The critical importance of antimicrobial stewardship (AMS) to contain health care costs, combat antimicrobial resistance, and avoid unnecessary medication-related adverse events has become well accepted within the medical community. This widespread recognition has fostered the development of robust, outcome-driven, multi-disciplinary AMS programs across a wide range of health care settings, from small, rural community hospitals to large, tertiary health care systems.

Formal AMS programs have evolved and remained largely established within acute care hospitals given the prevalence of broad-spectrum antimicrobial use, higher rates of multidrug antimicrobial resistance, and risks of hospital-acquired infections. Though the majority of AMS efforts have been directed toward inpatient practices, 60% of all antibiotic expenditures in the United States occur in the outpatient setting. In the United States alone during 2013, 269 million antibiotic prescriptions were dispensed from outpatient pharmacies. It has been estimated that up

Acute Infections

More Than Surviving Sepsis: Everything Old Is New Again
By Lauren A. Irgner, PharmD, BCPS, BCCCP

Because of numerous failed attempts at novel or targeted therapies in sepsis over the past 20 years, investigators have been compelled to step back in time and repurpose old agents, including angiotensin II and ascorbic acid, for the treatment of sepsis and septic shock. Both medications have historically shown promise in animal shock models. However, it was not until the publication of recent clinical investigations in humans that investigators’ interest piqued regarding their use in refractory vasodilatory shock.

Emerging/Re-Emerging Infections

Tick, Tick, Tick: Vector-Borne Diseases Ramp Up
By Ilia Rochlin, PhD, and Alvaro Toledo, PhD

Pathogens transmitted by ticks cause the vast majority of vector-borne diseases in temperate North America, Europe, and Asia. In the continental United States, more than 95% of reported human cases of vector-borne diseases are caused by tick bites. Lyme disease may exceed 300,000 cases annually, about 10-fold higher than the number of reported cases, ranking it among the most common infections in the United States, second only to sexually transmitted diseases.

HIV/AIDS

What’s in the Pipeline?
By Rakshanda Akram, MD, and Joseph DeSimone Jr, MD

Although advances in combination antiretroviral therapy (ART) have greatly reduced morbidity and mortality associated with HIV, the pipeline for development of novel drug mechanisms and new agents in the existing drug classes remains full. This article presents a review of investigational drugs furthest along in development with propitious results in human subjects.
Indication

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

Important Safety Information

Boxed Warning: Post Treatment Acute Exacerbation of Hepatitis B

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

Contraindications

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

Warnings and Precautions

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

Treatment-naïve Study Designs:

The efficacy and safety of BIKTARVY for treatment-naïve adults were evaluated in Study 1489 and Study 1490. In Study 1489, a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥50 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=314) or ABC/DTG/3TC (n=315) once daily. In Study 1490, a phase 3, randomized, double-blind, active-controlled study, treatment-naïve adults with an eGFR ≥30 mL/min were randomized in a 1:1 ratio to receive either BIKTARVY (n=320) or FTC/TAF+DTG (n=325) once daily. The primary endpoint for both trials was the proportion of adults with HIV-1 RNA <50 copies/mL at Week 48. Secondary endpoints included efficacy, safety, and tolerability at Week 96.
BIKTARVY® combines the FTC/TAF® backbone with bictegravir, a novel and unboosted INSTI—for a powerful STR with a high barrier to resistance1,6

No Treatment-Emergent Resistance Associated With BIKTARVY Through Week 961,4,5,7

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

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

Powerful Efficacy in Treatment-Naïve Adults1-5,7

Results noninferior to comparators at Week 481-3

Virologic Response

Results noninferior to comparators at Week 964,5,7

Virologic Response

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

IMPORTANT SAFETY INFORMATION (continued)

Warnings and precautions (continued)

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

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

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

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

Drug interactions
- **Prescribing information**: Consult the full prescribing information for BIKTARVY for more information on Contraindications, Warnings, and potentially significant drug interactions, including clinical comments.
- **Enzymes/transporters**: Drugs that induce P-gp or induce both CYP3A and UGT1A1 can substantially decrease the concentration of components of BIKTARVY. Drugs that inhibit P-gp, BCRP, or inhibit both CYP3A and UGT1A1 may significantly increase the concentrations of components of BIKTARVY. BIKTARVY can increase the concentration of drugs that are substrates of OCT2 or MATE1.
- **Drugs affecting renal function**: Coadministration of BIKTARVY with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC and tenofovir and the risk of adverse reactions.

Dosage and administration
- **Dosage**: 1 tablet taken once daily with or without food.
- **Renal impairment**: Not recommended in patients with CrCl <30 mL/min.
- **Hepatic impairment**: Not recommended in patients with severe hepatic impairment.
- **Prior to or when initiating**: Test patients for HBV infection.
- **Prior to or when initiating, and during treatment**: As clinically appropriate, assess serum creatinine, CrCl, urine glucose, and urine protein in all patients. In patients with chronic kidney disease, assess serum phosphorus.

Pregnancy and lactation
- **Pregnancy**: There is insufficient human data on the use of BIKTARVY during pregnancy. An Antiretroviral Pregnancy Registry (APR) has been established. Available data from the APR for FTC shows no difference in the rates of birth defects compared with a US reference population.
- **Lactation**: Women infected with HIV-1 should be instructed not to breastfeed, due to the potential for HIV-1 transmission.

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

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

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

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

WARNING: POST TREATMENT ACUTE EXACERBATION OF HEPATITIS B

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

INDICATIONS AND USAGE

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

DOSEAGE AND ADMINISTRATION

Also see Warnings and Precautions and Use in Specific Populations.

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

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

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

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

CONTRAINDICATIONS

Also see Drug Interactions.

BIKTARVY is contraindicated to be co-administered with:
• dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events
• rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

ADVERSE REACTIONS

Also see BOXED WARNING and Warnings and Precautions.

In Adults with No ARV Treatment History:

The safety assessment of BIKTARVY is based on Week 48 data from two randomized, double-blind, active-controlled trials: 1489 (n=314) and 1490 (n=320), in HIV-1 infected, ARV treatment-naive adults. Through Week 48, 1% of subjects discontinued BIKTARVY due to adverse events, regardless of severity.

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

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

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

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

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

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS
Also see Dosage and Administration, Warnings and Precautions, and Adverse Reactions.

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

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

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

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

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

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

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

210251-GS-000 February 2018
Questions related to editorial content and submissions should be sent to Managing Editor Alexandra Ward, MA: AWARD@CONTAGIONLIVE.COM.
MULTIDRUG-RESISTANT INFECTIONS

Incorporating Culture-Independent Diagnostic Tests for Bloodstream Infections

These tests have the potential to transform patient care and antimicrobial stewardship, but they have not gained widespread acceptance, partly because of uncertainty over how to use them clinically.

BY CORNELIUS J. CLANCY, MD, AND M. HONG NGUYEN, MD

PEER EXCHANGE

Experts Survey the Landscape of HIV Screening, Treatment

BY GINA BATTAGLIA, PHD

MEETING COVERAGE


CASE STUDY

An Unusual Case of Testicular Swelling in a Patient With HIV

Being immunocompromised increases risk of rare Mycobacterium tuberculosis epididymo-orchitis.

BY JANE ABERNETHY, MD CANDIDATE; SUSAN A. INNIS, MD; LAUREL J. GLASER, MD, PHD; AND WILLIAM R. SHORT, MD, MPH

Follow Us

@ContagionLive @Contagion_Live

Contagion_Live Contagion_Live
EDITOR-IN-CHIEF’S LETTER

Achaogen—Canary in the Coal Mine or Developer of an Unwanted Product?

In April, the infectious diseases world received bad news when Achaogen, the developers of plazomicin (Zemdri), announced that they were filing for bankruptcy. The company’s demise serves notice that the recent boom in antibiotic development, which led to the incredible success of the Infectious Diseases Society of America’s 10 x ’20 drug development initiative, comes with a notorious asterisk.

I am still amazed by the success of the focus on the desperate need for new antimicrobials. The goal of “10 new antibiotics by 2020” was reached ahead of schedule, and the pipeline contains several new agents with possible approvals in 2019 and 2020. Push incentives, which encourage antibiotic development by helping to reduce research and development costs, have been effective in lowering barriers of entry to the market for new entities, such as plazomicin. With the abandonment of antibiotic development by nearly all large pharmaceutical companies, small companies such as Achaogen with limited resources are left as the driving forces of drug development. I am thankful for these small companies and their interest in creating new antibiotics, but they are vulnerable to setbacks and are dependent on venture capitalists in ways that more robust companies are not.

Achaogen faced several setbacks. Their prospective study of plazomicin for carbapenem-resistant Enterobacteriaceae (CRE) infections was Dogged by low enrollment, though it showed a significant difference in mortality, at the level of a 90% confidence interval. The US Food and Drug Administration ultimately did not grant the indication for CRE infections, leaving plazomicin with only the ubiquitous “complicated urinary tract infection” indication in its label. Although the results showed that fewer relapses occurred than with the β-lactam comparator, most of the pathogens studied were not the highly resistant organisms that clinicians would actually use the drug to treat.

On the other side, plazomicin is an aminoglycoside, and I think it should have been expected that any uptake of a new drug in this class would be slow. Aminoglycosides have well-known toxicity, which has probably become magnified in the minds of clinicians as more time passes from when they were commonly used. It was the third of 3 drugs with activity against CRE to be approved this decade, losing a race to establish a foothold in a limited market to 2 β-lactams with likely better safety margins (ceftazidime-avibactam and meropenem-vaborbactam). Plazomicin faced an uphill battle.

So what’s the lesson here? Now that we finally have new antibiotics, does the Achaogen story portend a future in which the companies fail after they are approved, or is it the tale of a company with an antibiotic that was a reach in the first place? I feel that it is a little bit of both. Other antibiotic companies with newly approved products have seen their stock prices drop and may face difficulty generating the investment they require. Achaogen’s fate more closely resembles the tale of a company with an antibiotic that was a reach in the first place? I feel that it is

Copyright © 2019 by Intellisphere, LLC. All rights reserved.

The content contained in this publication is for general information purposes only. The reader is encouraged to confirm the information presented with other sources. Contagion® makes no representations or warranties of any kind about the completeness, accuracy, timeliness, reliability, or suitability of any of the information, including content or advertisements, contained in this publication and expressly disclaims liability for any errors or omissions that may be presented in this publication. Contagion® reserves the right to alter or correct any error or omission in the information it provides in this publication, without any obligations. Contagion® further disclaims any and all liability for any direct, indirect, consequential, special, exemplary, or other damages arising from the use of misuse of any material or information presented in this publication. The views expressed in this publication are those of the authors and do not necessarily reflect the opinion or policy of Contagion®.
Optimal Vancomycin Dosing in Obese Patients: Moving Toward the AUC

BY ANDREW J. HALE, MD; DANIELA DIMARCO, MD; AND JOHN W. AHERN, PHARMD

Vancomycin is the principal antimicrobial agent used to treat methicillin-resistant *Staphylococcus aureus* (MRSA)—associated invasive infections. The 2011 Infectious Diseases Society of America (IDSA) MRSA guidelines recommend that vancomycin be dosed at 15 to 20 mg/kg/dose (actual body weight) every 8 to 12 hours, not to exceed 2 g per dose, in patients with normal renal function.1 These guidelines state that “trough vancomycin concentrations are the most accurate and practical method to guide vancomycin dosing...Monitoring of peak vancomycin concentrations is not recommended.” However, obesity presents a unique dilemma, as actual body weight dosing of vancomycin could lead to large, potentially nephrotoxic doses.

Various studies have attempted to address the conundrum of weight-based dosing in obese patients.2-5 Important to this debate is the concept that the actual pharmacokinetic goal in vancomycin dosing is an AUC (area under the curve) >400 mg∙h/L, which a vancomycin trough concentration of 15 to 20 mg/L approximates. However, this trough goal can result in significant variability in the AUC achieved, particularly in obese patients.6 With this in mind, it may be preferable to directly target the AUC, which reflects a patient’s total exposure to a drug over a given time, as opposed to using the trough concentration as a proxy measure.7

Crass and colleagues have provided a noteworthy pharmacokinetic study that helps address this issue (Table). The goal of the research was to develop an initial dosage strategy that produces an AUC that is efficacious (>400 mg∙h/L) but not toxic (defined by the authors as <700 mg∙h/L). They conducted a study using peak (1 hour after infusion) and trough (30 minutes prior to next infusion) levels in obese patients. Then, via Monte Carlo simulation, they identified doses that were predicted to meet AUC goals. A total of 346 nonpregnant adults receiving vancomycin for >48 hours were included, with body weights of 69.6 to 293.6 kg and body mass indexes of 30.1 to 85.7 kg/m². Patients with creatinine clearance <30 mL/min or serum creatinine increase of 0.5 mg/dL (or 50%) above baseline were excluded. Monte Carlo simulations with a goal AUC of >2400 mg∙h/L and <700 mg∙h/L were run with a wide variety of potential dosing schemes. Based on this simulation, the authors proposed a vancomycin dosage nomogram that can be safely used to achieve pharmacodynamic end points. This uses vancomycin clearance, which is calculated from a regression equation using Cockcroft-Gault variables, to calculate maintenance dosages that range from 500 mg every 24 hours to 2250 mg every 12 hours.

Implementing this would result in very few patients receiving maintenance vancomycin dosage in excess of 4.5 g per day. The authors make 3 major recommendations, the first of which is a shift away from empiric weight-based nomograms to nomograms specifically targeting AUC. The second suggestion is to perform subsequent therapeutic drug monitoring using the AUC via a peak and trough strategy rather than a trough-only approach. The final recommendation is that less is more; the algorithm led to significantly lower overall vancomycin doses than would have been used in dosing based on actual body weight yet had a higher chance of AUC target attainment. The study has several limitations: First, the patient clinical status and the indication to provide vancomycin were excluded. Additionally, monitoring of peak and trough serum vancomycin levels requires additional phlebotomy. Alternatively, Bayesian software programs can estimate the AUC with a single drug concentration.2 The exclusion of patients with fluctuating renal function is significant, as this is not an uncommon occurrence in hospitalized patients with severe infections and likely represents a group at increased risk of vancomycin nephrotoxicity. Most important, this is a modeling study, and prospective clinical trials in obese patients looking at hard outcomes—microbiological cure and drug-toxicity rates—are much needed. The authors have provided the opportunity to reassess current guidelines and traditional vancomycin therapeutic drug monitoring strategies. Their study aligns well with expected updated IDSA vancomycin guidelines, set to be released in 2019, which are predicted to advocate for AUC-based dosing.

References available at ContagionLive.com.

### HIGHLIGHTED STUDY

**Dosing Vancomycin in the Super Obese: Less Is More**

[Published online November 1, 2018]

Daptomycin Dosing in Obesity: Consideration for a Fixed-Dose Strategy

BY KATHERINE LUSARDI, PHARMD, BCPS-AQ ID, BCIDP

Daptomycin is an important antibiotic with action against methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococci (VRE). Per the US Food and Drug Administration labeling, daptomycin is recommended to be dosed based on total body weight (TBW). This involves pharmacokinetic assumptions, including that clearance (CL) and volume of distribution (Vd) change proportionately with TBW—making TBW dosing appropriate in obese patients. If CL doesn’t change proportionately in obese patients, a higher drug exposure can result. Currently varied recommendations for dosing go beyond the labeled 4 to 6 mg/kg/TBW dosing, up to 10 to 12 mg/kg/TBW. There is also literature that debates the correct weight that should be used for dosing, with some arguing for ideal body weight and others supporting an adjusted body weight in obese patients.

Butterfield-Cowper et al aimed to determine whether weight-based daptomycin dosing results in the same exposures in obese and nonobese patients. The investigators used serum level data from a prior study to build pharmacokinetic models and a Monte Carlo simulation. In a prior study, 7 patients were given a 4 mg/kg dose of daptomycin, with 8 serum samples taken 0.5 hours through 24 hours after dosing. This study analyzed those samples in a population pharmacokinetic (PK) model, stratifying by obese and nonobese patients. A 2-compartment model was used, with zero-order infusion and first-order elimination from the central compartment. The median PK estimates were compared (morbidly obese vs nonobese), and linear regression was used to find the association between the daptomycin CL and Vd and TBW.

