EMERGING & RE-EMERGING INFECTIONS

What the 2018 DRC Ebola Epidemic Taught Us About Outbreak Response and Experimental Countermeasures

How has treating infections changed with the availability of experimental vaccines and therapeutics, and how can we apply this to COVID-19 today?

By Brayden Schindell; Jason Kindrachuk, PhD; and Krutika Kuppalli, MD

On August 1, 2018, the Ministry of Health of the Democratic Republic of the Congo (DRC) declared the country’s 10th Ebola virus disease (EVD) outbreak after a cluster of 26 cases of acute hemorrhagic fever that led to 20 deaths in Mabalako Health Zone was confirmed to be due to Ebola virus. Over the past 20 months, the EVD outbreak in North Kivu and Ituri provinces has developed into the largest and most complex in the country’s history, and only recently has it appeared that there might be an end in sight. The most recent data from March 3, 2020, report 3444 cumulative cases (3310 confirmed and 134 probable), with 2264 deaths (2130 confirmed and 134 probable) and 1168 survivors, for a fatality rate of 65.7%. Although the DRC has successfully contained more EVD outbreaks than any other country in the world, efforts to end the current one have been arduous given its occurrence in a war zone.
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TABLE OF CONTENTS

EMERGING & RE-EMERGING INFECTIONS

What the 2018 DRC Ebola Epidemic Taught Us About Outbreak Response and Experimental Countermeasures

How has treating infections changed with the availability of experimental vaccines and therapeutics, and how can we apply this to COVID-19 today?

BY BRAYDEN SCHINDELL; JASON KINDRACHUK, PHD; AND KRUTIKA KUPPALLI, MD

IN THE LITERATURE

5 Piperacillin/Tazobactam for the Treatment of ESBL Pyelonephritis: A Redemption Arc
BY TIFFANY LEE, PHARMD

6 Living and Aging With HIV: Recognition and Management of Common Prescribing Pitfalls
BY ANIRUDDHA (ANU) HAZRA, MD

MEDICAL WORLD NEWS

7 Learn more about important and trending infectious disease news from around the world.

NEWS & BREAKTHROUGHS

9 Progress in the 10 x ‘20 Initiative?
IDS reached its goal, but nobody’s buying. Can the drowning antimicrobial pipeline be saved?
BY HELEN W. BOUCHER, MD, FACP, FIDSA

ACUTE INFECTIONS

11 Amid Coronavirus Confusion, Tried-and-True Prevention Measures Matter
Christina Tan, MD, MPH, from the New Jersey Department of Health discusses COVID-19.
BY JARED KALTWASSER

HIV/ AIDS

15 Ending the HIV Epidemic Initiative: A Snapshot From the Trenches, 1 Year Later
Funded jurisdictions scramble to meet daunting deadlines yet maintain optimism.
BY MELANIE THOMPSON, MD

MULTIDRUG-RESISTANT INFECTIONS

17 The Search Continues for How to Best Treat Non–Carbapenemase-Producing CRE Infections
Given the limited clinical data, the preferred therapeutic approach remains unknown.
BY BEJOY PAUL MANIARA, PHARMD, BCPS, BCIDP

STEWARDSHIP & PREVENTION

19 New Rules Expand Application of the NTAP Program for Innovative Antibiotics
To better support the use of critical antibiotics, the Centers for Medicare & Medicaid Services revised the rules governing reimbursement for qualifying products.
BY MONIKA SCHNEIDER, PHD

INSIGHTS

21 Optimizing Treatment and Reducing Costs for Acute Bacterial Skin and Skin Structure Infections
BY GINA BATTAGLIA, PHD

MEETING COVERAGE

23 Coverage from the Transplantation & Cellular Therapies Meetings 2020 and the 49th Critical Care Congress.

CASE STUDY

25 A Case of Disseminated Nocardia farcinica Presenting as Fever of Unknown Origin in a Transplant Patient
Outcomes in disseminated nocardiosis are variable and depend on patient factors.
BY STEPHANIE SPIVACK, MD, AND PAUL LEONE, MD

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Active member of the Society of Infectious Diseases Pharmacists
COVID-19 Is Moving Quickly, but Let’s Take Notes

AS MY DEADLINE for turning in this column approached, I had no doubt what its topic would be. Anyone who follows me on Twitter knows that coronavirus disease 2019 (COVID-19) bumped antimicrobial resistance as the focus of my attention. However, I knew that whatever I wrote would be immediately out-of-date. That concern in itself has become the focus. As we address the challenges ahead, let’s take care to record the history to guide us next time.

As the pandemic presses on, each day brings more updates. Practitioners making quick patient care and policy decisions while keeping up with advancing literature and monitoring their own health are hard-pressed to do anything else. However, I believe it is crucial that we document the advance of COVID-19 and our successes and failures along the way.

We are encountering COVID-19 with an inter-connected, international society that presents new opportunities and obstacles. Social media is ubiquitous, offering a platform for the dissemination of good ideas (such as a shared Google document on treatment possibilities, started by Dr. Neil Glasser, Officer at Contagion). As part of our commitment to providing clinicians with the tools required to prevent disease transmission and optimize patient outcomes, we will continue to work alongside our Strategic Alliance Partners and Editorial Advisory Board to deliver a product that offers true utility to the infectious diseases community, and now is a key time for us to deliver.

Be well, and thank you for reading Contagion.

JASON C. GALLAGHER, PHARMD, FCCP, FIDP, FIDSA, BCPS

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When a Novel Pathogen emerges, it is likely to incite panic throughout the globe, and that is exactly what has happened in reaction to coronavirus disease 2019 (COVID-19).

In the wake of the pandemic, we have seen disrupted daily activities, voluntary quarantines, and travel restrictions. COVID-19 also has upset our spring conference season and inhibited our ability to gather together to share science.

In response to the outbreak, we launched the Contagion Live News Network, a video series featuring regular updates on COVID-19, filmed by our editorial staff at MJH Studios. We also developed a coronavirus resource center on our website, updated daily with news stories, literature reviews, and clinician-authored content.

Chairman's Letter

In the Face of a Pandemic, Educated Clinicians Bring More Value Than Ever

WE have seen the unprecedented impact of COVID-19 on our work as clinicians. As the pandemic presses on, each day brings more updates. Practitioners making quick patient care and policy decisions while keeping up with advancing literature and monitoring their own health are hard-pressed to do anything else. However, I believe it is crucial that we document the advance of COVID-19 and our successes and failures along the way.

We are encountering COVID-19 with an inter-connected, international society that presents new opportunities and obstacles. Social media is ubiquitous, offering a platform for the dissemination of good ideas (such as a shared Google document on treatment possibilities, started by Dr. Neil Glasser, Officer at Contagion). As part of our commitment to providing clinicians with the tools required to prevent disease transmission and optimize patient outcomes, we will continue to work alongside our Strategic Alliance Partners and Editorial Advisory Board to deliver a product that offers true utility to the infectious diseases community, and now is a key time for us to deliver.

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In the wake of the pandemic, we have seen disrupted daily activities, voluntary quarantines, and travel restrictions. COVID-19 also has upset our spring conference season and inhibited our ability to gather together to share science.

Our audience is uniquely affected by this situation. As infectious disease clinicians, scientists, and investigators, our readers are on the front lines of the COVID-19 response. At MJH Life Sciences®, we are committed to providing our readers with up-to-date news on COVID-19 as more information becomes available. Our goal is to educate our readers with the facts about the novel coronavirus and cut down on unnecessary hysteria.

In response to the outbreak, we launched the Contagion Live News Network, a video series featuring regular updates on COVID-19, filmed by our editorial staff at MJH Studios. We also developed a coronavirus resource center on our website, updated daily with news stories, literature reviews, and clinician-authored content.

As part of our commitment to providing clinicians with the tools required to prevent disease transmission and optimize patient outcomes, we will continue to work alongside our Strategic Alliance Partners and Editorial Advisory Board to develop informative articles about COVID-19.

In times like these, we cannot underestimate the value of an informed clinician.

Make sure you visit our website and use the Outbreak Monitor to track the spread of COVID-19 in the United States and abroad. You can keep up with us on Facebook (@ContagionLive), Twitter (@Contagion_Live), and LinkedIn (@Contagion_Live).

Please contact Senior Editor Michaela Fleming at mfleming@contagionlive.com if you have any questions or comments.

Stay informed, stay well, and thank you for reading.

Michael Hennessy Sr Chairman and Founder
G ram-negative bacteria that produce extended-spectrum β-lactamase (ESBL) enzymes are a prevalent global threat because of their efficiency in hydrolyzing and rendering many β-lactam antibiotics ineffective. Carbapenems, over time, became the treatment of choice for ESBL infections. However, interests have recently skewed toward the use of carbapenem-sparing regimens in light of growing selection for carbapenem-resistant organisms.1

Piperacillin/tazobactam, a commonly used agent, retains a broad spectrum of activity against many gram-negative pathogens. Tazobactam, a β-lactamate inhibitor, restores in vitro activity to piperacillin particularly in the presence of ESBL genes.2 Prior clinical experience with using piperacillin/tazobactam for invasive ESBL infections resulted in mixed conclusions until the MERINO trial (NCT02176122).3 In MERINO, piperacillin/tazobactam failed to reach noninferiority in 30-day mortality rates compared with meropenem for the treatment of ESBL bacteremia.4

Despite these results, the utility of piperacillin/tazobactam for less complicated ESBL infections is still debated. Its use in urinary infections is particularly appealing, due to both the prevalence of infections and the concentration of drug. Piperacillin/tazobactam displays a high degree of renal drug excretion, theoretically providing a high enough concentration to overcome resistance mechanisms in the urine. In a retrospective study, Sharara and colleagues further explored this by comparing piperacillin/tazobactam and carbapenems for upper urinary tract infections.5

Patients were included following a diagnosis of pyelonephritis caused by a molecularly confirmed ESBL-producing Enterobacterales and receipt of either piperacillin/tazobactam or a carbapenem within 48 hours from initial urine culture. Medications had to be continued for at least 72 hours, unless transitioned to a fluoroquinolone or trimethoprim-sulfamethoxazole for the remainder of therapy. Relevant exclusion criteria included receipt of antibiotics not susceptible to the uropathogen or with suboptimal penetration into renal parenchyma, receipt of the alternative study drug following 72 hours of initial therapy, and presence of concomitant infections including bacteremia and renal abscess.

The primary outcome was the rate of 30-day recurrence of cystitis or pyelonephritis with the index organism. Secondary outcomes included rates of symptom resolution by day 7 of therapy, 30-day mortality, and identification of carbapenem-resistant organisms in the 60 days following the start of antibiotics.

Authors used inverse probability weighting to account for baseline population differences between the 2 treatment arms. In brief, multivariate logistic regression is performed to identify influential patient characteristics that may broadly affect receipt of 1 of the 2 treatment arms. Taking into consideration these factors, a separate population is created to balance the propensity for high-risk or tenuous patients to preferentially receive meropenem in light of an ESBL-producing pathogen and provide more weight to those receiving the “unexpected” drug.

Overall, 188 patients met inclusion, with 47 (25%) receiving piperacillin/tazobactam and 141 (75%) receiving a carbapenem. The process of inverse probability weighting included 45 (24%) patients receiving piperacillin/tazobactam and 141 (76%) receiving a carbapenem. Patients in both treatment arms had a median age of about 63 years, with a slight female predominance (~68%). Overall baseline demographics were notable for fairly high rates of immunosuppression (48%), urologic abnormalities (45%), and intensive care unit admission (27%). The most common uropathogens were Escherichia coli (56%) and Klebsiella pneumoniae (30%), with most harboring a CTX-M (87%) or SHV-type (24%) ESBL gene. Median minimum inhibitory concentration for study medications were 2 mcg/mL (interquartile range [IQR]: 2-8) and 2 mcg/mL (IQR: 2-16) mcg/mL in the piperacillin/tazobactam and carbapenem groups, respectively. Details on the initial antibiotics used, including durations and rates of oral step-down, are listed in Table 1.

Results of the primary and secondary outcomes within the weighted cohort are summarized in Table 2 online. Ultimately, there were no differences seen between the arms across all outcomes. Notably, there was a higher numerical but not statistical rate of subsequent carbapenem-resistant isolates observed in the carbapenem arm compared with the piperacillin/tazobactam arm, particularly with non–lactose fermenting rods.

