), hypertension (6%), and cardiovascular disease (6%). Common symptoms at the onset of illness included fever (98% of cases), cough (76%), and myalgia or fatigue (44%). Less common symptoms that were recorded included sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%).

Dyspnea developed in 55% of patients (median time for illness onset to dyspnea 8.0 days [IQR: 5-13]). In 63% of the patients, lymphopenia was observed. Abnormal findings on chest CTs were observed for all 41 patients.

According to the authors, complications of the infection included acute respiratory distress syndrome (25%), RNAemia (15%), acute cardiac injury (12%), and secondary infection (10%). Among the 41 patients, 13 were admitted to an intensive care unit (ICU) and 6 patients died.

“Compared with non-ICU patients, ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFa,” the investigators wrote.

As of January 22, 2020, 28 of the 41 patients have been discharged from the hospital. Decision for discharge was based on reduction of fever for at least 10 days, improvement of chest radiographic evidence, and viral clearance in respiratory samples from the upper respiratory tract.

“Major gaps in our knowledge of the origin, epidemiology, duration of human transmission and clinical spectrum of disease need fulfillment by future studies,” the authors of the article concluded.

The World Health Organization (WHO) advises clinicians to gather travel history information from patients with suspected 2019-nCoV infection.

Case definitions from the WHO include standards for patients with severe acute respiratory infection as well as acute respiratory illness.

A suspect case applies to patients with severe acute respiratory infection when there is no other etiology which fully explains clinical presentation and travel to or residence in Wuhan, or no other etiology and status as health care worker in an environment where severe acute respiratory infections of unknown etiology are being cared for.

A suspect case also applies to patients with any acute respiratory illness and close contact with a confirmed or probable case of novel coronavirus, working in an animal market, or working in a health care facility with reports of novel coronavirus in the 14 days prior to onset of symptoms.

Probable cases are defined as suspect cases where novel coronavirus testing is inconclusive or testing was positive on a pan-coronavirus assay. Confirmed cases are defined by laboratory confirmation of novel coronavirus infection.

“Since there is much we still do not know about the 2019 novel coronavirus, such as the source, how easily it spreads, or the range of clinical severity I believe we will continue to see cases globally,” Krutika Kuppalli, MD, vice chair of the Infectious Diseases Society of America’s Global Health Committee and an affiliated assistant clinical professor at Stanford Healthcare, told Contagion®.

For the most recent case counts in the 2019-nCoV outbreak, check out the Contagion® Outbreak Monitor.

CDC Details First Shewanella haliotis Case in the Americas

BY GRANT M. GALLAGHER

Shewanella haliotis is an emerging human pathogen that was first isolated from the gut microflora of abalone in 2007. Previous cases of human infection have been concentrated in Asia, particularly China, South Korea, Japan, and Thailand.

The US Centers for Disease Control and Prevention (CDC) is currently detailing the first reported case of S haliotis in the region of the Americas, describing a 2018 case in Flushing, New York. Details appeared in the December 20th Morbidity and Mortality Weekly Report (MMWR).

On December 18, 2018, an 87-year-old man reporting abdominal pain was seen in a hospital emergency department. A computed tomography scan showed acute appendicitis with abscesses measuring <3 cm, and the patient was admitted to the hospital.

Upon admission, a percutaneous drain was placed, and 5 mL of what the MMWR describes as an “opaque, jelly-like substance” was removed. The substance was aspirated and sent for culture and antimicrobial sensitivity testing.

A Gram stain of the isolate showed gram-negative rods. The culture contained monomicrobial 1- to 2-mm yellow-brown mucoid colonies. When sequencing of the isolate’s 16S ribosomal RNA was evaluated using the GenBank database, results showed a >99.8% homology with S haliotis strain DW01.

Antimicrobial sensitivity testing showed susceptibility to fluoroquinolones, aminoglycosides, some penicillins, and broad-spectrum cephalosporins. Phylogenetic analysis confirmed S haliotis strain DW01 as the most recent ancestor of the culture.

The patient was treated with intravenous piperacillin-tazobactam during his hospital stay. He was subsequently sent home with a prescription for oral amoxicillin-clavulanic acid. At a 13-day follow-up visit, the patient was recovering well.

This is not only the first documented case in the Americas but also the first documented case of an S haliotis appendix infection.

“This case highlights the importance of preventing seafood-associated infections and the need to consider rare human pathogens in elderly or immunocompromised marine-exposed populations, as well as persons who might consume at-risk food that might have been imported from outside the United States and persons who might have been infected outside the United States when traveling,” the CDC authors wrote.
**Survey Results: Few US Child Care Centers Require Flu Vaccine**

**BY CONTAGION® EDITORIAL STAFF**

Children have higher risk for serious complications from influenza, making vaccination key to preventing unnecessary hospitalizations and mortality.

However, a study published in the *Journal of Pediatric Infectious Diseases Society* reports that child care centers in the United States rarely require children or adult care workers to be vaccinated against influenza. Of 518 child care centers surveyed, 24.5% and 13.1% reported an influenza vaccine requirement for children and adult child care workers, respectively.

A nationwide telephone survey was developed by a group working on infectious disease management in child care centers. The questionnaire was designed for child care center directors and piloted in 2008, prior to the recent study, which was conducted in 2016.

The survey was distributed to 2500 centers derived from simple random sampling of 180,000 centers and was completed by 518 respondents.

Only 24.5% of respondents reported their care center as having an influenza vaccine requirement for children, and only 13.1% had a similar requirement for child care workers.

The US Centers for Disease Control and Prevention Advisory Committee on Immunization Practices has recommended influenza vaccination for children 6 to 23 months of age since 2004, children aged 24 to 59 months since 2006, and everyone 6 months and older since 2008. But at the time of the study, only 4 states had influenza vaccine requirement laws in child care centers.

Notably, 37 respondents from states with a child care influenza vaccination law were more likely (52.8%) to report having a vaccine requirement than those from states that did not require vaccination (22.3%).

Yet even among such states, there was variation, with 85.7% of Connecticut and New Jersey center directors reporting an influenza vaccine requirement versus 6.7% of Ohio center directors. Study authors pointed to a variety of possible explanations, especially that Ohio’s requirements were established more recently.

Investigators were also aware of 2 states with influenza vaccine requirement laws for child care workers, but effects were not measureable in the study because there were not respondents from Rhode Island and the California law had only recently been enacted.

Investigators encouraged the passage of state legislation around influenza vaccines for children and workers in child care centers. Although few states have such legislation from which to draw empirical conclusions, respondents from those states had a statistically significant higher likelihood of reporting child care center vaccine requirements. ▲

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**FDA Declines Approval for Cabotegravir/Rilpivirine**

**BY MICHAELA FLEMING**

ViiV Healthcare’s cabotegravir and rilpivirine long-acting injectable antiretroviral therapy received a complete response letter from the US Food and Drug Administration (FDA), the company said. The therapy is being developed to treat HIV-1 in virologically suppressed adults.

Cabotegravir is an integrase strand transfer inhibitor developed by ViiV Healthcare and rilpivirine is a nonnucleoside reverse transcriptase inhibitor developed by Janssen Sciences. The cabotegravir and rilpivirine long-acting regimen is investigational and is not yet approved anywhere in the world.

According to the company, the reasons given in the complete response letter relate to chemistry manufacturing and controls. However, ViiV reports that there have been no reported safety issues related to chemistry manufacturing and controls and that there is no change to the safety profile of the products used in clinical trials to date.

In April, the FDA accepted the new drug application for the product.

The submission was based on the global ATLAS (Antiretroviral Therapy as Long-Acting Suppression) and FLAIR (First Long-Acting Injectable Regimen) phase 3 studies. Combined, the studies included more than 1100 patients from 16 countries and demonstrated that when injected monthly, cabotegravir/rilpivirine was as effective as a standard-of-care, daily, oral, 3-drug regimen in maintaining viral suppression throughout the 48-week study period. These results were presented in March at the 2019 Conference on Retroviruses and Opportunistic Infections.

ViiV Healthcare will work closely with the FDA to determine the appropriate next steps. ▲

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**FDA Approves Merck’s Ebola Vaccine**

**BY CONTAGION® EDITORIAL STAFF**

The US Food and Drug Administration has announced that the Ebola vaccine Ervebo has been approved for administration in individuals 18 years of age and older. This is the first vaccine for the prevention of Ebola virus disease that has been authorized in the United States. The approval was granted to Merck & Co, Inc. It is administered as a single-dose injection and is a live, attenuated vaccine.

Ervebo was used as an investigational vaccine in the Democratic Republic of the Congo where the second largest Ebola outbreak is ongoing. The vaccine was authorized by the World Health Organization under an expanded access program to help mitigate the outbreak.