A Monte Carlo simulation was used to model 2 doses, 6 mg/kg TBW/day and 500 mg/day, from which the steady-state area under the curve (AUC_{0-24ss}), maximum concentration (C_{max}), and minimum concentration (C_{min}) were determined.

For the PK analysis, obese and nonobese patients were well matched at baseline. Although differences were not found for CL, Vd, and terminal half-life, differences were detected in intercompartmental transfer rate constants, which were higher in the morbidly obese. Given that the rates were the same, because the Vd and CL did not change proportionally with weight, the obese patients would have higher drug exposure. To look at the drug exposure, the investigators used a Monte Carlo simulation.

For the Monte Carlo simulation, with the use of TBW dosing, the AUC_{0-24ss}, C_{max}, and C_{min} were 2-fold higher in morbidly obese patients compared with nonobese patients. The fixed-dose modeling showed similar AUC_{0-24ss}, C_{max}, and C_{min} between the groups. The study also looked at how the modeled dosing resulted in C_{min} over 24.3 mg/L, levels that were previously associated with creatine kinase elevation. The weight-based dosing exceeded 24.3 mg/L 10.8% of the time but just 2% in the fixed-dose model.

This is not the first study to identify higher daptomycin exposure in obese patients. Previously, it was shown that daptomycin dosing on actual body weight gave ~50% to 60% higher exposure in obese patients, which is similar to the 2-fold increased exposure seen in this present study. Studies that have examined the differences in exposure do have differences in how they control for renal function and other patient characteristics, making an apples-to-apples comparison between the findings difficult. What does appear to be consistent is that TBW dosing in obesity leads to increased exposure. Although therapeutically, we are pushing daptomycin doses higher and higher (>10 mg/kg TBW for VRE and MRSA), there can be concerns that the safety versus efficacy balance is affected.

Prior daptomycin studies also called into question the safety of daptomycin dosing in obese patients, with a more recent study identifying obesity (BMI >40) as an independent risk factor for myopathy and rhabdomyolysis.

Overall, although this study does not set a recommended fixed dose for obese patients, it does find that a fixed dose has merit for keeping drug exposure and safety profiles in obese patients similar to those of normal-weight patients. As daptomycin doses continue to be pushed for the sake of efficacy, studies for dosing strategies will need to keep pace and continue to fill the literature void.

References available at Contagionlive.com.

HIGHLIGHTED STUDY

A Fixed Versus Weight-Based Dosing Strategy of Daptomycin May Improve Safety in Obese Adults

Measles Cases Hit All-Time Annual High Since Elimination in United States
By Michaela Fleming

As of April 24, 2019, the United States has officially documented the greatest number of measles cases in a given year since the disease was declared eliminated in 2000.

The US Centers for Disease Control and Prevention (CDC) reported that 695 cases of measles have been detected across 22 states so far this year. The agency attributes the high counts primarily to a few large outbreaks on the West Coast in Washington State and on the East Coast in both New York City and New York State.

Outbreaks are also being monitored in New Jersey and Michigan and in Butte County, California. On April 22, the Los Angeles County Department of Public Health released a statement announcing an outbreak investigation following the confirmation of 4 measles cases, all linked to international travel.

According to the CDC, one of the largest barriers to controlling these outbreaks has been the spread of misinformation about the measles-mumps-rubella (MMR) vaccine. “We have to remember that one of the big messages that we have to get out there is that there isn’t any evidence that shows vaccines have long-term impact or adverse effects on people,” Christina Tan, MD, MPH, a state epidemiologist and an assistant commissioner with the New Jersey Department of Health, said in a recent segment of a Contagion® video program. “But you do run the risk of impacting your life with a vaccine-preventable disease. If you’re not vaccinated, you could have long-term sequelae related to, say, encephalitis or related to measles that will last you a lifetime.”

The Infectious Disease Physician Well Begins to Run Dry
By Saskia V. Popescu

There is a growing shortage of infectious disease physicians in the United States, according to The New York Times. In a time of increasing antimicrobial resistance, emerging infectious diseases, and continued outbreaks of vaccine-preventable diseases, these specialists are a critical asset to the medical and public health communities.

According to the report, from 2009 to 2017, hospitals able to fill all their adult infectious disease training programs fell by 40%. These gaps are reportedly due to challenges with insurance reimbursement and the fact that infectious disease physicians are consult-only providers. Ultimately, what does this shortage mean?

We rely on infectious disease physicians for managing complex antibiotic regimens with comorbidities. Moreover, they are often the only providers with experience in identifying these vaccine-preventable diseases.

Each year, 2 million Americans experience an antibiotic-resistant infection, 23,000 of whom will die. Poor antimicrobial stewardship is a critical part of resistance and, increasingly, poor prescribing practices are carried out by noninfectious disease physicians. As control measures against antimicrobial resistance struggle, the role of infectious disease physicians will grow, especially because they are often the only providers with the skills to use newer antimicrobial medications.

The shortage of infectious disease physicians has global implications in our fight against infectious disease threats, whether they originate from nature, laboratory accidents, or intentional acts of terror.

Investigators Link Receipt of PrEP at Study Enrollment With Rise of STIs
By: Contagion® Editorial Staff

As pre-exposure prophylaxis (PrEP) is recommended to populations at a higher risk of acquiring HIV, some clinicians have grown concerned that use of PrEP could be associated with an increased incidence of bacterial sexually transmitted infections (STIs).

New study findings by a team of Australian investigators published in the Journal of the American Medical Association show that, among gay and bisexual men, receipt of PrEP was linked with a higher incidence of STIs compared with before the study period.

A total of 2982 participants were enrolled across 5 clinics. Upon enrollment, the participants received daily oral tenofovir disoproxil fumarate and emtricitabine, along with quarterly HIV and STI testing and clinical monitoring. Each participant and had at least 1 follow-up visit.

The investigators found that during a mean follow-up of 1.1 years (3185 person-years), there were 2928 STIs diagnosed (1434 chlamydia cases, 1242 gonorrhea, 252 syphilis) among 1427 (48%) of the total participants. Overall, the STI incidence was 91.9 per 100 person-years, with 736 participants (25%) accounting for 2237 (76%) of all STIs.

According to multivariable analysis, younger age, greater number of sexual partners, and group sex were associated with greater STI risk, but condom use was not.

Based on preenrollment testing data that were available for 1378 participants, STI incidence increased from 69.5 per 100 person-years prior to the study to 98.4 per 100 person-years during follow-up (incidence rate ratio, 1.41; 95% CI, 1.29-1.56).

The investigators concluded that in gay and bisexual men using PrEP, STIs were highly concentrated among a subset of study participants. Additionally, receipt of PrEP at enrollment was associated with an increased incidence of STIs compared with preenrollment.
Peggy Lillis Foundation: Creating Public Awareness and Engagement to Fight C diff

By Alexandra Ward, MA

The Peggy Lillis Foundation brought together 100 leaders in April in Washington, DC, for its fourth National C diff Summit and Lobby Day.

The foundation was started after the 2010 death of a 56-year-old kindergarten teacher who died from complications of a Clostridioides difficile infection.

Contagion sat down with Christian Lillis, executive director of the Peggy Lillis Foundation to learn about the organization’s recent efforts, what obstacles it’s facing, and how providers can help in the fight against C diff.

CONTAGION®: WHAT ARE THE MOST URGENT PRIORITIES WHEN IT COMES TO REDUCING RATES OF C DIFFICILE INFECTION?

Lillis: For us, it all comes down to public awareness and engagement. A challenge with infectious diseases, as opposed to chronic ones, is that they are mostly acute. People either get well or they die. If they have a mild C diff infection, they generally just go about their lives. Of course, when someone perishes from an infection, they’re no longer present to raise awareness or advocate for better policies. We would like to see federal and state agencies taking an active role in raising awareness of preventable infections.

WHAT IS THE MOST IMPORTANT MESSAGE FOR HEALTH CARE PROVIDERS WHO ARE ON THE FRONT LINES OF C DIFFICILE TREATMENT?

C diff and other antibiotic-resistant infections are largely preventable if we all do our part, and work together: health care workers, policymakers, and patients and caregivers. We need real investment in terminal cleaning that ensures people responsible for that work are well trained and compensated. We also need health care workers to be open to patients and caregivers having greater participation in our care.

WHO Updates 2019-2020 Influenza Vaccine Recommendations

By Einav Keet

The World Health Organization (WHO) announced the recommendation of a new influenza A (H3N2) component for the 2019-2020 seasonal flu vaccine.

Because of recent changes in the proportions of genetically and antigenically diverse A (H3N2) viruses, in February, the members of the WHO Global Influenza Surveillance and Response System postponed the recommendation of the A (H3N2) component.

On March 21, WHO released an addendum to the February report with a decision to recommend an A/Kansas/14/2017 (H3N2)–like virus for use in flu vaccines during the northern hemisphere’s 2019-2020 flu season. The new component replaces an A/Singapore/INFIMH-16-0019/2016 (H3N2)–like virus in use in the northern hemisphere flu vaccine for the 2018-2019 flu season.

In an interview with Contagion®, WHO spokes-person Christian Lindmeier explained the delay and the ultimate decision. "Influenza A (H3N2) viruses have presented an increasing challenge for vaccine virus selection due to frequent changes in the virus and difficulties in generating candidate vaccine viruses for use in egg-based manufacturing," Lindmeier said, noting that experts reviewed data on virus surveillance, antigenic characterization, and virus fitness forecasts and identified multiple cocirculating influenza A (H3N2) virus groups before making the recommendation.

PrEP May Ease Fears of HIV Risk, Study Results Suggest

By Jonna Lorenz

Pre-exposure prophylaxis (PrEP) use may have psychological benefits for gay and bisexual men, according to results from a recent study.

"For many gay and bisexual men, the fear of HIV is still very real, and this fear may be negatively impacting their mental health," Thomas Whitfield, a graduate student at City University of New York and first author of the study, told Contagion®. "PrEP may put some of these men’s minds at ease and allow them to enjoy their sex lives better."

The study, published in The Journal of Sex Research, involved more than 1000 gay and bisexual men who completed a questionnaire before and after beginning a PrEP regimen.

The results found an average decrease of sexual anxiety by 0.27 points when participants were on PrEP compared with before treatment. No significant changes were reported in sexual esteem or satisfaction.

"To me, one of the most important aspects of these findings is that PrEP might finally provide a turning point for sexual minority men who have spent decades worrying about sexual risk," senior author Jonathon Rendina, PhD, MPH, director of quantitative methods at the Center for HIV Educational Studies & Training at Hunter College of City University of New York, told Contagion®.

The study noted that anxiety can persist for months and that some men avoid HIV testing for fear of a positive result. Addressing that anxiety may be a reason in itself to consider PrEP.

“A lot of focus has been put on HIV risk criteria for starting PrEP, which I think makes sense, but these findings also suggest that simply being worried about HIV risk may be reason enough to put a patient on PrEP,” Rendina said. “Assuming we can get access and costs figured out—which is a major assumption—we know PrEP is safe, it’ll reduce any risk should it eventually arise, and it might be what they need to reduce their worries about sex regardless of whether they are objectively at risk.”

Along with highlighting other reasons to consider PrEP, the study suggests that patients may benefit from broader conversations with providers that include psychological aspects.

Further studies are needed to replicate the results and determine whether anxiety continues to decrease over even longer periods of time, Whitfield said. Further investigations also are needed to examine whether psychological benefits may increase uptake of PrEP.

CONTAGION®. © 2020 Contagion Live, LLC. All rights reserved.
In 2016, the US Centers for Disease Control and Prevention estimated that 45% of all people living with HIV in the United States are over age 50.¹ This patient population continues to age due to advances in HIV antiretroviral therapy (ART); with tolerable, highly effective pharmacotherapy options, there is a shift in focus to minimize long-term toxicities of lifelong ART.

**CLINICAL TRIALS**

This new 2-drug regimen (2DR) comprises dolutegravir and lamivudine (DTG/3TC, [Dovato]) coformulated into 1 daily tablet. It received US Food and Drug Administration (FDA) approval on April 9, 2019, for treatment of HIV in adults with no prior ART history and no known resistance to the individual components. It is the second FDA-approved 2DR (it follows dolutegravir/rilpivirine [Juluca]) but the first approved for use in HIV treatment-naïve patients with no known mutations to the individual components. This medication, though not yet included in HIV treatment guidelines, changes what we know about combination ART and the historically recommended use of at least 3 drugs from at least 2 classes.

DTG/3TC received its approval after the completion of 2 identical phase 3 studies: GEMINI 1 and GEMINI 2.² Both studies are multicenter, double-blind, randomized, noninferiority, phase 3 trials that enrolled a total of 1441 patients from 192 centers across 21 countries. Participants were treatment-naïve individuals living with HIV who were 18 years or older with an HIV viral load less than 500,000 copies/mL. Patients were excluded if they had preexisting drug resistance mutations to nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs, or protease inhibitors. Women of childbearing potential were included if they were not pregnant or lactating and were using approved contraception. Patients were randomly assigned (1:1) to receive a 2-drug regimen of dolutegravir plus lamivudine (as 2 tablets) or a 3-drug regimen (3DR) of dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (as 2 tablets). Both the participants and the investigators were blinded to treatment assignment, made possible by over-encapsulating the lamivudine and emtricitabine/tenofovir disoproxil fumarate. The primary objective of the GEMINI studies was to prove noninferior virological efficacy of the 2DR when compared with guideline-recommended 3-drug ART.

The pooled analysis of the intention-to-treat-exposed populations of the GEMINI trials showed that dolutegravir/lamivudine met its primary endpoint, with 91% of patients achieving HIV-1 RNA of less than 50 copies/mL by week 48 compared with 93% of patients in the dolutegravir plus emtricitabine/tenofovir disoproxil fumarate group. Of the 10 (<1%) participants (6 in the 2DR group, 4 in the 3DR group) who met criteria for virological withdrawal, defined as a decrease of HIV-1 RNA of less than 1 log₁₀ copies/mL decrease from baseline or HIV-1 RNA greater than 200 copies/mL after week 24 or confirmed rebound of HIV-1 RNA greater than 20 copies/mL, no patients developed any treatment-emergent resistance as confirmed by genotypic testing.

**ADVERSE REACTIONS AND PRECAUTIONS**

Pooled analysis of the GEMINI 1 and 2 trials shows low incidence of reported drug-related adverse events (AEs), with
Per the labeling of DTG/3TC, other precautions include patients coinfected with HIV and hepatitis B virus (HBV), hypersensitivity reactions, hepatotoxicity, lactic acidosis and severe hepatomegaly with steatosis, and immune reconstitution syndrome. When managing patients who are coinfected with HIV and HBV, an additional agent such as entecavir or tenofovir should be added on for treatment of HBV if using DTG/3TC for HIV treatment. HBV resistance to lamivudine monotherapy reaches 90% at 4 years and is no longer a preferred antiviral therapy for HBV treatment. Other more serious AEs, like lactic acidosis and severe hepatomegaly with steatosis, is a precaution that is historically associated with nucleoside analogues but not commonly seen with currently used NRTIs like lamivudine.

Risk of drug–drug interactions with DTG/3TC is minimal compared with other antiretroviral (ARVs) such as boosted-protease inhibitor-based therapies. Common drug interactions seen with the dolutegravir component of DTG/3TC include metformin (increased metformin levels) and polyvalent cations (decreased dolutegravir levels). More serious and less commonly seen drug interactions can occur with dofetilide (increased dofetilide levels) and rifampin (decreased dolutegravir levels; less commonly seen in the United States).

**SWITCH FROM TRIPLE TO DUAL THERAPY**

Studies prior to the GEMINI 1 and 2 trials evaluated dolutegravir/lamivudine as a switch strategy for treatment-experienced patients who have been virally suppressed. DTG/3TC, however, was not studied in this patient population and is indicated only for treatment-naïve patients. De-escalation or switch studies have all been successful; however, patient sample sizes were small, and not all studies were prospective, randomized controlled trials.1-3 Future larger studies to confirm the results are warranted before using DTG/3TC as a simplification or switch strategy.

