MULTIDRUG-RESISTANT INFECTIONS

Dawn of a New Age: Novel Agents for the Treatment of Carbapenem-Resistant A baumannii

Targeting this bacterium with only our currently available antimicrobials is not enough.

BY NICOLE C. GRIFFITH, PHARMD, AAHIVP; AND JACINDA C. ABDUL-MUTAKABBIR, PHARMD, MPH, AAHIVP

Acinetobacter baumannii is a nonfermenting gram-negative (GN) organism with the capacity to cause severe infections that are untreatable by most antibiotic drug classes. For this reason, A baumannii has been identified by the World Health Organization as 1 of 6 organisms responsible for increased patient morbidity and mortality. Multidrug-resistant (MDR) A baumannii has become more prevalent, necessitating the use of carbapenems to aid in infection management. Nonetheless, molecular genotypes represented by the emergence of carbapenem-resistant A baumannii has become more prevalent necessitating the use of carbapenems.

Acute Infections

COVID-19–Associated Infections During ECMO
By Mehrnaz Sadrolashrafi, PharmD, BCCCP

SARS-CoV-2 infection has led to a drastic increase in the utilization of extracorporeal membrane oxygenation (ECMO) for supportive care. Based on data reported in the Extracorporeal Life Support Organization (ELSO) data set—from

(continued on page 14)

HIV/AIDS

Long-Acting Antiretroviral Therapies for HIV Treatment and Prevention
By Eric F. Egelund, PharmD, PhD; and Jessica Huston, PharmD

In January, the FDA approved cabotegravir/rilpivirine (Cabenuva), the first long-acting medication used for treating HIV infection. Several long-acting modalities are currently under investigation for both HIV treatment and prophylaxis, including oral, injectable, implant, antibody therapy, and vaginal ring.

(continued on page 10)

Stewardship & Prevention

How Do You Measure the Success of Your Stewardship Program?
By Jason Chao, PharmD; and Nicola Clayton, PharmD, BCIDP

Antimicrobial use data are essential for informing and assessing the progress of a stewardship program, but there are multiple challenges to collecting and analyzing the data in a meaningful, useful way. Data can be obtained from electronic health records, internal pharmacy

(continued on page 18)
The Tough Talks of Pediatric COVID-19 Vaccination

WE’VE AFFORDED OURSELVES, to some extent, the luxury of opportunity.

As of mid-May, more than 45% of Americans have received at least one dose of the COVID-19 vaccine, with supply for vaccination finally exceeding demand. We have the tools proven to curb the pandemic.

What’s more, we have begun the process of allotting vaccination for our younger generations. The FDA granted emergency use authorization (EUA) to Pfizer-BioNTech for use of their mRNA vaccine BNT162b2 in children and adolescents aged 12 to 15 years.

The EUA, which is the first granted to a COVID-19 vaccine for persons younger than 16 years old, is supported by ongoing clinical trial data that showed the 2-dose vaccine was associated with 100% prevention of symptomatic COVID-19 in adolescents 7 days after their second dose.

The data is substantial enough to warrant the EUA, and the assurances of continued federal agency monitoring of adverse events and vaccine-related risks have been proven by iterations of rollout and research pauses throughout this process. And greater vaccine availability should bring our population closer to the coveted vaccinated rates that would define herd immunity.

But the discussion of pediatric vaccination is a more difficult one, with the added element of parental decision-making. Yes, our data from the pandemic this past year show children are at less risk of SARS-CoV-2 infection as well as COVID-19 severity. And evidenced arguments have supported school reopenings and resumption of safe gatherings of children for the sake of their mental and behavioral development.

But the challenge to curb the virus’ progression from pandemic to endemic—or maybe even lesser—status implies the need for mitigated spread of SARS-CoV-2 from children to adults.

For parents and guardians, COVID-19 pediatric vaccination is an entirely different decision than the one to vaccinate themselves. And for our physicians and caregivers, it’s a different series of questions and concerns to field.

But what doesn’t change in the shift of focus from adult to pediatric vaccination is the absolute goal: a better future, removed from COVID-19. For the sake of the very same children becoming eligible for immunization, we must not lose sight of that goal while navigating these tricky conversations.

Mike Hennessy Sr
Chairman and founder

Learning the Wrong Lessons

AS THE US APPROACHES the second half of 2021, amazing progress against COVID-19 has been made. Most of the adult population has received at least one dose of vaccine and case rates have fallen substantially. Though the potential for seasonal spikes and new variants of concern remain as issues, it appears the worst of the pandemic is behind us in the US.

I feel that we were lucky. It seems wrong to write that for a disease that has claimed approximately 600,000 American lives, causes lingering effects in many people, and both harmed and altered the economy in ways that are still being assessed. However, it could have been much worse. An illness that combines the infectivity and asymptomatic spread of COVID-19 with the lethality of SARS-CoV-1 would have been beyond devastating.

Despite many missteps in our COVID-19 response, the US hit a grand slam with vaccine development. The widespread availability of COVID-19 vaccines across the country makes it easy to forget that these agents became available only a few short months ago. Any one of the many steps in vaccine development could have gone wrong. Although not every vaccine that entered clinical trials was successful, multiple agents were, and they have efficacy that is well above the expected threshold to limit spread. Safety of our available vaccines is now well understood and severe adverse events are exceedingly rare, particularly for the mRNA vaccines.

The spike protein of SARS-CoV-2, which is the antigen targeted by every single one of the vaccines currently available, turned out to be an effective target for vaccine-induced neutralizing antibodies. The US government funding of several vaccine manufacturer programs led to useful vaccines (with others still possible), and the “go-it-alone” approach of Pfizer led to another success.

Imagine some scenarios where things went differently. In one, multiple vaccines were not efficacious, and the one that succeeds in a trial has a measured efficacy of 50% but only for severe disease and only mildly blunts asymptomatic disease, leading to a limited effect on decreasing transmission. Vaccine availability is low due to high demand and limited production capabilities. Deaths decrease, but the pandemic rages.

Or, an approved vaccine is effective, but has a less-safe adverse effect profile that causes severe adverse effects in 1000 times as many people as the current vaccines. The adverse effects are still much rarer than deaths from COVID-19, but due to a different risk-benefit balance, only older adults and health care practitioners receive it. Deaths decrease, but the pandemic rages.

Or, imagine if the spike protein ended up being a poor target after all. Every single vaccine currently on the international market would fail. The pandemic rages.

None of these scenarios occurred. We are on track to control a rapidly emergent pandemic through vaccination for the first time in our history. It has not been easy, and because we have not implemented the more basic tenets of public health for infectious diseases well, we are fortunate. Humans have a tendency to forget history’s lessons as crises abate, and this is where I fear we are learning the wrong lesson now.

A process that began many years ago with vaccine development on multiple fronts culminated in the amazing therapeutics that we are putting into arms now. It is an enormous success. We cannot assume that the next challenge will be addressed successfully with technology at the same pace. The time to fund disease surveillance, bolster scant public health infrastructure, and develop our ability to respond to novel viruses is now, before the next shiny object takes our focus away.

Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS
Gallagher is a clinical professor at Temple University School of Pharmacy and clinical pharmacy specialist in infectious diseases at Temple University Hospital, both in Philadelphia, Pennsylvania. He is also the director of the PGY2 residency in infectious diseases pharmacy at Temple.

Active member of the Society of Infectious Diseases Pharmacists (SIDP)
## STEWARDSHIP & PREVENTION

18 How Do You Measure the Success of Your Stewardship Program?

The search continues for a metric that effectively evaluates an ASP's direct impact on appropriate antimicrobial use and improved patient outcomes.

**BY JASON CHAO, PHARMD; AND NICOLA CLAYTON, PHARMD, BCIDP**

### IN THE LITERATURE

4 Does Patient Insurance Influence *Staphylococcus aureus* Care Capability?

**BY KATHERINE T. LUSARDI, PHARMD, BCPS-AQ ID, BCIDP**

5 Treatment of Spinal Epidural Abscesses: Is Cefazolin Now a Close Contender?

**BY MIRANDA MONK, PHARMD, BCPS & MEAGAN ADAMSICK, PHARMD, BCIDP**

### MEDICAL WORLD NEWS®

6 Learn more about COVID-19 health care transformation and respiratory effects, plus a new tuberculosis clinical trial.

### NEWS & BREAKTHROUGHS

8 Treating Zaire ebolavirus With Ansuvimab-zykl

**BY LAUREN BLACK, PHARMD CANDIDATE; MATTHEW WITTMAN, PHARMD CANDIDATE; AND JAMIE WAGNER, PHARMD, BCPS**

### ACUTE INFECTIONS

10 COVID-19-Associated Infections During ECMO

Examining pharmacological management in COVID-19 patients with ARDS requiring antifungal therapy during extracorporeal life support.

**BY MEHRNAZ SADROLASHRAFI, PHARMD, BCCCP**

### EMERGING & REEMERGING INFECTIONS

12 10 Key Pillars to an Effective Ebola Response

EVD outbreaks this year serve as a reminder of the virus’ severity and the importance of having a containment strategy in place.

**BY SYRA MADAD, DHSC, MSC; AND VIKRAM MUKHERJEE, MD**

### HIV/AIDS

14 Long-Acting Antiretroviral Therapies for HIV Treatment and Prevention

More treatment options and modalities are now available for patients.

**BY ERIC F. EGELUND, PHARMD, PHD; AND JESSICA HUSTON, PHARMD**

### PEER EXCHANGE

20 Clostridioides difficile Infection: Diagnosis, Testing, Screening, and Treatment

**BY GINA BATTAGLIA, PHD**

### MEETING COVERAGE

22 Catch up on session coverage and featured interviews from SHEA Spring 2021

### CASE STUDY

24 A Case of Mycobacterium *Chimaera* Infective Endocarditis

Non-specific, nondolent symptoms make this disease difficult to diagnose.

**BY ZOHEIR KHAN, MD; AND JEREMY L. AGOSTINHO, MD**

### COVER IMAGE

COVER IMAGE CREDIT TO PRODUCTION PERIG, SEDA SERVET, THEVISUALSYOUNEED/ ADOBE STOCK

ILLUSTRATION BY PATRICK WELSH PAT@PATRICKWELSH.COM

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**TABLE OF CONTENTS**

**MULTIDRUG-RESISTANT INFECTIONS**

**Novel Agents for the Treatment of Carbapenem-Resistant *A baumannii***

*Targeting this bacterium with only currently available antimicrobials is not enough.*

**BY NICOLE C. GRIFFITH, PHARMD, AAHIVP; AND JACINDA C. ABDUL-MUTAKABBIR, PHARMD, MPH, AAHIVP**

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**ILLUSTRATION BY PATRICK WELSH PAT@PATRICKWELSH.COM**
Review the historical background on tetracycline discovery, emerging resistance, mechanism of action, and their spectrum of activity.

Learn about pharmacokinetic and pharmacodynamic similarities and differences of tetracyclines.

Discuss the clinical data supporting tetracycline use for common bacterial infections.

Identify applications for tetracycline-class antibiotics after assessing a patient case.
IN THE LITERATURE

Does Patient Insurance Influence Staphylococcus aureus Care Capability?

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

A study by McHale et al set out to look at the impact of patients’ insurance coverage on the receipt of appropriate or inappropriate management for Staphylococcus aureus bacteremia (SAB), an infection with high morbidity and mortality. The investigators hypothesized that patients without health insurance would receive a higher rate of inappropriate antibiotics at hospital discharge.

This was a retrospective study of adult patients with SAB conducted in a single academic hospital. Patients had to be discharged on antibiotics and could not have completed treatment as an inpatient. Postdischarge nursing care was categorized as “nursing service,” which included any facility placement or home health services, or “no nursing service.” Insurance status was placed into 4 categories: no insurance, Medicaid, Medicare, or commercial. The primary outcome was receipt of inappropriate therapy for SAB—determined by agent selection, route, and duration.

Appropriate antibiotics for methicillin-resistant S aureus (MRSA) included daptomycin and vancomycin, and appropriate antibiotics for methicillin-sensitive S aureus (MSSA) included β-lactams with antistaphylococcal activity. No oral antibiotics were considered appropriate. Antibiotic duration had to be more than 14 days to be considered appropriate, and categorization of complicated/uncomplicated SAB was not conducted.

Initially, 439 patients were identified, but only 273 were included. Of the 166 excluded patients, 35 completed therapy as inpatients, of whom 31.4% (n = 11) were uninsured compared with those who were included, uninsured, and completed treatment as outpatients (5.9%, n = 16). Thirty-nine patients (14.3%) of included patients received inappropriate therapy.

In the unadjusted model, both lack of infectious diseases (ID) consult and lack of nursing service after discharge were associated with inappropriate treatment. There was an increase in the rate of inappropriate therapy across the different insurance strata: commercial (4/76, 5.3%), Medicare (23/155, 14.8%), Medicaid (6/26, 23.1%), and no insurance (6/16, 37.5%). Having any insurance besides commercial was associated with inappropriate therapy (odds ratio [OR], 2.08; 95% CI, 1.39-3.13; P<.001), and having no insurance was more strongly associated with inappropriate therapy (OR, 4.07; 95% CI, 1.29-12; P=.0167).