Many nuances and factors affect a clinician’s choice of antibiotics in the setting of an ESBL pathogen, including infection severity and site. This study suggests that for urinary ESBL infections, piperacillin/tazobactam may still be a treatment option. However, external validity and applicability rest on methods of ESBL identification (ie, genotypic vs phenotypic) and regional distributions of resistance genes, as well as institutional differences in dosing and administering antibiotics (ie, intermittent vs extended infusion). Another commonly used antibiotic, cefepime, although structurally stable against many β-lactamases, has similarly conflicting data in treating ESBL infections.6 As increased pressure for carbapenem-sparing regimens develops, future prospective studies investigating both piperacillin/tazobactam and cefepime are needed to define their place in therapy for ESBL infections.7

References are available at ContagionLive.com.

TABLE 1. Initial and Step-down Antibiotic Treatment Regimens in the Inverse Probability Weighted Cohort

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Initial Antibiotics, n (%)</th>
<th>Median Duration, Days (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>2 (4.4)</td>
<td>9 (7-13)</td>
</tr>
<tr>
<td>Cefepime</td>
<td>0</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td>Piperacillin/ Tazobactam</td>
<td>43 (95.5)</td>
<td>9 (7-12)</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0</td>
<td>8 (7-10)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>4 (2.8)</td>
<td>10 (7-14)</td>
</tr>
</tbody>
</table>

IQR indicates interquartile range.

HIGHLIGHTED STUDY

Is piperacillin-tazobactam effective for the treatment of pyelonephritis caused by ESBL-producing organisms?

Living and Aging With HIV: Recognition and Management of Common Prescribing Pitfalls

BY ANIRUDDHA (ANU) HAZRA, MD

With advancements in antiretroviral therapy (ART), people with HIV (PWH) are now living longer and developing age-related chronic conditions that require medications in addition to ART. Studies have demonstrated that older PWH have a substantially higher frequency of medication-related problems, polypharmacy, and potential drug-drug interactions (DDIs) compared not only with their younger counterparts but age-matched HIV-negative counterparts.1,2 To better serve our growing population of older PWH, we must assess prescribing patterns as they pertain to HIV and aging.

The Swiss HIV Cohort Study (SHCS) is a multicenter prospective cohort study that has been enrolling PWH in Switzerland since 1988. As a collaboration among the infectious disease outpatient clinics of all Swiss University Hospitals, 2 large regional hospitals, and affiliated smaller hospitals, the SHCS represents one of the largest cohorts of PWH followed in any country and one of the only ones prospectively analyzing prescriptions filled by PWH.2 Previously, the SHCS has found a higher number of comedications and more severe effects of DDIs in older PWH compared with their younger PWH counterparts.2,3

To better understand the prevalence of potentially inappropriate medications (PIMs), this study’s authors compared prescribed medications, polypharmacy, and potential DDIs between young and older PWH in 2 SHCS outpatient sites.5 Participants were contacted by mail 1 week prior to their twice-yearly SHCS appointment and asked to report all current medication names and doses. Those 65 years and older were classified as “older.” Drugs reported by participants included ARTs, prescription medications, and over-the-counter medications. If a drug contained 2 or more active agents, each substance was counted individually. Polypharmacy was defined as concurrent administration of 5 of more comedications in addition to ART. PIMs were assessed using the classical Beers Criteria, and anticholinergic burden was measured by the Anticholinergic Risk Scale.6,7

Because of data gleaned from prior SHCS research, this study focused on cardiovascular (CV) and central nervous system (CNS) medications; these 2 therapeutic classes were the most used by PWH and had the most clinically relevant potential DDIs with ARTs. All the returned forms indicating use of at least 1 CV or CNS comedication were included in the study, and potential DDIs were screened and flagged based on their clinical significance. All medication forms provided during the observed 24-month period were considered in the analysis.

Of the 996 PWH participating in the study, 874 (88%) were aged less than 65 years, with a median age of 49 years; the remaining 122 (12%) were 65 years and older, with a median age of 71 years. A total of 1610 forms were collected, with the majority of participants (57%) completing the form on 2 separate occasions. Older PWH were more likely to be prescribed a combined ART regimen in addition to their nucleoside reverse transcriptase inhibitor (NRTI) backbone. Combined ARTs were defined as boosted protease inhibitor (PI) plus integrase strand transfer inhibitor (INSTI), a boosted PI plus nonnucleoside reverse transcriptase inhibitor (NNRTI), or a boosted PI plus INSTI plus NNRTI. These regimens represented complex ARTs that were characterized by a higher potential to cause DDIs. Nearly 50% of all ART regimens included an INSTI, regardless of age group (Table). The number of comedications increased with age, with older PWH using a median of 4 comedications compared with a median of 1 in their younger counterparts. CV medications were more commonly prescribed to older PWH, whereas CNS medications were more commonly prescribed to younger PWH. A total of 38 older patients (31%) had been prescribed at least 1 PI, the majority of which were benzodiazepines and hypnotics.

Over the study period, 767 forms collected from 500 PWH contained at least 1 CV or CNS medication; the majority of forms (54%) did not contain any potential DDIs. Of those that did, there was no significant difference in potential DDI severity between PWH age groups. Similar to prescribing distribution, older PWH were more likely to have potential DDIs between ART and CV drugs, whereas younger

| Table. ART Regimens (Excluding NRTIs) for the Entire Period, Stratified by Age Group |
|----------------------------------|----------------------------------|
| Integrase strand transfer inhibitor (INSTI) | <65 years (n = 874) | 413 (47.3) |
| Combined regimen* | Combined regimen* | 136 (15.6) |
| Non-nucleoside reverse transcriptase inhibitor (NNRTI) | Non-nucleoside reverse transcriptase inhibitor (NNRTI) | 238 (27.2) |
| Protease inhibitor (PI) | Protease inhibitor (PI) | 85 (9.7) |

*PI + INSTI or PI + NNRTI or PI + NNRTI + INSTI.

PWH were more likely to have potential DDIs between ART and CNS drugs. Ritonavir-boosted darunavir, a boosted PI, was the most common ART involved in potential DDIs of higher severity. Of the potential DDIs between ARTs and CV or CNS medications nearly all were managed properly through dosage adjustments. These new data from the SHCS demonstrate that not only are older PWH prescribed a higher number of comedications, but they also receive more complex ART regimens. Interestingly, there was not a significantly higher frequency of potential DDIs in older PWH compared with younger patients; this could be explained by an overall low rate of potential DDIs and robust prescriber knowledge of these interactions. However, it is also important to note that this analysis focused on only 2 therapeutic classes, and potential DDIs were assessed between only 2 compounds; this does not fully address the complexity of DDIs noted in polymedicated patients. In addition to receiving potential DDIs, 31% of older PWH were prescribed at least 1 PI during the observed period. This is likely an underestimate, as the study could not include all criteria that define inappropriate prescribing.

This study’s results reinforce that potential DDIs and polypharmacy remain a common problem for older PWH. As the realms of HIV medicine and geriatric medicine continue to overlap, we must recognize and address these prescribing issues using well-established geriatric principles and approaches. ▲

References are available at ContagionLive.com.

HIGHLIGHTED STUDY

Polypharmacy, Drug-Drug Interactions, and Inappropriate Drugs: New Challenges in the Aging Population With HIV.

US Flu Cases Reach 36 Million; Pediatric Hospitalization Rates Hit Record High

BY MICHAELA FLEMING

Data from the US Centers for Disease Control and Prevention (CDC) indicate at least 36 million cases of influenza in the 2019-20 US flu season. As of March 7, 2020, there were 370,000 flu-related hospitalizations and 22,000 associated deaths.

According to the CDC, for the younger populations, hospitalization rates reached the highest on record since influenza reporting began in 2004-2005. The rate for children and young adults surpassed that documented during the second wave of the 2009 H1N1 pandemic.

At the end of the first week in March, influenza B/Victoria and A(H1N1)pdm09 viruses were approximately equal for the season overall, and continued increases in influenza A (H1N1)pdm09 viruses have been seen in recent weeks.

The predominant influenza virus continues to vary by age group. Nationally, influenza B viruses are the most common among children and young adults under 25 years, whereas influenza A viruses are most commonly reported among individuals 25 years and older.

The CDC continues to recommend vaccination with the seasonal flu shot.

The most recent data indicate that 174.1 million doses of the flu vaccine have been distributed. The February 21 issue of the CDC’s Morbidity and Mortality Weekly Report featured interim estimates of the effectiveness of 2019-20 flu shot. The report estimated that at that point in the season, the vaccine was 45% effective overall and 55% effective in children.

Although the authors of the report acknowledged that more effective vaccines are needed, they also noted that the currently available vaccines provide substantial health benefits. “Most years, the mortality rate from influenza is a U-shaped curve, where the mortality is the highest in the very young and in elderly patients, and that’s due to immune response but also comorbid diseases, particularly in the elderly,” said Jason Gallagher, PharmD, editor-in-chief of Contagion®.

“Comorbidities are really what put people at the highest risk of complications from influenza. [Patients with] asthma, COPD (chronic obstructive pulmonary disease), other pulmonary conditions, [and] even heart conditions and the immunocompromised population—all these patients are at a significantly higher risk of complications from influenza than the general population.”

How Are PEPFAR Countries Implementing PrEP?

BY GRANT M. GALLAGHER

The US Centers for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) periodically features reviews on HIV prevention and control efforts in countries supported by the President’s Emergency Plan for AIDS Relief (PEPFAR).

In December 2019, an MMWR article highlighted challenges to implementing case-based HIV surveillance in countries supported by PEPFAR. Among the 39 countries that responded to CDC inquiry, 20 had implemented case-based surveillance, 15 were planning implementation, and 4 were not planning it.

An article in the February 28, 2020, edition discusses the expansion of pre-exposure prophylaxis (PrEP) into the 35 PEPFAR-supported early program adopters from October 2016 to September 2018.

A key pillar of prevention efforts globally involves expanding PrEP uptake in the populations most at risk of HIV. PEPFAR “supports implementation of PrEP to reduce HIV incidence among persons at substantial risk for infection, including female sex workers, men who have sex with men (MSM), and transgender women,” the authors from the Division of Global HIV and TB (Tuberculosis) at the CDC’s Center for Global Health wrote.

In 2018, for example, 54% of new HIV transmission around the world occurred among individuals from key populations and their partners.

Implementation of PrEP programs across the 35 PEPFAR-supported countries examined in the analysis was assessed through the number of programs that reported new PrEP users quarterly from October 2016 through September 2018.

By September 2018, just 15 of the PEPFAR-supported countries had PrEP programs. However, among those 15, client volume increased by a substantial 335% during the analysis period.

"Scale-up of PrEP among general population clients was nearly 3 times that of key population clients,” the authors wrote.

Programs with more than 150 new key population clients were labeled early adopters of PrEP among key populations. Critical factors and scale-up accelerators were identified among the PrEP programs that experienced rapid growth, with feedback provided by implementing partners in the programs.

“Among all PEPFAR-supported programs, 6 (Asia region, Kenya, South Africa, Uganda, Vietnam, and Zimbabwe) were classified as early adopters of PrEP for key populations. Implementing partners in 5 of these programs (all except Vietnam) identified critical factors for early adoption of PrEP, including national and regional stakeholder meetings with strong ongoing engagement and advocacy from ministries of health, community advocates, and multilateral partners such as the World Health Organization and the Joint United Nations Programme on HIV/AIDS (UNAIDS),” the authors wrote.

Of these programs, 5 included PrEP programs in national treatment and prevention guidelines despite unfavorable national legal environments to protect key populations from stigma and violence.

Other factors that accelerated scale-up included active government ownership of the national PrEP program, developing training criteria for medical personnel, and collecting PrEP data. Key accelerators also included promoting HIV prevention outside the clinic on social media, at gay bars, and in the community via peer outreach.

The authors pointed out that because regular PrEP use is key to maintaining protection from HIV, these programs should monitor adherence.

To expand on their findings, the authors suggested using cost-effectiveness and mathematical modeling studies on PrEP implementation among PEPFAR-supported countries. This type of research could help identify populations in which PrEP delivery would have the greatest HIV prevention impact in the context of limited resources.
Phase 3 Trial Yields Positive Results for Cefepime-Enmetazobactam

BY GRANT M. GALLAGHER

More than 100 million people worldwide are affected by complicated urinary tract infections (cUTIs) each year, leading to sizable social costs and health burden on patients. Additionally, the global rise of antimicrobial resistance suggests a need for new treatment options.

Allecra Therapeutics has announced that its investigational antibiotic combination cefepime-enmetazobactam met the US Food and Drug Administration (FDA) prespecified primary end point in the phase 3 ALLIUM clinical trial.

The combination features enmetazobactam, a novel extended-spectrum β-lactamase inhibitor (ESBL), and cefepime, a fourth-generation cephalosporin.