The safety of Ervebo was assessed in approximately 15,000 individuals. The most commonly reported side effects were pain, swelling and injection site redness, as well as headache, fever, joint and muscle aches, and fatigue. ▲
β-Lactam antibiotics are the mainstays of treatment for many infectious diseases. Unsurprisingly, emerging resistance limits their use for some patient populations and infection types. There are multiple mechanisms of resistance demonstrated by gram-negative bacteria including the production of β-lactamases. β-Lactamases can be divided into the Ambler classification system and include class A enzymes (Klebsiella pneumoniae carbapenemase [KPCs], extended-spectrum β-lactamases [ESBLs]), class B metallo-β-lactamases (eg, New Delhi metallo-β-lactamase 1 enzyme, imipenemase), class C enzymes (AmpC), and class D enzymes (eg, oxacillin-hydrolysing).1,2

In the late 1960s, β-lactamase inhibitors were developed to overcome resistance due to β-lactamase–producing enzymes. Developed in 1972, clavulanic acid was the first β-lactamase inhibitor available.3 When administered with a β-lactam antibiotic, β-lactamase inhibitors bind to β-lactamases, protecting and preventing inactivation of the antibiotic. Currently available β-lactamase inhibitors have slightly differing spectra of activity.4

Relebactam, formerly known as MK-7655, is a novel non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor. It is structurally similar to avibactam but has the addition of a piperidine ring. In vitro, it is a potent inhibitor of class A and C β-lactamases, including KPC enzymes.5 The addition of relebactam to imipenem-cilastatin improves activity against gram-negative organisms by significantly reducing the minimum inhibitory concentrations, including imipenem-resistant strains of Pseudomonas aeruginosa and Enterobacteriaceae.1,5-7

Carbapenem-resistant Enterobacteriaceae is most commonly attributed to β-lactamase production including ESBLs and KPC-type carbapenemases. Relebactam inhibits ESBLs and KPC-type carbapenemases, therefore restoring imipenem activity.5 P aeruginosa demonstrates resistance to imipenem via downregulation of porin protein synthesis in combination with AmpC overproduction. Relebactam inhibits AmpC production, therefore lowering the minimum inhibitory concentration and improving imipenem activity against P aeruginosa.5 In contrast, meropenem-resistant P aeruginosa is a result of

Imipenem-Cilastatin-Relebactam: Imipenem Is Rele Back Again

The US Food and Drug Administration approved imipenem-cilastatin-relebactam to treat complicated intra-abdominal infections and complicated urinary tract infections in adults with limited treatment options.

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Imipenem-cilastatin-relebactam (IMI-REL) was granted US Food and Drug Administration (FDA) approval on July 16, 2019, for the treatment of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs) in patients 18 years of age or older who have limited or no alternative treatment options available. The typical dose is a total of 1.25 grams, which consists of 500 mg of imipenem, 500 mg of cilastatin, and 250 mg of relebactam, administered via intravenous infusion over 30 minutes every 6 hours. 8

**CLINICAL STUDIES**

IMI-REL has been studied in 2 active-controlled double-blind phase 2 clinical trials, 1 in patients with cUTIs and the other in patients with cIAIs. 9,10 Both trials met the FDA noninferiority end points. More clinically relevant data arise from 2 other studies: RESTORE-IMI 1 and RESTORE-IMI 2. RESTORE-IMI 1 compared IMI-REL with imipenem-cilastatin plus colistin (IMI+CST) in 47 adults with carbapenem-nonsusceptible cIAIs, cUTIs, hospital-acquired pneumonia, and ventilator-associated pneumonia. 11 This study demonstrated that IMI-REL was comparable to IMI+CST with similar efficacy outcomes. The favorable overall response rate was 71.4% and 70% in the modified microbiologic intent-to-treat IMI-REL and IMI+CST groups, respectively. Although not statistically significant, day 28 all-cause mortality was 20% lower in the IMI-REL group. Serious adverse events (AEs) occurred more frequently in the IMI+CST group, at 31.3% compared with the IMI-REL group at 9.7%. The results of RESTORE-IMI 1 support the conclusion that IMI-REL is an effective and well-tolerated option for the treatment of patients with carbapenem-nonsusceptible infections.

RESTORE-IMI 2 is a larger clinical trial that compares IMI-REL to piperacillin-tazobactam in patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in the intensive care unit. Data have not yet been published, but topline results demonstrate that IMI-REL met its primary and key secondary end points of noninferiority when compared with piperacillin-tazobactam in day 28 all-cause mortality and clinical response at early follow-up. 12

**PHARMACOKINETICS**

Pharmacokinetic parameters were similar for single- and multiple-dose administration of imipenem-cilastatin-relebactam due to minimal accumulation. The mean area under the concentration time curve from 0 to 24 hours was 573.9 μM/hr and 427.3 μM/hr for imipenem and relebactam, respectively. The mean steady-state maximum concentration was 104.3 μM and 64.0 μM for imipenem and relebactam, respectively. 9

The mean volume of distribution of imipenem, cilastatin, and relebactam is 24.3 L, 13.8 L, and 19.0 L, respectively. The area under the concentration-time curve from 0 to infinity in epithelial lining fluid relative to that in plasma for relebactam and imipenem is 54% and 55%, respectively. 13 Protein binding of relebactam is 22% and is minimally metabolized. Relebactam has a half-life of 1.2 hours and greater than 90% of drug is excreted unchanged in urine. IMI-REL requires dose adjustments in patients with renal impairment. 8

**ADVERSE REACTIONS, WARNINGS, AND PRECAUTIONS**

Imipenem-cilastatin-relebactam has similar warnings and precautions associated with other carbapenem antibiotics. Due to the inclusion of imipenem in this combination, adverse reactions may include seizures, states of confusion, and myoclonic activity. Concomitant use with valproic acid formulations can drastically decrease valproic acid concentrations, possibly leading to seizures. Generalized seizures have also been reported with concomitant use of ganciclovir. In the 2 clinical trials that led to FDA approval, the most commonly reported AEs included diarrhea, nausea, vomiting, headaches, elevated alanine aminotransferase levels, and elevated aspartate aminotransferase levels. 8,10 In the RESTORE-IMI 1 trial, reported drug-related AEs included decreased creatinine clearance, hyperglycemia, infusion site erythema, and pyrexia. 11

**PLACE IN THERAPY**

IMI-REL increases our armamentarium against multidrug-resistant gram-negative rods. In addition to restoring activity against many carbapenem-resistant Enterobacteriaceae, relebactam also improves activity of imipenem against many imipenem-resistant strains of *P aeruginosa*. (Table) whereas limited data suggest vaborbactam does not substantially do this for meropenem-resistant *P aeruginosa*. 11 IMI-REL is currently indicated for the treatment of cIAIs and cUTIs and has clinical data for treating infections caused by resistant pathogens. Clinical data regarding its use in nosocomial pneumonia are pending. ▲

References are available at ContagionLive.com.
Consequently, serious infections are associated with high rates of treatment failure and mortality. In 2017, in the United States, there were an estimated 120,000 cases of *Staphylococcus aureus* bacteremia, resulting in 20,000 deaths. Although the mortality rate from methicillin-resistant *S aureus* (MRSA) has been about double that of methicillin-susceptible *S aureus* (MSSA), this article focuses on optimal antibiotic therapy for MSSA infections.

The timely administration of appropriate antibiotic therapy is associated with improved clinical outcomes in serious systemic infections. Initial sepsis empiric regimens most often consist of vancomycin with either ceftriaxone, cefepime, or a carbapenem, depending on the site of infection and risk of health care–associated infection. Use of piperacillin/tazobactam with vancomycin carries a relative risk of acute kidney injury of approximately 3, so its use is discouraged.

The decisions surrounding the transitioning of empiric appropriate therapy to optimal targeted therapy in *S aureus* bacteremia involve the integration of patient risk stratification, assessing the rate of clinical response, and source control. Antimicrobial therapy for *S aureus* bacteremia should be viewed as consisting of an intensive “induction” early phase to achieve clinical and microbiological stability followed by a less intensive “consolidative” stage for outpatient completion.

During the early targeted therapy phase of treatment, once blood cultures identify “gram-positive cocci in clusters,” regimens should be focused on *S aureus* until cultures are processed by the clinical microbiology laboratory or, ideally, rapid diagnostic methods can discriminate MSSA from MRSA later that day. In cases of *S aureus* bacteremia due to soft tissue infection or pneumonia, which are easily identified through initial physical exam and radiology, single-therapy regimens are likely adequate. However, great concern should arise with *S aureus* bacteremia in the setting of an unclear source. Such patients usually present with protean symptoms, such as weakness, shortness of breath, and without fever. They may have nonspecific back and other joint pain, possibly as an acute exacerbation of previous long-standing chronic pain. Patients with end-stage renal disease and other immunocompromising comorbidities and bioprostheses, clinical instability, and a history of intravenous drug abuse should also be paid very close attention.

We advocate early combination therapy with daptomycin plus cefaroline until MRSA is ruled out microbiologically (either through rapid diagnostics or through standard susceptibility testing) based on a small but randomized prospective study showing reduced mortality in high-risk patients treated with this regimen compared with standard-of-care monotherapy. Vancomycin plus anti-staphylococcal β-lactam (ASBL) treatment has demonstrated more rapid *S aureus* bacteremia clearance but at the price of acute kidney injury, recapitulating the recommendation against vancomycin plus piperacillin/tazobactam. Vancomycin-plus-cefazolin and vancomycin-plus-ceftaroline regimens may be considered, but improved outcomes with these regimens have not been demonstrated clinically. The combination of daptomycin plus fosfomycin has shown favorable data in Spain, but parental fosfomycin is not available in the United States.

In cases where combination therapy for “gram-positive cocci in clusters” has not been adopted and the patient has remained on vancomycin, strong clinical evidence supports rapid transition from empiric vancomycin to β-lactam therapy as soon as MSSA is identified. The ability of rapid diagnostics to shorten the empiric window...
between the initial "gram-positive cocci in clusters" reported by the laboratory to either MSSA or MRSA has been associated with more timely β-lactam therapy, decreased length of stay, and decreased hospitalization costs, driven largely by prompt initiation of β-lactam therapy for MSSA.14 Beyond the generally accepted need to switch from vancomycin to a β-lactam, other antibiotic choices afford the opportunity for interpretation.