In the adjusted model, controlling for ID consult and nursing service, lack of insurance was weakly associated (but not statistically significant) with increase in inappropriate therapy (OR, 1.57; 95% CI, 0.98-2.53; P=.0644). The strongest variable associated with inappropriate therapy was lack of ID consult (OR, 59.2; 95% CI, 11.4-306.9; P<.001). ID was consulted in 94.5% of all patients.

Thirty-day readmission and 30-day mortality were not higher in patients with inappropriate therapy, and in general in the study, were either the same as or lower than would be expected: 67/273 (24.5%) patients were readmitted, and 14/273 (5.1%) patients died. A study looking at 30-day readmission and mortality rates from SAB in 2014 in the United States found similar readmission rates (22%) as this study but higher mortality rates: 13% in-hospital death.

An older study placed 90-day mortality from bacteremia and complications at 26% (MSSA) to 44% (MRSA).

Lack of nursing service was associated with inappropriate therapy but could also be a further marker of the lack of adequate insurance. When this was controlled for in multivariate analysis, the association between insurance and inappropriate therapy dropped to be just under statistically significant (P = .064).

The study by McHale et al had several limitations. Addressing the role of oral medications in contributing to inappropriate therapy should be done, and because inappropriate therapy was not associated with worse outcomes, additional analysis of what caused therapy to be deemed inappropriate could have helped shed light on the lack of difference. This study was not chart-level review, so the determination of complicated/uncomplicated infection was not present and could have been different between the groups.

As more data come out to support oral antibiotics for diseases states like endocarditis and osteomyelitis, it becomes harder to dismiss the role of oral antibiotics in facilitating transitions of care. This study also continues to emphasize the connection between ID consult and appropriate management of SAB (ID consult was not present in only 5.1% of patients).

Despite some of the limitations, this study does have an important place in our libraries. It starts to quantify something that can be of concern for clinicians: Does our patient’s insurance impact our ability to choose the best medications in contributing to inappropriate therapy? The correlation that was initially seen faded away in the multivariate analysis, but considering the proportion of uninsured patients kept in hospital to finish their treatment, the answer is likely “yes,” and this area continues to require research.

References are available at ContagionLive.com.

Highlighted Study
Treatment of Spinal Epidural Abscesses: Is Cefazolin Now a Close Contender?

BY MIRANDA MONK, PHARM.D, BCPS ©, AND MEAGAN ADAMSKICH, PHARM.D, BCIDP ©

Current management of spinal epidural abscesses (SEAs) caused by methicillin-susceptible Staphylococcus aureus (MSSA) includes anti-staphylococcal penicillins (ASPs) as first-line agents and cefazolin as an alternative, without a well-defined optimal duration of therapy.

Clinical hesitancy for cefazolin for SEAs with MSSA involves in vitro evidence of the inoculum effect due to β-lactamase hydrolysis, leading to increased treatment failures, as well as conflicting evidence surrounding cefazolin’s penetration into the central nervous system space. Currently, no data specifically compare ASPs and cefazolin in SEAs. However, current data do support the use of cefazolin for MSSA bloodstream infection (BSI), because many SEAs are often caused by hematogenous spread.1-3

A multicenter, retrospective cohort trial at Mayo Clinic sites included patients from 2004 to 2020 who had a MSSA SEA diagnosed through epidural fluid collection and either CT or MRI. Antibiotic regimens included cefazolin 2 grams intravenous (IV) every 4 hours, oxacillin 2 grams IV every 4 hours, or nafcillin 2 grams IV every 4 hours. Patients were in the cefazolin or ASP group based on which treatment they received for more than 50% of their total treatment duration (defined as extending therapy) at 6 weeks.

Seventy-nine patients were included: 45 patients received cefazolin, 29 received nafcillin, and 5 received oxacillin. See Table for baseline characteristics and outcomes among groups. The majority of patients in both groups had multilevel epidural involvement. There was no difference in treatment failure at 6 weeks; most patients received treatment beyond 6 weeks (82.4% vs 75.6% in the ASP vs cefazolin groups, respectively; P=.58). Along with antimicrobial medical management, 92.4% of patients also underwent surgical management of SEA.

Additionally, no difference was detected between groups for other outcomes such as 30-day mortality (5.9% ASP vs 2% cefazolin) and 90-day recurrence (9.4% ASPs vs 11.4% cefazolin). Total duration of therapy was not statistically different in ASP vs cefazolin groups (median [interquartile range], 67.5 [45-93.7] days vs 55.5 [42.2-96] days; P=.44). However, patients with multilevel epidural involvement were treated with longer antibiotic courses compared to those with single-level involvement (85 [45-110] days vs 41 [41-60] days; P<.01).

This study, albeit small and retrospective, supports the use of cefazolin in SEAs compared to ASPs, with no detectable difference in treatment outcomes. Although similar rates of discontinuation due to adverse events were seen in this study, cefazolin is often chosen over ASPs for improved tolerability and safety or for patients with preexisting kidney or liver impairment. Cost is another consideration often favoring cefazolin when treating SEAs—given the prolonged duration.

The different dosing frequency of each antibiotic allows for selection of a treatment that will best fit each individual patient’s lifestyle. The study also highlighted the importance of surgical treatment of SEAs (>90% of patients underwent aspiration or surgical debridement). Finally, cefazolin can be considered an initial agent of choice in patients with concomitant BSI, infective endocarditis, and/or SEA, as data support its outcomes when compared to ASPs. However, a patient’s risk factors, surgical management plan, and epidural involvement must be carefully considered to decide appropriate treatment duration, which is still underdetermined for SEAs. ▲

See references at ContagionLive.com

Highlighted Study

TABLE. Baseline Characteristics and Patient Outcomes Adapted From Campioli et al 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cefazolin (n = 45)</th>
<th>Nafcillin/Oxacillin (n = 34)</th>
<th>P value</th>
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<tr>
<td><strong>Baseline characteristics</strong></td>
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<td>Age, median (IQR)</td>
<td>64.5 (55-73.2)</td>
<td>59.6 (47.2-64)</td>
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<td>Male, n (%)</td>
<td>26 (57.7%)</td>
<td>19 (55.9%)</td>
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<td>Charlson Comorbidity Index</td>
<td>3 (2-4)</td>
<td>2 (1-4)</td>
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<td>ICU admission</td>
<td>5 (11%)</td>
<td>10 (29.4%)</td>
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<td>Community-acquired infections</td>
<td>27 (60%)</td>
<td>19 (55.9%)</td>
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<td>History of spinal/epidural intervention</td>
<td>21 (47%)</td>
<td>15 (44.1%)</td>
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<td>Multilevel epidural involvement</td>
<td>30 (67%)</td>
<td>26 (76.5%)</td>
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<td>Concurrent Staphylococcus aureus bacteremia</td>
<td>31 (69%)</td>
<td>24 (70.6%)</td>
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<td>Duration of BSI, days</td>
<td>3 (2.5)</td>
<td>4.5 (2-8)</td>
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<td>Infective endocarditis</td>
<td>0</td>
<td>2 (5.9%)</td>
<td>0.18</td>
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<td>Aspiration or IR-guided procedure</td>
<td>13 (29%)</td>
<td>5 (14.7%)</td>
<td>0.18</td>
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<td>Surgical debridement</td>
<td>32 (71%)</td>
<td>28 (82.4%)</td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td>Hospital length of stay, days</td>
<td>9 (5.5-15.5)</td>
<td>13 (6-25)</td>
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<tr>
<td>Total antibiotic duration, days</td>
<td>55.5 (42.2-96)</td>
<td>67.5 (45-93.75)</td>
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<td>Extension due to clinical failure at week 6</td>
<td>37 (75.6%)</td>
<td>25 (82.4%)</td>
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<tr>
<td>SEA-related death</td>
<td>2 (4%)</td>
<td>2 (5.9%)</td>
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<tr>
<td>Mortality</td>
<td>7 (15.6%)</td>
<td>4 (11.8%)</td>
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<td>30-d mortality</td>
<td>1 (2%)</td>
<td>2 (5.9%)</td>
<td>0.57</td>
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<tr>
<td>90-d recurrence</td>
<td>5 (11.4%)</td>
<td>3 (9.4%)</td>
<td>1</td>
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<tr>
<td>Treatment interruption from adverse drug event</td>
<td>1 (2%)</td>
<td>2 (2.9%)</td>
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</tbody>
</table>

BSI, bloodstream infection; ICU, intensive care unit; IQR, interquartile range; IR, interventional radiology; SEA, spinal epidural abscess.
Will the Health Care Transformation Sparked by COVID-19 Be Permanent?

BY DESSIREE PAOLI

After months upon months of anxiety and uncertainty, a light at the end of the COVID-19 pandemic tunnel appears to be in sight.

In the US, the average number of daily deaths attributed to COVID-19 fell from 3,400 in mid-January to 940 by late March. Most Americans 65 years and older (the largest at-risk group) are now protected from the virus, with 52% having been fully vaccinated and 74% having received the first of 2 doses. With all adults in the US now eligible to receive the vaccine, it should only be a matter of time before we reach herd immunity and some semblance of normalcy.

As we all transition into a postpandemic reality, it will be crucial to note which industries regress to past practices and which ones are forever altered by this monumental global event.

When analyzing the current landscape, it’s clear that this health care transformation is permanent—and perhaps for the better.

HOW HEALTH CARE ADAPTED TO COVID-19

More than any other industry, health care felt the effects of the pandemic. As a worldwide health emergency continued to persist, care providers had to meet that overwhelming demand while protecting frontline personnel from the virus.

Health care workers adapted efficiently and creatively with strategies that are shaping the future of care delivery. Health care isn’t known for using technology enthusiastically or innovatively, evidenced by the fact that health care can take as long as 18 months to make seemingly minor tech changes.

The pandemic forced many hospitals and clinics to pivot and quickly implement new offerings, such as telehealth services. It was a calculated move considering that many health care providers didn’t have the infrastructure to support these services early in the pandemic.

Part of the need to move toward telehealth solutions was due to social distancing requirements and public health measures, but insurance reimbursements also played a significant role. Payers increased reimbursements above the previous rate of 20% of in-person visits, making telehealth economically viable in new ways. For physicians, telehealth solutions allow them to provide more accessible and flexible treatment.

This begs the question: Are telehealth and similar solutions here to stay, even after the pandemic ends?

THE NEW NORMAL

No matter what health care transformation looks like in the postpandemic period, there are compelling reasons to think virtual health care will play an ongoing role. For one, health care organizations have spent the past year accruing the equipment and expertise needed to make telehealth, remote work, video conferences, and all kinds of digital interactions possible on a vast scale. They have a natural incentive to continue leveraging these new resources instead of scrapping them for the status quo.

Health care providers will also face pushback if they move away from telehealth solutions now that we’ve seen how effective they can be. Physicians, patients, and even health care administrators know that telehealth replicates in-person visits and improves them in many ways. Physicians experience less stress and burnout, patients have easy access to doctors, and health care delivery takes fewer resources. It’s a win for everyone involved.

If the pandemic contains a silver lining, it’s how the health care industry learned to trust technology in new ways. People have been calling for change for years, but now it finally seems possible. The coming months and years in the health care industry promise to be fascinating.

REIMAGINING HEALTH CARE DELIVERY

Some health care delivery experiments undertaken during the pandemic proved so successful they are likely to become permanent. What follows are a few we see continuing to emerge:

• Digital monitoring: By implementing a telehealth program, any interaction that doesn’t require direct contact could realistically become a virtual session. Telehealth especially becomes useful when digital tools can monitor items like heart rate, blood sugar, and cholesterol—and then send the data to the health care organization for ongoing monitoring and analysis.

• Parking lot appointments: Offering COVID-19 tests and vaccinations in parking lots proved an effective defense against infectious disease and an efficient health care delivery model. Some form of drive-through care could become common, as health care workers try to provide care while keeping infectious patients out of waiting rooms. This is precisely the kind of outside-the-box idea that would have been off-limits pre-pandemic. Now, it’s a proven commodity. Everyone acknowledges the health care transformation was overdue long before 2020, but the pandemic forced the issue. Although COVID-19 has taken a terrible toll, it may result in some lasting good: Health care that works better for patients, providers, and payers. ▲
One-Third of Patients Hospitalized for COVID-19 Show Reduced Lung Function 1 Year Later

BY KILLIAN MEARA

Findings from a recent study conducted by investigators from the University of Southampton in collaboration with investigators from Wuhan, China, show that 1 year after infection, up to 33% of patients hospitalized for severe COVID-19 infection have evidence of effects on their lungs.

Results from the study were published in the journal *The Lancet Respiratory Medicine*.

“The majority of patients with severe COVID-19 pneumonia appeared to fully recover, although for some patients, this took many months,” said Mark Jones, PhD, an associate professor in respiratory medicine at the University of Southampton and National Institute for Health Research (NIHR) Southampton Biomedical Research Centre, who co-led the study. “Women were more likely to have persistent reductions in lung-function tests, and further investigation is needed to understand if there is a sex-specific difference in how patients recover. We also don’t yet know what happens beyond 12 months, and this will need ongoing study.”