The ALLIUM trial compared cefepime-enmetazobactam with piperacillin-tazobactam in patients with cUTIs, including acute pyelonephritis.

In addition to meeting the primary end point, cefepime-enmetazobactam displayed superiority over piperacillin-tazobactam alongside a comparable safety profile.

The phase 3 study was a multicenter, randomized, controlled, double-blind, global investigation across 112 sites within 19 countries. The investigators enrolled 1034 patients who were randomized to receive either cefepime 2 g plus enmetazobactam 0.5 g or piperacillin 4 g plus tazobactam 0.5 g every 8 hours as a 2-hour continuous intravenous infusion.

The primary end point was defined by both clinical cure, as reflected by symptom resolution, and microbiological eradication at the test-of-cure visit.

Overall success was 79.1% for cefepime-enmetazobactam compared with 58.9% for piperacillin-tazobactam (adjusted stratified difference, 21.2% [95% stratified Newcombe CI, 14.3%-27.9%]).

Treatment discontinuation was comparable in both combinations, at 5.2% in cefepime-enmetazobactam and 4.0% in piperacillin-tazobactam. Serious adverse events were reported by 4.3% of patients in the cefepime-enmetazobactam group and 3.7% in the piperacillin-tazobactam group.

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FLAIR Trial Findings Advance Possibility of Long-Acting ART

BY LAURIE SALOMAN, MS

One of the hurdles faced by people living with HIV who are on antiretroviral therapy (ART) is the necessity of taking daily pills: Nonadherence can prevent the virus from being suppressed. Scientists have been working on solutions, including a long-acting injectable drug or drugs that would free patients from the burden and possible stigma of sticking to an oral medication regimen.

In a new study published in The New England Journal of Medicine, investigators in the Department of Infection and Immunity at Queen Mary University of London in England and colleagues set out to determine whether a long-acting injectable formulation consisting of the integrase inhibitor cabotegravir and nonnucleoside reverse transcriptase inhibitor rilpivirine is noninferior to a daily pill consisting of dolutegravir, abacavir, and lamivudine.

The First Long-Acting Injectable Regimen (FLAIR) study (NCT02938520) consisted of 566 adults with HIV who had never taken ART before and had viral RNA levels of at least 1000 copies/ml at the beginning of the trial. The median age was 34 years, and 22% were female patients. All received dolutegravir/abacavir/lamivudine oral induction therapy for 20 weeks, then were randomly split into 2 arms: One continued with the daily oral therapy and the other switched to the long-acting injectable formulation, receiving monthly shots.

At 48 weeks, there was scant difference between the 2 groups in terms of viral suppression. In the oral therapy group, 2.5% had HIV RNA levels of 50 copies/ml or higher compared with 2.1% in the injectable group, indicating that long-acting injectables are noninferior to oral therapy for maintaining viral suppression.

Injection-site reactions were the most common adverse effect (AE) in the injectables arm, with 86% of participants experiencing at least 1 reaction, typically pain. Most AEs reported were mild or moderate, peaking approximately during week 4 injections and noted by 71% of patients and decreasing substantially by week 48 (20%). The injection-site reactions lasted a median of 3 days and led to 2 participants dropping out of the trial. Other AEs considered to be drug related, such as headache and fever, were experienced by 28% of those receiving the injectables versus 10% of those taking the oral medication.

“The results of this trial show a pathway for patients who have not previously received antiretroviral therapy to reach and maintain HIV-1 suppression with oral induction therapy and a subsequent transition to monthly injectable therapy,” the FLAIR authors wrote. They added that even though the participants in the injectables arm experienced AEs at a higher rate than those in the oral therapy arm, “effects associated with starting a new treatment (as opposed to continuing the same treatment) may have contributed to the observed differences—a possibility consistent with observations in previous switch studies.”

The investigators noted that 91% of participants preferred the long-acting injectables to the oral regimen, even after receiving the injection a dozen times; however, the investigators pointed out the possibility of selection bias because the participants had expressed a willingness to be given the injectables at the start of the trial.

“The potential clinical role of the long-acting regimen remains to be fully defined for the spectrum of patients with HIV-1 infection, particularly those who have adherence challenges, in different practice settings,” the authors wrote. Additional trials continue to explore the adoption of long-acting ART regimens in patients who previously took ART and those who demonstrated difficulty with adherence and are following participants for longer than 48 weeks.
Have We Made Progress in the 10 ×’20 Initiative?

IDSA reached its goal, but nobody’s buying. Can the drowning antimicrobial pipeline be saved?

BY HELEN W. BOUCHER, MD, FACP, FIDSA

At least 2 million people are infected with antibiotic-resistant bacteria, and more than 35,900 die each year in the United States, costing over $20 billion per year. Combating this evolving threat requires multiple stakeholders working together via a One Health approach. Antibiotics make procedures including joint replacement, transplantation, cancer chemotherapy, and premature newborn care possible. Recent reports have warned of the dangerously failing antibiotic pipeline; on January 18, the World Health Organization issued an unprecedented warning, declaring that “only government intervention can fix the broken market for antimicrobial drugs.”

The Infectious Diseases Society of America (IDSA) has worked since 2002 to sound the alarm about the antimicrobial resistance crisis and the need for progress in developing medicines to treat resistant infections. The 2004 report “Bad Bugs, No Drugs: As Antibiotic R&D Stagnates...a Public Health Crisis Brews” proposed legislative, regulatory, and funding solutions. IDSA then published an update on the concerning status of the development pipeline and a call to action from the medical community. Major pharmaceutical companies left the antibiotics space, and most research and development work moved to small biotech companies with limited capacity and budgets. Leaders reported difficulty in securing funding for antibiotic development because the return on investment was low.

In 2010, IDSA issued a call for 10 new efficacious and safe antibacterial agents by the year 2020. With 14 new systemically available antibiotics becoming available from 2010 to 2019, IDSA’s 10×’20 goal was achieved (Figure). However, these medications are entering a failing market. Achaogen filed for bankruptcy protection in April 2019, shortly after the US Food and Drug Administration (FDA) approval of their drug, sending a chill across the antibiotic marketplace. Limited use and poor reimbursement, as well as the cost of maintaining the supply chain and mandatory postapproval work, were cited as contributing causes. In June 2019, a foreign company purchased Achaogen’s assets for $16 million, and Tetraphase Pharmaceuticals announced significant layoffs. In December 2019, Melinta Therapeutics declared bankruptcy, bringing the total to 4 recently FDA-approved antibiotics in jeopardy.

Reasons for the broken market are complex and include the relatively low price of antibiotics and delayed uptake of newly approved antimicrobials, as well as the fact that they are held in reserve in the interest of good stewardship and preserving efficacy. IDSA leaders and others have called for a rapid “fix” of the broken antibiotic market via pull incentives, in addition to addressing delayed uptake and the other areas of policy work and advocacy already advancing.

Prior to the bankruptcies of Achaogen and Melinta, stakeholders worked to advance policy and regulatory solutions. Accomplishments included the 2012 Generating Antibiotic Incentives Now (GAIN) Act, an important first step toward support of antibiotic research and development. GAIN granted an additional 5 years of exclusivity to new antibiotics and antifungals that treat serious or life-threatening infections. The 21st Century Cures Act established the Limited Population Antibacterial Drug (LPAD) pathway in 2016. Under LPAD, such antibiotics can be studied in smaller, more rapid clinical trials. Paired with these efforts were measures to preserve and optimally use the few available antibiotics via antibiotic stewardship and optimize infection prevention and surveillance.

At the same time, efforts were made to facilitate study of drugs for resistant pathogens, narrow-spectrum indications, and unmet medical needs. To date, it has proved difficult for new antibiotics to achieve indications for MDR organisms. IDSA is working closely with other organizations and the federal government on initiatives to streamline clinical trials for agents that treat serious or life-threatening infections. This collaboration also led to progress in incentives for antibiotic development, including push incentives such as the Antibacterial Resistance Leadership Group of the National Institutes of Health (NIH) and the public-private partnership Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), both of which have significantly stimulated discovery and early-phase development. We now have evidence of promise in the antimicrobial discovery pipeline: CARB-X lists 36 early-development programs, including...
At the same time, clinicians must understand the power of standard FDA indications. Modern noninferiority studies are powerful tools; they detect inferior agents, provide clear safety and efficacy comparisons, facilitate initial FDA approval, and provide a basis for additional indications in more severe infections. Goals of future work include better use of other data that are available or can be readily obtained; learning to “borrow” data across indications, using different thresholds for different settings; and applying patient-oriented outcome measures.14

Antimicrobial stewardship programs provide “coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal antibiotic drug regimen including dosing, duration of therapy, and route of administration.”15 Benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events, and optimized resource use. Successful stewardship programs often help save money, but cost savings are not included in official definitions. Vickers et al and others have suggested that an unintended consequence of some stewardship programs may be focusing too much on cost savings and thereby discouraging appropriate use of newly FDA-approved antimicrobial agents.15

Delayed publication of pivotal trials and updating of guidelines, as well as failure to update antimicrobial susceptibility breakpoints, also contribute to delayed uptake of newly approved antimicrobial agents.13,16 In addition, failure to update breakpoints can affect uptake of new agents. In the case of colistin, an old and toxic drug, breakpoints had not been updated in years. Recently, the Clinical & Laboratory Standards Institute updated colistin breakpoints for key gram-negative pathogens. As a result, virtually all resistant gram-negative pathogens now test as colistin intermediate susceptible or resistant.17

Finally, fixing the broken market will require financial incentives. IDSA supports robust, predictable, and understandable incentives that target areas of greatest unmet need and align fully with principles of antibiotic stewardship and appropriate access. Incentives including reimbursement reform and market entry rewards seem to have gained the most traction to date. Importantly, both of theseunlink the incentive from sales of antibiotics, thereby supporting stewardship and avoiding overuse.

In August 2019, CMS released its final Hospital Inpatient Prospective Payment System rule for fiscal year 2020.18 It includes an increase in the Medicare bundled payment (also known as Diagnosis Related Group, or DRG) severity level designation for the diagnosis codes that specify antimicrobial drug resistance, which should result in higher Medicare payments to the hospital for these cases, hopefully allowing the use of newer, costlier drugs when necessary.19 The rule also provides for an increase in the new technology add-on payment (NTAP) and automatically considers all qualified infectious diseases product antibiotics as meeting the substantial clinical improvement criterion. This makes it easier for antibiotics to qualify for NTAP, but many hospitals still find the associated administrative burden too great and do not seek these payments except in cases of very costly drugs or devices (not antibiotics).

The bipartisan Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act was introduced in the House and Senate in 2019. This bill would carve new antibiotics that treat serious or life-threatening infections out of the DRG and pay for them separately to boost their reimbursement, require hospitals to establish antibiotic stewardship programs that align with US Centers for Disease Control and Prevention recommendations, and require hospitals to report antibiotic use and resistance data to the CDC. The goal is to help ensure that patients can access new antibiotics when necessary, as well as stabilize the antibiotics market for developers and ensure that these precious resources are used in the best way possible.

Although reimbursement reform and the proposed DISARM Act are encouraging first steps, salvaging the antibiotic research and development infrastructure will require more. Long-term solutions such as market entry rewards are gaining traction but require further work. The time is now for clinicians to be the voice for patients, telling patients’ stories and urging action. Advocate for prompt publishing of data and updating of guidelines and for availability of new drugs. Most of all, reach out to legislators in support of DISARM and get colleagues involved. Antimicrobial resistance affects us all, and we each have a role in responding to the crisis.

References are available at ContagionLive.com.
“Take those easy steps,” Tan, the state epidemiologist for the New Jersey Department of Health, told Contagion®, “Cover your coughs and sneezes. Make sure you wash your hands all the time. Stay home when you’re sick.”

However, this past January also proved very different from previous ones for Tan and other public health officials. This year, the routine precautions are urgent for a new and startling reason: the novel coronavirus and the fast-spreading illness it causes, coronavirus disease 2019 (COVID-19).

“Late last year, we started to see a cluster of unusual pneumonias come up in China,” she said. “That’s when we first started to get an indication that there might be some sort of new, novel emerging infection that was going on.”

In the weeks that followed, more information came out, and the epidemiological story evolved along with it. By late February, more than 2500 people in China had died from COVID-19, and some 20 cases had been detected by health care providers in the United States. As February closed, the US Centers for Disease Control and Prevention (CDC) announced the first death of a patient who had tested positive for the illness in the United States, a serious milestone for a disease that initially was centralized in a single province in China.

THE QUESTION OF CONTAGIOUSNESS
When a new virus emerges, one of the most pressing questions facing Tan and other public health officials is: Just how contagious is it?