Optimal therapy for confirmed MSSA bacteremia has traditionally favored an ASBL (eg, nafcillin, oxacillin, flucloxacillin, cloxacillin) over cefazolin. One primary argument that favors ASBLs is that some MSSA strains exhibit a so-called cefazolin inoculum effect, whereby cefazolin is hydrolyzed when a dense inoculum of bacteria is present. Strains with an inoculum effect show cefazolin minimum inhibitory concentrations (MICs) that increase >3 dilutions when 10^7 cfu/mL of organisms is tested rather than the standard 10^6 cfu/mL recommended by susceptibility testing guidelines. Like selection of susceptibility testing media itself, susceptibility testing inocula standards were not designed for simulation of in vivo conditions or bacterial counts seen in clinical infection, so the translation of susceptibility testing differences based on inocula to clinical response is unknown. However, several cases of clinical failure in cases of severe invasive S aureus infections have been documented in the literature.15-18

One major limitation of ASBL therapy is the real-world concern of the tolerability for the weeks-long duration of therapy required for many invasive S aureus infections such as endocarditis, osteomyelitis, and other deep-space infections. Long-term administration of ASBLs has been associated with myelosuppression, hepatitis, phlebitis, and interstitial nephritis superimposed on an already cumbersome every-4-hour dosing regimen.19 These concerns have increased over the years due to the higher risk of complications among elderly patients and the increasing number of patients who are quickly discharged on outpatient parenteral antibiotic therapy (OPAT) with less supervision of adverse effects than would be available in a hospital setting. Recent retrospective data, while vulnerable to treatment selection bias, have shown similar outcomes in patients treated with cefazolin and ASBLs for MSSA bacteremia with better tolerability.19 Cefazolin also allows for placement of a midline rather than a peripherally inserted central catheter for treatments of 4 weeks or less, due to its reduced propensity to cause phlebitis. Midlines are less invasive, have reduced risk of thrombosis, and are less anxiety-provoking for some patients. Finally, in patients on hemodialysis, placement of a venous access can be avoided with cefazolin; the drug can be administered 3 times weekly after hemodialysis sessions. Some employ a regimen of 2 g, 2 g, 3 g, where the 3 g covers the longer 3-day gap between Friday–Monday or Saturday–Tuesday sessions, although data supporting that approach over standard 2 g dosing are lacking.

We believe that both concerns are valid and need to be incorporated into the decision-making process of prescribing antibiotics to treat MSSA bacteremia. In cases of MSSA, we favor ASBL therapy while the patient is in the hospital to bridge them through bacteremia clearance, source control, and clinical stability. Use of ASBL therapy early on reduces risk of the inoculum effect in cases with high organism burden infections. The inpatient period also allows for placement of a venous midline catheter for cefazolin OPAT (Table). On occasion, we have encountered persistent MSSA bacteremia on cefazolin or ASBL monotherapy (frequently due to endocarditis) that we have successfully cleared with cefazolin plus ertapenem.20 Again, once stability is achieved, monotherapy is employed, with a preference for ASBL for OPAT in these more challenging circumstances, especially if the patient is being discharged to a skilled nursing facility where closer monitoring is enabled and the 4-hour dosing interval of ASBLs imposes less inconvenience than in the case of a more mobile patient being discharged to their home. Although case reports describe successful use of ceftriaxone in MSSA bacteremia, a recent comparative study showed inferior outcomes of ceftriaxone compared with cefazolin.21 Given the pharmacokinetics (ie, protein binding) and MICs of MSSA to ceftriaxone, routine use of ceftriaxone in MSSA is not recommended.

Table: Proposed Treatment of Documented or Suspected High Organism Burden or Complicated Staphylococcus aureus Infections

<table>
<thead>
<tr>
<th>EMPRIC</th>
<th>GRAM-POSITIVE COCCI IN CLUSTERS</th>
<th>MSSA INDUCTION REGIMEN</th>
<th>MSSA CONSOLIDATION REGIMEN</th>
</tr>
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<tbody>
<tr>
<td>Vancomycin + β-lactam</td>
<td>Daptomycin + Cefaroline</td>
<td>ASBL</td>
<td>Cefazolin</td>
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<td>Daptomycin + Cefaroline</td>
<td>Monotherapy</td>
<td>Daptomycin + Cefaroline</td>
<td>Monotherapy</td>
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References are available at ContagionLive.com.
Five Ways ID Clinicians Can Take On Antibiotic Resistance: Highlights From the CDC’s Latest Report

A death from an antibiotic-resistant infection occurs about every 15 minutes in the United States. The CDC’s 2019 threat report dives into national infection estimates and actions we can take to combat this threat.

BY LACEY AVERY, MA; DENISE CARDO, MD; KATY CAPERS, MA; NICOLE COFFIN, MA; AND MICHAEL CRAIG, MPP

The second groundbreaking report from the US Centers for Disease Control and Prevention (CDC) concerning antibiotic resistance (AR) shows that more people are dying from AR in the United States than previously estimated in 2013—but underscores that infection prevention is saving lives.

AR can affect anyone at any time. More than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result. In addition, 223,900 cases of Clostridiodes difficile occurred in hospitalized patients in 2017 and at least 12,800 people died. These data are not merely statistics—they represent people. In November 2019, the CDC released Antibiotic Resistance Threats in the United States, 2019, calling for continued action to combat this threat and save lives.

Although this threat is never ending, this report and other data sources show that with the right tools and practices, we can protect people from infections and related complications. Since the first AR Threats Report released in 2013, the number of deaths caused by antibiotic-resistant infections has been reduced by 18% overall and by nearly 30% in hospitals alone. This success is driven by public-private partnerships to prevent infections in the first place, slow the development of resistance through better antibiotic use, and stop the spread of resistance when it does develop.

Yet the number of people facing AR in the United States is still too high. The report lists 18 antibiotic-resistant bacteria and fungi into 3 categories based on level of concern to human health—urgent, serious, and concerning. Pathogens will continue to develop resistance and, without continued action, could undo the nation’s progress. The CDC’s report calls out many areas needing enhanced action, and 5 are included in this article.

INCREASE PREVENTION IN YOUR COMMUNITY

The CDC is concerned about rising antibiotic-resistant infections in the community, including those that can lead to sepsis. This can put many people at risk, make the spread of germs more difficult to contain, and threaten the progress made to protect patients. For example, 2 pathogens listed in the report causing infections have more than doubled since the last report—drug-resistant gonorrhea and group A Streptococcus. Also, certain types of Enterobacteriaeae, which can cause antibiotic-resistant urinary tract infections, are on the rise.

Stopping the spread of resistant threats in the community requires specific interventions. Health care providers can talk to patients about proper hygiene, routine vaccination, safer sex practices, safe food preparation, and ways to prevent spread. Many of these interventions have already proven successful. For example, family doctors recommending vaccines have protected their patients from pneumococcal infections. The PCV13 vaccine, which the US Food and Drug Administration (FDA) licensed in 2010, protects people from 13 types of pneumococcus, including resistant forms. This vaccine prevented more than 30,000 cases of invasive pneumococcal disease and 3000 deaths from 2010 to 2013 alone.

TAKE AGGRESSIVE ACTION IN HEALTH CARE

Antibiotic-resistant health care–associated pathogens can spread from patient to patient and across facilities. Infection prevention programs in hospitals have been critical to helping decrease antibiotic-resistant infections and their spread, but these gains will only be temporary without continued action and without similar control efforts in other health care facilities such as long-term care. Antibiotic-resistant pathogens can move back and
forth between health care facilities and communities, becoming much harder to control.

Health care providers can follow infection prevention and control recommendations, including screening at-risk patients when indicated, to stop infections before they begin. This step includes staying informed of current outbreaks and alerting receiving facilities when transferring patients who are colonized or infected with antibiotic-resistant germs.

If new or rare resistance is identified, the CDC’s Containment Strategy—aggressive detection and response activities—can keep these uncommon antibiotic-resistant genes or germs from spreading when launched at the first sign of a problem. For the "nightmare bacteria” carbapenem-resistant Enterobacteriaceae alone, aggressive containment responses could prevent 1600 cases in just 1 state over 3 years.

WATCH FOR EMERGING THREATS
The report’s Watch List includes 3 threats that have not spread resistance widely or that are poorly understood in the United States and could become common without a continued aggressive approach. Comprehensive prevention and response are needed to ensure that the 3 Watch List threats—drug-resistant Aspergillus fumigatus, Mycoplasma genitalium, and Bordetella pertussis—do not become threats here. There is the potential for these resistant germs to spread among cities, states, and countries.

The CDC and other public health experts are closely monitoring these germs. CDC’s AR Laboratory Network provides health care facilities and public health departments access to gold-standard public health lab testing to help detect emerging threats and prevent the spread of antibiotic resistance. As of 2018, every 4 hours, the AR Lab Network detected a resistant germ carrying a mechanism that required a public health investigation.

The report also highlights a new urgent threat, the fungus Candida auris that was not listed in the 2013 report. Vigilant surveillance and aggressive action in health care by infectious disease experts nationwide have, in many cases, helped contain this threat, which kills more than 1 in 3 patients with invasive C. auris infection.

Health care providers need to ask patients if they recently received care in another facility or traveled to another country. Early detection of resistant germs within the United States, followed by implementation of prevention strategies, could reduce spread and public health impact.

REMEMBER MECHANISMS
The emergence and spread of new forms of resistance remains a concern. To survive the effects of antibiotics, pathogens are constantly finding new defense strategies, called “resistance mechanisms.” These mechanisms can change over time and lead to more resistant infections. Alarmingly, antibiotic-resistant pathogens can share their resistance genes with other pathogens that have not been exposed to antibiotics. Bacteria and fungi can carry genes for many types of resistance. When already hard-to-treat pathogens have the right combination of resistance genes, it can make all antibiotics ineffective, resulting in untreatable infections.