**PLACE IN TREATMENT**

Currently, the US Department of Health and Human Services HIV guidelines list DTG/3TC as an option for “initial therapy when abacavir, tenofovir alafenamide, and tenofovir disoproxil fumarate cannot be used or are not optimal.” This recommendation has not been updated since DTG/3TC was approved by the FDA. That approval gave a 2DR option for the initial treatment of patients newly infected with HIV without a history of ART or drug-resistant mutations affecting dolutegravir or lamivudine. With less HIV ARV drug exposure, there is the benefit of fewer long-term toxicities. Additionally, if half the potentially eligible treatment-naïve patient in the United States were initiated on DTG/3TC, the associated ART cost savings would amount to more than $500 million over 5 years.6

HIV treatment has made significant progress, from past regimens consisting of upward of 10 tablets in the mornings and evenings to the current availability of single-tablet regimens. This lowers the ART pill burden to 1 tablet daily, with even some HIV treatment regimens containing just 2 active agents. This shift toward 2DR for initiation and maintenance of HIV changes how we may approach HIV treatment moving forward. DTG/3TC is an effective regimen for patients with new HIV diagnoses who have no treatment or resistance history. Some advantages and disadvantages comparing it with current recommended initial regimens for most people with HIV can be found in the Table. When 2 drugs can do the same job as 3, why are we still using 3? ▲

References are available at ContagionLive.com.

---

**TABLE.** Advantages and Disadvantages of Dovato (DTG/3TC) Compared With Other Recommended Initial Regimens

<table>
<thead>
<tr>
<th>Drug classes</th>
<th>DTG/3TC</th>
<th>BIC/FTC/TAF</th>
<th>DTG/ABC/3TC</th>
<th>DTG + FTC/TDF OR FTC/TAF</th>
<th>RAL + FTC/TDF OR FTC/TAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily pill burden</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Once daily</td>
<td>RAL; twice daily</td>
</tr>
<tr>
<td>HBV efficacy</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Renal function cutoff for use</td>
<td>CrCl &lt;50 mL/min</td>
<td>CrCl &lt;30 mL/min</td>
<td>CrCl &lt;50 mL/min</td>
<td>If using TDF: CrCl &lt;50 mL/min</td>
<td>If using TDF: CrCl &lt;50 mL/min</td>
</tr>
<tr>
<td>Safety in pregnancy</td>
<td>Possible risk</td>
<td>Unknown</td>
<td>Possible risk</td>
<td>Possible risk</td>
<td>Safe</td>
</tr>
<tr>
<td>Other: HLA-B*5701 testing</td>
<td>No</td>
<td>No</td>
<td>Yes, required</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

ABC indicates abacavir; BIC, bictegravir; CrCl, creatinine clearance; DTG, dolutegravir; FTC, emtricitabine; HBV, hepatitis B virus; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RAL, raltegravir; HD, high dose; TAF, tenofovir alafenamide; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

126 (18%) in the 2DR group and 169 (24%) in the 3DR group. Commonly reported AEs were similar between the 2 groups, with headache, diarrhea, and nasopharyngitis being the 3 most common. Changes in renal and bone turnover biomarkers, which can be attributed to tenofovir disoproxil fumarate, were, not surprisingly, more favorable in the 2DR group compared with the 3DR group. Suicidal ideation and behavior was reported in 2% in both groups—17 participants in the 2DR group and 12 in the 3DR group. Of these patients who reported these toxicities, 13 (76%) and 7 (58%), respectively, had a positive history of depression or suicidal behavior at baseline.
ANGIOTENSIN II

Management of distributive shock focuses on early and adequate fluid resuscitation, timely antibiotic administration, and initiation of catecholamine (eg, norepinephrine, epinephrine) and/or noncatecholamine (eg, vasopressin) vasopressor therapy.1 Given the potential for dose-dependent adverse effects (AEs) from catecholamine-based vasopressor therapy (eg, tachycardia), noncatecholamine therapy has potential clinical benefits.

One promising therapeutic strategy involves using the renin-angiotensin-aldosterone system (RAAS) to generate noncatecholamine vasopressor effects. Angiotensin II binds a number of G-protein coupled receptors, including angiotensin II receptor type 1 (AGTR1), which notably results in vasoconstriction, aldosterone secretion, sodium and water retention, and vasopressin release.2

In 1962, Derrick and colleagues described the use of angiotensin II in 10 patients with shock who were unresponsive to standard catecholamine therapy. The authors commented that angiotensin II consistently increased blood pressure and reduced heart rate with no apparent AEs.3 Despite use in early clinical studies, synthetic human angiotensin II only gained US Food and Drug Administration approval in December 2017 after more robust clinical evaluation.

The Angiotensin II for the Treatment of High-Output Shock (ATHOS-3) trial randomized 344 patients with persistent vasodilatory shock despite at least 25 mL/kg fluid resuscitation in 24 hours and high-dose vasopressor therapy (>0.2 mcg/kg/min of norepinephrine equivalent) for >6 hours to receive titratable angiotensin II vs placebo in addition to background vasopressor therapy. Importantly, patients were excluded if they did not have adequate cardiac function (cardiac index of >2.3 L/min/m² or central venous oxygen saturation >70% with central venous pressure >8 mm Hg), had active bleeding, or were receiving high-dose glucocorticoid therapy.3

Patients included in the ATHOS-3 trial had a high risk of death, as demonstrated by a baseline median acute physiology and chronic health evaluation II score of 28. Significantly more patients in the angiotensin II group (69.9%) achieved the primary end point of mean arterial pressure (MAP) >75 mm Hg or MAP increase of >10 mm Hg from baseline at hour 3 compared with placebo (23.4%; OR, 7.95; 95% CI, 4.76-13.3; P < .001).4 A post hoc analysis demonstrated a significant increase in 28-day survival with angiotensin II (53.2%) versus placebo (29.6%; HR, 0.515; 95% CI, 0.304-0.817; P = .0118).5

Based on the findings from this study, the clinician might be eager to incorporate angiotensin II in the treatment of refractory vasodilatory shock. However, important safety issues must be considered. A total of 12.9% of patients receiving angiotensin II experienced an arterial or venous thromboembolic (VTE) event compared with 5.1% in placebo.6 Angiotensin II may cause development of thrombotic events through activation of AGTR1, which induces expression of plasminogen activator inhibitor-1 and causes platelet aggregation.2 Therefore, patients using angiotensin II should receive concomitant VTE prophylaxis. If there is a contraindication to prophylaxis, the risk–benefit ratio must be considered before initiating therapy with angiotensin II.

Additionally, patients with reduced cardiac output were excluded from the ATHOS-3 study because of concern that pure vasoconstrictor therapy may result in a reflexive bradycardia, thereby worsening cardiac output and potentially increasing mortality.7 In general, routine use of invasive cardiac monitoring has declined because of changes in clinical practice. However, patients with vasodilatory shock may progress to low-output states, and the subsequent impact of angiotensin II is unknown. Therefore, invasive cardiac monitoring may be considered in these patients.7

More Than Surviving Sepsis: Everything Old Is New Again

Investigators are dusting off angiotensin II and ascorbic acid for renewed use in treating sepsis and septic shock.

BY LAUREN A. IGNERI, PHARMD, BCPS, BCCCP

LAUREN A. IGNERI, PHARMD, BCPS, BCCCP

Ignieri is the critical care clinical pharmacy specialist at Cooper University Health Care in Camden, New Jersey. She earned her PharmD at Rutgers University in Piscataway, New Jersey, and went on to complete her PGY-1 at Temple University Hospital in Philadelphia, Pennsylvania, and PGY-2 critical care specialty residency at Philadelphia College of Pharmacy at University of the Sciences and Cooper University Hospital.
ACUTE INFECTIONS

Current clinical practice guidelines recommend the addition of vasopressin or epinephrine to first-line vasopressor therapy with norepinephrine. Angiotensin II costs approximately 6 times more than vasopressin per day when given at standard doses for septic shock. The significant increase in cost must be considered when deciding to use this agent for refractory vasodilatory shock.

Given these concerns, angiotensin II is likely a third-line vasopressor for the treatment of vasodilatory shock at this time. As more real-world, clinical experience is gained with this agent, it may prove to have a niche for refractory vasodilatory shock.

ASCORBIC ACID (VITAMIN C)

In addition to its role in a number of other biochemical interactions, ascorbic acid (vitamin C) serves as a cofactor for the enzymes peptidylglycine β-amidating monooxygenase and dopamine β-hydroxylase, which are responsible for production of vasopressin and norepinephrine in the adrenal gland. Although vitamin C is endogenously synthesized in most mammals, humans require adequate dietary consumption. Vitamin C deficiency is well described in patients with sepsis and may account for reduced production of these endogenous catecholamines.

Vitamin C deficiency has been shown to play an important role in animal models of sepsis. In 1971, vitamin C-deficient guinea pigs demonstrated a higher mortality compared with a replete cohort in an endotoxin shock model. L-gulono-γ-lactone oxidase (GULO) is a pivotal enzyme in the biosynthesis of vitamin C in mice. In a cecal ligation and puncture murine sepsis model, GULO-knockout mice had a reduced survival fraction compared with wild-type mice, but survival was improved in the GULO-knockout cohort that received vitamin C.

Despite these findings, there have been discordant outcomes in human clinical trials of vitamin C. Until recently, few single-center studies demonstrated reductions in sepsis and inflammatory biomarkers, Sequential Organ Failure Assessment (SOFA) scores, and mortality with administration of vitamin C in patients with sepsis. In a prospective study of 24 patients with septic shock randomized to vitamin C 50 mg/kg intravenous (IV) daily, 200 mg/kg IV daily, or placebo daily for 4 days, patients receiving either dose of vitamin C had reductions in SOFA scores, C-reactive protein, and procalcitonin. Another study of 28 patients with septic shock randomized to vitamin C 25 mg/kg IV every 6 hours for 72 hours had significant reductions in dose and duration of vasopressor therapy and 28-day mortality compared with placebo. These results laid the groundwork for future investigations.

Marik and colleagues enrolled 94 patients with severe sepsis or septic shock into a before-and-after study of usual care compared with usual care plus the combination of vitamin C 1.5 g IV every 6 hours (4 days), thiamine 200 mg every 12 hours (4 days), and hydrocortisone 50 mg every 6 hours (7 days, followed by a 3-day taper). A significant reduction in mortality was seen in the control (40.4%) versus intervention (8.5%) groups (P < .001), as well as duration of vasopressor therapy, SOFA scores, need for renal replacement therapy, and increased procalcitonin clearance. Although there were notable limitations, including the observational study design and use of combination therapy with hydrocortisone, a drug known to improve outcomes in septic shock, nearly 60% of patients in the control group also received hydrocortisone, signaling that the intervention effects were not attributable entirely to corticosteroid administration. Because cortisol levels were not reported, it is unknown whether patients had adrenal insufficiency at baseline.

Although no safety issues have been identified with high-dose vitamin C to date, questions regarding its place in therapy remain. As of April 10, 2019, there were 28 clinical trials listed on ClinicalTrials.gov for ascorbic acid/vitamin C in sepsis or toxemia. Select ongoing studies are described in the Table. A number of studies will evaluate vitamin C monotherapy, as well as the combination with thiamine and hydrocortisone in severe sepsis and septic shock. A pharmacokinetic evaluation may provide insight on the optimal dosing. The Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS) study is projected to be the most robust evaluation of vitamin C in sepsis treatment, with its randomized, double-blind study design and planned enrollment of 2000 participants. These future studies may elucidate the role of vitamin C as part of the treatment of sepsis and septic shock.

In conclusion, recent clinical data for the use of angiotensin II and vitamin C in patients with septic shock generate optimism for improving clinical outcomes. As we begin to dust off these old therapies, clinicians must realize that future clinical experience and investigations will likely better define their roles in the treatment of septic shock.

References are available at ContagionLive.com.

### TABLE. Select Ongoing Studies of Vitamin C in the Treatment of Sepsis and Septic Shock

<table>
<thead>
<tr>
<th>STUDY NAME (SPONSOR[S])</th>
<th>INTERVENTION</th>
<th>PRIMARY OUTCOME</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Dose Vitamin C in Severe Sepsis (Christiania Care Health Services)</td>
<td>Vitamin C 67 mg/kg IV every 8 hours (200 mg/kg/day) for 72 hours vs placebo</td>
<td>SOFA score at 4 days</td>
<td>Completed November 2017</td>
</tr>
<tr>
<td>Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury (CITRIS-ALI) (Virginia Commonwealth University, NHLBI)</td>
<td>Vitamin C 50 mg/kg IV every 6 hours (200 mg/kg/day) for 96 hours vs placebo</td>
<td>• SOFA score at 96 hours</td>
<td>Completed January 2018</td>
</tr>
<tr>
<td>Pharmacokinetics of Two Different High-Dose Regimens of Intravenous Vitamin C in Critically Ill Patients (VU University Medical Center, Netherlands)</td>
<td>• Vitamin C 1 g IV every 12 hours (total 4 g) • Vitamin C 5 g IV every 12 hours (total 20 g) • Vitamin C continuous infusion x 48 hours (total 4 g) • Vitamin C continuous infusion x 48 hours (total 20 g)</td>
<td>• Vitamin C plasma concentrations at baseline, 48, 96, 168 hours</td>
<td>Completed November 2016</td>
</tr>
<tr>
<td>Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Trial (Beth Israel Deaconess Medical Center)</td>
<td>Vitamin C 1.5 g every 6 hours, thiamine 100 mg every 6 hours, hydrocortisone 50 mg every 6 hours x 4 days vs placebo</td>
<td>Change in SOFA score at 72 hours</td>
<td>Recruiting; 200 participants</td>
</tr>
<tr>
<td>Vitamin C, Thiamine, and Steroids in Sepsis (VICTAS) (Emory University)</td>
<td>Vitamin C 1.5 g every 6 hours, thiamine 100 mg every 6 hours, hydrocortisone 50 mg every 6 hours x 4 days (or ICU discharge) vs placebo</td>
<td>Vasopressor-free and ventilator-free days at 30 days</td>
<td>Recruiting; 2000 participants</td>
</tr>
<tr>
<td>Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in Sepsis, (ORANGES) (Community Medical Center, Tomis River, NJ)</td>
<td>Vitamin C 1.5 g every 6 hours, thiamine 200 mg every 12 hours, hydrocortisone 50 mg every 6 hours x 4 days (or ICU discharge) vs placebo</td>
<td>Hospital mortality</td>
<td>Recruiting; 140 participants</td>
</tr>
</tbody>
</table>

ICU indicates intensive care unit; IV, intravenous; SOFA, NHLBI, National Heart, Lung, and Blood Institute; SOFA, Sequential Organ Failure Assessment.
Tick, Tick, Tick: Vector-Borne Diseases Ramp Up

Infections transmitted by these bloodsucking species are on the rise worldwide.

BY ILIA ROCHLIN, PHD, AND ALVARO TOLEDO, PHD

Ticks transmit a variety of infectious agents including viruses, bacteria, and protozoan parasites (see online Table). Tick-borne diseases are usually characterized by short incubation times and rapid onset of acute systemic symptoms such as chills, sweating, headache, myalgia, arthralgia, malaise, nausea, and vomiting. Many diseases are biphasic, with several days of illness followed by remission and then more severe acute symptoms. Tick-borne diseases range from brief and self-limited to protracted, relapsing, and life-threatening illnesses, depending on the pathogen implicated, as well as the immune status of the patient.

Treatment of tick-borne diseases is a complex and sometimes controversial subject covered in numerous publications and guidelines. Generally, treatments vary based on the type of pathogen but are similar within each group. For viral tick-borne pathogens, avoiding tick bites is the best and often only available course of action. The most notable exception is tick-borne encephalitis virus, for which several safe and effective vaccines are used in Europe, Russia, and China. All require several doses followed by booster vaccinations every 3 to 5 years to maintain immunity. Tick-borne bacterial diseases are typically treated with tetracyclines. Doxycycline is commonly recommended as the treatment of choice for Lyme disease, human granulocytic anaplasmosis, human monocytotropic ehrlichiosis, and Rocky Mountain spotted fever. The recommended therapy for babesiosis, a tick-borne disease caused by a protozoan parasite, consists of atovaquone and azithromycin or clindamycin and clindamycin combinations.