The investigators followed 83 patients discharged from a hospital after experiencing severe COVID-19 infection. Follow-up was conducted at 3, 6, and 12 months.

At each follow-up, the participants underwent a clinical assessment, including measures of how well their lungs were functioning, a walking test, and a CT scan of their chest.

Findings from the study demonstrated that over a 12-month period, most patients showed an improvement in symptoms, exercise capacity, and COVID-19–related CT changes. By the end of the study period, the majority fully recovered.

However, 33% of patients still showed reduced lung functioning, particularly in how efficiently their lungs transferred oxygen into their blood, and approximately 25% still showed signs of changes in their lungs on CT scans.

“Firstly, our research provides evidence that routine respiratory follow-up of patients hospitalized with COVID-19 pneumonia is required,” said study co-lead Yihua Wang, MBBS, a lecturer in biomedical sciences at the University of Southampton and NIHR Southampton Biomedical Research Centre. “Secondly, given the length of time it takes for some patients to recover, it suggests that research into whether exercise programs help patients recover more quickly is required. Finally, it highlights the need for treatment strategies to prevent the development of long-term COVID-19–related lung changes.”

New Tuberculosis Regimen Shortens Treatment by 2 Months

BY KENNETH BENDER, PHARMD, MA

Four months of treatment with a rifapentine-moxifloxacin-based antituberculosis regimen produced the same survival rate with absence of mycobacterium tuberculosis at 12 months as the conventional half-year regimen with rifampin-based treatment, according to findings from a phase 3 trial published in the *New England Journal of Medicine*. The trial evaluated rifapentine-based regimens with and without the fluoroquinolone in more than 2000 patients in 34 sites around the world.

Susan Dorman, MD, of the Medical University of South Carolina in Charleston, and colleagues of the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium conducted the trial comparing 2 rifapentine-based experimental regimens against conventional treatment in patients newly diagnosed with *Mycobacterium tuberculosis* not resistant to isoniazid, rifampin, or fluoroquinolones.

The participants were randomly assigned in equal numbers to receive either a conventional regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol or with rifampin replaced with either rifapentine or with rifapentine and moxifloxacin.

The investigators chose rifapentine, a cyclopentyl derivative of rifampin, as an alternative to rifampin because preclinical models suggest that increasing exposure to rifamycins could shorten the time course for treating tuberculosis.

“Rifapentine has activity against *M. tuberculosis*, and its longer half-life makes the drug an attractive option for increasing the duration of exposure to rifamycins while maintaining the once-daily dosing schedule that facilitates the completion of treatment,” Dorman and colleagues wrote.

The investigators also noted evidence that moxifloxacin exerts activity against *M. tuberculosis* and that its addition to antituberculosis regimens has accelerated sputum-culture conversion to negative status, albeit without yet shortening the requirement for 6 months of treatment.

Rifapentine was administered at a daily dose of 1200 mg, with moxifloxacin at 400 mg daily and the other drugs at standard doses adjusted for body weight. The medications in each regimen were administered 7 days per week, with the study protocol specifying direct observation of medications being administered at least 5 days per week. Because food affects the absorption of rifapentine and rifampin differently, rifapentine was administered within 1 hour after ingesting food and rifampin was taken on an empty stomach.

Dorman and colleagues reported that 4 months of treatment with the rifapentine-moxifloxacin–based regimen (but not without moxifloxacin) was noninferior (within a margin of 6.6 percentage points) to 6 months of the conventional rifampin-based treatment.

In the microbiologically eligible populations, 15.5% of those on the rifapentine-moxifloxacin–based regimen had an unfavorable outcome, compared to 14.6% on the longer rifampin-based regimen. Adverse events of grade 3 or higher occurred in 18.8% of the rifapentine-moxifloxacin group and in 19.3% of those receiving the rifampin-based treatment.

The results were welcomed in the accompanying editorial, “Shortening the Short Course of Tuberculosis Treatment,” by Valerie Mizrahi, PhD, director of the Institute of Infectious Disease and Molecular Medicine at the University of Cape Town in South Africa, and Eric Rubin, MD, PhD, an infectious disease specialist at Brigham and Women’s Hospital, a professor in the Department of Immunology and Infectious Diseases at the Harvard T.H. Chan School of Public Health, and editor in chief of the *New England Journal of Medicine*.

“It was almost as though 6 months represented some strict limit—that is, until now,” Mizrahi and Rubin wrote.

That this development has been long awaited is reflected in the years since Mizrahi’s previous editorial in the journal in 2014, “Shortening Treatment for Tuberculosis—Back to Basics,” in which she reviewed failure of 3 separate trials to achieve this outcome and called for a closer look at the characteristics and potential susceptibility of *M. tuberculosis*.

Although they welcomed the prospect of a shortened course of treatment, Mizrahi and Rubin shared some concerns about this regimen, including the need to take rifapentine after meals for maximize absorption. They also suggested that the conventional rifampin-based regimen has an advantage of comprising drugs that are not generally used for other infections. In addition to necessitating rapid drug-susceptibility testing for moxifloxacin, the widespread use of the antibiotic for tuberculosis could promote resistance to fluoroquinolones in other bacteria, they noted.

“This trial does, however, establish an important principle: There is no magic 6 months of therapy,” they concluded. “This trial not only proves that we can have a shorter short-course treatment but also suggests that an even shorter short-course treatment might one day be feasible.”
Zaire ebolavirus (EBOV) is 1 of 4 Ebolavirus species that can cause a potentially fatal disease in humans. The Ebola virus is thought to be introduced into humans through contact with blood, bodily secretions, or organs of infected animals, such as bats, apes, monkeys, antelope, or porcupines. Human-to-human transmission occurs through direct contact with blood, bodily fluids, and tissues of infected humans as well as contaminated surfaces and materials.

The 2014 to 2016 Ebola outbreak was the largest recorded, with a total of 28,652 cases reported in 10 countries and 11,325 deaths occurring in 6 of those countries. The World Bank reported that the outbreak cost an estimated $1.62 billion. Spurred by this outbreak, the World Health Organization initiated discussions to develop and utilize experimental therapeutics in the next Ebola outbreak. Development of ansuvimab-zykl (Ebanga) originated from a single monoclonal antibody isolated from immortalized B cells obtained from a survivor of the 1995 Ebola outbreak in the city of Kikwit in the Democratic Republic of the Congo. Ansuvimab-zykl is a single-dose, intravenous, recombinant human IgG1κ monoclonal antibody that binds to the glycoprotein 1 subunit of EBOV, preventing binding of EBOV to host cells and inhibiting viral entry into the host cell.

A phase 1, open-label, dose-escalation clinical trial for ansuvimab-zykl was conducted from March 2018 to September 2018 to evaluate its safety, tolerability, and pharmacokinetics. The trial included 18 subjects in 3 experimental arms (5 mg/kg, n = 3; 25 mg/kg, n = 5; and 50 mg/kg, n = 10), with the drug given as a single 30-minute infusion. Participants were followed for 24 weeks and assessed for infusion-site reactions and systemic symptoms through self-reporting, direct clinician assessment, and clinical laboratory data. The primary study outcome was safety and tolerability of ansuvimab-zykl; secondary outcomes included pharmacokinetic and antidrug antibody evaluation.

All doses were well tolerated, with no infusion-site reactions reported. Only 4 (22%) participants experienced systemic symptoms, including malaise (n = 3), myalgia (n = 2), headache (n = 4), chills (n = 2), nausea (n = 2), and joint pain (n = 2). There were no serious adverse events. Ansuvimab-zykl exhibited linear pharmacokinetics and had a half-life of 24 days, with no detection of antidrug antibodies noted.
When the next EBOV outbreak occurred in August 2018, the randomized, controlled PALM trial (NCT03719586) was initiated comparing MAb114 (now ansuvimab-zyk1), remdesivir, and REGN-EB3 to ZMapp (active control). Patients were enrolled from November 2018 through August 2019, and all were included if they had a positive reverse transcriptase–polymerase chain reaction (RT-PCR) assay positive for EBOV within 3 days prior to screening. The primary end point was death at 28 days, and the secondary efficacy end point was time to first negative PCR test.

Most patients (74.4%) enrolled were 18 years or older, and more than half (55.6%) identified as female (Table). A total of 673 participants were randomized as follows: 169 received ZMapp (50 mg/kg × 3 doses); 175 received remdesivir (200 mg × 1 dose, then 100 mg daily × 9-13 days); 174 received MAb114 (50 mg/kg × 1 dose); and 155 received REGN-EB3 (150 mg/kg × 1 dose). Twelve patients died prior to receiving the first dose: 1 in the ZMapp group, 3 in the remdesivir group, 3 in the MAb114 group, and 5 in the REGN-EB3 group.

Most participants received the study drugs within 6 hours of enrollment in the trial; however, 42 (6.2%) patients had therapy delayed for more than 6 hours. Participants in the ZMapp group were administered the drug in just over 3 hours, and participants in the MAb114 group received the drug in just over 2.5 hours. Twenty-nine participants experienced a serious adverse event related to the trial drugs: 7 who received ZMapp, 9 who received remdesivir, 10 who received MAb114, and 3 who received REGN-EB3. By day 28, 290 (43.1%) patients expired; however, MAb114 had significantly less deaths compared to ZMapp (35.1% vs 49.7%; 95% CI, –25.2 to –1.7). This result continued to hold true for patients of both high (69.9% vs 84.5%; 95% CI, –33.0 to –0.5) and low (9.9% vs 24.5%; 95% CI, –32.4 to –2.6) viral loads, as well as for those who received the drugs in less than 6 hours (34.5% vs 49%; 95% CI, –25.4 to –1.5).

When examining the impact of other variables through a logistic regression model for death at 28 days, MAb114 maintained superiority over ZMapp when considering duration of EBOV symptoms (odds ratio [OR], 0.49; 95% CI, 0.31-0.78), age (OR, 0.52; 95% CI, 0.33-0.82), and serum creatinine level (OR, 0.48; 95% CI, 0.27-0.84). Additionally, the secondary efficacy end point, median time to first negative PCR test, was shorter for patients receiving MAb114 than patients receiving ZMapp (16 days vs 27 days).

Ansuvimab-zykl was formally approved by the FDA on December 22, 2020, for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to a mother who is PCR positive for Zaire ebolavirus. (See Figure for the development timeline of ansuvimab-zykl.) The drug is recommended to be given as a single 50-mg/kg actual body weight dose infused through a 1.2-micron in-line filter extension set over 60 minutes.

Development of ansuvimab-zykl originated from a single monoclonal antibody isolated from immortalized B cells obtained from a survivor of the 1995 Ebola outbreak in the city of Kikwit, Democratic Republic of the Congo.

No studies have been done to determine the impact of infusion ansuvimab-zykl in a patient who has received or will receive the live Ebola vaccine; therefore, it is recommended to avoid concurrent administration of the vaccine with ansuvimab-zykl treatment. Ansuvimab-zykl is approved for use in special populations, including pregnant women and neonates. Although an insufficient number of patients older than 65 years were included in the PALM trial, there were no differences in responses compared to adults younger than 65 years.

With the current outbreaks of EVOD occurring in the Democratic Republic of the Congo and Guinea, patients of any age can receive ansuvimab-zykl to help increase their chances of survival. The only limitation to using this drug is the need to store product vials in a refrigerated condition prior to warming and reconstitution.

**TABLE.** Baseline Characteristics of Participants in the MAb114 and ZMapp Populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ZMapp (N = 169)</th>
<th>MAb114 (N = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>29.7 ± 16.8</td>
<td>27.4 ± 18.5</td>
</tr>
<tr>
<td>No. of females (%)</td>
<td>87 (51.5)</td>
<td>98 (56.3)</td>
</tr>
<tr>
<td>No. pregnant/total No. (%)</td>
<td>4/63 (6.3)</td>
<td>5/69 (7.2)</td>
</tr>
<tr>
<td>Days since symptom onset, mean ± SD</td>
<td>5.6 ± 3.6</td>
<td>5.5 ± 3.6</td>
</tr>
<tr>
<td>Serum creatinine level, mg/dL</td>
<td>2.9 ± 3.3</td>
<td>2.1 ± 2.6</td>
</tr>
</tbody>
</table>

References are available at ContagionLive.com.
COVID-19–Associated Fungal Infections During EMCO: Review of Epidemiology, Diagnosis, and Pharmacotherapy

Examining pharmacological management in COVID-19 patients with ARDS requiring antifungal therapy during extracorporeal life support.

BY MEHRNAZ SADROLASHRAFI, PHARMD, BCCCP

(continued from cover page)

the start of the pandemic in North America through April 2021—more than 4000 patients were initiated on ECMO, with a reported 50% in-hospital mortality rate.1 The median duration of ECMO support in the most recent ELSO publication was 13.9 days (interquartile range, 7.8–23.3).2 The longer duration of ECMO support begs the question: Are these patients at higher risk of nosocomial infections compared to other critically ill patients?