That’s a difficult question to answer in the context of the coronavirus, in part because it’s not clear how many individuals actually have COVID-19. Many will have relatively mild symptoms, so it’s possible that many more individuals have contracted the illness than have been tested and officially reported.

“The information is still evolving about the transmission of the virus that causes COVID-19 illness,” Tan said. “For instance, she added, of the first 15 cases reported in the United States, just 2 were associated with person-to-person spread in the United States; the rest were the result of travel to China.

The main symptoms of the illness include fever, shortness of breath, and cough. However, Tan said, it’s generally the degree of severity that distinguishes COVID-19. “This is a little bit different, a little bit more severe than what we’ve been seeing with your routine respiratory virus illnesses,” she said.

US PUBLIC HEALTH SURVEILLANCE
The disease’s emergence in the United States has put public health officials on high alert. Top priorities include getting a handle on the size and scope of the problem here. Physicians are on the front lines, and Tan said that to meet the challenge, clinicians must keep up with the latest news and public health advisories.

“In the United States, the CDC has issued guidance with regard to what clinicians can be looking for,” she said. “We always strongly encourage clinicians to go on the CDC website, because things are changing so rapidly, just to keep themselves abreast of the most up-to-date information, such as what the current criteria are that we’re looking for.”

Those criteria can change in definition and importance as time goes on. A data point that seems irrelevant at the beginning of the crisis might later prove extremely important. A patient who one day does not meet the requirements for COVID-19 testing might the following day if the criteria change. That can be a difficult needle for public health officials like Tan to thread.

“We always try to get the balance of ensuring that we get the message out there to clinicians that sometimes things will change,” she said. “Sometimes when you’re looking for illnesses, you might need to modify what you’re looking for based on the newest information.”

WARNING SIGNS AND SYMPTOMS
At present, clinicians are asked to look for symptoms of a respiratory infection plus particular risk factors. “For now, the criteria [involve] looking at individuals with a history of exposure to the hot zone, Hubei province in China, or contact with individuals who are confirmed cases of COVID and with clinical presentation of fever and respiratory tract illness,” she said.

Tan cautioned that those guidelines will likely be supplemented or amended in the coming days. “Right now, we’re asking health care providers to be really vigilant in looking for illnesses that might be compatible with COVID-19 illness,” she said. “We also encourage child care providers to take good travel histories.”
Physicians should be proactive, particularly when it comes to contacting local public health authorities, Tan said. "[If] you are concerned that you might have a patient with a reportable condition or with infection with an emerging infectious disease like COVID-19...contact your public health departments to then report that information and then take next steps," she said.

Health care facilities should also review their infection control plans, something they ought to do periodically even when there’s not a specific threat. Tan also said clinicians have a role to play in halting misinformation, including the perpetuation of unscientific stereotypes.

"Unfortunately, we’re hearing about cases of stigmatization and prejudice against certain populations, particularly related to travelers coming back from China,” she said. “We want to remind everybody that what we’re fighting right now is a virus. We’re not fighting against pockets of our population who might have had a risk factor that put them at risk for COVID-19 illness.”

**TREATMENT LIMITS**

If cases of COVID-19 are confirmed, there is no approved treatment explicitly for the illness. Instead, patients with the illness receive supportive care and symptom relief.

Patients who have underlying medical conditions and/or might be immunocompromised are at a higher risk of complications.

Meanwhile, as the virus continues its spread, much uncertainty remains. However, Tan said, the same disease prevention precautions that have long applied will continue to be important, whether the novel coronavirus ends up a pandemic or fades away quickly.

“We have to remind ourselves that every single year we see seasonal flu, we see respiratory illnesses emerge,” she said. “Keeping those infection control plans in mind and exercising those infection control protocols are really key to not only dealing with the routine but also [are] a step toward the prevention of emerging issues.”

The coronavirus might dominate the headlines, but flu season continues at full pace, and physicians shouldn’t put away all those flu prevention posters, Tan said. “Again, because we’re in the middle of flu season, we want to remind everybody: Get your flu shot,” she said. “That is one tool that we do have to protect against what is a common threat to us all right now.”

*References are available at ContagionLive.com.*
BACKGROUND OF THE EPIDEMIC
With approximately 80 million individuals, the DRC is the fourth most populous country in Africa. Decades of fighting between government forces and armed militia groups vyng for control in the eastern part of the country has led to one of the longest and most complex global humanitarian crises. Over 4 million Congolese have been displaced within the country, and over 800,000 have fled to surrounding countries. Exploitation of the region’s vast mineral and other resources has fueled conflict, leading to illegal trade and human rights violations, including massacres, kidnappings, violence against women and children, human trafficking, and forced recruit - ment of children into militant groups. Years of atrocities led to a frail economy, weak political system, and poor health care infrastructure, creating a dearth of basic public health services such as water sanitation hygiene programs, vaccinations, and communicable disease prevention and surveillance. The breakdown of basic services combined with ongoing violence has made it difficult to detect and control communicable diseases, allowing for ongoing cholera, measles, and polio outbreaks and creating a perfect storm for the emergence of an Ebola outbreak.

The DRC’s longstanding socioeconomic challenges combined with mistrust in the government because of prolonged violence also damaged community support of humanitarian agencies such as the World Health Organization (WHO) and Doctors Without Borders, or Médecins Sans Frontières (MSF). The deep-seated community mistrust led to rumors that Ebola is a myth and fear among patients and family members about accessing care, leading to forced removal of patients and attacks on Ebola treatment centers (ETCs).

A turning point of this epidemic was the death of WHO epidemiologist Richard Valery Mouzoko Kiboung, PhD, on April 19, 2019, during an attack on Butembo University Hospital after a series of health care worker attacks. Armed militia groups’ sustained attacks on frontline responders and ETCs resulted in the withdrawal of operations in eastern DRC by the US Centers for Disease Control and Prevention (CDC) and closure of ETCs by MSF.

Despite the challenges of the current Ebola outbreak, one of the greatest stories has been the development of medical countermeasures (MCMs). During the course of this epidemic, the Merck vaccine Ervebo obtained US Food and Drug Administration (FDA) approval, and a randomized clinical trial of therapeutics was stopped early because it showed efficacy for mAb114 and REGN-EB3n. The investment and development of these MCMs demonstrate what can be achieved when the scientific community unites against 1 cause.

IMPACT OF VACCINATIONS
Quick implementation of Merck’s recombinant vesicular stomatitis virus–Zaire ebolavirus (rVSV-ZEBOV) vaccine at the start of the North Kivu–Ituri EVD outbreak was instrumental in preventing a larger emergency on the African continent. The single-dose vaccine protects against Zaire ebolavirus and is a modified vesicular stomatitis virus vector loaded with the Ebola glycoprotein. The vaccine was initially
deployed during the 2018 Équateur Province EVD outbreak in northwest DRC that ended 7 days prior to declaration of the North Kivu–Ituri outbreak. Because appropriate regulatory approvals had been obtained, ring vaccination campaigns were initiated almost immediately after the outbreak was declared.

In April 2019, WHO released an interim data analysis of the vaccine’s effectiveness, announcing that it demonstrated a 97.5% protection rate. More than 90,000 individuals had received the vaccine’s effectiveness, announcing that it demonstrated a 97.5% protection rate. More than 90,000 individuals had received ZMapp. Overall, 96% of deaths occurred within 10 days of enrollment. Longer duration of symptoms, higher serum viral load, impaired renal function, and elevated aspartate aminotransferase/alanine aminotransferase were associated with greater risk of death. The extension phase of the study is ongoing in the DRC.

SUCCESS OF THERAPEUTICS

The development and evaluation of therapeutics against EVD has been the outbreak’s other great success story. The Pamoja Tulinde Maisha study was a large consortium therapeutics trial with the primary objective of looking at the 28-day mortality of investigational therapeutics (mAb114, remdesivir, REGN-EB3) compared with ZMapp as the control arm (Table). The study was designed to enroll patients equally stratified among all 4 arms who were confirmed to be Ebola polymerase chain reaction positive and began enrollment in November 2018. The study was monitored by an independent data safety and monitoring board, and on August 8, 2019, after reviewing the data, the board recommended stopping enrollment and continuing an extension phase with mAb114 and RGN-EB3.

The final analysis of 673 eligible patients demonstrated that 76.5% were at least 18 years old, 56% were female (17 pregnant) at the time of EVD diagnosis, and average duration of symptoms prior to enrollment was 5.5 days. The 28-day mortality was 50% (84 of 169) for ZMapp, 53% (93 of 175) for remdesivir, 35% (61 of 174) for mAb114, and 34% (52 of 155) for RGN-EB3. Patients who received mAb114 or RGN-EB3 cleared serum viremia faster than those who received ZMapp. Overall, 96% of deaths occurred within 10 days of enrollment. Longer duration of symptoms, higher serum viral load, impaired renal function, and elevated aspartate aminotransferase/alanine aminotransferase were associated with greater risk of death. The extension phase of the study is ongoing in the DRC.

A TESTAMENT TO UNITY

Although the DRC EVD outbreak has been plagued by community mistrust and violence that have prolonged this epidemic, we are, hopefully, in the waning days of this epidemic, it should be noted that this outcome would not be possible without the extraordinary international effort, particularly of the frontline workers who risked their lives to ensure that patients received appropriate medical attention. This is a testament to what can happen when we unite during a public health emergency. Now, can we apply what we’ve learned to respond to the coronavirus disease 2019 (COVID-19) pandemic? ▲

References are available at ContagionLive.com.
Ending the HIV Epidemic Initiative: A Snapshot From the Trenches, 1 Year Later

Funded jurisdictions scramble to meet daunting deadlines yet maintain optimism that the new federal initiative can end flat funding and catalyze progress.

BY MELANIE THOMPSON, MD

In March 2018, US Centers for Disease Control and Prevention (CDC) Director Robert Redfield, MD, said the United States could end its HIV epidemic “in 3 to 7 years if we put our minds to it,” and the 2019 State of the Union address promised to end the epidemic by 2030.1,2 Subsequently, the US Department of Health and Human Services (HHS) announced Ending the HIV Epidemic (EHE): A Plan for America, an initiative that built on the Obama administration’s groundbreaking 2010 and 2015 National HIV/AIDS Strategy.3,4 The plan’s 4 pillars—diagnose, treat, prevent, and respond (to outbreaks)—aim to reduce new HIV diagnoses by 75% in 2025 and 90% in 2030.5 Its initial phase includes 48 jurisdictions; Washington, DC; and San Juan, Puerto Rico, which account for over half of new diagnoses annually, as well as 7 states with predominantly rural epidemics. The 2020 budget includes $291 million for EHE.6

The CDC and the Health Resources Services Administration (HRSA) released multiple EHE funding opportunities (Table 1 online)6–15 and awarded 2019 funds for jump-start pilot projects and jurisdictional planning. The Indian Health Service funded 1 jump-start site in Oklahoma’s Cherokee Nation, and the National Institutes of Health and National Institute of Mental Health awarded implementation science research pilot grants through their Centers for AIDS Research and AIDS Research Centers, respectively.6,8,10 HRSA awarded implementation funds for the Ryan White HIV/AIDS Program in March, with CDC funding to follow in June. One year after the EHE announcement, a snapshot across 6 geographic areas—metro Atlanta, Georgia; Baltimore, Maryland; East Baton Rouge Parish, Louisiana; New York, New York; San Antonio, Texas; and San Francisco, California—found a torrent of energy directed toward planning, submission of funding applications, and early pilot activity.

INITIATION OF JUMP-START PILOT PROJECTS

The CDC and IHS announced in June 2019 that Baltimore; DeKalb County, Georgia; East Baton Rouge; and the Cherokee Nation would each receive $1.5 million to implement jump-start projects by December 31 (Table 2 online).7,8 CDC recipients had about 3 weeks to submit proposals. Baltimore rapidly engaged community partners to create 14 new programs. Community engagement is “a cross-cutting pillar” of Baltimore’s work. Innovative activities include expanding the reach of Johns Hopkins Medicine’s I Want The Kit website and adding HIV self-test kits to the sexually transmitted infection (STI) kits already available online, adding an HIV expert “warm line” for clinicians, creating a tool to allow clinicians to view patient panels stratified by viral load suppression, and offering enhanced case management services.9 Prevention programs include a social network strategy for pre-exposure prophylaxis (PrEP) recruitment. A hybrid disease intervention specialist/community health worker model to enhance care engagement will use Ryan White EHE funds.