Health care providers need to be aware of resistance patterns in the area and work with their clinical and public health labs to receive immediate notification when antibiotic-resistant germs are identified in patients. Knowing when to report cases and submit resistant isolates to the health department can drastically help identify unusual resistance or treatment failures.

DISCOVERING INNOVATIVE ALTERNATIVES
We need to develop new antibiotics and come up with new and better ways to prevent, detect, and treat infections. Bacteria and fungi continuously change and develop new ways to resist antibiotics. The report highlights the need for innovative alternatives, such as antibodies, bacteriophages, fecal microbiota transplant, and vaccines. Researchers are testing vaccines to prevent various types of Streptococcus infections (eg, those caused by groups A and B) and C difficile infection.

To support innovative efforts in diagnostics and drug development, the CDC & FDA AR Isolate Bank provides curated collections of resistant organisms gathered through CDC’s outbreak response and surveillance programs. The isolates represent samples from health care–associated, foodborne, gonorrhea, and community-associated infections. The AR Isolate Bank helps, for example, inform research and development, perform testing to ensure drug effectiveness, study mechanisms, and detect public health resistance threats. This work ultimately improves patient care and builds solutions against resistance threats.

Preventing infections in the first place, stopping the spread of resistance when it does develop, slowing the development of resistance through better antibiotic use, and supporting innovations for better outcomes will help protect people. We all have a role to play—be alert in your community and facility and act to protect patients.

References and full author bios available at ContagionLive.com.
Addressing Weight Gain That Follows Life-Saving Antiretroviral Therapy

Clinicians must identify when additional pounds cross the line of diminishing return.

BY KARAM MOUNZER, MD

There is growing evidence supporting greater weight gain when patients start or are switched off a stable regimen to integrate strand transfer inhibitors (INSTIs) compared with existing agents. This finding is clinically important, as INSTI-based regimens are now recommended first-line ART, and patients living with HIV (PLWH) are at an increasing risk for obesity, metabolic comorbidities, and cardiovascular disease.1 Separating weight gain due to improved health status from weight gain due to an undesired effect of therapy, understanding the pathogenesis of weight gain, and its health repercussions are of paramount importance.

The pathophysiology of such excessive weight gain among PLWH following ART is multifactorial in nature (FIGURE) and is governed by the interplay between demographic factors, HIV-related factors, the composition of ART regimens, and our current obesogenic environment. The mechanisms by which certain ART agents differentially contribute to weight gain remain unknown. Some clinical investigators speculate that INSTIs could interfere with central nervous system appetite regulation (melanocortin-4 receptor), insulin signaling, or may have a better penetration into adipose tissue where they could exert a direct impact on adipose tissue adipogenesis,2 fibrosis, and insulin resistance.

The magnitude of weight gain and body fat distribution associated with ART contribute to the growing metabolic and cardiovascular disease burden in PLWH. Results from a Veterans Affairs study showed that a 5% increase in weight gain in PLWH relates to a 14% increase in risk for developing diabetes mellitus compared with 8% of vets without HIV.4 More importantly, central adiposity associated with an increased waist circumference coupled with reduced muscle mass has been independently associated with an increased 5-year mortality rate in PLWH. Ectopic fat deposition known as visceral fat is 1 of the most important factors predisposing individuals to cardiometabolic complications (ie, diabetes mellitus, coronary artery disease, and fatty liver) and other comorbidities. Visceral fat is hard to evaluate, not routinely measured in our clinics, and may or may not be associated with central obesity.3

Both longitudinal prospective randomized studies and observational cohort studies showed a significant weight gain associated with INSTI-based regimens. Most of these studies were conducted in ART-naïve populations where some of the weight gain could be primarily driven by return to health. More importantly, however, many of these studies did not account for numerous confounding contributors to weight gain such as concomitant medications, diet, physical activity, marijuana use, or smoking, making it harder to fully assess the direct impact of each ART agent on weight gain. In addition, it is important to note that the majority of these observational studies examined dolutegravir (DTG) association to weight gain, but few included bicitegavir (BIC), as it was approved in February 2018 and has little longitudinal follow-up time.

PROSPECTIVE RANDOMIZED STUDIES THAT EXAMINED WEIGHT GAIN IN NAÏVE PATIENTS

ACTG 5257 randomized 1809 ART-naïve patients to atazanavir/ritonavir/tenofovir disoproxil fumarate/emtricitabine (ATV/r/TDF/FTC), darunavir/ritonavir/tenofovir disoproxil fumarate/emtricitabine (DRV/r/TDF/FTC), or raltegravir/tenofovir disoproxil fumarate/emtricitabine (RAL/TDF/FTC). Weight increased on average by 3.8 kg and body mass index (BMI) by 1.3 kg/m² over 96 weeks. Compared with RAL, patients prescribed ATV/r were less likely to experience a severe weight increase, and those prescribed DRV/r were less likely to experience a significant BMI increase.6

The ADVANCE trial conducted in South Africa recruited 1053 patients and compared 3 first-line regimens in PLWH starting 1 of the following current first-line regimens: TAF/FIC/DTG versus TDF/FTC/DTG, as compared with TDF/FTC (or lamivudine/efavirenz [EFV]) (comparator arm). At week 96, absolute weight gain and the percentage of patients in whom obesity emerged during treatment were highest in the TAF-based group (7.7 kg, 27% new obesity), but the values in the TDF-based group (4.2 kg, 17% new obesity) were also higher than those in the standard-care group (2.1 kg, 11% new obesity). The respective proportions of women who gained more than 10% of weight through 96 weeks, on these 3 regimens, were 51%, 32%, and 23%, and proportions of men totaled 42%, 27%, and 18%, respectively.7

In the NAMSAL study, conducted in adults PLWH in Cameroon, more weight gain was observed in the DTG group than those in the low dose efavirenz group (a 400-mg dose, known as, EFV-400) (median weight gain, 5.0 kg vs 3.0 kg; incidence of obesity, 12.3% vs 5.4%). Weight gain of at least 10% was observed in more women than men and in more participants who had a low BMI at baseline than participants who were in other BMI categories at baseline. A significantly greater increase in the cholesterol level in both groups, as well as a greater increase in the glucose level in the DTG group, was observed in participants who had weight gain of at least 10% compared with participants who did not.8

A recent pooled analysis of weight gain in 8 randomized controlled, phase 3 clinical trials in naïve patients and follow-up duration of 96 weeks or more, encompassed more than 5000 participants and 10,000 person-years of...
follow-up. This study conducted between 2013 and 2015 revealed that INSTI-containing regimens were associated with more weight gain than protease inhibitors or nonnucleoside reverse transcriptase inhibitors (NNRTIs), with DTG and BIC associated with more weight gain than elvitegravir/cobicistat (EVG/c). Among the NNRTIs, rilpivirine (RPV) was associated with more weight gain than efavirenz. A multivariate modeling analysis identified these baseline factors to be associated with incident obesity: lower CD4 count (most important single factor), higher viral load, female patients, and black race. Tenofovir alafenamide was associated with more weight gain than TDF, abacavir, or cART. Tenofovir alafenamide was associated with higher viral load, female patients, and black race. Tenofovir alafenamide was associated with more weight gain than TDF, abacavir, or cART.

The association of weight gain with INSTI is unequivocal and represents more than simply an improvement in health. Knowing the predisposing factors for weight gain (ART-naive patients, diet and other life style factors, genetic predisposition, black race, female sex, age, low CD4 count, high viral load, and persons with baseline obesity) will help clinicians inform their patients before initiating ART to be on the lookout for undesirable weight gain. It is important for clinicians to identify when such gain becomes detrimental. In general, 80% of weight gain observed in the first 3 years occurs during the first 12 months following ART initiation. However, when a patient has a weight gain greater than 5% over the first 6 months, especially if coupled with truncal adiposity (a likely surrogate of visceral fat deposition), this can increase the likelihood of downstream cardiovascular and other metabolic complications. To further complicate the situation, weight and BMI do not accurately estimate visceral and abdominal adiposity. Hence, there is a need for large-scale longitudinal prospective studies with more rigorous data to better characterize lean body mass gain and fat distribution associated with weight gain following INSTI-based ART, in order to better understand the significance of these changes and their relationship with subsequent cardiometabolic complications.

Pending further evidence, clinicians should remain cognizant of the life-saving value of ART and not reflexively alter their practice. Weight gain in PLWH should be approached the same way as for any individuals with obesity. Weight, waist-to-hip ratio, and waist circumference should be monitored in a standardized manner. Although the reversibility of weight gain post switch remains unknown at this time, it is reasonable to consider early treatment modification in those patients on an INSTI-based regimen who are on an extreme weight gain trajectory.

REFERENCES are available at ContagionLive.com.
MULTIDRUG-RESISTANT INFECTIONS

Bacteriophage-Antibiotic Combinations: A Promising Alternative for Refractory Infections?

Despite the initial abandonment of bacteriophages in most areas of the world, the era of antibiotic resistance has led to a resurgence of phage therapy in clinical practice.