Potential reasons for increased nosocomial infections in critically ill patients with COVID-19 include3,4:

1. Routine use of steroids for COVID-19 acute respiratory distress syndrome (ARDS) based on results from the RECOVERY trial (NCT04381936)

2. Use of interleukin 6 receptor antagonists based on REMAP-CAP trial (NCT02735707) investigators

3. Prolonged duration of supportive care (eg, mechanical ventilation, central lines) and increased utilization of the empiric broad-spectrum antimicrobial.

Per COVID-19 Real-Time Learning Network, the current data indicate less than 10% rates of bacterial coinfections in patients with the diagnosis of COVID-19 upon presentation. However, with prolonged duration of hospitalization or mechanical ventilation, patients are prone to acquiring nosocomial bacterial and fungal infections. Despite various case series, the epidemiology of COVID-19–associated pulmonary aspergillosis (CAPA) and other fungal coinfections in COVID-19 is not known. The primary focus of this article is to review the diagnosis of fungal infections in a population of COVID-19 patients with ARDS requiring support from ECMO and compare it to the previously published data on its incidence and diagnosis in other viral infections such as influenza-related ARDS. The secondary focus of this article is to review the published data on pharmacokinetics and pharmacodynamics of antifungal dosing in ECMO.

Data are lacking in studying the epidemiology of fungal infection in the subpopulation of critically ill patients on ECMO, including the type of ECMO support and variable criteria for clinical diagnosis of invasive fungal infections, which makes the application of these data to clinical practice difficult.

To study the prevalence of fungal infections in ECMO, we should first review its incidence in critically ill patients regardless of their ECMO status.

**ASPERGILLUS AND CANDIDA INFECTIONS IN ECMO**

*Candida* and *Aspergillus* are 2 commonly isolated fungi among critically ill patients.5 Schauwvlieghe and colleagues6 reported retrospective data on a cohort of mixed immunocompromised and nonimmunocompromised intensive care unit (ICU) patients to identify risk factors for invasive pulmonary aspergillosis (IPA) among polymerase chain reaction–positive influenza A/B patients (n = 432) vs patients with severe community-acquired pneumonia as a comparator group (n = 321). The diagnosis of IPA was made based on the presence of clinical, radiological, and mycological criteria (Table).4

In the subgroup analysis, 12% of patients in the influenza cohort were on ECMO. Within the ECMO subgroup, 19% were diagnosed with IPA. In this cohort, influenza was reported as an independent risk factor for IPA. The study reported a high prevalence of bronchoalveolar lavage (BAL) sampling in approximately half of the influenza cohort (n = 233), in which only 60% of the BAL samples were tested for the presence of galactomannan (GM).

To study if prevalence IPA is also applicable to patients with the diagnosis of COVID-19, Lahmer and colleagues recently published the results of the first randomized, controlled trial to study the prevalence of IPA in patients with severe

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**TABLE.** Modified AspICU Definition of IPA4

<table>
<thead>
<tr>
<th>CLINICAL CRITERIA</th>
<th>RADIOLOGICAL CRITERIA</th>
<th>MYCOLOGICAL CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more of the following signs or symptoms had to be present:</td>
<td>Any infiltrate on pulmonary imaging by portable chest x-ray or CT scan of the lungs. This radiological definition was different from the EORTC-defined radiological criteria (eg, halo sign or air-crescent sign) because these EORTC criteria apply to patients with prolonged neutropenia but are of little use for ICU patients.</td>
<td>One or more of the following had to be present:</td>
</tr>
<tr>
<td>• Fever refractory to at least 3 days of appropriate antibiotic therapy</td>
<td>• Histopathology or direct microscopic evidence of dichotomous septate hyphae with positive culture for <em>Aspergillus</em> from tissue</td>
<td>• A positive Aspergillus culture from BAL</td>
</tr>
<tr>
<td>• Recrudescence of fever after period of defervescence of at least 48 h while still on antibiotics and without other apparent cause</td>
<td>• A galactomannan optical index on BAL of ≥ 1</td>
<td>• A galactomannan optical index on serum of ≥ 0.5</td>
</tr>
<tr>
<td>• Dyspnea</td>
<td>Aspergillus species were identified by their culture characteristics and microscopic morphology.</td>
<td></td>
</tr>
<tr>
<td>• Hemoptysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pleural friction rub or chest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support1,2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BAL, bronchoalveolar lavage; EORTC, European Organization for Research and Treatment of Cancer; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis.
COVID-19 pneumonia (AspCOVID-19 study). Based on anecdotal reports on an increased rate of IPA in patients with COVID-19 and prior reports during the hemagglutinin type 1 and neuraminidase type 1 influenza pandemic, the authors utilized a modified AspCU algorithm for identifying patients with IPA and risk factors associated with this diagnosis. The Figure reviews the standardized diagnostic algorithm the AspCOVID-19 investigators utilized for screening and diagnosis of IPA.

Data are lacking in studying the epidemiology of fungal infection in the subpopulation of critically ill patients on ECMO.

Patients were screened for CAPA until extubation. Patients with the diagnosis of CAPA (positive GM antigen from respiratory and/or serum blood) continued to be followed for 28 days.

A total of 32 patients were included in the final analysis of this study, which found no difference in IPA between COVID-19 and severe influenza-pneumonia groups.

In a published ELSO registry data set from 2006 to 2016 (including both venoarterial ECMO and venovenous ECMO), solid organ transplant, mechanical ventilation, and influenza infection were found to be risk factors for aspergillosis, and renal replacement therapy and sepsis were independently associated with an increased risk of *Candida* bloodstream infection (C-BSI). In this cohort of patients, 10.8% were found to have fungal infection/diagnosis, 1.3% *Aspergillus*, and 1.2% C-BSI. This study reported its findings in a retrospective data set from cultures collected at the discretion of the clinicians rather than a protocolized approach (collecting cultures and conducting bronchoscopy or sending biomarkers when an infection is suspected). Although this study may underestimate the actual prevalence of IPA and/or *Candida* infections, the diagnostic algorithm for IPA proposed by Schauwvlieghe and colleagues may lead to inflating the number of actual patients with this diagnosis, secondary to overtesting and possible false-positive diagnoses. The balance between overtesting and risk stratification based on the patient’s baseline risk factors for C-BSI and IPA needs to be better studied. Prospective studies are needed to guide clinicians on empiric treatment without waiting for positive cultures versus conducting appropriate diagnostic imaging and microbiological studies first. (See table online: Studies in ECMO for Antifungal Agents)

**CHOICE OF ANTIFUNGAL AGENT WHILE ON ECMO FOR CAPA/C-BSI**

Drug pharmacokinetics may be altered in ECMO due to various factors such as drug sequestration in the ECMO circuit, increased volume of distribution, and altered clearance (organ dysfunction and/or need for continuous renal replacement therapy). If the diagnosis of CAPA/C-BSI is confirmed or highly suspected, timely initiation of antifungal therapy is prudent, as these infections have been associated with an increased rate of mortality and length of hospital stay.

Per the 2020 European Excellence Center for Medical Mycology/International Society for Human and Animal Mycology consensus criteria for research and clinical guidance, voriconazole or isavuconazole is recommended as a first-line treatment option for CAPA. This guideline recommends initiating liposomal amphotericin B in cases of azole resistance in CAPA.

Per Infectious Diseases Society of America guidelines, an echinocandin is recommended as a first-line treatment for C-BSI in critically ill patients, which can be later deescalated to an azole based on the isolate susceptibility. Liposomal amphotericin B is recommended in case of suspected/confirmed azole resistance. ▲

References are available at ContagionLive.com.
10 Key Pillars to an Effective Ebola Response

EVD outbreaks this year serve as a reminder of the virus’ severity and the importance of having a containment strategy in place.

By Syra Madad, DHSc, MSc, and Vikram Mukherjee, MD

As the world focuses on combatting COVID-19, we are reminded once again that dozens of outbreaks of other infectious diseases continue to occur. Many of these diseases are endemic like Ebola virus disease (EVD) in the Democratic Republic of the Congo (DRC) and can reemerge at any given time. In February, there were 2 Ebola outbreaks, one in the DRC and another in Guinea. The outbreak in the DRC was declared over on May 3. According to the World Health Organization, Guinea began a 42-day countdown to declaring an end to the EVD outbreak in early May.

The article’s authors are part of a special pathogens team tasked with ongoing preparedness and maintaining a state of readiness in health care for Ebola. This team is made up of physicians, nurses, technicians, infection preventionists, emergency management coordinators, administrators, and more.

What follows are their 10 core pillars to an effective Ebola-outbreak response.

1. THE 3 CS: COMMUNICATION, COORDINATION, AND COLLABORATION

The need for clear, concise, consistent, transparent, and science-based communication is essential, both for outbreak responders and the public. For those involved in Ebola response, ongoing communication, coordination, and collaboration must occur at all levels—from local to international.

The ability to conduct contact tracing relies on trust and cooperation from the public—hence the need for risk communication and community engagement. Previous epidemics of Ebola have been contained through successful contact tracing, isolation, and quarantine, which break the chain of infection.

2. BOX IN THE VIRUS: TESTING, CASE FINDING, AND CONTACT TRACING

To contain the virus, rapid and ongoing laboratory services to accurately diagnose individuals, identification of cases coupled with isolation, and contact tracing to find and quarantine exposed persons are critical to prevent transmission.

The ability to conduct contact tracing relies on trust and cooperation from the public—hence the need for risk communication and community engagement. Previous epidemics of Ebola have been contained through successful contact tracing, isolation, and quarantine, which break the chain of infection.

3. MONITORING AND SURVEILLANCE

A public health surveillance system should be in place to immediately detect and report cases of illness compatible with Ebola. Strong surveillance systems to track all suspected and confirmed cases of disease will allow for detection of new cases and monitoring spread. Upon detection of a possible Ebola event, a rapid-response team should investigate and implement initial mitigation measures, including systematic contact tracing. Technological advances can supplement traditional surveillance methods to accrue information in real time, offering the possibility of better outbreak management.

4. PATIENT CARE

All efforts should be made to provide usual standard of care to patients with suspected or confirmed Ebola. While such care should be provided in a safe and logical manner, planning and education should result in avoidance of altered standards of care due to the perceived risk to providers. Lastly, there should be synchrony among the multiple disciplines involved in the care of a patient with EVD, including physicians, nurses, laboratory personnel, environmental services, and infection control.
5. INFECTION PREVENTION AND CONTROL
The core of every Ebola response is basic infection prevention and control. This includes a combination of measures to prevent and minimize the transmission of Ebola, such as administrative controls and safer work practices (eg, protocols, processes for screening, limiting individuals who come in contact with suspected or confirmed persons with Ebola); engineering controls to prevent or minimize exposures (eg, physical barriers or designated rooms for patient care and designated equipment and supplies); and use of personal protective equipment to prevent and minimize exposure. This also includes safe and dignified burial practices and other environment-of-care strategies (eg, cleaning and disinfecting, waste management).

6. SOCIAL MOBILIZATION AND COMMUNITY ENGAGEMENT
Outbreak response starts and ends with the people. For people to change any behaviors (eg, burial rituals) and follow public health guidance, there must be community engagement. This starts with grassroots, boots-on-the-ground messengers who are part of the community and can serve as trusted emissaries. In previous and current Ebola outbreaks, community engagement has served as the backbone of successful responses.3

7. RISK COMMUNICATION
Risk communication refers to effective communication during an emergency.4 Effective risk communication helps the public make informed decisions regarding the event and helps rapid-response teams understand behavior changes to mitigate risks. Risk communication can occur through multiple channels including social media, government briefings, and press releases. Given the misinformation and disinformation that occur during Ebola outbreaks, which can result in mistrust and hostility toward responders,5 having experts who are trusted messengers provide ongoing risk communication (with science- and evidence-based information) is essential.

8. EPIDEMIOLOGICAL AND OUTBREAK ANALYTICS
Effective Ebola response relies on good data and analytics to provide information on current and projected case counts and where the outbreak is headed in terms of trajectory, map current progress and spread, assess populations at risk, and help with early detection and control of viral spread. Epidemiological and outbreak analytics are complex and multifaced and require collecting, analyzing, interpreting, modeling, and reporting of data. Effective data collection and analysis inform the outbreak response and help decision makers determine next steps (eg, mobilization of resources).

The ability to conduct contact tracing relies on trust and cooperation from the public.

9. LOGISTICS MANAGEMENT AND INCIDENT COMMAND
All Ebola outbreaks require resources including personnel, treatment centers, equipment and supplies, vaccines and therapeutics, and more. The assistance of an incident management structure can facilitate planning, logistic management (eg, supply chain), and the ability to operationalize a response. The complex task of coordinating and dispatching needed supplies, equipment, and human resources and maintaining a safe and hygienic environment is a massive undertaking that often requires all hands on deck.

10. GOVERNANCE
Leadership and governance can make or break Ebola response. A successful strategy requires responsiveness, accountability, and the ability to galvanize rapid response. Regions with civil unrest and unstable public health and health care systems pose additional challenges, but these hurdles can be overcome by effective leadership with trust between government and citizens. ▲

References are available at ContagionLive.com.
Long-Acting Antiretroviral Therapies for HIV Treatment and Prevention

More treatment options and modalities are now available for patients.