DeKalb County experienced challenges with contract execution and hiring, requiring an extension until June 2020. In November, it opened a sexual health clinic to provide HIV/STI screening and PrEP initiation in partnership with Rollins School of Public Health at Emory University in Atlanta. DeKalb also is expanding PrEP to an existing county clinic and 3 community organizations. HIV testing will expand through community organizations, a jail, an emergency department (ED), and a federally qualified health center (FQHC).

East Baton Rouge expanded HIV testing capacity through 5 community partners and 2 EDs, as well as enhanced HIV, syphilis, and hepatitis C population-level screening in prisons. The parish extended its health model patient incentive program to a new FQHC partner, employed a “rapid start” navigator to expedite linkage and treatment for individuals with new diagnoses, added a TelePrEP navigator, expanded syringe services program (SSP) capacity, and hired community health workers to link hot spot communities with basic resources and HIV testing.

The Cherokee Nation is expanding routine HIV screening, especially in clinical settings; increasing access to PrEP; advocating for SSPs; and aiming to reduce stigma. Omission from the 2020 federal budget, however, threatened sustainability, although funds now have been included in the proposed 2021 budget.

EHE PLANNING: ATTACKING INEQUITIES, DISPARITIES, AND STIGMA

San Francisco’s Getting to Zero consortium and New York City’s End the Epidemic blueprint led to substantial progress in controlling their epidemics, even before the federal EHE initiative.11,12 Both, however, have persistent new diagnoses concentrated in underserved populations.

As part of EHE, San Francisco will target health disparities and inequities that drive its remaining 197 annual new diagnoses, according to Diane Havlir, MD, cochair of Getting to Zeros steering committee and HIV/AIDS division chief at University of California, San Francisco. She said that a “rapid strategic-planning process” employs a racial and social justice lens to address housing, mental health, substance use, incarceration, and stigma while integrating HIV, STI, and hepatitis C prevention and treatment. Creating low-threshold, neighborhood-based services for priority populations and collaborating with Alameda County (Oakland) in the East Bay are important elements of the city’s strategy.

New York City’s EHE plan identifies overarching priorities of advancing equity and eliminating stigma and aims to confront “structural racism and other systems of oppression” that fuel the epidemic.13 The plan addresses
stigma, the HIV/STI syndemic, and the impact of social determinants of health. Funds support community engagement activities, including listening sessions in the 4 funded boroughs and among priority populations. Strategies include supporting priority populations directly through grassroots organizations.

THE SOUTH: EHE WITHOUT A SAFETY NET
Barbara Taylor, MD, cochair of the End Stigma End HIV Alliance, describes San Antonio’s safety net as “fragile” without Medicaid expansion and acknowledges that EHE requires tackling “giant structural problems like stigma, housing, substance use, and transportation and their intersection with HIV.” Planning funds support training on mental health and healing justice and transgender health, as well as creation of communitywide strategies for sexual health and confronting stigma. Roberto Villarreal, MD, who oversees Ryan White programs, says HRSA funds will support targeted communications strategies for care engagement, expansion of a successful nurse navigator program, rapid “test and treat” in EDs, and initiatives to increase the HIV workforce, including for mental health providers.

The draft plan for 4 metro Atlanta counties (Fulton, DeKalb, Cobb, and Gwinnett) includes expanding HIV testing, PrEP, and housing but focuses on care engagement. According to Jeff Cheek, director of the Fulton County Department of HIV Elimination, highest priorities are developing a 24/7 centralized linkage and reengagement system and an intake portal for eligibility documentation that service providers, including housing providers, can access; extending clinic hours; and creating rapid response teams to treat each new HIV diagnosis as a sentinel health event. Cross-pillar strategies emphasize client-centered services and policies through training on cultural humility, “People First” language, and trauma-informed care.

RECOMMENDATIONS: INCREASE MONEY, DISRUPT SILOS, PRIORITIZE COMMUNITY, CHANGE POLICIES
At all sites, leaders expressed that an influx of funds coupled with political support could benefit their jurisdictions, yet optimism was often tempered by the reality of life in the trenches. When local leaders were asked what they would recommend HHS do to improve EHE, common threads emerged. “Tell them it is going to be really, really expensive,” one said. Much more will be needed than the $716 million for year 2 in the 2021 White House budget. Particularly in the South, funding for core services must increase. “We simply can’t afford to take care of all of the people we plan to diagnose or bring back into the clinic,” one clinician observed.

More than one leader observed that the EHE rollout was “daunting and swift,” as one characterized it, because of short deadlines and the sheer number of proposals required. The yearlong development of a local EHE plan was abruptly changed to require a draft plan within 3 months, disparaged by some as “a plan without the planning.” Lack of coordination among HHS agencies frustrated most, because funding streams that “perpetuate the old, inefficient silos” required duplicative applications with unsynchronized submission and award timelines. Rapidly coordinating across multiple planning bodies with existing plans and ensuring meaningful community engagement was difficult. “Disruptive innovation,” as advocated by the CDC, “starts at home,” one leader said. HHS should issue joint funding opportunities across agencies and synchronize timelines, deliverables, and reporting to ensure interoperability, decrease administrative burden, and avoid the exhaustion and frustration generated by what one leader described as “Whac-A-Mole proposal writing,” jurisdictions also invite mechanisms for sharing best practices and implementation challenges.

Many credited long-standing community partnerships for their success. “Community engagement takes time and can’t be expected to happen overnight for a grant,” said Adena Greenbaum, MD, MPH, a Baltimore City Health assistant commissioner. “The source of innovation is not the health department. It comes from the communities we serve. We are the vessel for innovation that comes from the community.” Some said that HHS should mandate community integration into EHE decision-making bodies, as required in Ryan White programs. Many fear that EHE will be unachievable because of discriminatory policies against lesbian, gay, bisexual, transgender, queer, and gender diverse individuals; efforts to repeal the Affordable Care Act; work requirements and block grants for Medicaid; and budgets that decrease funding for health safety nets, housing, CDC, and NIH. All agree, though, that EHE represents a potentially transformative opportunity. “The end of the epidemic is not around the corner,” said Victoria Cargill, MD, a Baltimore City Health assistant commissioner. “But it’s not impossible either.”

WHERE DO WE GO FROM HERE?
The federal EHE initiative has provided new opportunities and challenges to both the initial 59 funded jurisdictions and HIV leaders at CDC and HRSA, all of whom are scrambling to translate political will into funding opportunities; awards; and, ultimately, programs. Now that the first round of deadlines is past, there is tremendous opportunity for HHS, CDC, and HRSA leaders to embrace a new paradigm, learning from the EHE initiative experience of the frontline HIV community, including both care providers and people with HIV, and to “think different,” as Steve Jobs said, about removing the significant structural barriers created by funding silos and uncoordinated timelines and deliverables.

Although it had its own challenges, the Care and Prevention in the US Demonstration Project, a single award offered jointly by the CDC, HRSA, and the Substance Abuse and Mental Health Services Administration, proved that true interagency collaboration could be accomplished. Moreover, HHS has power and a unique opportunity to stop stigmatizing and discriminatory policies before they become regulations that obstruct EHE efforts, and it should, regardless of political repercussions.

In the fast-moving era of COVID-19, a caveat should be added. We cannot allow EHE to falter because of lack of funding or depleted human resources. Renewed advocacy will be needed to protect current funding from diversion and ensure adequate future funding. The United States cannot afford to sacrifice EHE in the fight to curtail another outbreak. As we move past a bumpy start, therefore, there is cautious optimism that, with appropriate financial support and political will, motivated individuals and groups can catalyze real change toward bending the curve of the HIV epidemic.

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

The Search Continues for How to Best Treat Non–Carbapenemase-Producing CRE Infections

Infections caused by non–carbapenemase-producing carbapenem-resistant Enterobacteriaceae present challenges in the treatment paradigm. Given the limited clinical data, the preferred therapeutic approach remains unknown.

BY BEJOY PAUL MANIARA, PHARMD, BCPS, BCIDP

(continued from cover page)

The CDC estimated that CRE were responsible for approximately 13,100 hospitalizations, 1000 deaths, and $130 million in health care expenditures in 2017.

Unfortunately, the CDC does not currently stratify these statistics by 2 CRE classifications: carbapenemase-producing (CP-CRE) and non–carbapenemase-producing (NCP-CRE). Although both are daunting and encompass urgent threats, they differ significantly. Managing infections caused by CRE is arduous because many strains tend to be resistant to nearly all antibiotics, forcing clinicians to use less effective and/or more toxic antibiotics.

TWO PATHS OF RESISTANCE

The resistance mechanism by which CP-CRE and NCP-CRE confer resistance to carbapenems differs. As the name suggests, CP-CRE produce enzymes that hydrolyze and inactivate carbapenems. These enzymes are categorized as Ambler class A, B, or D β-lactamases and are typically carried on mobile genetic elements (MGEs; eg, plasmids, integrons, transposons), which can transfer carbapenemases to other Enterobacteriaceae. Their propensity to rapidly spread between organisms and patients has major infection control implications because CP-CRE are more likely associated with clinical outbreaks. This high-level carbapenem resistance may phenotypically be represented by elevated minimum inhibitory concentrations (MICs) to meropenem, generally >16 µg/mL in Klebsiella pneumoniae carbapenemase (KPC)–producing K pneumoniae. However, other CP-CRE (eg, KPC-producing Escherichia coli or Enterobacter spp) may present with lower MICs.

Conversely, NCP-CRE lack enzymes that hydrolyze carbapenems. Rather, they resist carbapenems through other chromosomal mechanisms (eg, porin channel and/or efflux pump mutations combined with β-lactamase production). These mechanisms make NCP-CRE appear to be a less daunting infection control concern. Additionally, NCP-CREs may exhibit lower carbapenem MICs. As a result, probability of target attainment against NCP-CRE with carbapenems is likely higher than it is against CP-CRE with carbapenems.

COMPARING RISKS OF CP-CRE AND NCP-CRE

Patient risk factors for CRE include indwelling devices (eg, catheters) and prolonged courses of antibiotic therapy, particularly if source control has not been achieved. However, CP-CRE and NCP-CRE risk factors also vary. Findings of an epidemiologic study by Marimuthu K et al on Singapore adults showed that prior carbapenem exposure and hematologic malignancies were more likely associated with NCP-CRE than with CP-CRE. Marimuthu K et al also conducted a national case-control study to assess risk of antecedent carbapenem exposure in patients with CRE. They concluded that patients with NCP-CRE had 3-fold higher odds of having been exposed to carbapenems 30 days prior compared with those with CP-CRE. Patients with CP-CRE were more likely to be men, have been in an intensive care unit (ICU), and have been hospitalized within 1 year prior.

Results of a French case-control study by Nicolas-Chanoine and colleagues determined that male gender, travel to Asia, hospitalization within 1 year prior, infection within 3 months prior, urine drainage, and mechanical ventilation...
were CRE risk factors: only CP-CRE cases had risk factors of previous travel and hospitalization abroad.\textsuperscript{11} Zou H et al also assessed CRE risk factors and found that old age, longer ICU stay, and cancer were more likely associated with CP-CRE compared with NCP-CRE, and NCP-CRE was more associated with longer ICU stay and venous catheterization compared with extended-spectrum β-lactamase phenotypes. Of note, they discovered that prior carbapenem exposure had 7-fold higher odds of CP-CRE in contrast with Marimuthu K et al’s findings.\textsuperscript{12}

Theoretically, CP-CREs may cause more severe disease and be more difficult to eradicate than NCP-CREs. Villegas MV et al assessed the impact of monomicrobial CP-CRE and NCP-CRE bacteremia in 7 Latin American countries and found that mortality was 4-fold higher in patients with CP-CRE. Survival rates were higher for patients with NCP-CRE at days 7 and 28. However, patients with CP-CRE were more likely to be critically ill, have undergone surgery, and be immunosuppressed. These patients were also less likely to have received active empiric and definitive therapy.\textsuperscript{13}

Tamma PD et al compared outcomes with monomicrobial CP-CRE and NCP-CRE and found that 14-day mortality was 4-fold greater in patients with CP-CRE. They also found that CP-CRE were less likely to be susceptible to other non–β-lactams (eg, aminoglycosides, fluoroquinolones, tigecycline, and polymyxins). As a result, empiric regimens were less likely to be active against CP-CRE. In the same cohort, meropenem MICs to CP-CRE were more likely to be ≥16 µg/mL, whereas meropenem MICs to NCP-CRE were more likely to be <1 µg/mL.\textsuperscript{7}