BY TAYLOR MORRISETTE, PHARMD; RAZIEH KEBRAEI, PHD; SANDRA MORALES, PHD; AND MICHAEL J. RYBAK, PHARMD, MPH, PHD

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INTRODUCTION TO BACTERIOPHAGES
Phage therapy was first implemented in the early 20th century, but the introduction of antibiotics, among other factors, overshadowed their therapeutic potential throughout the majority of the world.7,8 Despite this initial abandonment, the era of antibiotic resistance has led to a resurgence of phage therapy into clinical practice, primarily in refractory cases or to attack MDR organisms.2,3,8-9 Phages depend on their bacterial hosts for replication, and the 2 main life cycles for viral replication are the lytic, or virulent cycle (in which the phage kills the bacterial cell) and the lysogenic, or temperate cycle (in which the phage lays dormant within the bacterial genome and does not immediately kill the bacterial cell). In clinical practice, lytic phages are favored for use.10,11

Most phages used for therapy are viruses that consist of DNA within a prism-shaped head, spikes/tail fibers that attach to bacteria, and a tail sheath through which the DNA flows en route to injecting its host.11 The interaction of virulent phages and bacteria begins with the tail fibers of the phages adsorbing to their specific receptors on the surface of the bacteria. Following attachment, phages create a hole on the bacterial surface to propel their DNA through their tail sheath into the bacterial cytoplasm. The function of the DNA from the phages is to take over the bacterial host’s bacterial machinery to replicate and produce new phages within the bacterial cell. This process continues until the bacterial cell is lysed, at which point the phage offspring are released to reinitiate the cycle.10,11

Importantly, the use of "phage cocktails”—or combinations of phages—is typically recommended for therapy, although monophage therapy is sometimes employed. Because single phage activity is typically very specific, utilizing phage cocktails broadens the antibacterial activity. It has also been shown to reduce the development of phage-resistant bacteria.12-14

POSITIVE INTERACTIONS AGAINST BACTERIA WITH PHAGE-ANTIBIOTIC COMBINATIONS
Phages used alone have potential advantages over antibiotics. These include high specificity to bacteria, which limits potential damage to the normal flora of the host; self-limiting action, meaning that phage numbers decline as the bacterial infection resolves; and phages’ adaptability with the bacterial host, in that they may infect previously phage-resistant bacterial mutants. However, recently published research has shown promising results with phage-antibiotic combinations against bacteria.3-6,10,11,13 Currently, phage-antibiotic combinations seem to be particularly important when there are minimal or no antibiotic options due to antibiotic resistance, or in instances where there is minimal diffusion of antibiotic(s) to the infected area of interest. At present, phage therapy in place of antibiotics in critically ill patients is highly unlikely to occur until more evidence of efficacy through controlled studies becomes available. Although numerous positive interactions have been reported with phage-antibiotic combinations, selected interactions dealing with enhancement, with brief examples, are described below.
MULTIDRUG-RESISTANT INFECTIONS

1. Phage-antibiotic synergy (PAS) and reductions in bacterial growth or reductions in minimum inhibitory concentrations (MIC)

Comeau and colleagues coined the phrase PAS in describing how sublethal concentrations of antibiotics may stimulate the production of virulent phages. The investigators evaluated phage qMFP against *Escherichia coli* (strain MFP) with and without cefotaxime. The presence of cefotaxime at a concentration of 50 ng/mL exhibited a marked PAS effect that was not observed in the absence of cefotaxime. Another study performed by Oeschlin and colleagues evaluated phage cocktail PP1131 and various antibiotics against *Pseudomonas aeruginosa*. Within their in vitro analysis of static fibrin clots, meropenem and ciprofloxacin at 2.5x MIC in combination with phage cocktail PP1131 was associated with ≥3 log₉ colony forming units/mL bacterial reduction when compared with monotherapy with either antibiotic or phages.⁵

2. Biofilm eradication

Biofilms are polysaccharide matrices that shield pathogens from antibiotics and the host immune system. Phages can produce enzymes, such as depolymerases and endolysins, that can expedite the breakdown of the extracellular matrices of biofilms. An in vitro biofilm analysis performed by Chaudhry and colleagues evaluated *P aeruginosa* (strain PA14) against monotherapy and combination therapy with 2 phages (NP1 and NP3) and various antibiotics. After biofilm growth occurred, synergistic activity was noted when a combination of the phages and antibiotics was present; this activity occurred to a lesser degree when either agent was used alone.⁶

3. Alterations in the emergence of resistance

It has been shown that phages may impose a selective pressure on certain strains of bacteria. This “evolutionary trade-off” may be associated with a fitness cost (fitness is the ability of an organism to survive in a competitive environment) of inducing phage resistance, but with regaining bacterial susceptibility to antibiotics. Ho and colleagues described an example of this phenomenon in which an *epR* mutation led to a reduction in phage adsorption to a strain of *Enterococcus faecalis* (OG1RF); however, daptomycin susceptibility was enhanced in the presence of this mutation.⁷

There are fewer reports of clinical data than there are of in vitro data, but some clinical data have emerged from studies, with more to come. A report published by Schooley and colleagues describes the use of intravenous and intracavitary phage cocktail therapy to treat an MDR *Acinetobacter baumannii* infection. A 68-year-old man had an infection disseminated from pancreatic pseudocysts and necrotizing pancreatitis; he had received 2 intravenous phage cocktails and 1 locally administered phage cocktail, in combination with minocycline. This treatment led to clearance of infection and clinical improvement, in contrast to previous clinical deterioration after multiple rounds of source control and antibiotics. Other clinical reports have been described, in which phages have been used through compassionate use to complement the existing antibiotic arsenal in cases where traditional therapy with antibiotics had failed.⁸,⁹,¹⁰

Additionally, clinical trials are in progress examining the combination of phage endolysin and antibiotics. One trial already presented was a phase 2, placebo-controlled, double-blind, randomized clinical trial comparing Exebacase, formerly CF-301 (phage-derived endolysin) plus standard-of-care (SOC) versus SOC alone in patients with *Staphylococcus aureus* bacteremia. At day 14, higher clinical responder rates had occurred in the prespecified Methicillin-resistant *S aureus* subgroup analysis (~75% vs ~30%; *P = .010*).¹¹

**FINAL THOUGHTS**

In this troubling era of antibiotic resistance, the use of bacteriophages in combination with antibiotics is a very promising therapeutic approach. Additional randomized controlled trials comparing SOC versus SOC in combination with phages or phage derivatives are urgently needed. Among the facets of treatment that must be studied are optimal administration route, duration of phage therapy, and whether antibiotic or phage treatment can be de-escalated while the other is continued. The long-term effects of increased phage use on antibiotic resistance are currently unknown and must be evaluated, too. These considerations could lead the way for a new focus on “phage stewardship.” Despite the many unanswered questions and the additional intricacy phages would bring to the already complicated scenario of treating patients suffering from infectious diseases (Figure), phage-antibiotic combinations may enhance effectiveness via multiple mechanisms. Further research is most certainly warranted. ▲

References are available at ContagionLive.com.
Diagnostic Stewardship: Beyond Managing Bloodstream Infections

Diagnostic stewardship is a novel concept related to modifying the process of ordering, testing, and reporting with the goal of decreasing unnecessary testing and treatment, working upstream and synergistically with antimicrobial stewardship principles.

(continued from cover page)

Diagnostic stewardship, however, is a novel concept that has not been fully defined and elucidated and has, in fact, even been refuted.3,4 In particular, these interventions target the preanalytic phase (when tests are being ordered), analytic phase (the performance of the diagnostic test itself), and postanalytic phase (reporting of diagnostic results once the test has been complete).3 Interventions related to diagnostic stewardship are meant to alter the processes before antimicrobials are prescribed and thus work synergically with AMS initiatives (Figure).5

DIAGNOSTIC STEWARDSHIP AND URINARY TRACT INFECTIONS

Urinary tract infections (UTIs) represent one of the most commonly reported infectious diseases; however, inappropriate diagnosis and management are common.6,7 Differentiation of UTIs from asymptomatic bacteriuria (ASB) remains a common clinical challenge, as the presence of white blood cells or bacteria in the urine is not, in itself, indicative of a UTI.8 Evidence demonstrates that the presence of a high level of pyuria or a positive urine culture test result, despite a lack of signs and symptoms of infection, are major drivers for antimicrobial prescribing.9 From an AMS perspective, patients are often reviewed after the diagnosis has been made, limiting the ability to alter the course of care. As such, inappropriate treatment of ASB often leads to unnecessary antibiotic exposure and increases the risk of adverse drug events and development of resistance.10

Diagnostic stewardship initiatives to decrease inappropriate treatment of ASB target all 3 phases, from preanalytic to postanalytic.11 In the preanalytic phase, it is imperative to limit the unwarranted ordering of urinalyses and urine cultures—in particular, urinalyses that reflex to culture when there was no intent to culture. Decreasing inappropriate ordering of urine cultures can be achieved through a combination of educational initiatives, written guidance, and electronic alerts while ordering. Through a combination of these initiatives and provider feedback, investigators have been able to demonstrate significant reductions in both rates of urine cultures ordered and treatment of ASB.12,13 Additional clinical decision support with best practice alerts or requirements for documentation of symptoms in the electronic medical record can also be used to discourage inappropriate ordering of urine cultures.14,15 Another novel approach is the implementation of conditional urine reflex culture policies. When urinalysis and culture are ordered, the culture is not completed unless meeting specific criteria such as WBC > 10 cells per high-power field.16 Several quasi-experimental studies have shown an immediate decrease in rates of urine cultures performed.
after implementing conditional urine reflex; however, implications for antimicrobial prescribing have not been extensively studied. In the postanalytic phase, there are published methods aimed at decreasing treatment after an inappropriate urine culture has been ordered—including educational memoranda, selective susceptibility reporting, and complete cessation of urine culture results—reporting requires a separate call to the clinical microbiology laboratory.