BY ERIC F. EGELUND, PHARMD, PHD; AND JESSICA HUSTON, PHARMD

Long-acting formulations are being developed to overcome barriers—primarily, adherence—presented by daily oral therapy. Encouraging results regarding adherence from the phase 2b LATTE-2 study (NCT02120352) that evaluated long-acting cabotegravir/rilpivirine for HIV treatment showed that 99% of participants preferred to continue with injectable therapy compared with 78% on oral treatment. The purpose of this article is to provide an overview of the various antiretroviral (ART) therapies being studied and are available for prevention and treatment of HIV.

Cabotegravir/rilpivirine

Cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a nonnucleoside reverse transcriptase inhibitor were approved and copackaged as the first injectable treatment option for adults with HIV-1. Following an oral lead-in therapy, the cabotegravir/rilpivirine long-acting extended-release injectable suspensions are currently administered once monthly and are expected to replace the current regimen for those who are infected, have no history of treatment failure, and are virologically suppressed (HIV-1 RNA < 50 copies/mL). This long-acting injectable was approved based on the results of the phase 3 FLAIR (NCT02938520) and ATLAS (NCT02951052) studies, which evaluated virologic suppression in ART-naive and ART-experienced individuals, respectively.

Cabotegravir

In addition to the previously mentioned clinical trials (ATLAS, FLAIR) examining long-acting cabotegravir in the treatment of HIV, injectable cabotegravir is also being studied for preexposure prophylaxis (PrEP) in the HPTN 083 (NCT02720094) and HPTN 084 (NCT03164564) studies. Promising results emerged using injectable cabotegravir every 2 months for PrEP in the HPTN 083 study, which enrolled cisgender men and transgender women who have sex with men. As with the ATLAS and FLAIR studies, an oral lead-in therapy was utilized. The study was halted early due to the superiority of injectable cabotegravir versus oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Of the 52 HIV infections seen in HPTN 083, 13 infections were in the cabotegravir arm (0.41% incidence rate) compared to 39 infections in the TDF/FTC arm (1.22% incidence rate).

The interim analysis for the phase 3 HPTN 084 study, which enrolled HIV-uninfected women at increased risk for HIV, showed that women in the cabotegravir arm had an 89% lower risk of HIV infection compared with those receiving TDF/FTC. In addition, HPTN 084 showed superior efficacy for long-acting injectable cabotegravir in an interim review meeting, with the HIV incidence rate in those receiving cabotegravir at 0.21% compared with 1.79% in those receiving oral TDF/FTC. Because of the positive study outcomes at that point, it was recommended to stop the blinded phase and offer subjects in both arms of the study long-acting cabotegravir once available.

Dapivirine

A dapivirine intravaginal ring (IVR) for HIV-1 prevention is currently on the World Health Organization’s prequalification list following the positive opinion from the European Medicines Agency in July 2020. The dapivirine intravaginal silicone ring is designed to slowly release dapivirine over the course of 1 month to reduce the risk of HIV acquisition.

In 2 phase 3 studies, the dapivirine IVR was shown to be well tolerated and reduced HIV-1 acquisition risk by 30% compared with placebo. The HOPE study (NCT02858037), an open-label extension of the ASPIRE study (NCT01617096), aimed to assess the uptake and use of the IVR in women who had participated in the ASPIRE study and remained HIV-1 negative. Acceptance of the dapivirine IVR was high; 92.2% of women accepted the ring at enrollment, and 97.9% of follow-up visits were completed. Adherence was also measured by testing residual dapivirine amounts in the rings; overall, 89.3% of the returned rings had more than 0.9 mg of dapivirine released, which indicated use.

Due to its cost effectiveness, acceptability, and feasibility, the IVR will provide benefit to sexually active at-risk women. Studies that include IVRs with both contraceptive and HIV preventative medications are underway.

Islatravir

One of the most promising long-acting oral antiretrovirals is islatravir, a first-in-class nonnucleoside reverse transcriptase translocation inhibitor. Islatravir’s long intracellular half-life in peripheral blood mononuclear cells (PBMCs) allows for extended dosing intervals. Interim results from a phase 2a study (NCT04003103) comparing once-monthly islatravir 60 mg tablets, 120 mg tablets, and placebo for PrEP showed no serious adverse events or deaths; in addition, the drug was well tolerated. Tissue kinetics showed rapid and sustained distribution to cervical, rectal, and vaginal tissues, with both tested doses achieving trough concentrations above the prespecified threshold (0.05 pmol/106 cells).

Based on the favorable results from this phase 2 study, two phase 3 studies will compare islatravir once monthly at the 60-mg dose to current PrEP therapy: TDF/FTC in cisgender women (IMPPOWER-022)
Lenacapavir acts as a capsid inhibitor, with additional in vitro data showing disruption of multiple stages in HIV’s life cycle; thus, it has the potential to work against HIV strains that have developed resistance to multiple other classes. In the phase 2/3 CAPELLA study (NCT04150068), 36 adults with multidrug-resistant HIV received either placebo or daily lenacapavir for 14 days as an add-on to a failing regimen. At the end of 14 days, the lenacapavir cohort met the primary end point (0.5 log10 copies/mL decrease in viral load; 88%) compared with the placebo group (17%).

The aforementioned subcutaneous injectable formulation of lenacapavir displays a long half-life and is being investigated as a twice-yearly injectable for PrEP. A phase 1b study supported sustained therapeutic concentrations following a single 900 mg dose administered in three 1-mL injections (also studied were two 1.5-mL injections).

For treatment purposes, interim efficacy results from the CAPELLA study showed high rates of viral suppression through 26 weeks in study participants receiving lenacapavir injection (following the 2-week oral lead-in) in combination with an optimized background regimen in treatment-experienced people living with HIV (PLWH). Nineteen of the 26 subjects followed through the 26 weeks achieved viral suppression, with an average CD4 count increase of 72 cells/mm³. Gilead Sciences, Inc and Merck have announced plans to codevelop lenacapavir and islatravir as a combination injectable regimen; a coformulated oral regimen is also being studied.

**VRC01**

Broadly neutralizing monoclonal antibodies (bNAbs) are potential agents for long-acting HIV prevention due to their ability to decrease viral load by neutralizing many strains of the pathogen and possibly reducing the viral reservoir. VRC01 was discovered in the blood of a PLWH and is directed at the HIV-1 envelope protein CD4-binding site. This bNAb was manufactured for the Antibody Mediated Prevention (AMP) studies (NCT04801758, NCT04860323) to assess its ability to prevent HIV-1 acquisition.

The 2 double-blind, placebo-controlled phase 2b AMP studies enrolled more than 4000 patients collectively. HPTN 081 (NCT02568215) enrolled cisgender women, and HPTN 085 (NCT02716675) enrolled MSM and transgender persons who have sex with men. HVTN 703/ HPTN 081 (NCT04860323) included heterosexual women from sub-Saharan Africa, and HVTN 704/HPTN 085 (NCT04801758) included men and transgender persons from the Americas and Europe who have sex with men.

In each study, subjects were randomized to receive VRC01 by intravenous infusion at a dose of 10 mg/kg or 30 mg/kg every 8 weeks or a control infusion every 8 weeks. The outcome of both studies was to compare documented HIV-1 infection by week 80. Overall, acquisition of HIV-1 was not significantly lower with VRC01 compared with placebo in either study.

Unfortunately, viruses in persons receiving the bNAb showed greater resistance. Furthermore, as compared to other potential long-acting modalities, cost—as well as the necessity of intravenous infusions—may preclude the use of bNAbs for the immediate future. Instead, bNAbs may have a place in vaccine design and development. Future studies will examine combinations of bNAbs and bNAb-based vaccines.

**SUMMARY**

The modalities currently under study, once realized, will allow a wide variety of options for both treatment and prophylaxis (Table). Adherence, which is especially challenging for at-risk populations, could improve dramatically. Daily adherence to an oral regimen would be replaced by longer intervals between clinic visits—reducing dosing frequency, pill fatigue, and oral absorption issues (e.g., drug-drug interactions, short bowel syndrome) as well as the potential avoidance of HIV-related stigma.

However, the potential impact that delayed clinic visits could have on resistance to long-acting formulations in a real-world setting requires further study. Other barriers also will need to be overcome for long-acting formulations to reach their full potential, such as cost effectiveness, cotreating comorbidities (e.g., hepatitis B, substance abuse), and ensuring overall availability to at-risk populations.

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**TABLE.** Sample of Long-Acting Formulations for Treatment and PrEP Under Development With Proposed Regimens

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MOA</th>
<th>FORMULATION</th>
<th>PREP/TREATMENT</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabotegravir</td>
<td>Integrate inhibitor</td>
<td>Injectable</td>
<td>Treatment</td>
<td>Every 4 weeks Every 8 weeks</td>
</tr>
<tr>
<td>Dapivirine</td>
<td>NNRTI</td>
<td>Vaginal Ring</td>
<td>PrEP</td>
<td>Every 3 months</td>
</tr>
<tr>
<td>Islatravir</td>
<td>NRTTI</td>
<td>Oral</td>
<td>Treatment</td>
<td>Once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Treatment PrEP</td>
<td>Once weekly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Once monthly</td>
</tr>
<tr>
<td>Islatravir</td>
<td>NRTTI</td>
<td>Implant</td>
<td>PrEP</td>
<td>Once yearly</td>
</tr>
<tr>
<td>Lenacapavir</td>
<td>Capsid inhibitor</td>
<td>Oral</td>
<td>Treatment</td>
<td>Once weekly</td>
</tr>
<tr>
<td>Lenacapavir</td>
<td>Capsid inhibitor</td>
<td>Injectable</td>
<td>PrEP</td>
<td>Twice yearly</td>
</tr>
<tr>
<td>VRC01</td>
<td>bNAb</td>
<td>Intravenous</td>
<td>PrEP</td>
<td>Every 8 weeks</td>
</tr>
</tbody>
</table>

bNAb, broadly neutralizing antibody; MOA, mechanism of action; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTTI, nucleoside reverse transcriptase translation inhibitor; PrEP, preexposure prophylaxis.
Targeting this bacterium with only our currently available antimicrobials is not enough.

BY NICOLE C. GRIFFITH, PHARMD, AAHIVP; AND JACINDA C. ABDUL-MUTAKABBIR, PHARMD, MPH, AAHIVP

Dawn of a New Age: Novel Agents for the Treatment of Carbapenem-Resistant A baumannii

Tetracyclines have shown utility against CRAB.

(continued from cover page)

of blaOXA-23, blaOXA-24, and blaOXA-51 genes, which are class D β-lactamases (oxacillinase, or OXA), have contributed to an increase in carbapenem-resistant A baumannii (CRAB). Additionally, extended-spectrum Acinetobacter-derived cephalosporinas (ADCs) as well as select class A β-lactamases further complicate the use of cephalosporins and other carbapenem-sparing agents in A baumannii-mediated infections. Sulbactam, a β-lactamase inhibitor that binds to PBP2 in A baumannii, has shown some activity against CRAB; however, it also falls prey to the aforementioned resistance mechanisms.

Tetracyclines (tigecycline and minocycline) have been shown to have utility against CRAB; however, pharmacokinetic limitations, clinical toxicity, and challenges with interpreting susceptibility results impede placement within CRAB treatment regimens. Aminoglycosides demonstrate minimal in vitro activity against CRAB, attributed to the presence of aminoglycoside-modifying enzymes, and clinical results are often less promising than in vitro reports. Thus, last-line antimicrobials, such as the polymyxins (polymyxin B and colistin), have become the agents of choice against CRAB. However, the ill-defined pharmacokinetic/pharmacodynamic parameters of the polymyxins translate to the over- and underdosing of the agents, leading to toxicity and poor efficacy, respectively. Moreover, an increase in polymyxin-resistant and heteroresistant A baumannii organisms has been reported.

In short, the most appropriate monotherapy agents for the management of CRAB have yet to be elucidated. Combination-therapy options, often with a carbapenem backbone, have shown some promise against CRAB. The basis of success with combination therapy is typically attributed to antibiotic synergy provided by the use of multiple antimicrobials with differing mechanisms of activity against CRAB.

Nevertheless, clinical efficacy has not been consistently reported, and combination approaches are not devoid of collateral damage. Further, the use of combination therapy does not allow for a decline in the dosing of the single agents; therefore, developing toxicities associated with each antimicrobial (ie, Clostridiodes difficile infections, renal toxicity, etc) is a risk. Because of the mechanisms of resistance, associated toxicities, and ultimate uncertainty with the currently utilized treatment regimens for CRAB, the development and availability of novel therapies for CRAB management are imperative.

Targeting our currently available antimicrobials against CRAB mechanisms of resistance is a commendable approach but is not adequate for optimal treatment of CRAB. Currently, 3 agents have recent phase 3 trial data available or in progress: eravacycline, ceferodocol, and sulbactam-durlobactam; in addition, there is a renewed focus on the utility of bacteriophage therapy. Although these agents have shown promising in vitro activity against CRAB, clinical outcomes studies have reported variable results.