VIRAL

Tick-borne encephalitis (TBE) complex (Flavivirus) is arguably the most significant viral infection transmitted by ticks, with more than 10,000 hospitalized cases per year, mainly in Europe, Russia, China, and Japan. Members of this group, such as TBE virus, louping-ill virus, and Powassan virus.
(POW), cause encephalitis.\textsuperscript{11} Omsk hemorrhagic fever is febrile with hemorrhagic symptoms,\textsuperscript{13} whereas Kyasanur Forest disease (KFD) causes both encephalitis and hemorrhages.\textsuperscript{13} TBE virus is emerging in parts of Europe due to climate and land use changes.\textsuperscript{14} However, the most significant recent trends represent the rise of TBE group viruses outside the typical temperate Eurasian range.\textsuperscript{15} In North America, POW virus is now considered an emerging disease,\textsuperscript{16} and on the Indian subcontinent, KFD is on the rise.\textsuperscript{14}

Bunyavirales (formerly Bunyaviridae) is another important group and perhaps the most daunting among the emerging tick-borne viruses. Crimean-Congo hemorrhagic fever virus (CCHFV), associated with more than a dozen tick species and multiple wildlife hosts, is the most geographically widespread of all tick-borne viruses in Eurasia and Africa.\textsuperscript{17,18} CCHFV and its transmission cycles are well characterized and understood; nonetheless, it remains an important emerging pathogen over much of its range.\textsuperscript{17,18} CCHFV is a disease of the nervous system, with neurological symptoms preceding more dramatic hemorrhagic symptoms.\textsuperscript{19} The incubation period is short, with rapid onset of a severe headache, dizziness, neck pain, and vomiting.\textsuperscript{17,19} After a few days, hemorrhagic symptoms on mucous membranes and skin, as well as external and internal bleeding, are common. Mortality can be very high (at least 30%), especially when nosocomial transmission occurs.\textsuperscript{17,18}

Unlike the long epidemiological record of CCHFV, closely related viruses from a different Bunyavirales genus, Phlebovirus, are among the most recent but noteworthy emerging pathogens. A new Phlebovirus transmitted by ticks, first described in 2009, causes severe fever with thrombocytopenia syndrome (SFTS) characterized by fever, thrombocytopenia, leukopenia, and gastrointestinal symptoms.\textsuperscript{19,21} There are approximately 1000 cases per year of SFTS virus (SFTSV), with 6% to 30% mortality in China, as well as sporadic cases in Japan and South Korea.\textsuperscript{19,20} The Asian longhorned tick (Haemaphysalis longicornis) is the main vector.\textsuperscript{21} Until recently, this species was present only within its native range in East Asia (China, Korea, Japan), as well as in Australia, New Zealand, and some Pacific Islands, where it was previously introduced.\textsuperscript{22} In 2017, an established Asian longhorned tick population was found in New Jersey,\textsuperscript{22} quickly followed by several other states. Based on climatic factors, \textit{H longicornis} has the potential to spread to the eastern United States and parts of the West Coast.\textsuperscript{22} Particularly suitable for this species are areas of the Midwestern United States, where another novel Phlebovirus, the Heartland virus, which is closely related to SFTSV, was isolated in 2009 from 2 patients, and several more confirmed cases presented over the following years.\textsuperscript{25} Symptoms are similar to those of other tick-borne diseases, including fever, leukopenia, and thrombocytopenia. However, this virus can also cause rapidly fatal, widely disseminated infection, with severe shock and multisystem organ failure.\textsuperscript{26,22}

**BACTERIAL**

Lyme borreliosis, the most important vector-borne disease in the northern hemisphere, is caused by various strains or genospecies of \textit{Borrelia burgdorferi}.\textsuperscript{1,17,28} A new member of this group, \textit{Borrelia mayonii}, was recently described in patients and ticks from the upper Midwest.\textsuperscript{29} Interestingly, \textit{B mayonii} was found in high numbers in patients’ blood, which is atypical in individuals infected with other genospecies of \textit{B burgdorferi}. Some \textit{Borrelia} species cause tick-borne relapsing fever, which is usually transmitted by soft ticks.\textsuperscript{30} One exception is \textit{Borrelia miyamotoi}, which is vectored by the same \textit{Ixodes} species that transmit Lyme borreliosis. The number of diagnosed human cases is low, in part because the disease generally runs its course like a limited febrile illness.\textsuperscript{31} Usually, patients experience an influenza-like illness, with high fever, leukopenia, and thrombocytopenia, followed by a relapse about a week later in about 10% of patients.\textsuperscript{31,32}

Another important group, tick-borne rickettsial diseases such as spotted fevers and tick typhus, have a worldwide distribution with many emerging pathogens.\textsuperscript{13,25,24} In the United States, Rocky Mountain spotted fever is the most common (several thousand cases) and lethal (<20% mortality) rickettsiosis, causing frequent hospitalizations and even death in untreated patients.\textsuperscript{44} Two less severe rickettsial diseases are now recognized in the United States. \textit{Rickettsia parkeri} is found in the southeastern part of the country and vectored by the Gulf Coast tick (\textit{Amblyomma maculatum}). The disease’s onset is characterized by the presence of an eschar or a vesicular or pustular rash and the relative absence of nausea, vomiting, and diarrhea.\textsuperscript{35} It is also an emerging disease in South America.\textsuperscript{46} Similarly, on the West Coast, \textit{Rickettsia philipii} is transmitted by the Pacific Coast tick (\textit{Dermacentor occidentalis}) and can be differentially diagnosed by presence of eschar.\textsuperscript{37}

Other representatives of the order Rickettsiales, \textit{Anaplasma} and \textit{Ehrlichia} species, are emerging human pathogens. \textit{Anaplasma phagocytophilum} is the most prevalent pathogen within this group, causing close to 6000 cases of human granulocytic anaplasmosis (HGA) per year in the United States.\textsuperscript{48} The disease is transmitted by \textit{Ixodes scapularis} ticks in the northeastern United States and \textit{Ixodes pacificus} in California. HGA generally presents with nonspecific symptoms including fever, chills, malaise, headache, and myalgia; if not treated appropriately and on time, some patients can develop life-threatening complications.\textsuperscript{49,50}

Although rare, \textit{Ehrlichia muris eauclairensis} has been detected in patients with thrombocytopenia and lymphopenia in Minnesota and Wisconsin.\textsuperscript{51,52} Unlike other \textit{Ehrlichia} species that are vectored by lone star ticks (\textit{Amblyomma americanum}), \textit{E muris eauclairensis} is transmitted by the black-legged tick (\textit{I scapularis}). Another yet to be cultured \textit{Ehrlichia} bacterium, \textit{Candidatus Neoehrlichia mikurensis}, has been detected in the blood of patients who developed prolonged fever, erysipelaslike rashes, thromboembolic complications, or septicemia in Europe and parts of Asia, where it is vectored by \textit{Ixodes ricinus} and \textit{Ixodes persulcatus} ticks.\textsuperscript{53,14}

**PROTOZOAN**

Human babesiosis is caused by intraerythrocytic \textit{Babesia} species, an emerging tick-borne disease in the temperate northern hemisphere.\textsuperscript{13,28,45} In North America, \textit{Babesia microti} is common in the northeastern United States, whereas \textit{Babesia duncanii} is an emerging pathogen along the Pacific Coast.\textsuperscript{45,46} Patients experience flu-like symptoms and hemolytic anemia; however, elderly and splenectomy patients are at higher risk of serious or fatal disease, especially from \textit{Babesia divergens} infections in Europe.\textsuperscript{54,49}

**TICK BITE-ASSOCIATED COMPLICATIONS**

Red meat allergy mediated by IgE antibody directed against a mammalian oligosacchideride epitope, galactose-\textalpha-1, 3-galactose, is an emerging condition in many parts of the world and attributed to tick bites.\textsuperscript{47,48} Urticarial or anaphylactic reactions occur several hours after eating red meat such as pork, lamb, beef, or kangaroo. In the United States, the lone star tick has been implicated as the main culprit in case reports of delayed angioedema, a painful and pruritic urticarial rash, and also causes abdominal pain, diarrhea, and sore throat.\textsuperscript{49,50} With its recent introduction in the United States, the Asian longhorned tick was identified as the most probable cause of red meat allergy in Japan.\textsuperscript{55}

**CONCLUSIONS**

Expanding vector tick populations are driving resurgence of tick-borne diseases worldwide, especially in temperate America, Europe, and Asia. Much of North America is endemic for a confounding variety of tick-borne diseases. However, tick-borne pathogens are easily categorized into viral, bacterial, and protozoan infections, with similar clinical picture and treatments within each group. In high-risk areas, public health practitioners should become familiar with tick species of medical importance, their stages, and established or emerging tick-borne pathogens.\textsuperscript{1}

References are available at ContagionLive.com.
What’s in the Pipeline?
A look at up-and-coming HIV drugs in development

BY RAKHSANDA AKRAM, MD, AND JOSEPH DESIMONE JR, MD

(continued from cover page)

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI)

GS-9131 is a prodrug of the nucleotide analogue GS-9148. It inhibits reverse transcription by chain termination. GS-9131 was shown to have broad in vitro activity against HIV-1 and HIV-2 and was not significantly affected by the presence of reverse transcriptase mutations K65R, L74V, M184V, or their combinations. In vitro resistance selection studies have shown a high barrier to resistance. GS-9131 has low potential for mitochondrial toxicity and renal accumulation. It is a promising candidate with once-daily dosing in combination with other ART in patients with NRTI resistance and limited treatment options.

NUCLEOSIDE REVERSE TRANSCRIPTASE TRANSLocation INHIBitor (NRTTI)

MK-8591 (Efda) is an adenosine analogue that both acts as a reverse transcriptase chain terminator and prevents DNA translocation. It has a prolonged half-life of 150 to 160 hours. In early clinical studies, single oral doses of 0.5 to 30 mg of MK-8591 resulted in >1.2-log viral load decline by day 7. This suggests the NRTTI’s potential for once-weekly dosing, with high potency, at a very low dose. However, because of its high intrinsic aqueous solubility, an injectable formulation is not considered feasible. Studies in rat models using nondegradable polymer implants have shown a plasma half-life of up to 100 days, so the possibility of human implants with a dosing interval of 1 year or longer is being explored.

Initial pharmacokinetic data show that inhibitory quotients of MK-8591 for both wild-type and NRTI-resistant HIV-1 at low once-daily and once-weekly doses are substantially higher than those of any currently approved NRTIs. Common NRTI mutations, including M184I/V, thymidine analogue mutations, K65R, and K70E, confer just low-fold shifts in antiviral potency of MK-8591. Currently, a phase 2b clinical trial is under way to test MK-8591 for the treatment of HIV-1 infection with once-daily administration of 0.25, 0.75, or 2.25 mg in combination with doravirine. In addition, no clinically meaningful effect on the pharmacokinetics of MK-8591 was observed when coadministered with dolutegravir and tenofovir. In a prevention study in animals, weekly oral dosing of MK-8591 completely protected rhesus macaques from repeated rectal HIV challenges.

These findings raise the possibility of exploring the use of MK-8591 administered as a long-term implant for both treatment and prevention of HIV infection.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI)

Elsulfavirine (VM1500A) is a long-acting NNRTI with a half-life that allows for once-weekly dosing. A phase 2b clinical trial tested Elpida (a prodrug of elsulfavirine) at a dose of 20 mg orally once daily against efavirenz, both in combination with tenofovir disoproxil fumarate/emtricitabine in treatment-naïve patients living with HIV. Viral suppression was attained in 81% of Elpida recipients compared with 74% in the efavirenz arm. A higher response rate was noted in Elpida recipients with a baseline viral load of >100,000 copies/mL (78% vs 68%). No virologic failure (defined as 2 consecutive HIV RNA plasma levels of >400 copies/mL) was experienced. Drug-related adverse effects (AEs) were about half as frequent in the Elpida group compared with the efavirenz group (36.7% vs 77.6%, respectively).

Elsulfavirine received its first global approval in Russia in June 2017. Given its excellent tolerability and long half-life, its developer, Viroim, initiated a phase 1b clinical trial of once-weekly oral dosing of elsulfavirine (Elida, VM1500) in 36 HIV-uninfected volunteers for an 8-week treatment period in Moscow. Participants were randomized to a 40-, 80-, or 160-mg treatment group. A phase 2a trial of once-weekly oral elsulfavirine in combination with other antiretroviral agents in patients infected with HIV is now being planned by Viroim.

Preclinical pharmacokinetic studies have also shown the potential of VM1500A nano suspensions for developing long-acting injectable formulations.
INTEGRASE STRAND TRANSFER INHIBITOR (INSTI)

Clobentegravir is an INSTI with a structure and resistance profile similar to that of dolutegravir. Its availability in nano formulation with a half-life of 21 to 50 days makes it an option for monthly or bimonthly parenteral administration. Results from 2 phase 3 trials are now available. The ATLAS (Antiretroviral Therapy as Long-Acting Suppression) study evaluated monthly injectable clobentegravir plus rilpivirine in 616 treatment-experienced people who switched from a standard oral antiretroviral combination with an undetectable viral load to injectable clobentegravir plus rilpivirine. The injectable formulation was found to be noninferior to continued oral therapy. The FLAIR (First Long-Acting Injectable Regimen) study tested the injectable formulation of clobentegravir plus rilpivirine in treatment-naive individuals. Patients were first started on induction dolutegravir/abacavir/lamivudine for 20 weeks and then randomized to either continued oral therapy or switched to injectable clobentegravir plus rilpivirine. Virological success rates were 93.3% in the continued oral therapy group versus 93.6% in the injectable group. Injection site reactions, predominantly pain, were noted in 20% to 30% of participants. Both studies had 3 individuals, each with virological failure (defined as HIV-1 RNA ≥200c/mL in consecutive samples). All individuals had HIV subtype A virus with evidence of mutations in the NNRTI and INSTI domains.

In assessing patient satisfaction with injectable formulations, many patients were found to prefer monthly injections over daily oral medications.

Long-acting injectable cabotegravir is also being evaluated for pre-exposure prophylaxis in HIV-uninfected individuals.

CD4 ATTACHMENT INHIBITOR

Fostemsavir targets the first step of HIV entry by binding HIV envelope glycoprotein 120, thus inhibiting the virus from binding to the CD4 receptor. It is first in its class, thus offering an option for individuals with highly drug-resistant HIV. It is an oral produg of temsavir and can be dosed once daily. Twelve percent of participants in a phase 1 trial had baseline envelope polymorphisms that lowered susceptibility to fostemsavir. This raises the issue of the need for patient screening for polymorphisms prior to therapy. Based on encouraging efficacy results and good tolerability obtained in phase 2 studies, the ongoing BRIGHTHE phase 3 study is evaluating the utility of fostemsavir as a salvage therapy with an optimized background regimen (OBR) in individuals failing ART. Initial results at 48 weeks have shown a 0.8 log copies/mL drop (about a 6.5-fold drop) in viral load compared with an 0.2 log drop in those on placebo with OBR. These results support the further development of fostemsavir as a therapeutic option for HIV-1-infected, highly treatment-experienced with multidrug resistance.

CCR5 ANTAGONISTS

Leronlimab (PRO 140) is a humanized IgG4 monoclonal antibody that blocks the CCR5 coreceptor. It does not appear to interfere with the normal function of CCR5 in mediating immune responses. Weekly subcutaneous injections resulted in ≥1.65 log10 mean viral load reduction when tested as a single agent maintenance therapy after initial ART. A 92% response rate was seen at a 700-mg dose in a phase 3 trial. Patients who failed to respond to leronlimab safely achieved viral suppression upon resuming the ART regimen they maintained prior to enrollment.

Cenicriviroc (CVC) is another CCR5 antagonist. It also has an inhibitory effect on CCR2. This additional anti-inflammatory effect may lead to an improvement in HIV-associated neurocognitive impairment by reducing monocytic immune activation. Phase 2b study results showed noninferiority and better tolerability compared with efavirenz when coadministered with tenofovir/emtricitabine. A phase 3 clinical trial is already under way to evaluate its role in the treatment of nonalcoholic steatohepatitis, and a phase 3 clinical trial is being planned to investigate a fixed-dose combination ART tablet containing cenicriviroc plus lamivudine.