**DIAGNOSTIC STEWARDSHIP AND CLOSTRIDIODES DIFFICILE INFECTION**

Health care professionals are increasingly recognizing the importance of differentiating true *Clostridioides difficile* infection (CDI) from colonization, representing a prime opportunity to implement diagnostic stewardship initiatives. For instance, although the gold standard for identifying *C difficile* is cell culture cytotoxicity neutralization assay, it is a labor-intensive method and not commonly employed. Instead, nucleic acid amplification tests (e.g., polymerase chain reaction and loop-mediated isothermal amplification) tend to be used in routine clinical practice. These molecular tests detect the genes responsible for toxin production and have reported sensitivities greater than 99%. These tests with extremely high sensitivity have the risk of low positive predictive values as the prevalence of true infection decreases. As such, when there is low pretest probability, a false-positive test result becomes more likely (Figure 2 online). This is particularly true in patients with unclear signs and symptoms of infection. The 2016 European Society of Clinical Microbiology and Infectious Diseases and 2018 IDSA guidance for the diagnosis and management of CDI recommend, in conjunction with clinical signs and symptoms of infection, a 2-step diagnostic algorithm to improve positive predictive performance. To help differentiate colonization from true infection and decrease diagnosis and treatment of false positives, infection control programs have started to implement these multistep testing algorithms, requiring both a polymerase chain reaction and toxin-positive test result to diagnose true infection.

Other diagnostic stewardship interventions to limit the incorrect diagnosis of CDI have also been successfully implemented in the preanalytic phase. Clinical decision support, such as best practice alerts, hard-stops, and requirements to document signs and symptoms of infection while ordering have all shown potential benefit in limiting inappropriate test ordering. Best practice alerts and hard-stops can be applied in particular situations, for instance when a test is ordered within 48 hours of laxative use or within 7 days of a previously negative *C difficile* test result. The most commonly reported interaction is implementing best practice alerts to notify ordering providers of laxative use within 48 hours before ordering the test.

**DIAGNOSTIC STEWARDSHIP AND LOWER RESPIRATORY TRACT INFECTIONS**

There is considerably less literature specifically focused on diagnostic stewardship initiatives for the management of lower respiratory tract infections (LRTIs). A major challenge faced with the treatment of LRTIs is the differentiation of causative pathogens, with organism identification occurring in less than 40% of infections and 50% of infections caused by viral as opposed to bacterial pathogens. Treatment of viral LRTIs with antimicrobial agents is likely commonplace. Molecular rapid diagnostic tests, including multiplex syndromic viral panels have been shown to assist in the identification of causative pathogens and implementation of patient isolation; however, their impact on antimicrobial management has been limited. Several studies have demonstrated that days of antimicrobial utilization or the proportion of patients continued on antimicrobials after identifying viral pathogens remain largely unchanged. Publications have also examined the impact of rapid diagnostic tests in combination with procalcitonin monitoring, demonstrating the ability to decrease overall antibiotic use in several studies. In the postanalytic phase, microbiological nudges have demonstrated success in de-escalating antimicrobial therapy, in particular highlighting the lack of drug-resistant pathogens isolated. Selective release of antimicrobial susceptibility information demonstrated the ability to prevent initiation of antimicrobials.

**CONCLUSIONS**

Interventions related to diagnostic stewardship, with and without active AMS involvement, have shown the ability to decrease inappropriate diagnosis of a variety of infections ultimately leading to a decline in unnecessary antimicrobial use. Opportunities exist in all 3 phases of diagnostics from pre- to postanalytical, but it remains imperative that an emphasis be placed on ensuring a high pretest probability to increase diagnostic accuracy and ensure appropriate use of diagnostics as well. Collaboration between AMS and the clinical microbiology laboratory is key to advance best practices in the management of bacterial infections.

References are available at ContagionLive.com.
Updates to Clinical Practice Guidelines for Community-Acquired Bacterial Pneumonia

BY GINA BATTAGLIA, PHD

Thomas Lodise, PharmD, PhD, professor at the Albany College of Pharmacy, discussed some of the key updates to clinical practice guidelines for community-acquired pneumonia (CAP), ways to reduce the cost of care for community-acquired bacterial pneumonia (CABP), and ongoing clinical challenges for the management of CABP in a recent IDWeek 2019 News Network video series.

INITIAL REACTIONS TO UPDATED CAP GUIDELINES

Lodise discussed some of his initial reactions to the updated clinical practice guidelines for the management of CAP, developed by a multidisciplinary panel from the American Thoracic Society and Infectious Diseases Society of America. He noted that, like previous iterations, the most recent update to the guidelines stratify recommendations for outpatient management based on the presence of comorbidities, whereas it classified recommendations for inpatient management based on whether the patient is in the hospital ward or intensive care unit (ICU).

One key change in the recent update was the recommendation against the use of macrolides as monotherapy for *Streptococcus pneumoniae*, the leading cause of CABP, in regions with greater than 25% resistance to the drug class. Although the surveillance data for *S pneumoniae* are sparse, Lodise said that most regions likely have a level of resistance well above the 25% threshold—closer to 40%.

“The guidelines indicate that macrolides should not be used alone, which is a new recommendation in contrast with [the 2007 guidelines],” said Lodise. He added that otherwise, the treatment choices are largely unchanged, with β-lactam with a macrolide, or respiratory fluoroquinolones for patients in the hospital ward, and β-lactam plus a macrolide, or β-lactam with a fluoroquinolone for patients in the ICU. However, he noted that the guidelines have mentioned multiple boxed warnings for fluoroquinolones over the years (eg, QTC prolongation, tendinitis, and tendon rupture), with the most recent update including a warning about the increased risk of aortic aneurysm, particularly among patients with cardiac risk factors.

“They do discuss that there appears to be some advantage in our ICU patients using a β-lactam with a macrolide over with a fluoroquinolone,” said Lodise. “However, they said either one is an acceptable recommendation.”

Lodise also said that the recent update to the guidelines recommended against using the prior categorization of health care–associated pneumonia to guide selection of extended antibiotic coverage and instead discuss treatment of CAP in patients at risk for methicillin-resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa*. The updated guidelines recommend that inpatients who are in septic shock and have had prior infection or colonization with MRSA or *P aeruginosa* receive empiric treatment for these pathogens while waiting for culture data.

“If patients do have risk factors for MRSA or *Pseudomonas*, those are the ones that tend to be admitted who have high acute disease severity,” said Lodise. By contrast, he stated that the guidelines only recommend coverage for MRSA or *Pseudomonas* for patients in the hospital ward if the pathogen is identified, either by patient history of infection, polymerase chain reaction testing (for MRSA), or clinical culture (for *Pseudomonas*). Vancomycin or linezolid are the guideline-recommended agents for MRSA treatment, whereas an antipseudomonal β-lactam is recommended for coverage of *Pseudomonas*.

Lodise concluded that although the guidelines recommended that the risk of MRSA in hospitalized patients should be predicated on validated institution-specific clinical prediction rules, these are not widely available and remain an area that needs further research moving forward.

REDUCING COST FOR CABP AND EXPLORING NEW AGENTS

Lodise discussed possible ways of lowering the expense of managing CABP and found that reducing the hospital length of stay is a potentially significant approach to save on costs.

“We need to be more acutely aware when we standardize admission practices for patients who present to the [emergency department] with suspected or documented community-acquired bacterial pneumonia,” he said. “If there’s an opportunity to treat the patient briefly in the observation unit, that should be preferred over a short hospital admission.”
Additionally, Lodise identified several studies (many of which were outside of the United States) showing that many patients with infections stay in the hospital longer than necessary, which can significantly drive up the cost.

"If one considers each day of hospitalization for a CABP patient is $2500, even a 1- or 2-day hospital stay reduction could have a substantial impact on the overall cost of care," said Lodise.

Key strategies that could reduce costs associated with hospitalization include improving the triage of patients who present to the emergency department, the selection of patients who require admission, and identifying when admitted patients can be discharged following treatment of their infection—often 24 hours after clinical stabilization and improvement in some symptoms.

ASSESSING CHALLENGES TO TREATING CABP
Lodise noted that although the general community perceives that many options exist for CABP treatment, the guidelines identify a limited number of drug classes. He noted that recent approval of lefamulin (a pleuromutilin antibiotic) and omadacycline (a next-generation tetracycline-like antibiotic) for the treatment of CABP provides much-needed additions to the list of treatment options.

"Largely, we’re left with the use of a β-lactam and for our inpatients in combination with a macrolide," he said. "There are the respiratory fluoroquinolones—and most of us are aware of many of the increased box warnings associated with them. Doxycycline is a drug that is considered in the guidelines but has limited evidence for use in CABP, and our 2 newer agents omadacycline and lefamulin [are potential options]."

He added that although broader-spectrum antibiotics, such as vancomycin, linezolid, and antipseudomonal β-lactams may also be considered, these should be avoided whenever possible, particularly among patients with CABP, to promote responsible antibiotic stewardship.

Lodise also pointed out that the empiric treatment of CABP also poses a challenge in that physicians generally do not know exactly what pathogen they are treating and may start with a broad-spectrum antibiotic, which provides limited opportunities for de-escalation. Furthermore, he noted that the class effect of antibiotics can make it difficult to choose a therapy if a patient has a contraindication to a particular drug class.

"For example, if someone’s allergic to penicillin, you can’t use ampicillin-sulbactam, amoxicillin; and you may or may not be using some of the cephalosporin antibiotics," said Lodise. "If someone has an allergy to a fluoroquinolone, or they’re in a high-risk group for one of its adverse events, this is a class effect."

The increase in macrolide resistance across the United States has also effectively eliminated macrolide monotherapy as a therapeutic option, according to Lodise.