ERAVACYCLINE

Modifying the original tetracycline pharmacophore, eravacycline potentiates activity through the inhibition of the 30S ribosomal subunit. To date, clinical trials evaluating eravacycline have focused solely on infection site rather than causative pathogen. This, unfortunately, has resulted in the reporting of extremely low rates of infection due to A baumannii, let alone CRAB, precluding the ability to determine any potential utility against the carbapenem-resistant isolates. Furthermore, the lack of trial data is mirrored with no published post-marketing clinical experience.

CEFIDEROCOL

Cefiderocol is a novel siderophore cephalosporin that utilizes the bacteria’s active transport system to evade common mechanisms of A baumannii resistance. Cefiderocol therapy was evaluated against GN-complicated urinary tract infections (UTIs) and GN pneumonias in the APEKS-cUTI (NCT02321800) and APEKS-NP (NCT03032380) trials, respectively. Although cefiderocol proved to
be noninferior to the comparator therapy in both studies, neither patient population included an appreciable amount of patients infected with CRAB to draw conclusions from these studies.14,15

The CREDIBLE-CR trial (NCT02714595) aimed to resolve this discrepancy, but the results, unfortunately, only further confounded CRAB treatment.16 Overall, clinical cure rates between patients randomized to receive cefiderocol or best-available therapy were similar.16 However, participants randomized to cefiderocol treatment had a significantly higher rate of all-cause mortality, a result driven by the study population infected with CRAB.16 Of importance, all-cause mortality was not the primary outcome of the study, and the patients with CRAB were older (≥ 65 years) and more commonly diagnosed with ongoing septic shock and/or requiring treatment in an intensive-care setting compared with the rest of the study population, although these factors were not determined to be causative of the increased mortality findings.16 In addition to concerns for increased mortality, 5 isolates of A baumannii displayed an increase in the minimum inhibitory concentration of cefiderocol during the study, potentially foreshadowing rapid resistance against cefiderocol therapy in practice.16

Despite cefiderocol’s promise as a new agent with utility against GN pathogens, its role against CRAB remains undetermined.

**SULBACTAM-DURLOBACTAM**

Sulbactam-durlobactam, a combined β-lactam/β-lactamase inhibitor (BL/BLI) agent, is currently being evaluated in a phase 3 trial that corrects some of the obstacles previously faced in determining efficacy against CRAB.17 Designed to study infections caused by A baumannii-calcoaceticus complex infections, the trial compares sulbactam-durlobactam with imipenem/cilastatin versus colistin with imipenem/cilastatin, thereby evaluating combination regimens that are reflective of actual clinical practice.17 Although this will provide a better picture of real-world efficacy, this design will lead to difficulty in interpreting the true efficacy of the novel BL/BLI and any potential for monotherapy.

**PHAGE THERAPY**

Bacteriophages are viruses that can be administered locally or systemically to parasitize specific bacterial species or even individual bacterial strains. The phages are typically administered in “cocktails” designed to target particular pathogens or isolates. To date, phage therapy has generally been utilized as a last-line option in conjunction with antimicrobial therapy to treat multidrug-resistant infections, but antimicrobial resistance threats worldwide are leading to increased focus on and development of this novel therapy.

A baumannii–targeted bacteriophages were first introduced in 2010, but phage therapy presents many unique challenges surrounding controlled-trial evaluation, standardization, and regulatory approval that have delayed widespread use.18 Ongoing clinical trials will begin to provide information on efficacy as well as optimal route, dosage form, dose, and duration of therapy for phage therapy, but to date, the best data are based on case reports. Two published patient cases detail the use of phage therapy in patients infected with CRAB, both treated with bacteriophages in conjunction with antimicrobials after failure of antimicrobial therapy.19,20 The addition of phage therapy both locally and systemically resulted in clinical improvement in a 68-year-old man infected with MDR A baumannii from a comatose, intubated state that required vasopressor support to clinical success and subsequent discharge.19 A second patient received systemic phage therapy for a cranectomy with intraoperative cultures positive for MDR A baumannii. The local site improved, but unfortunately, the patient did not survive.20 Based on case report findings, phage therapy resulted in increased A baumannii sensitivity to antibiotic therapy; however, drug resistance to the individual phages did develop during therapy.19,20

**FINAL THOUGHTS**

CRAB continues to be a troublesome GN organism due to its ability to develop advanced mechanisms of resistance, resulting in variable activity of available antimicrobial agents, both as monotherapies and in combination regimens. Thus, novel agents such as eravacycline, cefiderocol, and sulbactam-durlobactam are of supreme interest, given their ability to evade commonly characterized resistance mechanisms. Although these agents have potential as treatment options against CRAB, additional agents earlier in the pipeline are being evaluated in clinical and animal studies and hold interest as potential CRAB-mitigating options (Table).

Nonetheless, it is necessary to confront the lack of clinical data for the aforementioned novel therapies as well as the potential for the emergence of A baumannii resistance, which in turn influences the placement of these antibiotics in CRAB treatment algorithms. Of note, it is not currently recommended that these agents be used as initial monotherapy treatments against CRAB. Further, the inevitable emergence of resistance has been shown by the decreased A baumannii susceptibility of cefiderocol in the presence of ADC-type cephalosporinases and with A baumannii phages, with the requirement of multiple phages to overcome quickly emerging bacteriophage cocktail resistance.19,21

Factors such as these are an impediment on the use of newer agents, but they also present an avenue for the use of combination therapy—with these novel therapies serving as the backbone. This could ultimately revolutionize CRAB therapy and possibly serve as a sparing mechanism for the older agents used in CRAB treatment. Nevertheless, the present gaps reinforce the necessity for more clinical and in vitro studies targeted to determine the best approach to mitigating CRAB infections. ▲

### TABLE. Agents in the Pipeline for Carbapenem-Resistant A baumannii

<table>
<thead>
<tr>
<th>STAGE OF DEVELOPMENT</th>
<th>AGENT (CLASS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro studies</td>
<td>LN-1-255 (BL-lactamase inhibitor)* Apramycin (aminoglycoside)</td>
</tr>
<tr>
<td>Phase 1</td>
<td>VRNX-5113 (BL-lactamase inhibitor) WCK-5153 + zidebactam (BL-lactam enhancers) AIC-499 (BL-lactam) SPR741 (polymyxin B derivative)</td>
</tr>
</tbody>
</table>

*Outcome studies.
How Do You Measure the Success of Your Stewardship Program?

The search continues for a metric that effectively evaluates an ASP’s direct impact on appropriate antimicrobial use and improved patient outcomes.

BY JASON CHAO, PHARMD; AND NICOLA CLAYTON, PHARMD, BCIDP

(continued from cover page)

documentation, or, most tediously, manual chart review.

Regulatory bodies such as the Centers for Medicare & Medicaid Services (CMS), Centers for Disease Control and Prevention (CDC), and the Joint Commission have developed several standards to guide the development and implementation of antimicrobial stewardship programs (ASPs). These standards define what elements of a stewardship program, including the tracking and reporting of metrics, must be met for reimbursement. Although antibiotic use data must be collected by each facility to receive CMS funding, reporting of facility-specific data to the CDC’s National Healthcare Safety Network (NHSN) remains optional, in contrast to hospital-acquired infection data, for which reporting is mandatory.1

Current metrics are typically categorized broadly as either a process-of-care measure or an outcome measure. Process measures such as duration of therapy or proportion of patients compliant with facility-based guidelines are used to assess the impact of ASP interventions on antimicrobial use, whereas outcome measures like hospital length of stay are centered around the end effect on patients (or hospitals).2,3

EXAMINING CURRENT METRICS

The 2016 Infectious Diseases Society of America (IDSA), Society for Healthcare Epidemiology of America (SHEA), and Pediatric Infectious Diseases Society (PIDS) ASP implementation guidelines suggest measurement of antibiotic use as the best overall reflection of ASP impact versus antimicrobial cost (Table 1).2 ASP interventions may incidentally lead to cost savings (eg, by decreasing unnecessary antimicrobial use) and help garner administrative support for the program, but antibiotic costs are not always congruent with patient outcomes or antibiotic appropriateness. In fact, appropriate ASP interventions can sometimes increase antimicrobial costs.2,4

Antimicrobial consumption data are available to hospitals and allow for internal (at the same institution over time) and external (across institutions) comparison. External comparison is limited, however, by the variation in reported metrics.1 Defined daily doses (DDDs) is a consumption metric determined by dividing the amount of each antimicrobial used by its corresponding World Health Organization (WHO) standard daily dose; the sum of these amounts is then typically normalized by dividing by a volume measure such as 1000 patient-days. Although measurement of DDDs is recommended by the WHO and widely used outside the United States, it is heavily reliant on the WHO definition of standard daily dose.1,5 This can lead to contrasting results when indication-specific, weight-based, or renally adjusted doses are used.2,4

Days of therapy (DOT) is the preferred metric in the United States and endorsed by the IDSA/SHEA/PIDS ASP guidelines.2 It is a count of the number of individual antimicrobial agents given to a patient on each calendar day multiplied by the total number of days of therapy, which is then standardized to account for volume by dividing by 1000 patient-days. Length of therapy (LOT) is a similar metric but considers the duration of overall antimicrobial therapy without accounting for the number of antimicrobials administered each day.1,3 DOT can be considered to account for the total burden of antimicrobial use while LOT accounts for the days of antimicrobial exposure. Both metrics are most useful as a tool for comparing an ASP’s performance against its own historical performance, but comparison to other facilities is limited because DOT and LOT do not account for differences in patient populations. Notably, measures of consumption should be used cautiously to avoid confusing the goal of therapy optimization with unjustified antimicrobial reduction. Although quantitative measures such as DOT and antimicrobial costs are commonly utilized performance metrics, they are only peripherally related to the impact of ASP interventions on patient quality of care and outcomes.

The most recently developed ASP metric is the NHSN SAAR, or standardized antimicrobial administration ratio; WHO, World Health Organization

<table>
<thead>
<tr>
<th>METRIC</th>
<th>BENEFITS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial cost</td>
<td>Easily quantified, supports ASP implementation and maintenance</td>
<td>Impacted by rising drug costs, drug shortages, and new or generic antimicrobials entering the market</td>
</tr>
<tr>
<td>DDD</td>
<td>Easily estimate DOT from purchasing data when EMR data are not readily available, moderate benchmarking capability</td>
<td>Heavily dependent on dosing strategies and WHO standard daily doses, cannot use in pediatric patients</td>
</tr>
<tr>
<td>DOT/LOT</td>
<td>Not impacted by dose, can be used for pediatric patients, moderate benchmarking capability</td>
<td>Does not account for drugs with long half-lives (eg, vancomycin in dialysis patients)</td>
</tr>
<tr>
<td>SAAR</td>
<td>Can be broken down by location or antimicrobial spectrum, accounts for differences in patient populations, high benchmarking capability</td>
<td>Relies on hospital-submitted data, does not assess appropriateness, requires substantial IT infrastructure and support</td>
</tr>
</tbody>
</table>

ASP, antimicrobial stewardship program; DDD, defined daily doses; DOT, days of therapy; EMR, electronic medical record; IT, information technology; LOT, length of therapy; SAAR, standardized antimicrobial administration ratio; WHO, World Health Organization
TABLE 2. CDC Guidance for Tracking and Reporting of Metrics in Non–Hospital-Based Settings\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>SETTING</th>
<th>SUGGESTED METRICS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small/critical access</td>
<td>1. DOT via NHSN AU option</td>
<td>Robust EMR and IT analyst support is needed to develop the capability to upload data to NHSN.</td>
</tr>
<tr>
<td>hospitals</td>
<td>2. Adherence to treatment recommendations (eg, for CAP, UTI, and SSTI)</td>
<td>Alternatives: Calculate defined daily dose for the 5 most commonly used antimicrobials (eg, ceftriaxone, azithromycin, vancomycin, piperacillin-tazobactam, fluoroquinolones).</td>
</tr>
<tr>
<td></td>
<td>3. Performance of interventions such as antimicrobial time-outs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Antimicrobial use at the clinician level</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>1. Antimicrobial prescribing at the individual clinician level</td>
<td>Data can be used to provide feedback that compares clinician’s performance with that of peers.</td>
</tr>
<tr>
<td></td>
<td>2. High priority-condition audits</td>
<td>Diagnosis shifting may result in missed prescribing when tracking and reporting are done only for high-priority conditions. This is solved by tracking percentage of visits for which antimicrobials are prescribed, but the comparability of clinicians’ patient populations should be considered.</td>
</tr>
<tr>
<td></td>
<td>— Diagnostic criteria met?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>— Selected antimicrobial recommended for disease state?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>— Dose and duration are correct?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Percentage of visits for which an individual clinician prescribes antimicrobials</td>
<td></td>
</tr>
<tr>
<td>Nursing homes</td>
<td>1. Rate of antimicrobial DOT per 1000 resident days = (total monthly DOT ÷ total monthly resident days) × 1000</td>
<td>Data are easiest to collect and analyze if the nursing home has implemented an EMR.</td>
</tr>
<tr>
<td></td>
<td>2. Antimicrobial starts</td>
<td>Antimicrobial prescribing may be complex with one antimicrobial course being associated with multiple antimicrobial order or pharmacy transactions.</td>
</tr>
<tr>
<td></td>
<td>3. Point prevalence surveys of antimicrobial use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. CDC NHSN AU reporting for nursing homes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Rates of \textit{Clostridium difficile} infections or antimicrobial-resistant organisms</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}AU, antimicrobial use; CAP, community-acquired pneumonia; CDC, Centers for Disease Control; DOT, days of therapy; EMR, electronic medical record; IT, information technology; NHSN, National Healthcare Safety Network; SSTI, skin and soft tissue infection; UTI, urinary tract infection.

an ASP’s performance to its expected performance based on the given patient population. The predicted number of antimicrobial days are calculated using statistical models based on nationally aggregated data from the CDC. A SAAR ratio less than 1 indicates antimicrobial use was less than predicted, a SAAR of 1 indicates use was equivalent to predicted use, and a SAAR of more than 1 indicates use was greater than expected.