Seo H et al compared mortality between monomicrobial CP-CRE and NCP-CRE bactere mia and contrarily found that carbapenemase production was not a mortality risk factor. However, patients who achieved source control in the CP-CRE group were more likely to survive than those who did not achieve source control in the NCP-CRE group. This lack of source control in the NCP-CRE group may explain why the authors did not find carbapenemase production to be a mortality risk factor.\textsuperscript{5}

The data from the recently published study, Consortium on Resistance Against Carbapenemases in Klebsiella pneumoniae and Other Enterobacteriaceae II (CRACKLE-II) demonstrate that there was no difference in patient outcomes (dead versus alive without events versus alive with 1 event versus alive with 2 or 3 events), via desirability of outcome ranking analysis, between patients infected with CP-CRE, NCP-CRE, or unconfirmed CRE.\textsuperscript{14}

### CHOOSING AMONG TREATMENTS

Although investigators discovered varying clinical outcomes between CP-CRE and NCP-CRE, therapeutic options should be predicated upon CRE type and underlying mechanism of resistance. Tests to detect CP include chromogenic assays, modified Hodge test, and metallo-β-lactamase Etest, but these tests do not identify specific carbapenemases. Various rapid diagnostic phenotypic tests (eg, Carba NP, mCIM, eCIM, and MALDI-TOF MS) may detect carbapenemase-production, whereas several rapid diagnostic genotypic tests (eg, Biofire FilmArray, Verigene System, Xpert Carba-R, GenMark ePlex) may identify specific carbapenemases.\textsuperscript{15}

Current literature does not clarify optimal methods of treating NCP-CRE versus CP-CRE. Because currently available data suggest that CP-CRE may cause more severe infections and be more prognostically important than NCP-CRE, it may be reasonable to treat NCP-CRE less aggressively by prioritizing novel agents for patients with CP-CRE.\textsuperscript{2,3} Authors of several studies discuss potential treatment options against NCP-CRE (Table). Importantly, novel β-lactam/β-lactamase inhibitors (BLBLIs; eg, ceftazidime/avibactam, meropenem/vaborbactam,imipenem/relebactam) were designed to inhibit serine carbapenemases and may not be appropriate against NCP-CRE.

In addition, because these agents do not address or bypass the resistance mechanism, unnecessarily administering them may inadvertently accelerate resistance development. Although these novel BLBLIs may not be necessary against all NCP-CREs, ceftazidime/avibactam and imipenem/relebactam may still remain effective against NCP-CREs that produce ESBL and/or AmpC. Zou H et al found that ceftazidime/avibactam was effective in vitro against NCP-CRE with low-level resistance. The investigators also found aztreonam/avibactam effective in vitro against all strains of NCP-CRE, including more resistant strains with combined carbapenemase production and porin loss.\textsuperscript{12} However, this has yet to be studied in humans to produce outcomes data.

Although the majority of study findings demonstrate use of combination therapy more likely to be administered against CRE, particularly CP-CRE, monotherapy versus combination therapy efficacy against NCP-CRE is yet to be elucidated. Su C et al assessed treatment outcomes against NCP-CRE K pneumoniae infections in Taiwanese hospitals. Among 67 patients receiving appropriate therapy, 61 received monotherapy (most commonly tigecycline, colistin, and carbapenems), of whom 21.3% experienced 14-day mortality versus 37.5% who experienced 14-day mortality with inappropriate therapy.\textsuperscript{16}

Most studies use carbapenems in combination with polymyxins, tigecycline, aminoglycosides, and/or fluoroquinolones. Seo H et al associated definitive combination therapy with decreased mortality.\textsuperscript{6} Findings have shown that carbapenems may be effective against CRE with MICs up to 16 µg/mL if dosing regimens are optimized, though CRE type was not differentiated.\textsuperscript{17,18} Using these data, Tamma PD et al used standard-infusion meropenem 2 g every 8 hours for CRE with MIC ≤4 µg/mL (more likely NCP-CRE) and extended-infusion meropenem 2 g every 8 hours, infused over 3 hours, for CRE with MIC >8 µg/mL (more likely CP-CRE). Carbapenems were used in combination with another agent in 84% of patients with CP-CRE and 95% of patients with NCP-CRE.\textsuperscript{7} Other antibiotics may be viable alternatives against NCP-CRE as long as they are susceptible and the isolate does not have resistance mechanisms against it (eg, antibiotic-modifying enzymes or target site, porin, and/or efflux pump mutations), potentially permitting novel non–β-lactams (eg, eravacycline, plazomicin) and β-lactams with novel mechanisms (eg, ceferodrol).

Treating CRE infections is complex. Evaluating patient-specific risk factors may help clinicians select appropriate empiric therapy against specific CRE types. Determining CRE type is important for infection control because CP-CRE spread more rapidly, and it is paramount for treatment purposes because NCP-CRE may cause less severe disease and potentially be managed without novel BLBLIs, allowing these agents to be reserved for CP-CREs. Further studies are needed to elucidate optimal antibiotic treatment against NCP-CRE.\textsuperscript{19}

References are available at ContagionLive.com.
Continued availability and effectiveness of these drugs are critical to public health, but increasing resistance and diminished development of innovative antibiotics raise concerns about the ability to treat future infections.2,3

THE IMPEDIMENT OF LIMITED REVENUES

For many developers, there is not a clear path to sustainable revenue generation for innovative antibiotics, in large part due to limited use.4 Stewardship programs appropriately restrict the use of novel classes of antibiotics or those with new mechanisms of action when they reach the market, helping preserve their effectiveness. Similarly, physicians may wait for diagnostic results before prescribing some types of antibiotics. Although these actions contribute to the life span of the available antibiotic arsenal, they may limit the revenues generated by manufacturers, potentially making it difficult to maintain products on the market.5,6

Although stewardship protocols place appropriate limits on prescribing, disadvantageous payment mechanisms may also restrict use of innovative antibiotics. For Medicare and Medicaid beneficiaries, hospital reimbursements are made through a diagnosis-related group (DRG) that covers the costs of all care administered and medical products used during an episode of care. These reimbursements are a set rate based on average costs of a specific condition, giving physicians the flexibility to provide the care that they deem most appropriate. However, the use of new, high-priced drugs has the potential to exceed the set reimbursement amount for the DRG, resulting in a financial loss for the hospital. The price of newly approved antibiotics often exceeds the DRG reimbursement, creating an added disincentive for use by hospitals, which in turn further limits potential revenue for the manufacturer.

SUPPORTING INNOVATION THROUGH REIMBURSEMENT REFORMS

The Centers for Medicare & Medicaid Services’ (CMS) new technology add-on payment (NTAP) program is intended to reduce this financial disincentive. The program provides additional reimbursement for new drugs or devices that demonstrate substantial improvement over existing technologies but
have costs that exceed the standard DRG amount. A medical 
product may receive these payments for 2 to 3 years, and as 
products are adopted among providers, the applicable DRGs 
are expected to adjust upward as updates incorporate the cost 
of the new technology.

Few antibiotics have qualified for an NTAP during the 
years it has been available, but recent changes in the inpa-
tient prospective payment system (IPPS) are designed to 
increase the number of new antibiotics that may qualify and 
tient prospective payment system (IPPS) are designed to 
reduce the financial disincentive that hospitals may face 
when using these drugs. CMS made 3 important changes: First, 
the requirement for substantial clinical improvement is 
waived in NTAP applications for qualifying antibiotics, 
so the only requirements are newness and exceeding the 
cost of the DRG. Second, hospitals using qualifying antibi-
otics with an NTAP are reimbursed the lesser value of 
75% of the costs that exceed the DRG or the cost of the 
antibiotic (in contrast to 65% for other medical products). 
Finally, CMS changed the severity scores for 18 types of 
resistant infections, resulting in higher reimbursement rates 
for episodes of care that involve those infections.

Although these are promising actions from CMS, their 
potential impact on antibiotic revenues is limited, and 
there are concerns that these actions will not be enough to 
reverse the downward trend. For one, the NTAP period 
is finite, making this a temporary boost in reimbursement 
for qualifying drugs. This reimbursement mechanism is also 
still volume based, and even if it influences a change in 
how new antibiotics are used, there is a ceiling on how 
much additional use and therefore revenue a given drug 
might generate.

However, the effect of the NTAP changes will also be 
influenced by hospital and pharmacy practices, especially 
by how frequently the NTAP is used. In hospitals where the 
NTAP for antibiotics has not been widely adopted, there 
may be opportunities for change that can increase this 
program’s impact for both providers and manufacturers.

ADDRESSING ANTIBIOTIC-SPECIFIC LIMITATIONS
Since the program’s inception in 2000, just 3 antibiotics 
(fidaxomicin, meropenem-vaborbactam, and plazomicin) 
have qualified for the NTAP. For this reason, many hospi-
tals, pharmacy departments, and infectious disease clini-
cians may be unfamiliar with the NTAP mechanism for 
antibiotic products. Until there is greater understanding of 
what drugs have qualified for NTAP and how to process the 
reimbursement documentation, there likely will be limited 
changes in formulary placement, coverage, or prescribing. 
Manufacturers can raise awareness of these programs if 
they have a qualifying product on the market but may not 
have the resources to do so on a large scale. As the NTAP 
program expands, better monitoring and stronger awareness 
campaigns may be the first step toward increasing usage of 
this mechanism.

Receiving reimbursement through the NTAP mechanism 
may be administratively burdensome, particularly for small 
or rural hospitals. Large health care organizations may have 
processes within their electronic medical record systems to 
facilitate coding and reimbursement, and these processes 
are likely critical for the NTAP mechanism’s use with antibi-
otics. A new antibiotic might be appropriate for use under 
a large number of DRGs, so without a system in place to 
trigger the NTAP reimbursement process, hospitals may 
miss opportunities to receive additional reimbursement.

In hospitals where the NTAP has not been widely adopted, 
there may be opportunities for change that can increase 
this program’s impact for both providers and manufacturers.

OUTLOOK FOR SUSTAINABLE REIMBURSEMENT AND USE
Ultimately, although CMS’ changes to antibiotic reimburse-
ment are a promising next step, they provide only an incre-
mental improvement in revenue for antibiotic developers.

Even if hospitals fully use the NTAP mechanism to enhance 
appropriate prescribing of new antibiotics, it is unlikely that 
sales will reach the levels needed to sustain a market for 
innovative antibiotics. Further, physicians and pharmacists 
will continue to rely on practice guidelines driven by ongoing 
product data to make prescribing decisions, so continued 
evidence generation will be critical to support appropriate 
use. For long-term sustainability, payment for this drug 
category will need to shift away from volume-based reim-
bursement. CMS should continue to work with providers 
and other relevant stakeholders to explore reimbursement 
mechanisms that delink antibiotic revenue from volume 
sales while also supporting strong stewardship programs 
and encouraging data generation.

References are available at ContagionLive.com.
Optimizing Treatment and Reducing Costs for Acute Bacterial Skin and Skin Structure Infections

BY GINA BATTAGLIA, PHD

The introduction of intravenous (IV) long-acting lipoglycopeptides for acute bacterial skin and skin structure infections (ABSSSI) has helped shift care to the outpatient setting in an effort to reduce unnecessary hospital admissions and minimize hospital length of stay. However, refinements in care pathways and algorithms are needed to improve the identification of patients most likely to benefit from outpatient treatment and care for special populations (such as immunocompromised patients and people who use IV drugs), Krutika N. Mediwalla, PharmD, said during a recent Contagion® News Network interview at the American Society of Health-System Pharmacists Midyear Meeting. Mediwalla discussed the need to improve access to IV lipoglycopeptides in all sites of care, reduce hospital readmission rates and length of stay, and address unmet needs of special populations and current challenges of treatment in ABSSSI.

At the American Society of Health-System Pharmacists Midyear Meeting, Krutika N. Mediwal, PharmD, discussed best practices for treating acute bacterial skin and skin structure infections.

SITE OF CARE FOR ABSSSI

Health care systems have recently pushed to reduce unnecessary hospital admissions and move site of care to the outpatient setting in patients with ABSSSI, with the goals of reducing costs and improving efficiency of care. A retrospective analysis of hospital admissions for skin and soft tissue infections at 520 US hospitals showed that approximately 60% of admissions were for patients without life-threatening conditions and Charlson Comorbidity Index (CCI) scores of 0 or 1 (indicating a low risk for mortality within the next 10 years). The analysis also showed that patients with a CCI score of 0 or 1 were treated in the hospital for an average of 4 days and incurred an average cost of $6000 to $7000. Furthermore, the results of a prospective study of adult patients presenting to the emergency department (ED) at 12 US sites in August 2008 showed that the need for IV antibiotics was the only reason for admission in 41.5% of patients, which led the authors to conclude that many patients with ABSSSI could be managed safely and effectively in the outpatient setting.