They have shown some increased survival benefit in some of our sicker CABP patients, but we have lost the macrolides as a monotherapy agent in the outpatient setting in patients without comorbidities,” he said.

Lodise concluded that identifying the most appropriate site of care in a standardized way is a continual challenge, although triage tools such as the PSI/PORT score have helped with risk stratification of patients with CAP in the outpatient clinic or emergency department. Although he acknowledged that clinical judgment should be the primary deciding factor, he noted the considerable variability in admission of patients with CABP among institutions that needs to be reduced to lower costs of care.

"The single decision to admit a patient with CABP, whether they needed to or not or could be managed in an observation unit for 48 hours, is associated with costs upwards of $10 to $15,000,” said Lodise. ▲

References are available at ContagionLive.com.
Evaluating Meropenem and Piperacillin/Tazobactam for Empiric Sepsis Treatment

BY MICHAELA FLEMING

Every year, at least 1.7 million adults in the United States develop sepsis, according to the US Centers for Disease Control and Prevention. Of these individuals, nearly 270,000 will die from the condition. It is estimated that 1 in 3 patients who die in a hospital setting have sepsis, making the condition a common finding in the intensive care units (ICUs) in the United States. However, administration of appropriate antibiotics in a timely manner has been associated with improved clinical outcomes among patients with sepsis. Piperacillin/tazobactam and meropenem are both accepted as options for empirical antibiotic therapy due to their broad-spectrum activity.

In a new study, a team of investigators set out to evaluate whether there is a difference in clinical outcomes between adults receiving piperacillin/tazobactam and meropenem for empiric sepsis treatment in the ICU. Their findings were presented in a poster session at the American Society of Health-Systems Pharmacists (ASHP) Midyear Clinical Meeting.

The investigators conducted a retrospective data review from 122 adult patients with sepsis who were admitted to the ICU between January 2015 and December 2017. In total, 82 patients were treated with piperacillin/tazobactam and 40 individuals received meropenem.

The investigators assessed information including demographic data, underlying comorbidities, potential infection sources, along with culture results and susceptibility to piperacillin/tazobactam and to meropenem. The study team performed propensity score matching analysis and multivariate analysis to control for all potential confounders.

The primary outcomes were ICU length of stay and 30-day mortality. After adjusting for confounders, the investigators found that there was no significant difference in ICU length of stay between piperacillin/tazobactam- (median, 12; interquartile range, 7, 20) and meropenem-treated groups (median, 15.5; interquartile range, 8.5, 27) (P = .2).

Additionally, the investigators report that 30-day mortality was not significantly different between individuals treated with piperacillin/tazobactam (73%) and meropenem (76.3%), respectively (P = .6).

Secondary outcomes included the delta Sequential Organ Function Assessment score, C-reactive protein ratio, and the difference between serum procalcitonin concentrations and white blood cell count on admission and 48 to 72 hours later. According to the investigators, there were no significant differences between the 2 groups among secondary outcomes.

“The propensity score matching analysis confirmed these findings, with no significant difference in the average treatment effect nor the average treatment effect among [those] treated both for mortality and length of stay in the ICU,” the authors wrote.

Based on these findings, the authors conclude that there was no difference in ICU length of stay or 30-day mortality among patients with sepsis treated with either piperacillin/tazobactam or meropenem.

“These findings support the use of a carbapenem-sparing agent, such as piperacillin/tazobactam, as an initial empiric antibiotic therapy to treat sepsis in the ICU and avoid meropenem overuse,” the authors noted in their conclusion.

However, the authors have indicated that there is a need for a prospective multicenter study comparing the 2 agents that could provide more information on the impact of empirical use for sepsis treatment.

The abstract, “Clinical Outcomes of Empirical Use of Piperacillin/Tazobactam Versus Meropenem in Adult Patients Admitted to the Intensive Care Unit With Sepsis,” was presented in a poster session on Monday, December 9, 2019, at ASHP Midyear Clinical Meeting in Las Vegas, Nevada.

Can Improving Penicillin Allergy Documentation Cut Costs?

BY CONTAGION® EDITORIAL STAFF

Penicillin allergies are the most commonly reported β-lactam allergy, yet true allergies are rare, with the estimated frequency of anaphylaxis less than 0.05% in the general population.

It has been hypothesized that the high rate of reported penicillin allergies could be attributable to inaccurate allergy documentation. In patients with reported penicillin allergies, β-lactam antibiotics are typically avoided despite minimal cross-reactivity.

A team of pharmacists at Baptist Hospital in Miami, Florida, set out to evaluate the impact of a pharmacy-driven allergy assessment on improving allergy documentation and decreasing the use of non-β-lactam alternatives in patients with reported penicillin allergies. Their findings were presented in a poster session at the American Society of Health-Systems Pharmacists (ASHP) Midyear Clinical Meeting.

The study included patients who were admitted to the hospital with a reported penicillin allergy between February 6 and April 30, 2019. Patients who met inclusion criteria were interviewed about their allergy history to improve documentation and optimize antibiotic selection. Investigators also evaluated medical records to assess prior tolerance of β-lactam antibiotics.

The study team recommended treatment with a β-lactam antibiotic for patients with mild-to-moderate penicillin allergies and/or patients with prior tolerance of β-lactam antibiotics.

The primary end point was the number of patients with a reported penicillin allergy who switched to treatment with a β-lactam antibiotic. Investigators also looked at the cost of therapy recommended by the pharmacist compared with the agent initially selected by the prescriber, as well as prescribing trends before and after the allergy assessment and adverse events.

“Working together, pharmacists and other medical professionals can find alternatives that work for some patients. A multidisciplinary approach is key to optimizing therapy in patients with a reported penicillin allergy,” Rita Chamoun, PharmD, clinical staff pharmacist at Baptist Hospital of Miami and lead author of the study, said in a statement.

Sixty-three patients met inclusion criteria, and 43 of these individuals were switched from a non-β-lactam antibiotic to a β-lactam antibiotic. The investigators noted that prior β-lactam use was confirmed in 57% of patients and allergy documentation was updated in 83%.

The study authors also write that over a 3-month period, a potential cost savings of $21,468 was estimated.

“Conducting a pharmacy-driven allergy assessment led to improved allergy documentation, increased use of β-lactam antibiotics, and associated cost savings for patients with a reported penicillin allergy,” the authors concluded.

The abstract, “Improving Penicillin Allergy Documentation and its Effect on Antibiotic Prescribing at a Community Hospital,” was presented in a poster session on Monday, December 9, 2019, at the ASHP Midyear Clinical Meeting in Las Vegas, Nevada.
Speed of Processing Training Results in Significant Improvements for Individuals With HAND

BY ALEXANDRA WARD, MA

There is a vast unmet need for nonpharmacological treatment strategies to protect and improve cognitive function in the approximately 50% of adults living with HIV who experience HIV-associated neurocognitive disorder (HAND).

Speed of processing (SOP) training (a particular computerized cognitive training program) has been shown to improve neurocognitive function in older adults as well as adults living with HIV, and now investigators with the University of Alabama at Birmingham are evaluating whether SOP boosts the rate of visual information processing in adults with HAND. The results from the ongoing THINKFAST study were presented in a poster at the 2019 Association of Nurses in AIDS Care Conference (ANAC 2019).

In an interview at the conference, Contagion® sat down with presenting author David Vance, PhD, MGS, MA, associate dean for research at the School of Nursing at the University of Alabama at Birmingham, to discuss the data.

A cognitive battery test was used to determine whether participants (adults who were HIV+, 40 years of age and older) had HAND or borderline HAND. If they did, participants were then randomized to 1 of 3 study groups: (1) 10 hours of SOP training (n = 52); (2) 20 hours of SOP training (n = 54); or (3) 10 hours of internet (control) training (n = 53). Using the Useful Field of View test, investigators performed assessments at baseline and after testing to evaluate rates of visual processing.

Participants randomized into the 20-hour SOP training arm showed significant improvement (P < .001) in visual SOP after controlling at baseline for Useful Field of View performance. Participants in the 10-hour SOP training group showed the next best improvement.

"Other studies in older adults without HIV have also observed improvements in locus of control, driving safety, health-related quality of life, and self-rated health after receiving SOP training," investigators concluded. "As it is hypothesized that this cognitive training provides widespread neural activation in the brain that provides these transfer effects, the aim of the THINKFAST study will also examine whether improvements in these other therapeutic benefits are observed."

The poster, "Does Speed of Processing Training Improve Cognitive Efficiency in Adults With HIV-Associated Neurocognitive Disorder? Findings From the THINKFAST Study," was presented Thursday, November 7, 2019, at ANAC 2019 in Portland, Oregon.
Never Ignore a New Rash in a Patient With AIDS
A case of Kaposi sarcoma with immune reconstitution inflammatory syndrome.

BY NATALIE DICENZO; AMY FORRESTEL, MD; AND DAGAN COPPOCK, MD

Final Diagnosis: Kaposi Sarcoma

HISTORY OF PRESENT ILLNESS
The patient is a 28-year-old man with a history of newly diagnosed HIV/AIDS, complaining of a new rash on his abdomen and right arm. Initially, he presented to the emergency department with fever, weakness, and diarrhea and was admitted with sepsis. Upon admission, his serum creatinine level was 4.49 mg/dL and his serum sodium level was 117 mEq/L. A computed tomography scan of the abdomen and pelvis showed evidence of pancolitis. The patient was started on intravenous fluid and antibiotics. Although he was improving clinically, he left against medical advice, 1 day after admission. At that time, he was provided with prescriptions for levofloxacin and metronidazole, both of which he reported taking as directed.