FUSION INHIBITOR

Albusviride is a long-acting injectable fusion inhibitor that inhibits HIV virus from entering CD4 cells by attaching to an envelope glycoprotein, gp41, on the outer surface of HIV. It was tested in the Test Albusviride in Experienced Patients (TALENT) study, the first phase 3 licensing study of a new antiretroviral drug conducted in China, where it was approved in 2018.

Investigators randomized 389 treatment-experienced individuals with virological failure on a first-line regimen to receive either a weekly infusion of albusviride (dose unspecified) plus twice-daily dosing of the boosted protease inhibitor lopinavir/ritonavir or a regimen of lopinavir/ritonavir twice daily plus 2 NRTIs; lamivudine and either tenofovir, abacavir, or zidovudine, depending on previous treatment history (72% received tenofovir; 26%, zidovudine; 1%, abacavir; and 1%, tenofovir and zidovudine). At 48 weeks, 80.4% of the albusviride group had a viral load below 50 copies/mL by intent-to-treat analysis compared with 66% in the triple-drug group. The albusviride arm was noninferior to the standard triple-drug regimen in second-line treatment. No resistance to albusviride was detected, and it was well tolerated.

A US phase 2 multicenter, 3-part study was initiated in October 2018 to establish the dosage, safety, and antiviral activity of combination therapy with albusviride and 3BNC117 (a broadly neutralizing antibody) as long-acting maintenance therapy in virologically suppressed subjects with HIV-1 infection.

CAPSID INHIBITOR

GS-CA1 is the first capsid inhibitor to enter preclinical studies. The capsid is a cone-shaped structure that encloses the viral genome and is vital to HIV replication. GS-CA1 interferes with the disassembly of the capsid protein and transport of viral genetic material into the host cell nucleus. It also interferes with the assembly of capsids of the newly produced virus, resulting in immature viral particles unable to infect new cells. It is a highly potent inhibitor of HIV-1 replication in T-cell lines (EC50 = 0.24nM), with full activity against HIV-1 mutants resistant to licensed antiretroviral drugs. It has shown high in vitro metabolic stability, low systemic drug clearance, and a long half-life (7.2-18.7 hours). Its low aqueous solubility allows for an extended-release preclinical pharmacokinetic profile after subcutaneous administration of a solid depot formulation.

GS-6207 is a modified version of GS-CA1. A first human study showed that a single subcutaneous injection of GS-6207 resulted in sustained concentrations for at least 24 weeks. The sustained delivery pharmacokinetic profile of a subcutaneous formulation may allow for a 3-monthly dosing interval. Safety data are still blinded; however, no serious AEs or deaths have been noted. Based on these findings, a proof-of-concept study is under way to determine the optimal dose and frequency of administration in HIV-infected individuals. Efforts are also being made to develop an oral formulation of GS-6207.

REV INHIBITOR

ABX464 is an orally available small molecule that stops viral replication by interfering with the activity of Rev, an HIV protein essential for making RNA strands. Exposure to ABX464, therefore, produces shorter RNA fragments, rendering them useless to produce new viruses. Small peptides produced by these RNA fragments alert the immune system, which can then eliminate the HIV-infected cells. This may help reduce the reservoir of HIV DNA in the body, with the hopes of achieving a “functional cure” without the need for lifelong treatment. Reductions of greater than 25% in integrated HIV DNA (HIV DNA most likely to lead to HIV replication) were observed in 41% of individuals in the ABX464 arm of a phase 2a randomized trial. Viral rebound, however, was noted with treatment interruption. Viral load reduction >0.5 log was observed in 1 of 6 HIV treatment-naive patients in the 75-mg cohort, 2 of 6 in the 100-mg cohort, and 4 of 6 in the 150-mg cohort. ABX464 was well tolerated in this first study in HIV-infected patients.

References are available at ContagionLive.com.
Blood cultures remain the gold standard for diagnosing bacterial and Candida bloodstream infections (BSIs), but they are limited by slow turnaround and suboptimal sensitivity.1,2 Data from some but not all retrospective studies suggest that rapid initiation of active antimicrobial therapy correlates with reduced mortality among patients with bacterial or Candida BSIs.3-8 Although such findings have not been validated in prospective studies,5 the limitations of blood cultures and quality standards for sepsis and septic shock provide a rationale for aggressive empiric broad-spectrum antimicrobial therapy.5,9 These practices may promote unnecessary antimicrobial usage, drug toxicity, and emergence of resistance. 5,10,11

Culture-independent diagnostic tests (CIDTs) that detect pathogens and antimicrobial resistance genes within clinical samples are transforming clinical practice.2,12 Syndromic CIDT panels for respiratory specimens, stool, and cerebrospinal fluid facilitate rapid identification or exclusion of infections due to particular organisms and antimicrobial initiation or de-escalation strategies.12 Likewise, commercial molecular tests of positive blood cultures for pathogen or resistance determinant identification are valuable patient care and stewardship tools.10-14 CIDTs of whole blood samples from patients with suspected BSIs have not gained widespread acceptance, in part because costs are high and clinicians are unsure how to incorporate testing into rational management paradigms.12,15 This paper reviews the performance of blood cultures and direct-from-whole-blood CIDTs for bacterial and Candida BSIs and provides a conceptual framework for using CIDTs in the clinic.

PERFORMANCE OF BLOOD CULTURES AND CIDTS
Blood culture sensitivity for detecting bacteremia is ~73%, 90%, and 98% if 1, 2 and 3 sets of aerobic and anaerobic bottles, respectively, are collected in the absence of antimicrobial treatment.16 Such performance is contingent upon collecting ≥20 mL of blood in each culture set. Smaller volumes, as often collected in hospitalized patients, increase false negativity.2 Blood cultures may require several days for bacteria to achieve detectable concentrations and additional time for species identification and resistance testing.2 Blood cultures are ~50% sensitive for diagnosing invasive candidiasis.1 Moreover, blood cultures become positive late in the course of invasive candidiasis, and incubation times prior to positivity are typically longer than those for detecting bacteria.1 Antimicrobial treatment reduces sensitivity for bacteria and Candida by ~50%,17-20 which is notable because 28% to 63% of blood cultures are collected from patients who are receiving antimicrobial agents.2

Several direct-from-whole-blood CIDTs couple nucleic acid amplification with novel technologies for target detection, including Iridica, SeptiFast, SepsisTest, Magicplex, and T2Direct (T2Bacteria, T2Candida) assays.2 T2Direct is the only FDA-cleared system.17,21,22 Assay characteristics and performance are summarized in the Table.2,17,21,26,36,37 Interpretation of performance is complicated by study heterogeneity and limitations of blood cultures as gold standard. CIDTs require ≤5 mL of blood and provide results within 4 to 10 hours. In general, DNA amplification-based technologies are more sensitive than blood cultures in patients receiving antimicrobials.17,23-25

Bringing Culture-Independent Diagnostic Tests for Bloodstream Infections Into Rational Patient Management

These tests have the potential to transform patient care and antimicrobial stewardship, but they have not gained widespread acceptance, partly because of uncertainty over how to use them clinically.

BY CORNELIUS J. CLANCY, MD, AND M. HONG NGUYEN, MD

CORNELIUS J. CLANCY, MD
Clancy is chief of infectious diseases at the VA Pittsburgh Healthcare System and director of the XDR Pathogen Laboratory at the University of Pittsburgh. His research lab is funded by the Department of Veterans Affairs and National Institutes of Health.

M. HONG NGUYEN, MD
Nguyen is director of the Antimicrobial Stewardship and Transplant Infectious Diseases programs at the University of Pittsburgh Medical Center. Her translational and basic science research lab is funded by the National Institutes of Health and other sources.
MULTIDRUG-RESISTANT INFECTIONS

We will focus on SeptiFast and T2Direct as examples of broad- and narrow-spectrum platforms, respectively.27-32,34,35 Concepts presented here can be applied to other tests.

**CIDTs AS BAYESIAN DIAGNOSTICS**

CIDTs assign a probability of BSI due to a given pathogen.27-29 Positive and negative predictive values (PPVs, NPVs) are determined by sensitivity and specificity of the test and the patient's likelihood of BSI. Anticipated PPVs and NPVs in different types of patients can be calculated for pathogens targeted by SeptiFast (sensitivity/specificity: 75%/90%), T2Bacteria (85%/95%), and T2Candida (90%/98%; see online Table). Tests are unlikely to be useful if performed every time a blood culture is collected,28 because false positivity exceeds true positivity, and excellent NPVs provide only marginal value over already low pretest likelihoods.

In patients presenting to the hospital with fever or those with sepsis in the absence of septic shock, anticipated SeptiFast and T2Bacteria PPVs for targeted bacteria are each ~50% to 75%. SeptiFast offers an advantage of detecting ~85% to 90% of bacteria and fungi that cause BSIs, whereas T2Bacteria detects 5 bacteria that account for ~50% of BSIs.28,30-33 A potential disadvantage of broad-spectrum panels is that some targets are uncommon causes of BSI and therefore more likely to generate false-positive results. Although T2Bacteria NPVs are excellent for targeted bacteria, they are inferior to SeptiFast NPVs in excluding BSIs due to any bacterium. Candida are typically rare causes of BSI in these populations,15,27-29 and T2Candida PPVs and NPVs are unlikely to be useful in most cases. Anticipated T2Candida PPVs may approach 67%, and NPVs are 99.7% among septic patients with risk factors for candidemia in whom a causative bacterium is not identified. T2Candida detects species that account for >95% of candidemia at most centers.17,21

The likelihood of bacterial or Candida BSI increases in septic shock, and anticipated PPVs of each test are ~70%. However, SeptiFast and T2Bacteria NPVs are just 78% and 62%, respectively, for excluding BSIs in the setting of septic shock; T2Candida NPV remains excellent (99.5%).

**INTEGRATING CIDTS INTO CLINICAL AND STEWARDSHIP PRACTICES**

Surviving Sepsis guidelines endorse empiric broad-spectrum antibiotic therapy within 1 hour of triage for suspected sepsis and septic shock and rapid de-escalation based on susceptibility of causative organisms or if infection is excluded.9 Other experts propose more nuanced, case-by-case approaches, in which empiric antibiotics are administered immediately for suspected septic shock, but clinical observation and diagnostic testing may be undertaken prior to treatment decisions in at least some patients with suspected sepsis in the absence of shock.5,10,11

In patients with possible sepsis in whom treatment decisions have been deferred pending workup, positive SeptiFast or T2Bacteria results may shorten the time to antibiotic treatment compared with waiting for positive blood cultures. If blood or other cultures are negative and an alternative, noninfectious diagnosis is not established, there is a good chance based on predictive values that a positive CIDT has identified a BSI that would have been missed otherwise. In such cases, continuing antibiotic treatment against the CIDT-identified pathogen is reasonable. Detection of resistance genes by SeptiFast may guide early selection of active antibiotics. T2Bacteria does not include resistance genes, but the panel is directed against ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterobacter species) that are often resistant to first-line antibiotics.22,24 In high-risk patients, such as those colonized by a resistant pathogen included in the panel, a positive T2Bacteria result may justify use of an alternative agent.

If SeptiFast or T2Bacteria results are negative and a patient with suspected sepsis is stable, clinicians may decide to withhold antimicrobials pending blood and other culture results. This strategy is reasonable because empiric treatment has not proved superior to culture-directed treatment of BSIs or suspected sepsis, and ~50% of suspected sepsis is ultimately ascribed to noninfectious etiologies.5,10,11 If antimicrobials have been administered, combined negative CIDT and culture results may offer an argument for de-escalation. Approaches to using CIDTs similar to those described for possible sepsis also may be useful for managing febrile patients in the emergency department.

In patients with presumed septic shock, clinicians will not wait for CIDT results before initiating broad-spectrum antibiotics (often in combination). In these patients, SeptiFast and T2Bacteria may have value if antibiotics are administered before blood cultures or whole blood samples are collected. Positive CIDT results may help in streamlining empiric antibiotic regimens. T2Candida is likely to be useful in septic shock (and perhaps in sepsis with risk factors for candidemia),22 since empiric antifungals are not recommended routinely. T2Candida PPVs and NPVs would justify initiating and withholding (or discontinuing) antifungal therapy, respectively. Sensitivity and specificity of SeptiFast are lower than T2Candida for Candida species,17,22,23 but the former test still may have value in patients with septic shock who are at risk of candidemia.

**CONCLUSIONS**

We propose a conceptual framework for thinking about how to incorporate CIDTs for BSIs into rational patient management and antimicrobial stewardship strategies. Similar exercises can be undertaken for other populations at risk of BSIs, such as patients with neutropenic fever or transplant recipients with sepsis, CIDT-based management paradigms will require validation in clinical trials. An important question is whether shorter turnaround times and identification of more potential pathogens and resistance determinants using direct-from-whole-blood CIDTs can lead to improved patient outcomes compared with those obtained with molecular testing of positive blood cultures. ▲

References are available at ContagionLive.com.

---

**Table. Culture-Independent Diagnostic Tests for Bloodstream Infections**

<table>
<thead>
<tr>
<th>SYSTEM (MANUFACTURER)</th>
<th>TECHNOLOGY</th>
<th>TARGETS</th>
<th>TIME TO RESULTS</th>
<th>SENSITIVITY/SPECIFICITY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iridica (Abbott)</td>
<td>Multiplex PCR with ESI-MS</td>
<td>780 bacteria and fungi; meca, vanA, vanB, blaKPC</td>
<td>6 hours</td>
<td>45%-83%/69%-94%</td>
<td>Withdrawn from market</td>
</tr>
<tr>
<td>SeptiFast (Roche)</td>
<td>Multiplex real-time PCR with probe hybridization, DNA melting analysis</td>
<td>25 bacteria and fungi; meca</td>
<td>4-6 hours</td>
<td>63%-83%/83%-95%</td>
<td>Current market status unclear</td>
</tr>
<tr>
<td>SepsiTest (Molzym)</td>
<td>Universal PCR with Sanger sequencing</td>
<td>&gt;345 bacteria, 13 fungi</td>
<td>8-10 hours</td>
<td>11%-87%/83%-96%</td>
<td>Currently available in Europe</td>
</tr>
<tr>
<td>Magicplex (Seegene)</td>
<td>Multiplex real-time PCR</td>
<td>&gt;85 bacteria and fungi; meca, vanA, vanB</td>
<td>6 hours</td>
<td>37%-67%/66%-92%</td>
<td>Current market status unclear</td>
</tr>
<tr>
<td>T2Direct (T2 Biosystems)</td>
<td>Microbial cell-associated PCR with T2 magnetic resonance</td>
<td>T2Bacteria: Staphylococcus aureus, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, T2Candida: Candida albicans/tropicalis, Candida glabrata/krusei, Candida parapsilosis</td>
<td>4-6 hours</td>
<td>T2Bacteria: 85%/95% T2Candida: 90%/98%</td>
<td>Only tests that are FDA cleared; tests also have CE mark</td>
</tr>
</tbody>
</table>

CE indicates Conformité Européenne; ESI-MS, electrospray ionization mass spectrometry; PCR, polymerase chain reaction.
Outpatient Antimicrobial Stewardship: Field of Dreams or Land of Opportunity for Pharmacists?

Relevant existing reports, though limited, demonstrated positive outcomes and suggest a promising space for pharmacy practice growth in outpatient antimicrobial stewardship.

BY CHRISTINA G. RIVERA, PHARMD, BCPS, AAHIV-M

(continued from cover page)

to 30% of outpatient antibiotic prescriptions may be inappropriate, based upon professional society endorsed national guidelines for infectious syndromes. Further, the burden of community acquired *Clostridioides difficile* is significant, with up to 35% of adult and 70% of pediatric *C. difficile* cases occurring in patients who had no recent overnight stay in a health care facility. In response to the need for systematic outpatient AMS, the US Centers for Disease Control and Prevention (CDC) released the Core Elements of Outpatient Antibiotic Stewardship in 2016. The recommendations center around 4 cornerstone elements: commitment, action for policy and practice, tracking and reporting, and education and expertise.