The US Food and Drug Administration (FDA) approval of dalbavancin and oritavancin (long-acting intravenous lipoglycopeptides) for ABSSSI allows some patients to receive the entire therapy in a single dose in the ED or outpatient setting and thus avoid hospital admission. Identifying patients who can safely receive treatment outside of the hospital will be instrumental for cutting overall costs of health care, according to Mediwal.

“The whole point is to identify these patients in the [ED] or an outpatient setting and administer the drugs so we avoid them getting admitted in the hospital and [incurring] all those costs, as well as possible adverse events,” Mediwal said.

However, she also noted that expanding access to IV lipoglycopeptides in both the inpatient, and the ambulatory settings is also important for patients who live far from an ED.

“My institution specifically takes care of a lot of the indigenous population from rural South Carolina,” Mediwal said. “Outpatient stewardship can help with that so they don’t have to come all the way to my institution just to come to the ED, get this drug, and then have to go drive back.”

CUTTING READMISSION RATES

In addition to the high rates of unnecessary hospital admission, high rates of readmission after treatment with oral antibiotics are also a problem for patients with ABSSSI and likely indicate a need to modify current treatment algorithms, according to Mediwal. The results of a retrospective observational cohort study of patients who presented to an ED for ABSSSI from July 2012 to June 2013 showed similar rates of all-cause and skin infection–related unplanned ED visits or hospital readmissions within 30 days after the initial episode of care between admitted and nonadmitted patients.

“The indirect costs of these patients getting admitted for [5-7 days of treatment] because of them having failed oral antibiotics is a lot more than for other hospital-acquired infections,” she said. “Cost is a great aspect for both the patient [and] health care institution.”

She also noted that education is important for setting up patients for success and avoiding readmission, as well as refining criteria to identify patients most likely to benefit from long-acting lipoglycopeptides. These include patients with uncomplicated cellulitis who can be followed closely by their primary care physician and patients with ABSSSI that did not respond to oral antibiotics. However, she added that access to these IV lipoglycopeptides in the inpatient setting is still difficult and often requires multiple communications with the insurance company to obtain coverage.
"I've had it used in a patient [in the] inpatient setting, and I had to fax 3 different things, get them on the phone, and be like, 'Hey, we need a 24 hour turnaround; I really need you guys to look at this patient' for the insurance and the co-pay," Mediwala said.

She added that the recent focus on outpatient antibiotic stewardship also provides an important opportunity for using evidence-based methods to identify patients with ABSSSI who can benefit from outpatient therapy.

DECREASING LENGTH OF STAY
For eligible patients with ABSSSI who do require hospital admission, use of long-acting IV lipoglycopeptides can be instrumental for reducing length of stay and patient quality of life, according to Mediwala. Data from the ENHANCE trial, a pre- versus postperiod pragmatic trial that evaluated consecutively admitted patients with ABSSSI at New YorkPresbyterian/Weill-Cornell Medical Center, showed that identification and treatment of eligible patients with dalbavancin in the postperiod significantly reduced the mean infection-related length of stay compared with the usual care administered during an observational period (ie, preperiod) prior to use of dalbavancin (3.2 days vs 4.8 days; P = .003). Furthermore, work productivity and activity impairment outcomes were significantly better in the group that received dalbavancin.

"From an adherence point of view, patients are able to get this dose very quickly and move on with their lives," Mediwala said.

Use of long-acting lipoglycopeptides in the ED may also increase throughput rate and translate into improved efficiency and reduced costs. Findings from another study using discrete-event simulation showed that implementation of a long-acting antibiotics treatment pathway in the ED for patients with ABSSSI improved throughput rate by 350% and reduced length of stay in the ED by 68%, with the improvements driven by the reduced infusion time needed for long-acting antibiotics. The study authors concluded that implementation of similar pathways would likely decrease treatment time for ABSSSI, which may translate into improved efficiency and economic value of care.

The potential for long-acting IV lipoglycopeptides to reduce length of stay and improve value of care has prompted studies of these agents for other types of infection, such as osteomyelitis and endocarditis, with the goal of providing more options for patients who are "not really fit for the hospital but still have [an] infection to deal with," according to Mediwala.

THE LANDSCAPE OF TREATMENT
In her interview, Mediwala stated that "plenty of antibiotics" are available to treat ABSSSI, including doxycycline, cephalaxin, and sulfamethoxazole/trimethoprim, as well as the IV antibiotics vancomycin, daptomycin, and ceftaroline. However, she reiterated the benefits of the long-acting lipoglycopeptides dalbavancin and oritavancin for improving patient compliance, because they only require a single dose.

"The most important thing that we worry about with our skin is soft tissue infection patients is [adherence]," Mediwala said. "Giving someone a drug that you know has [adverse] effects such as diarrhea can really change someone's [adherence]. Not having to worry about that is really helpful."

Although Mediwala said that the options for antibiotics are usually sufficient in the general population, she noted that immunocompromised patients are often treated with broad-spectrum agents that may not be necessary. Therefore, developing algorithms to identify immunocompromised patients who could be treated safely with a normal protocol, rather than a protocol designed for immunocompromised patients, could help minimize the use of broad-spectrum antibiotics. She added that individuals who use IV drugs and present with cellulitis often have additional complications, such as bacteremia or osteomyelitis, and early identification of patients who would benefit from some of the new agents for ABSSSI could be instrumental for treating these patients.

CHALLENGES WITH TREATMENT
Mediwala concluded her interview with a discussion of key challenges with treatment of ABSSSI—namely nuances with the FDA definition of ABSSSI, source control, and hospital readmissions. The FDA definition of ABSSSI, a bacterial infection of the skin (including cellulitis/erysipelas, wound infections, and major cutaneous abscesses) with a lesion size area of ≥75 cm², was established as a guidance to identify infections for which a reliable control drug treatment can be estimated in clinical trials. Although these criteria may be useful for standardizing enrollment of patients for clinical trials, Mediwala suggested that this definition may be too abstract for use in the clinical setting to determine whether a patient meets the criteria for ABSSSI treatment.

She pointed out that source control may also be an issue for infections, such as cellulitis, that do not have a well-defined source that can be evacuated. "It’s very elusive when you have cellulitis because [I] don’t necessarily have a source that I could point to," she said. "That can sometimes be difficult to treat."

She added that reducing hospital admissions is important for patients who initially received oral antibiotics but end up needing IV antibiotics and may be accomplished by restructuring the treatment algorithms and identifying patients who qualify for IV treatment up front followed by oral antibiotics. Prescribing oral antibiotics up front to patients who need "a little bit more help" and eventually required readmission reduces the treatment options available for that patient and negatively affects the hospital’s metrics," Mediwala said.

References are available at ContagionLive.com.

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Can Enteral Vancomycin *C Difficile* Prophylaxis Improve Outcomes in HSCT Recipients?

If an individual who has undergone autologous and allogenic hematopoietic stem cell transplantation (HSCT) becomes infected with *Clostridioides difficile*, the consequences can be severe. *C difficile* may compromise nutrition following HSCT and can cause complicated gastrointestinal mucositis, resulting in mucosal barrier infections or sepsis. The infection can also play into gastrointestinal acute graft-vs-host disease (GVHD) and reduce survival rates in patients who have undergone allogeneic HSCT.

Using enteral vancomycin for *C difficile* prophylaxis may be the key to reducing morbidity and improving outcomes in HSCT recipients. A team of investigators from Texas Transplant Institute/Methodist Children's Hospital in San Antonio presented their research on this topic in a session at the 2020 Transplantation & Cellular Therapy Meetings of American Society for Transplantation and Cellular Therapy (ASBMT) and Center for International Blood & Marrow Transplant Research (CIBMTR).

According to the abstract, Methodist Children's Hospital initiated enteral vancomycin for *C difficile* prophylaxis in all recipients of autologous and allogenic HSCT as a quality improvement initiative in February 2019.

Patients were prescribed 125 mg of vancomycin oral/enteral twice daily from the point of HSCT admission through discharge. Those who were readmitted within the first 100 days following HSCT returned to the enteral vancomycin regimen while hospitalized.

All patients were monitored for *C difficile* and vancomycin-resistant *Enterococcus* according to institutional policy. For this study, the investigators retrospectively reviewed pre- and postimplementation data. Specifically, the team used 2-sided Fisher exact test to compare occurrences of *C difficile*.

During the preimplementation period of January 5, 2018, through February 12, 2019, the rate of *C difficile* was 29% (9 of 31). In the postimplementation period of February 13, 2019, through September 16, 2019, the rate was 0% (0 of 23). Enteral vancomycin resulted in a significant reduction in the number of *C difficile* cases (*P* = .0068), the authors wrote.

In the preimplementation period, 26% (7 of 27) of the recipients of allogeneic HSCT developed gastrointestinal acute GVHD. Of these 7 individuals, 6 had a history of *C difficile*.

In the postimplementation period, 7% (1 of 14) of recipients of allogeneic HSCT recipients developed gastrointestinal acute GVHD.

The study team also reports that there were no vancomycin-resistant *Enterococcus* positive screens or infections or adverse events related to enteral vancomycin.

"Enteral vancomycin appears to be safe and effective *C difficile* prophylaxis in pediatric, adolescent, and young adult HSCT recipients," the authors wrote. "Since institution of enteral vancomycin prophylaxis, there has been a significant reduction of *C difficile* in our HSCT patients.

The investigators also noted that this quality improvement project is ongoing and that future work will compare gastrointestinal acute GVHD and overall survival with the pre- and postimplementation of enteral vancomycin prophylaxis.

The abstract, "Enteral Vancomycin Is Effective *Clostridium Difficile* Prophylaxis in Pediatric, Adolescent, and Young Adult Hematopoietic Stem Cell Transplant Recipients," was presented in a poster session Wednesday, February 19, at the 2020 Transplantation & Cellular Therapy Meetings of ASBMT and CIBMTR in Orlando, Florida.

### Antibiotic Exposure After HCT Raises Risk of Respiratory Viral Disease Progression

For patients who have undergone allogenic hematopoietic cell transplantation (HCT), exposure to antibiotics prior to respiratory viral infection can increase the risk of disease progression.

This new finding was announced by a team of investigators from the University of Washington, Fred Hutchinson Cancer Research Center, and Seattle Children's Hospital in a poster presentation session at the 2020 Transplantation & Cellular Therapy Meetings of American Society for Transplantation and Cellular Therapy (ASBMT) and Center for International Blood & Marrow Transplant Research (CIBMTR).

Previously, findings from animal model research showed that immunomodulate effects of changes in the microbiota were likely linked to the increased risk of disease progression following antibiotic exposure.

To address knowledge gaps, the team set out to identify specific antibiotics that may be associated with progression of select respiratory viral diseases. The investigators analyzed data from 469 individuals who underwent allogenic HCT between April 2008 and September 2018 and had a subsequent respiratory viral infection within the first 100 days following the transplant.

Specifically, the investigators looked at individuals who had parainfluenza (93), respiratory syncytial virus (54), human metapneumovirus (27), or human rhinovirus (295). Of these individuals, 124 experienced progression to lower respiratory tract disease.

The team assessed antibiotic exposure, looking at any versus no use of specific antibiotics and the total number of antibiotic days in the 21 days prior to onset of respiratory viral infection.

Using cumulative incidence curves, the investigators estimated the probability of disease progression, with death classified as a competing risk. They also used Cox proportional hazard models to examine associations between antibiotic exposure and disease progression risks, adjusting for type of respiratory infection, age, steroid use, lymphopenia, and neutropenia before infection onset. The data were censored at point of death, discharge, or 30 days after the infection resolved.

According to the results, the cumulative incidence or disease progression during the 21 days prior to onset of illness was a median of 11 (range, 0-56).

The investigators also reported that progression to lower respiratory tract disease was associated with more antibiotic days, use of antibiotics with broad anaerobic activity, and use of cephalosporins with limited anaerobic activity.

"This study suggests that cumulative exposure to antibiotics prior to respiratory viral infection is a risk factor for respiratory viral disease progression," the investigators wrote in their abstract. "Despite complex antibiotic use patterns in HCT recipients, our findings also suggest antibiotics of varying spectra may be associated with respiratory viral disease progression."
Newly Developed Algorithm for Pediatric Sepsis Surveillance Proves Successful

A n algorithm that uses clinical data successfully provided an efficient tool for pediatric sepsis surveillance.

Investigators from the University of Pennsylvania Perelman School of Medicine and Children’s Hospital of Philadelphia conducted a retrospective observational study at a single academic children’s hospital to test the surveillance algorithm. The findings were published in Pediatric Critical Care Medicine and presented as a late breaker at the 49th Critical Care Congress.