In 2017, SAAR baselines were established for 13 adult and pediatric medical, surgical, medical-surgical intensive care units (ICUs), wards, step-down units, and oncology units, with 15 antimicrobial categories for which an institution could receive SAAR information back from the NHSN. For example, one could choose to see how their gram-positive–targeted antimicrobial use (eg, vancomycin, daptomycin, linezolid, etc) compared with the expected use for a certain unit type such as a medical ICU. NHSN allows for reporting of 89 specific antimicrobials and includes new drugs as they become FDA approved. However, because the system does not allow for manual data input, significant information technology infrastructure and investment are required to submit reportable data to NHSN. In addition, certain specialized unit types such as burn ICUs are not yet validated by NHSN and do not have a SAAR baseline to provide predicted antimicrobial days.\textsuperscript{3}

The CDC also provides guidance on suggested metrics for non–hospital-based stewardship programs (Table 2\textsuperscript{a,b}). Irrespective of site, recommendations emphasize that even though savings in drug costs after implementation of a stewardship program may be used to justify the cost of the ASP, antimicrobial expenditures should not be used to track the effectiveness of stewardship efforts.\textsuperscript{6-8}

Certain settings allow for unique metrics. For example, informing outpatient clinicians that they prescribe more antimicrobials than 80% of their peers or comparing them to peers who perform in the top 10% on quality measures can result in overall reductions in antimicrobial prescribing.\textsuperscript{2} Smaller settings may be better able to track prescribing at the clinician level; however, they may also make tracking the complications of antimicrobial use (eg, \textit{Clostridium difficile} infection, drug interactions, and adverse drug reactions) less reliable or useful due to small sample sizes.\textsuperscript{8} Nursing homes or long-term care (LTC) facilities may choose to do point prevalence surveys of antimicrobial use, which track the proportion of residents receiving antimicrobials during a given period, to get a snapshot of the burden of antimicrobial use in the facility.\textsuperscript{4} A unique challenge for nursing homes is that antimicrobials are often provided by LTC pharmacy vendors, which may create an additional layer of complexity when trying to assess antimicrobial use and limit the reporting of antimicrobial use available to a facility (eg, antimicrobial start dates or indications).\textsuperscript{8}

CONSIDER GOALS TO DETERMINE BENCHMARK

The ideal benchmark would be centered around the primary goal(s) of ASPs: to improve patient outcomes via appropriate use of antimicrobials and to optimize antimicrobial regimens, including dosing, duration of therapy, and route of administration.\textsuperscript{7}

Although CMS and the Joint Commission similarly call for evidence-based antimicrobial use as well as minimization of adverse events, resistance, and hospital-acquired infections, it is difficult to measure these outcomes, and little data connect them to our most commonly collected metrics.

Key stakeholders also want metrics that correlate more with patient care. A survey of physicians and pharmacists identified that they favored patient-centered outcomes such as infection-related mortality and considered these disparate from the metrics reportedly used at their institution.\textsuperscript{9}

There is no perfect metric by which to judge the success of one’s stewardship program. More and more facilities are, however, opting to share their antimicrobial use data with the CDC NHSN. In turn, this provides better, higher-quality data for future SAAR baseline validations and a way for stewardship programs to benchmark their institutions against others with a similar patient population. ▲

References are available at ContagionLive.com.
Clostridioides difficile Infection: Diagnosis, Testing, Screening, and Treatment

Investigators apply guidelines into practical management strategies.

BY GINA BATTAGLIA, PHD

Identification of patients to undergo testing for *Clostridioides difficile* infection (CDI) is largely based on a high index of suspicion, although the role of asymptomatic carriage in transmission highlights the importance of infection control in inpatient and outpatient settings, according to experts who participated in a *Contagion®* Peer Exchange panel. The panel, moderated by Peter L. Salgo, MD, also discussed recommendations for treatment of recurrent CDI and considerations for selecting the most appropriate treatment method.

**C DIFFICILE: A DIFFERENTIAL DIAGNOSIS**

The 2017 guidelines from the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) state that patients with unexplained and recent onset of at least 3 unformed stools in a 24-hour period are the “preferred target population for testing” of CDI.1 However, Teena Chopra, MD, MPH, noted that presentation of CDI can range from mild symptoms to severe sepsis, fulminating colitis, or death and that clinical judgment is the most important consideration when selecting patients for testing. She said that presence of risk factors for CDI along with fever, elevated white blood cell (WBC) count, and frequent diarheal stools increases suspicion; however, she added that diarrhea can also be associated with antibiotics, parasites, or consumption of contaminated food or water and that testing every patient with diarrhea would likely lead to overdiagnosis because individuals may be colonized with nontoxigenic forms of *C difficile*.

Joseph Reilly, PharmD, noted that with the increase in pay-for-performance initiatives and public reporting of CDI rates, hospitals are particularly motivated to ensure the CDI rates are low to prevent financial penalties and that positive tests for patients who are colonized with nontoxigenic *C difficile* would artificially inflate the rates. Paul Feuerstadt, MD, added that, rather than testing for CDI in any patient with diarrhea as a “knee-jerk reaction,” clinicians should broaden the differential diagnosis and evaluate the clinical presentation, such as assessing for the presence of blood in the diarrhea or whether the diarrhea is secretory or osmotic.

He added that irritable bowel syndrome (IBS) and postinfection IBS can complicate the clinical picture and that it is important to determine whether another bout of diarrhea indicates a recurrent infection or an alternative issue in a patient with a history of CDI to direct therapy appropriately. However, Feuerstadt said that patients with inflammatory bowel disease (IBD) are an exception, so all patients with IBD who experience an exacerbation should undergo testing for CDI because of the high incidence in this population.

**TESTING FOR CDI**

Feuerstadt said that in addition to the IDSA/SHEA guidelines that provide recommendations for selecting candidates for testing, factors such as WBC count, creatinine level, and recent history of antimicrobials are also helpful to consider.

“If a patient has loose stools and recently received antimicrobials, they’re in the [intensive care unit], and their white [blood cell] count is 40,000, you probably know what’s going on there,” he said. “That might be a circumstance where time is of the essence and you might send off a stool assay before starting antimicrobials, but you may also want to empirically start antimicrobials due to your suspicion that [*C difficile* infection] is present.”

Dale N. Gerding, MD, also pointed out that the work-up for a patient with community-acquired diarrhea needs to be different than for a patient with health care–associated diarrhea, in which CDI is high on the list of probable causes. For example, he recommended a multiplex polymerase chain reaction platform for patients with community-associated diarrhea to rule out multiple other potential causes.

In general, tests for CDI detect the organism itself or its primary toxins (toxin A and/or B). Commonly available options include toxigenic culture, nucleic acid amplification test (NAAT), glutamate dehydrogenase (GDH) assay, cell culture cytotoxicity neutralization assay, and toxin A and B enzyme immunoassays. Gerding noted, however, that the cell culture cytotoxicity neutralization assay has become obsolete because it is time consuming and difficult to perform.1

The NAAT is among the more commonly used tests in the United States and detects several toxin gene targets in the organism, although it has a low to moderate specificity and may pick up cases of patients colonized with *C difficile*, according to Gerding. He added that specific toxin tests, typically...
performed using enzyme immunoassays for toxin A and/or B, identify toxigenic C. difficile strains but have low sensitivity and that GDH assays are commonly used but need paired with another diagnostic test because GDH is found in toxigenic and nontoxigenic strains.

The IDSA/SHEA guidelines recommend using a stool toxin test as part of a multistep algorithm for diagnosis, which may involve GDH plus toxin test, GDH plus toxin test followed by NAAT as an arbitration test, or NAAT plus toxin test. However, Gerding noted that the difference in diagnostic yield among the algorithms may be introducing inconsistencies with diagnosis of CDI in current practice.

SCREENING FOR C. DIFFICILE
According to Chopra, asymptomatic carriage is an important consideration because carriers can act as reservoirs of transmission and probable vehicles of transmission to other patients. She added that the rate of asymptomatic carriage varies, with rates as high as 50% among older adults and approximately 5% to 10% among healthy adults.

“It’s important that we understand and realize that...these asymptomatic carriers don’t have diarrhea, but we are detecting [Clostridoides] difficile and they can transmit it,” she said, emphasizing the importance of infection control with hand hygiene and contact precautions in outpatient care settings and dialysis units as well as inpatient care settings. However, Chopra added that testing asymptomatic patients for carriage in the hospital setting is not routinely performed and would be a poor use of resources, and that even hospitalized patients with risk factors for asymptomatic carriage are only put in contact isolation to prevent transmission if the hospital is facing an outbreak. Gerding noted that the data are currently insufficient to recommend universal screening for CDI, in part, because testing is invasive and isolation of positive patients would use a large number of isolation rooms. “I think we need more data before we jump on the colonization bandwagon, even in hospitals,” he said.

C. DIFFICILE: CLINICAL PRACTICE GUIDELINES AND TREATMENT OPTIONS
According to the 2018 IDSA/SHEA guidelines, the recommendations for management of the first recurrence of CDI are a prolonged tapered and pulsed vancomycin regimen or fidaxomicin (if a standard vancomycin regimen was used previously) or a standard vancomycin regimen (if metronidazole was used for the previous infection). However, Thomas Lodise, PharmD, PhD, noted that metronidazole has largely fallen out of favor for CDI infection because it has a broad spectrum of coverage (likely eliminating gut bacteria that are protective against CDI) and has been shown to have lower rates of efficacy than vancomycin. The inferior response rate of metronidazole to vancomycin was demonstrated in a pooled analysis of 2 multinational trials designed to compare clinical success of tolevamer, a nonantibiotic toxin-binding polymer, with vancomycin and metronidazole, respectively, in patients with CDI. Tolevamer was found to be inferior to both antibiotics, and rates of clinical success were higher with vancomycin than with metronidazole (81.1% vs 72.7%).

“That’s what built up this concept on the clinical side [that] metronidazole is less targeted and alters the gut microbiota, which leads to higher risk for recurrence,” Feuerstadt said.

For second or subsequent recurrences, regimens recommended by the 2018 IDSA/SHEA guidelines include tapered and pulsed regimen of vancomycin, standard vancomycin regimen followed by rifaximin, fidaxomicin (if not used for prior infections), and microbiota replacement therapy or fecal microbiota transplantation (although the expert panel recommended appropriate antibiotic regimens for at least 3 episodes of CDI prior to trying this strategy). Feuerstadt noted that these recommendations in the 2018 guidelines have changed substantially from 2010, as metronidazole was largely removed from 2018 guidelines in favor of vancomycin or fidaxomicin in the first-line setting and fidaxomicin was introduced as an option for treatment of first recurrence.

Reilly concluded that assessing the likelihood of patient compliance with the regimens, particularly the 8-week pulsed tapered vancomycin regimen, is important when selecting a treatment plan. He said in his experience, compliance tends to drop off after getting past the twice-per-day portion of the regimen. Salgo added that compliance is particularly difficult when dosing frequency drops to once every 2 to 3 days.

“We have to think about the patients we see who have [C. difficile infection],” Reilly said. “Are they going to be compliant with this, taking vancomycin 4 times per day for possibly 2 weeks, then another 2 times per day for a week, once per day for another week, and every 2 to 3 days for up to 8 weeks? That’s a demanding regimen that we have to put a patient on. I understand the efficacy behind it, but we shouldn’t approach it and say, ‘Oh, I’ll just use that’ when there’s an alternative available that might be easier [and] that the patient might be more compliant with.”

References are available at ContagionLive.com.
Social-Role Identity Influences Communication in Hospital-Based Antimicrobial Stewardship

BY JOHN PARKINSON

Antimicrobial stewardship is a paramount issue that needs greater recognition and effort to combat preventable bacterial infections. In addition, the people who take on the role of antimicrobial stewards within their hospitals and medical centers need to realize that how they view their position within the social context of their health care organization influences how they approach communication with providers who prescribe medication.

This important finding was presented at the session, “The Impact of Social Role Identity on Communication in Hospital-Based Antimicrobial Stewardship,” during the Society for Healthcare Epidemiology of America Spring 2021 Virtual Conference.

The investigators conducted interviews with 58 antimicrobial stewards, including 25 physicians and 33 pharmacists at 10 hospitals. The breakdown of the types of institutions included 4 academic medical centers, 4 community hospitals, and 2 children’s hospitals.