THE PHARMACIST’S ROLE

Pharmacists have garnered an established role on inpatient AMS teams, as evident in the CDC’s Core Elements of Hospital Antibiotic Stewardship Programs. The drug expertise element states that a pharmacist leader should be appointed to improve antibiotic use. In contrast, the proposed involvement of pharmacists in outpatient-based AMS as described by the Core Elements of Outpatient Antibiotic Stewardship is more subtle. The document’s intended audience members represent several areas that pharmacists commonly work in, such as primary care clinics, emergency departments, retail health clinics in pharmacies, and health care systems, though pharmacists themselves are not specifically mentioned in these settings. Community pharmacies and pharmacists are described as a potential partner for outpatient AMS activities, along with health insurance companies, local microbiology laboratories, long-term care facilities, and others. Certainly, community-based pharmacists are well situated to be key players in outpatient AMS. Most outpatient antibiotic prescriptions in the United States are dispensed at community pharmacies, and virtually all of those for acute infectious syndromes would be processed through a local pharmacy.

COMMUNITY PHARMACY AMS

To date, published literature focusing on pharmacist-led AMS interventions in community pharmacies centers around the use of pharmacist–prescriber collaborative practice agreements (CPAs) and point-of-care testing. CPAs create a formal practice agreement between the pharmacist(s) and prescriber(s) that specifies the functions a pharmacist can perform outside the usual scope of practice. Although legal throughout most of the United States, rules and regulations governing CPAs vary from state to state. Of interest within the realm of outpatient AMS, CPAs may grant pharmacists prescribing authority within predefined infection-related clinical scenarios or specifically for antimicrobials. Point-of-care testing dovetails nicely with community pharmacist CPAs. In nearly all states, pharmacists can use Clinical Laboratory Improvement Amendments (CLIA)–waived tests, which are defined by the FDA as “so simple and accurate as to render the likelihood of erroneous results negligible; or pose no reasonable risk of harm to the patient if the test is performed incorrectly.” Two such examples of CLIA-waived tests used in pharmacist-led outpatient AMS are the rapid influenza diagnostic test (RIDT) and group A *Streptococcus* (GAS) testing.
From December 2013 to April 2014, a pilot program involving 55 community pharmacies in 3 states (Michigan, Nebraska, and Minnesota) used a pharmacist CPA and RIDT with the aim of shortening the time to receipt of antivirals and reducing inappropriate antimicrobial use in patients with suspected influenza infection.\(^{10}\) Of the 75 adult patients included in the study, just 8 (11%) were positive for influenza by RIDT and, per CPA, were dispensed oral oseltamivir by the pharmacist. Patients with a negative test were counseled on symptomatic management without provision of an antiviral or antibiotic. All patients were followed up in 24 to 48 hours, and no adverse events were reported. Interestingly, patient satisfaction was \(>90\)% despite the majority of patients not receiving an antibacterial or antiviral medication. The authors suggest this program demonstrated that a physician–pharmacist collaboration for seasonal influenza-like illness can improve appropriate use of antivirals and decrease unnecessary antibiotic prescribing. Given that a large proportion of patients presented after regular physician office hours or had no primary care physician (39% and 35%, respectively), the authors hypothesized that emergency department and urgent care visits were also avoided.\(^{10,11}\)

During the same time frame, this group of investigators evaluated the use of a pharmacist CPA and GAS testing coupled with a bacterial pharyngitis scoring tool in patients who presented with pharyngitis symptoms.\(^{11,12}\) Adult patients with a Centor score of 1 or greater, younger than 46 years, and clinically stable with a positive GAS test qualified for treatment with amoxicillin or azithromycin per protocol. Of 316 patients screened, 273 were eligible for testing, of which 48 (17.5%) were positive and received antimicrobial treatment. Similar to the pharmacist–physician collaborative pilot program, the literature suggests rates of 60% to 80% antimicrobial prescribing for adult pharyngitis in usual care. Taken together, these studies offer evidence that community pharmacists armed with the right tools can be a significant asset in guiding the judicious use of outpatient antimicrobials.\(^{13,15}\)

**Table.** Outpatient Antimicrobial Stewardship (AMS) Potential Areas for Pharmacists’ Involvement

<table>
<thead>
<tr>
<th>AMS INTERVENTION</th>
<th>PHARMACIST OPPORTUNITY</th>
<th>INTENDED AUDIENCE</th>
<th>TARGET GOALS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education/ Reeducation</strong></td>
<td>Newsletters, Brochures, Formal or informal didactics, Webinars, Electronic medical record alerts, Antibiotic counseling</td>
<td>Primacy care providers, Specialists commonly prescribing antibiotics, Community- or clinic-based pharmacists, Patients</td>
<td>Decrease unnecessary prescribing, Decrease patient perceptions of antibiotic needs, Increase correct patient antibiotic administration.</td>
</tr>
<tr>
<td><strong>Electronic medical record and decision support</strong></td>
<td>Electronic alerts, Antibiotic order sets, Embedded clinical decision support tools, Required indications on antibiotic prescriptions</td>
<td>Antibiotic prescribers</td>
<td>Decrease unnecessary prescribing, Direct toward best prescribing, Antibiotic use tracking.</td>
</tr>
<tr>
<td><strong>Delayed prescribing</strong></td>
<td>Follow-up clinical assessment phone calls</td>
<td>Patients</td>
<td>Decrease unnecessary antibiotic use.</td>
</tr>
<tr>
<td><strong>Implement guidelines for common infectious syndromes</strong></td>
<td>Develop, review, maintain guidelines, Disseminate guidelines</td>
<td>Primary care providers, Community- and clinic-based pharmacists</td>
<td>Direct toward best prescribing.</td>
</tr>
<tr>
<td><strong>Pharmacy-based programs and practices</strong></td>
<td>Vaccination, Medication take back, Allergy history documentation, Exclusion of antibiotics from free/discounted medication lists, Commitment posters</td>
<td>Patients</td>
<td>Prevent infectious illness. Dispose excess antimicrobials. Avoid unneeded use of second-line antibiotics. Avoid promoting antibiotic overuse.</td>
</tr>
<tr>
<td><strong>Policies</strong></td>
<td>Formulary restrictions on certain outpatient antibiotics</td>
<td>Managed-care pharmacists, Pharmacy and therapeutics committees</td>
<td>Limit broad-spectrum antibiotic overuse</td>
</tr>
</tbody>
</table>

**EMERGENCY DEPARTMENTS AND ACADEMIC DETAILING AMS**

Data also demonstrate that emergency department (ED) pharmacists can play a key role in AMS efforts. From October 2011 to September 2012 at The University of Utah, ED pharmacists retrospectively reviewed 180 positive urine culture results (>100,000 CFU/mL), patient symptoms, diagnosis, and discharge antibiotics for patients discharged from the ED. Following an ED protocol, the pharmacists determined that 42 (23%) of empiric discharge antibiotics were considered inappropriate and required pharmacist intervention. All but 7 patients (17%), who were lost to follow-up, had a change made in their therapies.\(^{14}\) The authors concluded that ED pharmacists can improve patient care and reduce inappropriate antimicrobial use after discharge. Tailored education delivered to health care professionals by a content expert to encourage best practices, also known as academic detailing,\(^{17}\) is a typical component of inpatient antimicrobial stewardship programs. Outpatient AMS–focused academic detailing had mixed results, with 1 study showing a decrease in cephalaxin prescribing after a face-to-face meeting with a pharmacist and others showing no statistically significant change with pharmacist education efforts.\(^{18-22}\) AMS education is generally recommended to combine with a corresponding AMS intervention such as audit and feedback, clinical decision support, delayed prescribing, and/or public display of provider pledges to AMS.\(^{23}\)

**FUTURE DIRECTIONS**

In fall 2018, the Society of Infectious Diseases Pharmacists released a position statement on the essential role of pharmacists in outpatient AMS and, the summer preceding, a call to action for outpatient antimicrobial stewardship in *Journal of American Pharmacists Association.*\(^{24-26}\) The aforementioned studies, among others, are cited as evidence that pharmacists must be leaders in outpatient AMS.\(^{24}\) Road maps and other diverse potential areas for outpatient AMS programs, from vaccination to direct patient education (*Table*), are discussed, along with barriers to outpatient AMS, including perceived lack of financial incentives.

In conclusion, there is widespread recognition of the need for outcomes-based, systematic outpatient AMS programs. Pharmacists, particularly those enabled with a CPA and point-of-care testing, are poised to be change leaders in the betterment of outpatient infectious diseases care. ▲

References are available at ContagionLive.com.
Although the incidence of new HIV infections has stabilized over the past few years and screening has been introduced into the community setting, barriers remain in the screening of some subpopulations and uptake of pre-exposure prophylaxis (PrEP) in high-risk individuals, according to panelists who participated in a recent *Contagion®* Peer Exchange panel.

The panelists also discussed the potential for HIV outbreaks associated with the opioid epidemic, the lingering stigma associated with HIV screening, and ways to reduce the medical burden of using PrEP to increase use.

**THE HIV TREATMENT LANDSCAPE**

Recent data from the US Centers for Disease Control and Prevention (CDC) estimate that the prevalence of HIV infection in the United States is approximately 1.1 million individuals.1 Although the overall annual incidence remained stable from 2012 to 2016,2 Paul Sax, MD, pointed out that it slightly increased among men who have sex with men (MSM), particularly among black and Hispanic MSM. Ian Frank, MD, estimated that up to 20% of new diagnoses are made in individuals ≥55 years old (generally thought to be at lower risk of new infection than younger individuals), emphasizing the importance of testing high-risk individuals of all ages.

The panelists also warned that although the incidence of infection has remained relatively stable, the current opioid epidemic may lead to a rise in the number of new infections, as evidenced by recent outbreaks in Boston and other parts of the United States. Sax also explained that the increase in use of opiates with a short half-life, such as fentanyl, raises risk of infection because individuals may inject themselves up to 20 times per day, increasing potential exposure to infected needles. “In that context, there’s really a chance for explosive spread of HIV,” Sax said.

**HIV SCREENING AND DIAGNOSIS**

Although the panelists stated that the fourth-generation antigen–antibody combination assay is typically used for screening, Eric S. Daar, MD, emphasized that an HIV viral load test should be performed in patients who test negative on the fourth-generation antigen–antibody assay if the clinician has a high index of suspicion.

Sax added that a positive antigen–antibody test does not have enough specificity to conclusively diagnose HIV and needs to be confirmed with a differentiation assay. “In our hospital, where we have a large obstetric service and a lot of women who are pretty low risk getting screened, it’s actually just as common for their screening test, once positive, to be not confirmed as it is for it to be confirmed,” he said.

Although patients occasionally come in with acute infection, Daar said that the majority of people he and his colleagues see received their HIV diagnoses through increased use of routine screening in the hospital, sexually transmitted disease (STD) clinics, and urgent care centers. “Anecdotally, we are catching people earlier because our threshold [for screening] is now, if you’re a warm body and we think of [screening], we should do it,” he said.

W. David Hardy, MD, added that removing obstacles to HIV testing, such as requirements for consent forms and counseling, and bringing the screening tests from the testing center into the community has helped
increase uptake of HIV screening. "For many years, they tested people at the [Department of Motor Vehicles] in [Washington], DC, because the incidence was so high," he said. "They stopped doing it because the pickup rate was so small, but it really normalized HIV testing, which is so important."

The panelists also discussed possible reasons for missing early diagnosis in patients with advanced disease. "In my experience, African Americans are coming in very late because even though they may know they’re positive, they’re not accessing treatment because of the stigma of taking the treatment and what that means in their community," Hardy said.

Panel moderator Joseph Eron, MD, added that patients may present to the hospital with opportunistic infections but not be tested for HIV because they are perceived to be at low risk. "They might be a little bit older," he said, "so the diagnosis isn’t necessarily considered."

Frank added that general practitioners or other subspecialists may not be familiar with signs of advanced-stage HIV infection, such as opportunistic infections, that clearly indicate the need for HIV testing.

**HIV US PREVENTIVE TASK FORCE SCREENING RECOMMENDATIONS**
The US Preventive Services Task Force gives a grade A (highest) recommendation for HIV testing in individuals aged 15 to 65 years, adolescents <15 years and adults >65 years with additional risk factors, and all pregnant women. However, Hardy noted that the stigma around HIV screening remains a barrier to obtaining consent from individuals and recommended using language to allow individuals to opt out of screening. "The wording can be as simple as ‘I test all my patients for HIV. I’m going to test you today, too, unless you say no,’” he said. "It assumes that [screening] is a good thing.”

The panelists added that pregnant women can be screened up to the time of delivery, and the panelists added that testing twice during pregnancy is ideal. "[In the] very few cases of HIV transmission in newborns, when you look back, they often had a negative test early in pregnancy and then a positive one later on," Sax said.

**HIV PREP THERAPY**
According to Frank, the use of antiretroviral therapy (ART) to prevent HIV infection is one of the major recent advances in this field, and use of daily tenofovir/emtricitabine as PrEP can prevent nearly all HIV transmissions. "We should be talking about PrEP with anybody who has had a sexually transmitted infection [and] in men who have sex with men who are not in monogamous relationships," he said. "It’s really an easy conversation to have. The combination is very safe. There are very few serious toxicities."

Despite its general safety, Frank warned, the tenofovir/emtricitabine combination can reactivate the hepatitis B virus and cause acute liver injury in patients with chronic hepatitis B infection, and it should not be used in patients with acute HIV infection because of the high risk of developing resistance. He recommended confirming the patient’s hepatitis B infection status and performing viral load and serological assay for individuals with symptoms of acute HIV infection.

However, the panelists noted that the uptake of PrEP is often low among the individuals at highest risk of HIV transmission. "A lot of the people we have prescribed PrEP to would fall into the category of the worried...They may be in a monogamous relationship with an HIV-infected partner, but that person is taking [ARTs] already, so their risk is actually really low, if not zero, but they still want to take PrEP just because,” Sax said. "Those are not the people at highest risk of getting HIV, and really, that’s where PrEP needs to be rolled out.”

Daar estimated that just 10% of the candidates for PrEP are receiving the regimen, adding that practitioners need to communicate the simplicity of using PrEP. "We have to stop making this sound as difficult as treating somebody with HIV," he said. "It’s simple [and] easy to take, [and] the screening is very straightforward. As long as we don’t give it to someone who has HIV, we’re probably going to do mostly good.”

The panelists added that finding ways to reduce the medicalization of using PrEP, which currently requires follow-up appointments with a medical care provider every 3 months, will help increase uptake in the target population. "In most cases, the medical interactions many people who are on PrEP have is with their PrEP provider," Hardy said. "Why make that more complex, more difficult, [and] more time-consuming for a prevention of the disease?"

He suggested developing innovative ways of performing follow-up, such as having a knowledgeable pharmacist interpret the follow-up results, to potentially reduce the medicalization of the disease.

The panelists also stated that sustaining PrEP can be a challenge, especially with the current recommendations of not refilling a prescription until the follow-up HIV test comes back negative. "We have to be a little looser with our follow-ups, allowing people to stay on PrEP without necessarily doing everything that is in the guidelines every 3 months like clockwork,” Sax said.

In conclusion, Hardy said that unlike medications for HIV infection, PrEP can be taken intermittently, depending on the patient’s sexual activity and lifestyle, and procedures for follow-up should account for this discontinuous use. "We have to be aware of that and also be flexible to let people say, ‘I’m going to be off for the next 3 months, so don’t expect to see me. But when I’m ready to go back on, I’ll go back on,’” he said. ▲

References are available at ContagionLive.com.
OUTBREAK MONITOR

The Contagion® Outbreak Monitor provides details and trends on the number of confirmed cases and deaths of infectious disease outbreaks, matched with recent coverage related to each outbreak. Use the Contagion® Outbreak Monitor to learn about infectious disease outbreaks in your geographical region, and manipulate the map to find out the latest information on global outbreaks. The new Map Key lets you easily find the outbreak that you're looking for, and hone in on the details specific to that outbreak. To view information on past outbreaks that have occurred in specific regions, click on the new Resolved Outbreaks tab.