The investigators acknowledged the lack of a method to identify the occurrence of sepsis that is not affected by a change in diagnosis or claims-based coding practices. To address this need, the team derived an algorithm using routine clinical data to identify infection and concurrent organ dysfunction and applied it to study longitudinal trends in the epidemiology of sepsis. To evaluate the algorithm, the investigators looked at hospital encounters to determine trends in incidence and mortality from January 2011 through January 2019.

Among 93,987 hospital encounters and 1065 episodes of suspected sepsis in the derivation period, the surveillance algorithm yielded sensitivity of 78% (95% CI, 72%-84%), specificity of 76% (95% CI, 74%-79%), positive predictive value of 41% (95% CI, 36%-46%), and negative predictive value of 94% (95% CI, 92%-96%), the authors reported.

During the validation period, the algorithm yielded an observed sensitivity of 84% (95% CI, 77%-92%), specificity of 65% (95% CI, 59%-70%), positive predictive value of 43% (95% CI, 35%-50%), and negative predictive value of 93% (95% CI, 90%-97%).

The authors noted that most false-positive results should be deemed clinically relevant sepsis following manual review.

Overall, the hospital-wide incidence of sepsis was 0.69% (95% CI, 0.67%-0.71%), and inpatient incidence was 2.8% (95% CI, 2.7%-2.9%).

Risk-adjusted sepsis incidence also reportedly increased over time without bias from changing diagnosis or coding practices (adjusted incidence rate ratio per year, 1.07; 95% CI, 1.06-1.08; P < .001).

Mortality was 6.7% and did not change over time (adjusted OR per year, 0.98; 95% CI, 0.93-1.03; P = .38).

“An algorithm that uses routine clinical data available within the EHR [electronic health record] can provide an objective, efficient, and reliable method for pediatric sepsis surveillance across emergency and inpatient hospital settings,” the authors concluded.

“An increased sepsis incidence and stable mortality, free from influence of changes in diagnosis or billing practices, were evident.”

The study, “Identification of Pediatric Sepsis for Epidemiologic Surveillance Using Electronic Clinical Data,” was presented at the 49th Critical Care Congress Monday, February 17, 2020, in Orlando, Florida.

Findings Link OUD, Sepsis to High Death Totals of Young, Healthy Patients

I ndividuals with opioid use disorder (OUD) are more likely to acquire fungal and bacterial infections, including skin and skin structure, soft tissue, bone/joint, and bloodstream infections. These infections are also likely to occur in individuals who use injection drugs.

According to new research presented at the 49th Critical Care Congress, individuals with OUD are more likely to be hospitalized for sepsis and die if they are young and otherwise healthy.

“Sepsis is an increasing problem among people with OUD, especially those who are young and healthy,” Mohammad Alrawashdeh, MSN, PhD, postdoctoral research fellow in therapeutics research and infectious disease epidemiology at Harvard Medical School and Harvard Pilgrim Health Care Institute in Boston, Massachusetts, said in a statement. “People with OUD who inject the drugs are at risk for a serious and potentially deadly infection if they use nonsterile needles.”

The investigators analyzed more than 6.7 million records of hospitalization that occurred between 2009 and 2015. The team discovered that 375,479 patients had sepsis (5.6%), 164,891 had OUD (2.5%), and 11,861 (0.2%) had both.

Over the 7-year period, 1 in 14 hospitalized patients with OUD had sepsis, the investigators found, and sepsis was present in 1 in 3 patients with OUD who died in the hospital. The percentage of individuals with sepsis who also had OUD increased from 3% in 2009 to 4.2% in 2015.

Among hospitalized patients, those with OUD had a higher prevalence of sepsis compared with patients who did not have OUD (7.2% vs 5.6%).

Among all patients with sepsis, those who also had OUD were younger and healthier, with an average age of 53 years. In comparison, the average age of a patient with sepsis was 67 years. Additionally, patients with OUD and sepsis had an Elixhauser score of 7.3 versus 12.6, indicating fewer other health issues such as high blood pressure or diabetes.

The study team noted that patients with sepsis and OUD were more likely to have endocarditis (3.9% vs 0.7%), require mechanical ventilation (32.6% vs 24%), and stay in the intensive care unit longer (7.9 days vs 7 days, on average).

Overall, the investigators found that patients with OUD accounted for 2.1% of deaths among patients hospitalized for sepsis but 3.3% among healthy patients and 7.1% of those younger than 50 years.

Based on these findings, the investigators concluded that OUD contributed disproportionately to sepsis-associated deaths in younger and healthier patients. “In combating the opioid crisis, public health officials should also raise awareness with both patients and providers about the risk of death due to sepsis,” Alrawashdeh concluded.

The abstract, “Epidemiology, Outcomes and Trends of Sepsis in Patients Based on These Findings, the Investigators Concluded That OUD Contributed Disproportionately to Sepsis-Associated Deaths in Younger and Healthier Patients,” was presented in a late-breaking session at the 49th Critical Care Congress in Orlando, Florida.
A Case of Disseminated *Nocardiia farcinica* Presenting as Fever of Unknown Origin in a Transplant Patient

Outcomes in disseminated nocardiosis are variable and depend on patient factors.

**BY STEPHANIE SPIVACK, MD; AND PAUL LEONE, MD**

**FINAL DIAGNOSIS Nocardia farcinica**

**HISTORY OF THE PRESENT ILLNESS**

A 44-year-old woman with a medical history significant for end-stage renal disease underwent a deceased-donor kidney transplant. Nine months later, she presented to her nephrologist in the fall with fevers and chills, 2 days after returning from a trip to China. She was prescribed a course of azithromycin and had a chest x-ray and urine culture performed. The chest x-ray was unremarkable, and the urine culture grew *Proteus mirabilis*. She was then prescribed a course of levofloxacin. She continued to have fevers at home, so she was instructed to present to the hospital for further testing. On admission, she reported having had right-side flank pain, pleuritic chest pain, nonproductive cough, and myalgias for about 1 week.

**PAST MEDICAL HISTORY**

The patient had a history of end-stage renal disease due to presumed immunoglobulin A nephropathy. She had been receiving hemodialysis for several months via tunneled catheter followed by peritoneal dialysis for 3 years prior to her transplant. At the time of transplant, she demonstrated prior exposure to Epstein-Barr virus and cytomegalovirus (CMV). Her donor also demonstrated prior exposure to CMV. Her postoperative course was complicated by leukopenia, which required adjustment of her immune suppression, temporary cessation of *Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX), and administration of colony-stimulating factors.

She also had low-level CMV DNAemia, without evidence of organ involvement, treated with valganciclovir about 5 months after transplant. This condition, a form of leukopenia, was attributed to a combination of CMV and medications and resolved about 3 months prior to presentation.

She also had a history of hypertension, hypothyroidism, hyperparathyroidism, and gastroesophageal reflux disease.

**KEY MEDICATIONS**

At presentation, the patient was taking cyclosporine, mycophenolate mofetil, and prednisone for immunosuppression. She was also taking prophylactic TMP-SMX and recently completed a course of valganciclovir. In addition, she took amlodipine, levothyroxine, famotidine, aspirin, atorvastatin, and ferrous sulfate.

**EPIDEMIOLOGICAL HISTORY**

The patient was born in China and grew up in Brazil. She spent 3 weeks in the region of Canton in southern China and returned 2 days prior to symptom onset. While in China, she visited family and traveled to rural areas but denied outdoor activities, contact with animals, and insect bites. She did undergo a dental extraction during her trip. Normally, she lived at home in the United States with her husband and 2 adult children, none of whom had any recent illnesses. She was not employed. She had no history of alcohol, tobacco, or illicit drug use.

**PHYSICAL EXAMINATION**

On initial presentation, the patient was febrile with a temperature of 101.9°F. Her vital signs were otherwise within normal limits. She appeared well and in no distress. She was noted to have a grade 3/6 systolic murmur at the right upper sternal...
border that was not previously noted. Her exam was otherwise unremarkable.

STUDIES
Initial labs revealed a leukocytosis of 15.0 k/mm³ with a high absolute neutrophil count of 14.1 k/mm³ and low absolute lymphocyte count of 0.2 k/mm³. A comprehensive metabolic panel was unremarkable. Her cyclosporine level was elevated at 725 ng/mL (goal: 100-150 ng/mL). A D-dimer was elevated to 3468 ng/mL. An interferon-gamma release assay was negative. The remainder of her initial labs, including lactic acid, D-dimer was elevated to 725 ng/mL (goal: 100-150 ng/mL). A chest x-ray showed new subpleural irregularities. Light's criteria but grew Nocardia on culture. On imaging, she was also found to have a fluid collection around her transplanted kidney, which was drained by interventional radiology. The fluid cultures from this collection remained negative. Her blood cultures were persistently positive for 11 total days before clearing.

TREATMENT AND FOLLOW-UP
The Nocardia isolate was sent out for additional testing and returned as Nocardia farcinica. She was treated with TMP-SMX, meropenem, and linezolid while in the hospital. After her blood cultures cleared, she was transitioned to a 3-drug oral regimen consisting of amoxicillin/clavulanate, moxifloxacin, and TMP-SMX based on susceptibility testing (Figure 4 online).

Her CMV DNAemia was thought to be reactive in the setting of acute illness. Her viral load became undetectable on ganciclovir, and she was transitioned to oral valganciclovir. She was discharged after 20 days in the hospital. She was noted to be feeling well at follow-up visits.

DISCUSSION
Nocardia species are aerobic gram-positive branching rods that display weak acid-fast staining. The taxonomy of the genus Nocardia has been rapidly evolving because of improved molecular testing. The number of identified species is debatable, with some sources citing more than 90 species, including more than 50 recognized as causing disease in humans.

The most common human pathogens were members of what was once called the Nocardia asteroides complex, but many species that were formerly in this group have been reclassified. N nova, N farcinica, N cyriacigeorgica, N abscessus, and N brasiliensis are now among the most common species. In some case reviews, N farcinica has been observed to have higher rates of antibiotic resistance than other species. Studies in mice have also suggested that N farcinica may be more virulent and likely to cause disseminated infection than other species.

Nocardia are not part of the normal human flora, but they are found in the environment worldwide and can be inhaled or directly inoculated into the skin. Immunosuppression, especially diminished cell-mediated immunity, is a well-documented risk factor for nocardiosis, with approximately two-thirds of cases occurring in patients with an underlying immunocompromised condition. However, immunocompetent hosts can develop nocardiosis as well; they tend to develop localized skin infections. Immune-compromised hosts are more likely to develop pulmonary or disseminated disease.

Pulmonary disease can have many presentations, with symptoms including cough, dyspnea, hemoptysis, and weight loss. Radiographic findings are nonspecific and include nodules and cavitary lesions. Nocardia can disseminate to nearly any organ, particularly the central nervous system. Therefore, MRI screening of all patients with pulmonary or disseminated disease is recommended. Bacteremia, as seen in this patient, is relatively rare.

In patients with solid organ transplant, multiple patient factors have been associated with a higher risk of nocardiosis, including high trough levels of calcineurin inhibitors, use of high-dose corticosteroids, history of CMV infection, patient age, and length of stay in the intensive care unit after transplant. Although many transplant patients take TMP-SMX as Pneumocystis prophylaxis and this drug is the mainstay of treatment for nocardiosis, it is not clear if taking prophylactic doses of TMP-SMX provide some protection against developing Nocardia-related infections. Patients who developed nocardiosis while on prophylactic TMP-SMX have not been found to have higher rates of TMP-SMX resistance, as is the case here.

Nocardia is slow growing, and routine plates and cultures are frequently discarded before growth is detected. If Nocardia is suspected, cultures can be held for a prolonged period of 2 to 3 weeks. Various selective media can also help isolate Nocardia from contaminated specimens, such as sputum.

Trimethoprim/sulfamethoxazole is generally used as first-line therapy for nocardiosis, but combination therapy is often used for severe or disseminated disease. Susceptibility varies greatly among species, so susceptibility testing is recommended for all cases to guide therapy. Antimicrobial therapy for at least 6 to 12 months is recommended. Lowering immune suppression as much as possible is also recommended.

Outcomes in disseminated nocardiosis are variable and depend on patient factors, including number of organs involved, as well as time to diagnosis and to initiation of appropriate therapy. Because nocardiosis can present in a variety of ways and be challenging to diagnose, a high level of clinical suspicion is required for this increasingly recognized pathogen as our population of immunosuppressed patients grows.

References are available at ContagionLive.com.
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