Shortly after the patient left the hospital, he was contacted regarding a positive HIV screening test result. The following day, he presented to the Partnership Comprehensive Care Practice for a new patient visit. During that visit, he reported his diarrhea had improved, but he continued to complain of fever, weakness, nausea, coughing, wheezing, and dyspnea. On physical examination, and his temperature was 99.9°F. His blood pressure was 88/59 mm Hg, his heart rate was 153 bpm, with normal respiratory rate and oxygen saturation. Given his hemodynamic instability, he was returned to the hospital via emergency medical services.

During the patient's second hospital stay, he was started on broad-spectrum antibiotics. The result of his chest x-ray was negative. Blood and urine cultures were negative. CD4 count was 3 cells/µL. The patient underwent a lumbar puncture, and the cerebrospinal fluid was remarkable for a positive Venereal Disease Research Lab test result. His antibiotics were narrowed to intravenous penicillin for neurosyphilis, and he received the full 14-day course as an inpatient. He defervesced and became hemodynamically stable. In the hospital, the patient was started on emtricitabine, tenofovir disoproxil fumarate, and dolutegravir as well as trimethoprim/sulfamethoxazole for prophylaxis. He was also started on gabapentin for lower extremity paresthesias and was discharged with these medications.

One day after discharge, the patient returned to the clinic for a hospital follow-up. He reported 100% adherence to all medications since discharge. He reported control of his lower extremity symptoms with gabapentin. His gastrointestinal (GI) symptoms and cough had resolved. However, he now complained of a new skin rash on the left side of his chest, left shin, and right forearm that developed during the course of his hospitalization. He did not know exactly when the lesions had appeared, but to his knowledge, they had not changed in size since he first noticed them. He did not complain of pain, itching, tenderness to touch, swelling, or redness and denied skin lesions anywhere else on his body. The patient denied fever, chills, night sweats, shortness of breath, difficulty breathing, nausea, vomiting, abdominal pain, diarrhea, or constipation.

PHYSICAL EXAM
The patient was afebrile and hemodynamically stable with a normal respiratory rate and normal oxygen saturation. Body mass index was 19.8. His skin exam was significant for red-purple nodules on the left side of his torso, right forearm, and left shin (Figure 1 a-c). In general, the patient was in no acute distress. His eyes were anicteric with normal conjunctivae. Pupils were equal, round, and reactive to light. He was awake, alert, and oriented with a normal mood and affect. His oropharynx was without erythema, exudates, or patches. His neck was supple and symmetric, with no palpable thyroid abnormality or cervical lymphadenopathy. Lungs were clear to auscultation with normal respiratory effort. His heart sounds were regular in rate and rhythm without murmurs, rubs, or gallops. He had no peripheral edema and his abdomen was soft, nontender, and nondistended, with normal bowel sounds. He had full range of motion in all extremities, with diminished strength in his bilateral lower extremities and ataxia.

STUDIES
The patient’s laboratory studies, collected during the initial outpatient visit were significant for HIV genotype without resistance, a viral load of 899,000 copies/mL, and a CD4 count of 4 cells/µL. Hepatitis C and hepatitis A antibody test results were negative. The hepatitis B surface antigen was negative and the hepatitis B surface antibody was positive. The patient had a negative toxoplasmosis immunoglobulin test result. His rapid plasma reagin test result was positive with a 1:128 titer and the fluorescent treponemal antibody test result was positive. His white blood cell count was 8.5 x 10^3 cells/µL; hemoglobin, 10.2 g/dL; hematocrit, 32.7%; and platelets, 183 x 10^3 cells/µL. His alkaline phosphatase level was 51 U/L; aspartate transaminase, 82 IU/L; and alanine transaminase, 33 IU/L. The patient had elevated triglycerides and low high-density lipoprotein cholesterol.

DIAGNOSTIC PROCEDURES AND RESULTS
The patient’s initial HIV regimen was discontinued, and he was started on bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy). All other medications were continued. The patient was referred to a dermatologist for suspicion of Kaposi sarcoma (KS). Based on the lesions’ appearance, the dermatologist believed that the patient’s lesions were cutaneous KS, likely worsened in the setting of immune reconstitution inflammatory syndrome (IRIS), and a biopsy was ordered. The biopsy confirmed the diagnosis of KS.

TREATMENT AND FOLLOW-UP
The patient was referred to an oncologist, who recommended management of the KS with antiretroviral therapy (ART) alone. One month after discharge, the lesions had decreased in size significantly and the patient’s CD4 count had recovered to 128 cells/µL. An outpatient colonoscopy is being arranged, given his initial symptoms.

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Natalie Dicenzo is a fourth-year medical student at Drexel University College of Medicine. She plans to pursue a residency in obstetrics and gynecology and is interested in family planning, HIV, harm reduction, and trauma-informed care.

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DISCUSSION

KS is a low-grade vascular tumor associated with infection with human herpesvirus 8. It is the most common type of tumor in individuals infected with HIV, is considered an AIDS-defining illness, and is a significant cause of morbidity and mortality. Among patients with HIV who were infected with both HIV and human herpesvirus 8 at baseline, the 10-year probability of developing KS was approximately 50%.2 Since the introduction of ART for patients with HIV infection, the incidence of all opportunistic infections including KS has significantly declined along with overall mortality.3 However, initiation of ART has also been shown to be associated with reactivation of indolent infections, including KS, in a process known as IRIS. IRIS is thought to be the direct result of a partially restored immune system recognizing pathogens or antigens that were previously present, but clinically asymptomatic.1 Here, we report a case of KS presenting in a patient upon ART initiation.

Cutaneous disease is the most common form of KS. The lesions most often appear on the lower extremities, face, oral mucosa, and genitalia. Lesions are not painful or pruritic, may be pink, red, purple, or brown due to their vascularity, are most often papular, and range from several millimeters to centimeters in diameter. Visceral disease most frequently presents in the GI and respiratory systems and can occur even without cutaneous disease.2 GI lesions may be asymptomatic or cause weight loss, abdominal pain, nausea, vomiting, upper or lower GI bleeding, malabsorption, intestinal obstruction, and/or diarrhea.3 Screening for GI involvement involves testing for stool occult blood, whereas endoscopy is reserved for patients who test positive for occult blood or have GI symptoms.4 Pulmonary KS lesions can cause shortness of breath, cough, fever, hemoptysis, or chest pain and are screened via chest x-ray. Bronchoscopy is reserved for those with abnormal imaging test results and persistent respiratory symptoms with no other cause.5 Diagnosis of cutaneous and visceral disease should be confirmed by biopsy.5

Combination ART is recommended for treatment of all patients with AIDS-related KS, and since its introduction, the incidence of KS in patients who are HIV positive has significantly declined.4 However, initiating HIV treatment has also been shown to be associated with progression of KS in the setting of presumed IRIS.3 IRIS is described as an intense inflammatory reaction to foreign antigens caused by the rapid recovery of the immune system upon ART initiation in patients with very advanced HIV, who often have presented late for care and may have AIDS-defining opportunistic infections. Patients with IRIS present with an “unmasking” flare-up of an underlying previously undiagnosed opportunistic infection or a “paradoxical” worsening of a previously treated opportunistic infection that causes progressive clinical deterioration.4 This flare-up occurs despite markers of clinical improvement in HIV infection such as decreased viral load and increased CD4 count. IRIS is usually self-limiting but can cause significant morbidity and even mortality if not promptly recognized and treated.6 Significant proportions (7%-30%) of patients with KS have been shown to develop IRIS, presenting with increased KS inflammation and/or edema in the initial weeks after ART initiation or change in ART regimen following treatment failure.7 In a study by Bower et al,7 of 150 therapy-naive patients who presented with KS, 10 (6.6%) developed progression of KS within 3 to 6 weeks of starting ART. In a study by Yanik et al,8 the incidence of KS was highest during the first 6 months after ART initiation and was associated with a lower CD4 count at ART initiation. The same study showed that the incidence of KS dropped significantly with continued treatment, supporting the recommendation that patients should continue ART in the event of developing IRIS-associated KS. One study found that nearly 1 out of 3 patients with KS developed IRIS, with a higher incidence in those with visceral compared with cutaneous disease and that visceral IRIS-KS was associated with significant mortality.9 These authors hypothesized that the widely varied rates of IRIS-KS reported among studies may be in part due to the lack of a standardized definition or diagnostic criteria for IRIS. Factors associated with an increased risk of IRIS-associated KS in patients initiating ART for HIV include more extensive KS, a higher HIV viral load, and the use of ART without chemotherapy9 as well as the use of glucocorticoids.7

In addition to ART, treatment can involve local or systemic therapy. Local symptomatic therapy manages existing lesions, but it does not prevent the development of new lesions in untreated areas. This includes intralesional chemotherapy, which induces regression of injected tumors and is preferable for small lesions, as well as radiation therapy for treating larger or more numerous lesions.12 Systemic chemotherapy is indicated in the event of extensive cutaneous disease (>25 lesions), symptomatic visceral involvement, cutaneous KS that is unresponsive to local therapy, and patients with progressive disease in the setting of IRIS.10 Several small randomized trials have investigated the treatment of KS with chemotherapy plus ART versus ART alone. For example, chemotherapy plus ART has been shown to increase rates of disease regression and reduce rates of disease progression, especially in the treatment of severe or progressive disease. However, to date, no increase in survival or overall morbidity has been demonstrated.11,12

In conclusion, this case report represents an additional example of the well-described phenomenon of progressive KS in the setting of IRIS upon ART initiation in a patient with AIDS. In resource-rich settings, further research is needed to diagnose such patients earlier, before the development of KS. ▲

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