Providing health care professionals who specialize in infectious disease with up-to-date, disease-specific information and resources to improve patient outcomes and positively impact the identification, diagnosis, treatment, and prevention of infectious diseases.
The Contagion® Outbreak Monitor provides details and trends on the number of confirmed cases and deaths of infectious disease outbreaks, matched with recent coverage related to each outbreak.

Use the Contagion® Outbreak Monitor to learn about infectious disease outbreaks in your geographical region, and manipulate the map to find out the latest information on global outbreaks. The new Map Key lets you easily find the outbreak that you’re looking for, and hone in on the details specific to that outbreak.

To view information on past outbreaks that have occurred in specific regions, click on the new Resolved Outbreaks tab.
**FURI Study Case: Ibrexafungerp Successfully Treats Esophageal Candidiasis**

**BY MICHAELA FLEMING**

Candida species are a common cause of mucosal and invasive candidiasis. In certain circumstances, patients may develop refractory candidiasis. While conducting a study evaluating the safety and efficacy of Ibrexafungerp (IBX), investigators observed that the drug successfully treated a case of severe refractory esophageal candidiasis. The details were presented by Jose Vazquez, MD, chief of infectious diseases at Augusta University's Medical College of Georgia, who is also a member of the Contagion® editorial advisory board, at this year’s European Congress for Clinical Microbiology and Infectious Diseases (ECCMID 2019).

IBX is being evaluated in SCYNEXIS Study 301, a FURI, an open-label clinical trial of patients either intolerant or refractory to antifungal therapy.

One patient, a 63-year-old man, was enrolled into the trial, with a history of esophageal strictures with 10-year history of recurrent esophageal candidiasis. Prior to enrollment, the patient experienced dysphagia, and a feeding tube was inserted. An esophagogastroduodenoscopy demonstrated severe candidiasis with a culture revealing Candida glabrata resistant to fluconazole (minimum inhibitory concentration, 64 mcg/mL).

The patient was enrolled and given a loading dose of oral IBX 750 mg twice a day for 2 days, followed by oral IBX 750 mg daily for a total of 54 days. While receiving treatment, the patient gradually improved and by day 54 was completely asymptomatic.

One month following the discontinuation of therapy, the patient remained symptom free. A follow-up esophagogastroduodenoscopy did not detect any esophageal candidiasis; 2 months later, the feeding tube was removed. At a 9-month follow-up, the patient remained asymptomatic and was gaining weight.

“This report demonstrates the efficacy of IBX in a patient with a severe recalcitrant and refractory [esophageal candidiasis] and highlights the potential for using IBX to manage difficult-to-treat azole resistant and refractory candidiasis,” the investigators concluded.

The study, “Use of Ibrexafungerp (Formerly SCY-078) To Treat Severe Azole-Refactory Esophageal Candidiasis: A Case Report From the FURI Study,” was presented on April 13 at ECCMID 2019 in Amsterdam, the Netherlands.

---

**CAMERA2: Combo Therapy for MRSA Bacteremia Is Effective but Linked to Higher Mortality, AKI Rates**

**BY ALEXANDRA WARD, MA**

In vitro studies, animal models, and observational studies in humans have demonstrated that combination therapy combining vancomycin, the current standard treatment, with a β-lactam appears to be more effective than monotherapy in treating methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. However, results from the largest clinical trial to date have raised concerns over the effects of combination therapy on mortality and rates of acute kidney injury (AKI).

The CAMERA2 study, presented at this year’s European Congress of Clinical Microbiology and Infectious Diseases (ECCMID 2019), sought to evaluate the combination therapy through an investigator-initiated randomized controlled trial of patients with MRSA bacteremia.

Between August 2015 and July 2018, the trial enrolled 352 participants across 27 sites in 4 countries (Australia, New Zealand, Singapore, and Israel) who were found to have MRSA bacteremia within 72 hours of index blood culture draw, were 18 years or older, and were likely to remain an inpatient for ≥7 days. Participants were randomized to either the standard treatment, vancomycin or daptomycin, or the standard treatment plus an antistaphylococcal β-lactam (flucloxacillin, cloxelacin, or cefazolin).

The primary end point was a composite outcome at 90 days of all-cause mortality, persistent bacteremia at day 5 or beyond, microbiological relapse, or microbiological treatment failure, as assessed by a blinded adjudication committee. Secondary end points included individual elements of the composite primary end point, bacteremia at day 2, and AKI or need for renal replacement therapy.

The total participants included 252 from New Zealand or Australia, 56 from Singapore, and 44 from Israel. The median age of participants was 64 years, 34% were women, 64% had a health care–associated infection, and 15% were receiving haemodialysis. The modified intent-to-treat analysis included 344 participants (standard care, n = 174; combination, n = 170). The trial was stopped early on the recommendation of the data and safety monitoring board.

“The main result was that we found no difference in the primary end point, which was a composite of 90-day mortality, persistent bacteremia at day 5, and microbiological failure and relapse,” Steven Tong, PhD, associate professor at the Doherty Institute and Menzies School of Health Research and the presenter of the CAMERA2 study, told Contagion®. “However, what we did find was that there was a markedly increased risk of acute kidney injury in the combination arm. Of patients who received combination therapy, 30% developed acute kidney injury versus 9% in the standard therapy arm.”

Investigators found increased mortality in the combination arm, in which 21% of patients died versus 16% in the standard therapy arm, although the number of patients with persistent bacteremia at day 5 in the combination arm was significantly reduced compared with standard therapy.

In a post hoc exploratory analysis, 7 patients in the combination group ended up on renal replacement therapy versus just 2 in the standard therapy group.

“In retrospect now, we’re really pleased in some ways that we found something out—something unexpected but that, I think, has clinical impact,” Tong said. “It’s very clear to me that we should not be using a combination of vancomycin plus flucloxacillin for treatment of MRSA bacteremia. We ended up doing more harm to patients through that combination than the standard therapy group. I think this should actually give us pause in our enthusiasm for combination therapy for Staphylococcus aureus bacteremia.”

“The other key message is [that] the duration of bacteremia may not be a good surrogate end point,” Tong continued. “We reduced the duration of bacteremia—that was very clear—with combination therapy, but that had no impact on overall results, which was no difference in the composite primary end point.”

The study, “Combination Antibiotic Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: The CAMERA2 Randomized Controlled Trial,” was presented in an oral session April 16 at ECCMID 2019 in Amsterdam, the Netherlands.
Investigators Pinpoint 5 Factors Associated With Candida auris Colonization in Nursing Homes

BY ALEXANDRA WARD, MA

Even before Candida auris made the front page of The New York Times, the emerging health care–associated fungal infection had providers worldwide worried because of its multidrug resistance and invasiveness.

New York State has the highest rate of colonization, with more than 500 infected individuals, most of whom reside in nursing homes and many of whom are mechanically ventilated.

To identify opportunities to reduce transmission, investigators with the US Centers for Disease Control and Prevention and the New York State Department of Health analyzed the factors that lead to Candida colonization. Their findings were presented at the Society for Healthcare Epidemiology of America Spring 2019 Conference (SHEA Spring 2019).

From 2016 to 2018, the research team conducted point prevalence surveys for C auris colonization among nursing home residents in New York State. Swabs were collected from residents’ axilla, groin, and nares, and data on facility transfers, antimicrobials, and medical history were extracted from medical records.

The team deployed a matched case–control investigation, in which a case was defined as C auris colonization in a resident and then matched with up to 4 residents with negative swabs during the same point prevalence survey.

In total, investigators used 12 point prevalence surveys at 6 nursing homes to identify 60 cases and 218 controls. The team controlled for age, underlying conditions, functional status, and infection with other multidrug-resistant organisms in the 90 days before screening.

Investigators determined that the following factors are associated with C auris colonization: having a urinary catheter (adjusted odds ratio [aOR], 2.5; 95% CI, 1.1-5.4), having a tracheostomy (aOR, 8.2; 95% CI, 1.1-58.8), being on a ventilator (aOR, 3.4; 95% CI, 1.2-9.2), receiving meropenem in the prior 90 days (aOR, 2.5; 95% CI, 1.2-5.3), and having ≥1 hospitalization in the prior 6 months (aOR, 4.3; 95% CI, 1.8-10.0).

“Targeted screening of patients with the above risk factors for C auris can help identify those who are colonized and facilitate implementation of infection control measures to prevent transmission,” investigators concluded.

“Antibiotic stewardship and interfacility communication may be important factors in the prevention of C auris colonization.”

The study, “Factors Associated With Candida auris Colonization Among Residents of Nursing Homes With Ventilator Units—New York, 2016-2018,” was presented in an oral session on April 24 at SHEA Spring 2019 in Boston, Massachusetts.

Can Stethoscopes Transmit Multidrug-Resistant Bacterial Pathogens?

BY MICHAELA FLEMING

With burdens of nosocomial infections steadily increasing, it is important to determine sources of direct contact transmission.

The diaphragm of a stethoscope has been regarded as the second-most contaminated area, after the fingertips, but stethoscopes have not been studied in depth as a vector of nosocomial infection. In the few studies that explored the link between these instruments and bacterial infection transmission, most of the findings were limited to Staphylococcus.

But now, investigators from the College of Medicine at the Catholic University of Korea in Seoul, South Korea, have conducted a prospective observational study to determine whether stethoscopes are a potential carrier of nosocomial multidrug-resistant (MDR) bacteria. They presented their findings in a poster presentation at the Society for Healthcare Epidemiology of America Spring 2019 Conference (SHEA Spring 2019).

As a part of a quasi-experimental study in a 450-bed hospital in South Korea, investigators sampled stethoscopes of 86 of the 89 doctors and nurses who agreed to participate. The investigators imprinted the diaphragm of each instrument for 6 to 10 seconds on blood agar plates. For each sample, bacterial loads were calculated by total colony-forming units (CFUs) and the potential nosocomial pathogens were identified. Of the 86 stethoscopes, 85 (98.8%) were contaminated, with a mean CFU of 27.91 ± 32.46.

According to the investigators, 20 of the 85 contaminated stethoscopes (23.5%) were confirmed to have at least 1 potential pathogen, with Staphylococcus aureus detected in 13. Other detected isolates include Enterococcus, Enterobacter, Klebsiella, methicillin-resistant Staphylococcus aureus, and extended-spectrum β-lactamase-producing Klebsiella pneumoniae. No isolates of vancomycin-resistant Enterococcus, carbapenemase-producing Enterobacteriaceae, MDR-Acinetobacter, or Pseudomonas were detected.

The health workers were also surveyed via questionnaire about their cleaning procedures. The results indicate that 58 of the 89 participants (65.2%) were women and 44 (49.4%) were doctors.

Just 19 of the 89 participants (21.3%) reported cleaning their stethoscopes regularly at least once a day. The investigators observed that physicians were less likely to clean their stethoscopes (gender adjusted; P = .001; OR, 12.750; 95% CI, 2.730-59.546) and more likely to use their own stethoscopes instead of using those designated for examining isolated patients infected with MDR pathogens (gender adjusted; P < .001; OR, 8.762; 95% CI, 2.911-26.373).

“There were no significant risk factors associated with the contamination rate and bacterial load when multivariate regression analysis was performed using variables such as gender, job, age group, department, cleaning method, and frequency of stethoscope cleaning,” investigators noted.

Although the study determined that most of the stethoscopes were contaminated, and contamination by nosocomial pathogens was 23.5%, MDR pathogens were detected in just a small proportion.

Based on this research, the investigators concluded that there is a need for an evidence-based disinfection manual for stethoscopes.

The study, “Stethoscope as a Potential Carrier of Multi-Drug Resistant Bacterial Pathogens? Preliminary Data of Quasi-experimental Study,” was presented April 24 at SHEA Spring 2019 in Boston, Massachusetts.
Can Outpatient Oritavancin Therapy Prevent Hospital Admissions?

O ritavancin (Orbactiv) was approved in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible gram-positive organisms, but can its use in the outpatient setting help prevent hospital admissions for patients with cellulitis?

In an institutional review board–exempt, retrospective chart review study presented at the Making a Difference in Infectious Diseases (MAD-ID) 2019 meeting, investigators at Huntsville Hospital in Alabama compared the standard-of-care treatment for managing cellulitis, which involves inpatient admission and intravenous (IV) therapy, with outpatient infusion clinic administration of oritavancin to determine which is more clinically and economically advantageous.

Between February 2015 and December 2018, a total of 1348 patients were included in the standard-of-care arm, with a payer mix of 415 privately insured, 613 government insured, and 320 noninsured patients. The average length of hospital stay for patients with ABSSSI in the inpatient group was 3.4 days, with an average loss per month of $45,888. The 30-day readmission rate for patients with cellulitis was 3.6%.

A total of 201 patients were included in the outpatient oritavancin arm, with a payer mix of 75 privately insured, 92 government insured, and 34 noninsured patients. Patients in the oritavancin arm experienced an average monthly gain of $1231, and the total number of bed days saved with outpatient oritavancin administration was 683 days throughout the study period. The 30-day readmission rate for cellulitis was 0.5% in the outpatient oritavancin arm.

“From an outcome perspective, we saw that readmission rates were actually much less—even though our readmission rates were already low,” Jonathan Edwards, PharmD, BCPS-AQ ID, BCGP, ID pharmacist at Huntsville Hospital in Alabama and an investigator on the study, told Contagion®.

“When we utilized Orbactiv in the outpatient setting, the admission rates at that time were actually less, so we saw both clinical and financial benefit even in that very noncritically ill population for skin and skin structure.”

The study “Clinical and Economic Outcomes of Inpatient Standard of Care Versus Outpatient Oritavancin Therapy for Patients with Cellulitis” was presented at MAD-ID 2019, held May 8 to 11, 2019, in Orlando, Florida.

Patients With Gram-Negative Skin Infections Are 6 Times More Likely to Receive Inappropriate Empiric Therapy

BY ALEXANDRA WARD, MA

G ram-negative pathogens are increasingly responsible for acute skin and skin structure infections (SSSIs), which in general account for nearly 2% of all hospitalizations in the United States.

Investigators with Melinta Therapeutics, EviMed Research Group, BD, and GST Micro sought to analyze how administering inappropriate empiric therapy (IET) for patients with SSSIs caused by gram-negative organisms affects outcomes. Their results were presented at the Making a Difference in Infectious Diseases (MAD-ID) 2019 meeting.

Using BD research data on culture-positive bacterial skin/wound isolates from consecutive patients treated with empiric antibiotic therapy at 68 US acute care hospitals between 2015 and 2017, the research team categorized SSSIs as abscess, cellulitis, chronic ulcer, wound, or other multiple infection types and stratified by bacterial pathogen into gram-negative, gram-positive, or mixed.

If the antibiotic that was started within 5 days prior to final culture result did not cover the organism(s) or was resistant, IET was considered present. Investigators used International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes to classify the SSSIs.

A total of 9853 admissions met inclusion criteria. Of those, 40.2% involved a gram-negative organism. Overall, IET was administered to 13% (1284). Patients with only a gram-negative infection (odds ratio [OR], 6.4; 95% CI, 5.3-7.7; P <.0001) and/or mixed gram-negative/gram-positive pathogens (OR, 6.6; 95% CI, 5.6-7.6; P <.0001) were more likely to receive IET (22.8% [270 of 1184] vs 22.8% [633 of 2778], respectively) compared with patients with infections caused by only gram-positive organisms (6.5% [381 of 5891]). This difference was noted across all SSSI categories.

The investigators concluded that, compared with those with a gram-positive SSSI, patients with a gram-negative or a mixed infection, irrespective of the type, have about 6 times the odds of being exposed to IET. Glenn Tillotson, PhD, a consultant with GST Micro and an investigator on the study, discussed the findings with Contagion® at MAD-ID 2019. “The main [observation] from our work was the fact that gram-negative pathogens, such as Pseudomonas aeruginosa [and Escherichia] coli, were actually more common in the skin infection area...than expected. Everyone seems to think and believe that gram-positives, such as [Staphylococcus] aureus of either methicillin-resistant or methicillin-susceptible group A strep [are associated] with skin infections,” Tillotson said.

“However, we looked at different categories of skin infection—abscess, cellulitis, wound—and saw a remarkably high incidence of gram-negatives...often in combination with the Staph aureus. If you believe the gram-positive-only story, you will miss the appropriate treatment of the gram-negatives, and those gram-negatives would lead to bad outcomes.”

The study "Pathogen Type and Inappropriate Empiric Therapy (IET) in Culture-Positive Skin and Soft Tissue Infection (SSI) Among Hospitalized Patients in the United States, 2015-2017" was presented at MAD-ID 2019, held May 8-11, 2019, in Orlando, Florida.
Previous research has shown that using a rapid diagnostic test for bloodstream infections can improve clinical outcomes—specifically, when accompanied by antimicrobial stewardship interventions for gram-positive bloodstream infections. However, scant data are available regarding outcomes of gram-negative bloodstream infections in the absence of antimicrobial stewardship involvement.

Now a team of investigators from the University of Maryland schools of Pharmacy and Medicine has conducted a retrospective, quasi-experimental study of patients with gram-negative bloodstream infections. The findings were presented in a poster session at the Making a Difference in Infectious Diseases (MAD-ID) 2019 annual meeting.

The Verigene Blood Culture Gram-Negative Test (VBC-GN) is a rapid diagnostic that can detect key gram-negatives, as well as resistance, within hours. For the study, the investigators followed patients with VBC-GN target gram-negative bloodstream infections between December 2014 and September 2015 for preimplementation information and between October 2015 and May 2017 for postimplementation data.

Of the 547 patients included in the study, 238 were identified as preimplementation and the remaining 309 were sorted into the postimplementation group. According to the investigators, the 2 groups had similar baseline characteristics. Among all participants, the median age was 58 years, and 62% of participants were men. The most commonly observed infections were Escherichia coli (38%) and urinary (31%) and intra-abdominal (22%).

In an interview at MAD-ID 2019, Contagion spoke with the presenter of the poster, Kimberly Claey, PharmD, an assistant professor of pharmacy practice at Maryland School of Pharmacy.

The investigators indicated that the appropriateness of antibiotics in the study was determined based on the final susceptibility results. They also noted that "optimal antibiotics were not overly broad, accounting for resistance, source of infection, and other infecting organisms." The study team reported that categorical variables were compared using Chi-squared/Fisher's exact and continuous variables with Mann-Whitney U tests, with time to event analyzed through Kaplan-Meier survival analysis.

Results indicate that postimplementation patients had higher rates of previous extended-spectrum beta-lactamases (3.8% vs 8.1%; P = .048). Appropriate therapy was achieved in 99% of patients, with time to appropriate therapy similar in both groups (2.7 [interquartile range (IQR), 1.5–3.9] vs 4.2 [IQR, 2.5–5.8] hours; P = .408).

Optimal therapy was reported to be achieved in 66% of the preimplementation population versus 79% postimplementation population (P < .001), with time to optimal therapy significantly shorter in the postimplementation group (47 [IQR, 5.3–61.2] vs 24 [IQR, 12.49]; P = .018). Time to de-escalation was noted as similar in both groups (62 [IQR, 48–84] vs 64 [IQR, 25.8–89.2]; P = .572). Time to escalation was significantly shorter post implementation (50.7 [IQR, 18.1–65.3] vs 20.6 [IQR, 14.9–30.2]; P < .001). Additionally, the median hospital and postbloodstream duration of stay, in days, were similar (16.9 [IQR, 6.4–32.3] vs 15.9 [7.8–29.4]; P = .738), (9.5 [IQR, 5.1–18.8] vs 9.8 [IQR, 5.4–19.6]; P = .509), respectively. Inpatient mortality was 15% in each group, as well.

"Implementation of VBC-GN without active antimicrobial stewardship intervention was shown to improve time to optimal therapy, which was primarily driven by decreased time to antibiotic escalation," the authors conclude, noting that stewardship intervention could further improve the time through optimal de-escalation.

Claey also told Contagion that there will be 3 phases of this research, and the third stage will include stewardship involvement. This research was funded by MAD-ID, Claey said.

The poster "Impact of Verigene Blood Culture Gram-Negative Without Active Stewardship Intervention" was presented May 9, 2019, at MAD-ID 2019 in Orlando, Florida.

Residents: The Lost Stakeholders in Stewardship

As antimicrobial stewardship becomes a critical element of improving patient care, a team of investigators from the University of Pittsburgh Medical Center (UPMC) Mercy and UPMC St. Margaret hospitals in Pennsylvania have noticed that some stakeholders may be underrepresented in stewardship programs. According to guidelines published by the Infectious Diseases Society of America in 2016, antimicrobial stewardship programs (ASPs) should be led by an infectious disease physician and infectious disease pharmacists with additional stewardship training. However, most of these programs feature additional stakeholders, including department representatives from infection control, microbiology, hospitalists, nursing, and hospital administration, the investigators noted.

The study team noticed that medical residents are among the underrepresented stakeholder groups that have the potential to play a critical role in the growth of ASPs and that very few programs have a resident champion program (RCP).

Therefore, the investigators designed a survey to evaluate the opinions and perceptions of ASPs by internal medicine and family medicine residents. The findings were presented in a poster session at the Making a Difference in Infectious Diseases (MAD-ID) 2019 annual meeting.

The 10-question survey was distributed to 133 residents across 3 hospitals within a large health system. "Interactions between residents and ASPs at a hospital with an RCP were compared with 2 hospitals without an RCP," the investigators said.

In total, 47 residents completed the survey (24 RCP, 23 non-RCP). All 24 RCP residents were aware of their hospital’s stewardship program compared with 9 of 23 (39.1%) non-RCP residents (P < .001). Additionally, 18 of 24 (75%) RCP residents were aware of the RC.

 Among residents aware of the stewardship program, 20 of 24 (83.3%) RCP residents reported interactions with ASP versus 3 of 9 (33.3%) non-RCP residents (P = .007). At the RCP, 23 of 24 (95.8%) residents knew at least 1 member of the ASP team compared with 2 of 9 (22.2%) non-RCP residents (P < .001). Further, increased satisfaction with ASP recommendations was reported by RCP residents, with 12 of 24 (50%) rating satisfaction as exceeding expectations or outstanding and 11 of 23 (47.9%) rating it as acceptable, whereas all 9 non-RCP residents responded with an acceptable rating (P = .027).

The authors concluded that for ASPs to be successful, they must be supported by all of the health system’s stakeholders. Residents can often be overlooked as stakeholders but are “frontline providers at a formative stage of their developing medical career,” the authors write, elaborating that “this presents a prime opportunity to educate and foster good stewardship practice behaviors that they will utilize throughout their careers.”

The authors said they hope that the study will provide a foundation for the inclusion of an RC in hospital ASPs, because these individuals can be a liaison to facilitate more frequent interactions and enhanced perception of stewardship teams. The poster "The Lost Stakeholders in Antimicrobial Stewardship" was presented May 9, 2019, at MAD-ID 2019 in Orlando, Florida.
An Unusual Case of Testicular Swelling in a Patient With HIV

Being immunocompromised increases risk of rare *Mycobacterium tuberculosis* epididymo-orchitis.

BY JANE ABERNETHY, MD CANDIDATE; SUSAN A. INNIS, MD; LAUREL J. GLASER, MD, PHD; AND WILLIAM R. SHORT, MD, MPH

**HISTORY OF PRESENT ILLNESS:**
A 42-year-old man presented to the hospital with approximately 2 weeks of right testicular pain and swelling. He received a diagnosis of epididymo-orchitis and was treated with ceftriaxone 250 mg intramuscularly and doxycycline 100 mg twice daily for 14 days. During a follow-up visit at his primary HIV provider’s office, the patient noted that he had less pain, but his swelling had not resolved. He denied any history of fever, weight loss, night sweats, cough, or hemoptysis.

**MEDICAL HISTORY:**
The patient had a history of HIV, which was diagnosed in 2014 and had been treated with abacavir/dolutegravir/lamivudine (Triumeq). One month prior to admission, his CD4 count was 304 (22%), and his HIV RNA by polymerase chain reaction (PCR) was undetectable. Early in his diagnosis, he had frequent episodes of syphilis, now with a nonreactive rapid plasma regain after adequate treatment.

**MEDICATION:**
Abacavir/dolutegravir/lamivudine

**ALLERGIES:**
No known drug allergies

**EPIDEMIOLOGIC HISTORY:**
The patient was born in the United States and lived on the East Coast. He denied any national or international travel. He denied smoking, alcohol, and illicit drug use. He had a pet dog. He had a history of incarceration for approximately 6 months many years ago.

**PHYSICAL EXAMINATION:**
The patient appeared well. His temperature was 98.6°F; heart rate, 75 beats per minute; blood pressure, 110/70 mm Hg; and respirations, 14 per minute. His lungs were clear to auscultation bilaterally. A cardiac exam showed normal S1 and S2, with no murmurs. An abdominal examination showed normoactive bowel sounds with no tenderness and no hepatosplenomegaly. On a genital exam, the patient’s right testicle was swollen and nontender; the left was normal. The inguinal lymph nodes were not palpable.

**STUDIES:**
Lab studies revealed normal leukocyte, hemoglobin, and platelet counts. The blood urea nitrogen was 12 mg/dL; creatinine level, 1.15 mg/dL; aspartate aminotransferase, 27 U/L; and alanine aminotransferase, 15 U/L. A urine nucleic acid amplification test for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* was negative, as was a urine culture. A computed tomography scan of his abdomen and pelvis with contrast showed a large right testicle measuring 8.3 × 3.5 × 3.5 cm with heterogeneous enhancement and adjacent fluid. The serum tumor markers β-human chorionic gonadotropin and β-fetoprotein were within normal limits.

**CLINICAL COURSE:**
The patient was referred to urology to rule out malignancy. After a long discussion, a decision was made to pursue a right inguinal exploration. Despite negative malignancy markers and due to the appearance of the testicle, the patient underwent a right orchiectomy. On gross examination, the testicle was 8 cm, with a smooth-walled cyst and 2 ill-defined masses/thickened areas in the testis and epididymis with purulent material.

**DIAGNOSTIC PROCEDURES AND RESULTS**
The operating room specimen was sent to pathology, and the right testicle and epididymis showed large areas of destruction by multiple caseating and noncaseating epithelioid granulomas with scattered foreign body giant cells and surrounding fibrosis (Figure 1). The auramine-rhodamine stain showed a few rodlike bacteria, highly suspicious for *Mycobacterium* species (Figures 2 and 3). There was not enough of the sample to be sent for an acid-fast bacilli (AFB) culture. The testicular specimen was sent to the US Centers for Disease Control and Prevention for PCR testing, and tuberculosis (TB) was confirmed. Because this was PCR, susceptibilities could not be performed. Three early-morning urine specimens were sent to the lab for AFB stain and culture. All urine specimens grew *Mycobacterium tuberculosis* (Mtb).
Being immunocompromised increases risk of rare An Unusual Case of Testicular Swelling in a Patient With HIV.

TREATMENT AND FOLLOW-UP:
The patient was started on a 4-drug treatment regimen of isoniazid, ethambutol, pyrazinamide, and rifabutin along with pyridoxine pending susceptibility testing. After 2 months, his susceptibility testing was available (Table), and the isolate was susceptible to all first-line drugs. Subsequently, ethambutol and pyrazinamide were discontinued.

<table>
<thead>
<tr>
<th>Organism ID: M tuberculosis complex</th>
<th>Drug, MIC</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin 1 mcg/mL</td>
<td>Susceptible</td>
<td></td>
</tr>
<tr>
<td>Isoniazid 0.1 mcg/mL</td>
<td>Susceptible</td>
<td></td>
</tr>
<tr>
<td>Rifampin 1 mcg/mL</td>
<td>Susceptible</td>
<td></td>
</tr>
<tr>
<td>Ethambutol 5 mcg/mL</td>
<td>Susceptible</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide mcg/mL</td>
<td>Susceptible</td>
<td></td>
</tr>
</tbody>
</table>

Tuberculosis: TB is a multisystem disease, it exclusively presents in the fourth and fifth decade. History of prior TB infection, close contact with TB infected individuals, travel to endemic areas, or immune system compromise may be helpful diagnostically, but these data points are not always present. Eighty percent of hosts infected with genital TB may develop a scrotal swelling, which is painful in approximately 44% of cases. It is often accompanied by ulceration or a draining sinus tract and may present with lower urinary tract symptoms such as dysuria and hematuria. Genital TB without evidence of pulmonary disease can occur, and systemic symptoms such as fever, chills, and night sweats are not reliably present. Presentation may mimic multiple conditions including testicular tumor, testicular torsion, hydrocele, acute infections, or testicular sarcoidosis.

Because of the disease’s nonspecific symptoms, it is recommended that TB always be considered in the differential diagnosis of cases with prolonged, unresolved urinary symptoms.

Early diagnosis is critical to preventing destruction and fibrosis, which can lead to infertility, contracted bladder, bilateral kidney injury, and end-stage renal disease. Microscopic analysis of the urine may yield nonspecific findings such as sterile pyuria, microscopic or macroscopic hematuria, or acidic urine. Definitive diagnosis can be made by urine acid-fast culture cultures, a method that is time intensive, with relatively low sensitivity due to sporadic shedding of bacilli. Due to these constraints, PCR testing can be performed on urine, expressed prostatic secretions, or ejaculate. PCR is less sensitive and similarly specific compared with culture, but it is advantageous due to its rapidity. PCR cannot, however, differentiate between live and dead organisms. In this case, histopathological examination should be attempted with inguinal exploration, yielding caseous necrosis or stained AFB testing for definitive diagnosis. Necrotizing granulomatous inflammation without evidence of AFB suggests TB but can also represent another infectious agent, such as species of Brucella or Blastomyces, Treponema pallidum, and nontuberculous mycobacteria, as well as others. For this reason, tissue PCR for TB is still useful in optimizing diagnostic precision.

Of the 10 million incident cases of TB in 2017, 9% were coinfected with HIV. Patients with HIV are more susceptible to all manifestations of TB infection, including epididymo-orchitis, due partly to the critical role of CD4-positive T lymphocytes in the control of the disease. First-line treatment for drug-susceptible strains in both immunocompetent and immunocompromised hosts is antimycobacterial chemotherapy including a course of isoniazid, rifampin, ethambutol, and pyrazinamide with pyridoxine.

A 6-month course is likely as effective in urogenital TB as it is in pulmonary TB because pulmonary TB is the more standard presentation. No randomized control trial has been performed to identify the ideal treatment duration. Despite the effectiveness of treatment with this regimen, regular annual follow-ups are recommended to evaluate for relapse.

References available at ContagionLive.com.
The healthcare industry is evolving at a rapid pace. The need for relevant expert-driven opinions and insights is crucial to continuing the advancement of patient outcomes. With platforms like HealthAdviser, physicians and healthcare professionals can empower their voice to make a difference in market research studies designed to have an impact on the pharmaceutical and healthcare industries. HealthAdviser is a community of nearly 20,000 healthcare professionals who are given an opportunity to participate in market research studies from HRA®, a trusted market research firm for over 40 years, and earn honoraria for their contributions.

“It empowers subject-experts by providing them with a platform to share knowledge unique to their experience as a HCP, patient, or caregiver”, said Ryan Pitcherello, Quantitative Operations Associate at HRA. “This gives them the opportunity to make a difference on a larger scale than would be possible in their day-to-day duties,” said Pitcherello.

Aside from earning honoraria, healthcare professionals can make a difference with an opportunity to shift the industry with their opinions and to further their relationships with their peers. “The importance of registering for the HealthAdviser panel is that it allows you as a customer or stakeholder the ability to participate in research studies, by providing your opinions. These opinions help others understand the needs for, new products and/or improvements on existing products,” said Patrick Chapman, Senior Manager, Qualitative Field Operations and Conference Controller at HRA. “Your participation in market research helps with decisions on goods and services and why customers may choose a brand or service over a competitor. Market research identifies new business opportunities and the change of market trends,” said Chapman.

With the advancement of technology and the critical need for expert insights, there has never been a better time to get involved. For more information on joining HealthAdviser, please visit www.health-adviser.com.