In looking at the interviewees’ responses, a dichotomy appeared to emerge between those stewards who felt included in a team environment, and those who felt like outsiders.

“Respondents who felt empowered in their interactions with prescribers explicitly adopted a social identity that conceptualized stewards and prescribers as being on the ‘same team’ with shared goals (in-group orientation),” the investigators wrote. “Drawing on the meaning conferred via this social role identity, respondents engaged in communication strategies to build and maintain common bonds with prescribers.”

Stewards worked with the clinicians, developing strategies for communication. These strategies included “moderating language to minimize defensive recommendations when delivering stewardship recommendations, aligning the goals of stewardship with the goals of the clinical team, communicating with prescribers about things other than stewardship, compromising for the sake of future interactions, and engaging in strategic face-to-face interaction.”

For the group that felt more like outsiders, the respondents said that they felt a more “us versus them” mentality and that the contentious atmosphere led to a less-than-desired communication between stewards and prescribers.

“These respondents expressed deference to hierarchy, a reluctance to engage in face-to-face interaction, a feeling of cynicism about the impact of stewardship, and a sense of low professional accomplishment within the role,” the investigators wrote.

The steward’s role needs to be shaped with consideration to the significant impact of their work, and with assistance and understanding from peers and encouragement from superiors. “Social role identity in stewardship is shaped by the influence of mentors and colleagues, indicating the importance of supportive relationships for the development of steward skill and confidence,” the investigators wrote.

Study Examines How COVID-19 Impacted Antimicrobial Stewardship

BY KILLIAN MEARA

The COVID-19 pandemic, an unanticipated and unprecedented global public health crisis, laid a heavy burden on health care systems around the world. The hallmarks of the disease—lower respiratory tract infections and hypoxia—lead to a strain in resources due to the exponential increase in hospitalizations.

A scarcity of data on bacterial coinfections and a lack of therapeutic options severely challenged antimicrobial stewardship programs and the use of antimicrobials during the early stages of the pandemic. In a new study presented at the Society for Healthcare Epidemiology of America Spring 2021 Virtual Conference, investigators set out to understand how COVID-19 impacted antimicrobial use and antimicrobial stewardship programs.

The team retrospectively reviewed cases during the first wave of COVID-19 in a 151-bed urban safety-net community hospital between March and June 2020. The study included 302 patients, of which 221 received empiric antimicrobials.

Findings from the study showed that the most common antimicrobials used were ceftriaxone and azithromycin. The use of ceftriaxone was shown to increase from 71 to 113 patients during the study period, with an average therapy duration of 6 days (8 days in the intensive care unit).

The use of procalcitonin was also documented in 37 cases and ranged from 0.09 to 12.57 days of duration, with an average duration of 1.21 days. None of the cases examined had a documented bacterial coinfection.

This study demonstrates the common prescription of antimicrobials during the first wave of the pandemic. Antimicrobial stewardship programs were shown to successfully guide clinicians toward recommended guidelines for selection and duration.
Examining COVID-19 Transmission After First Dose of Vaccine in Long-Term Care Facilities

BY JOHN PARKINSON

In the United States, residents and staff at long-term care facilities (LTCF) have had high rates of COVID-19 infection, with residents having one of the highest mortality rates in the country.

As states have rolled out their COVID-19 vaccine programs, a study from the Nebraska Department of Health & Human Services looked at COVID-19 transmission rates among staff and residents after the first dose of a 2-dose vaccine regimen in the state’s LTCFs.

The state began its COVID-19 vaccines at LTCFs on December 28, 2020, as part of the CDC Pharmacy Partnership for Long-term Care Program. By February 5, 159 skilled nursing facilities (SNF) had completed their first vaccine (clinic-1) and 7271 residents and 6768 staff had been administered their first dose.

The investigators used the Federal Retail Pharmacy Program for COVID-19 Vaccination database to gather the vaccination numbers of residents and staff. They followed the SNFs for 21 days after clinic-1 from December 28 to February 5 for any first-time COVID-19 positives. The National Healthcare Safety Network (NHSN) database was used to collect the information on the number of residents present at the facility on the day of clinic-1. The staff count for each facility was extracted from Nebraska licensure for LTCF. The investigators gathered case information from the state surveillance, NHSN, and the Test Nebraska platform.

The findings showed that staff vaccine coverage was associated with a reversal of cases, but no reversal of cases was found in resident vaccine coverage and new resident transmission.

For the staff, the results showed a progressive result. “[For] each percentage increase in staff vaccine coverage, the odds of having a new staff-positive case 7 days and 14 days after clinic-1 decreased by 26% and 48%, respectively,” the investigators reported. Investigators noted that possible confounding exists when infected residents “might have tested positive 7 to 14 days after clinic-1” that were not impacted by vaccination.

Although a positive association was witnessed in the staff population, the investigators wanted more data after the second dose. “Although we observed the association between lower case count with increased facility-level vaccine coverage, we would need to wait for the administration of the second dose of vaccine before assessing the level of association between coverage and new transmission,” the investigators wrote.

“Further initiatives are warranted to increase the suboptimal vaccine coverage for staff.”

Improving Urine Collection Poses Opportunity for Diagnostic Stewardship in Primary Care

BY KILLIAN MEARA

Urine cultures exhibit a significant influence on the treatment of suspected urinary tract infections (UTI) and are the most common microbiological tests in outpatient settings. Although results from urine cultures are typically needed for confirmation of a UTI diagnosis, physicians will often prescribe antibiotics before results are received.

This poses a threat to patient care because physicians will often need to make adjustments to treatment once they receive the testing results. In addition, although urine cultures are the gold standard for a UTI diagnosis, they can easily become contaminated during the collection process, according to investigators presenting data at the Society for Healthcare Epidemiology of America (SHEA) Spring 2021 Virtual Conference.

To determine the prevalence of contaminated cultures, along with predictors and antibiotic use associated with contaminated urine cultures, investigators analyzed data from 2 adult safety-net primary care clinics.

The study included 1265 patients and found that of those, 264 had no culture growth, 694 were contaminated, 159 had low counts of growth, and 148 had high counts of growth.

Additional findings showed that of the 694 with contaminated cultures, 153 were prescribed an antibiotic; of the 264 who showed no culture growth, 36 were prescribed an antibiotic.

This study demonstrates that more than half of urine cultures tend to be contaminated and that 1 in 5 patients were treated with an antibiotic.

Investigators concluded that reducing the contamination of urine cultures will almost certainly improve patient care and that more accurate records are relevant to managing any future UTI episodes.
A Case of *Mycobacterium Chimaera* Infective Endocarditis

Nonspecific, nondolent symptoms make this disease difficult to diagnose.

BY ZOHEIR KHAN, MD; AND JEREMY L. AGOSTINHO, MD

A 55-year-old man presented to our emergency department at the behest of his primary care physician after being evaluated for dysarthria and left upper-extremity weakness, which had been present for the past month. His symptoms were sudden in onset. His left upper-extremity weakness had gradually resolved over the past few weeks, but he continued to have mild dysarthria.

**PAST MEDICAL HISTORY**
The patient had a history of hypertension and mitral valve prolapse. Five years prior, he underwent a percutaneous balloon mitral valvuloplasty, followed by placement of an annuloplasty ring and a left atrial appendage clip.

**KEY MEDICATIONS**
None

**EPIDEMIOLOGICAL HISTORY**
The patient was born in New York, raised in Pittsburgh, Pennsylvania, and has lived in Philadelphia for the past 25 years. He is divorced and lives alone. He does not have pets. He works as a health advocate. He said he did not travel outside the country. He hikes occasionally but said he has had no animal contact. He is not sexually active. He smokes cigarettes daily and drinks beer occasionally. He claimed no intravenous drug use.

**PHYSICAL EXAMINATION**
On presentation, the patient was afebrile, and vitals were within normal limits. He was noted to have mild slurring of speech and a broken, decayed molar tooth. There were no stigmata of infective endocarditis. The rest of his exam was without obvious abnormalities.

**STUDIES**
Initial lab work showed no leukocytosis or renal/hepatic derangements. Blood cultures were sent and yielded no growth. An MRI showed acute ischemia in the midbrain with small chronic infarctions in the right thalamus and bilateral cerebellar hemispheres. A transesophageal echocardiogram (Figure 1) showed 2 large, mobile echo-densities attached to the mitral valve, emanating from the annuloplasty ring.

**CLINICAL COURSE**
The patient underwent bioprosthetic mitral valve replacement and explantation of the annuloplasty ring. Mitral valvular tissue was sent for surgical pathology along with acid-fast bacilli, fungal, and tissue cultures. In addition, a paraffin block of mitral valve tissue was sent to an outside laboratory for 16S ribosomal RNA (rRNA) sequencing. Surgical pathology showed variably intense acute and chronic inflammation suggestive of infective endocarditis. Serial blood cultures were negative throughout the hospital stay, and all surgical cultures yielded no growth. *Bartonella/Coxiella burnetii* species serologies were negative. 16S rRNA sequencing did not identify the culprit organism. The patient was discharged on ceftriaxone, doxycycline, and vancomycin. He was doing well on his outpatient follow-up visit after completing 6 weeks of antibiotic therapy.

The patient presented 1 year later with fevers, fatigue, dyspnea, and dry cough that had been present for 2 weeks. A CT...
scan of the chest showed diffuse, patchy ground-glass opacities and an 8-millimeter left lung apical nodule suspicious for malignancy. COVID-19 testing was negative. Lab work showed a white blood cell count of 4300/µL (normal range, 4.11 × 10^3/µL), platelet count of 42000/µL (normal range, 140-450 × 10^3/µL), hemoglobin level of 9.4 g/dL (normal range, 14-18 g/dL), lactate dehydrogenase level of 1179 IU/L (normal range, 125-220 IU/L), ferritin level of 9335 ng/mL (normal range, 22-275 ng/mL), and a fibrinogen level of 73 mg/dL (normal range, 200-600 mg/dL). A transthoracic echocardiogram showed a mobile echo-density on the anterior mitral leaflet. Blood cultures were negative throughout the admission. A bone marrow biopsy was performed due to suspicion of hemophagocytic lymphohistiocytosis (HLH) and showed macrophages engulfing nucleated red cells and myeloid cells, confirming the diagnosis. Special bone marrow stains for acid-fast bacilli and fungi were negative. In light of the HLH, the patient was deemed high risk for bleeding during valvular surgery and managed with medical therapy alone. He was subsequently discharged with doxycycline for 6 weeks and a corticosteroid taper for management of the HLH.

**DIAGNOSTIC PROCEDURES AND RESULTS**

An outpatient PET scan 1 month later again showed an apical nodule on the left lung suspicious for malignancy. Three weeks after the PET scan, the patient returned to the emergency department for fevers, chills, and drenching sweats. A transthoracic echocardiogram revealed a mobile echo-density (1.5 cm × 0.9 cm large) on the anterior mitral leaflet and severe prosthetic mitral valve stenosis. Blood cultures were once again negative. Interventional radiology performed a core biopsy of the lung nodule, and the patient was diagnosed with a large cell neuroendocrine tumor. A blood sample was sent to an outside laboratory for Karius cell-free DNA sequencing, which returned positive for *Mycobacterium chimaera*. Acid-fast bacilli blood cultures were collected, which were positive for acid-fast bacilli at 4 weeks and for *Mycobacterium avium* complex at 8 weeks.

**TREATMENT AND FOLLOW-UP**

The patient was started on azithromycin, ethambutol, rifabutin, and intravenous amikacin. He was deemed a poor candidate for repeat valve surgery due to his underlying comorbidities, started on radiation therapy for his neuroendocrine tumor, and discharged home. He returned to the hospital 2 weeks later with acute kidney injury secondary to aminoglycoside toxicity. Discussions with the patient and his family resulted in him being eventually discharged to home hospice.

**DISCUSSION**

*M. chimaera* is a member of the nontuberculous mycobacteria group found ubiquitously in nature. First described in 2004 by Tortoli et al., it is genetically related to the MAIS group (*M. avium, M. intracellulare*, and *M. scrofulaceum*) but different from all 3; hence, it is aptly named “Chimaera” after the Greek mythological hybrid creature.

In 2014, an outbreak of *M. chimaera* infections occurred in multiple European countries and the United States. These infections were linked to open-heart procedures, including valve replacement and aortic graft procedures, that utilized 3T heater-cooler units (HCUs). The most likely mechanism of infection appears to be transmission of mycobacteria via aerosolized particles from the cooler units, followed by inoculation of the surgical field. As of 2017, approximately 120 cases of *M. chimaera* have been associated with HCUs. According to Sommerstein et al., the incidence rate based on the current number of reported cases likely underestimates the true incidence of *M. chimaera* infections that complicate valve replacement surgery; they estimate an incidence rate of 156 to 282 cases worldwide, with 51 to 80 of those cases annually. *M. chimaera* has a long incubation period and tends to cause subclinical infection due to overall low virulence. In the HCU outbreak, patients presented with vague signs and symptoms including fever, fatigue, shortness of breath, cough, and weight loss, that did not develop until years after undergoing cardiac surgery; the earliest patient in the 3T HCU outbreak had undergone surgery in 2008. Hence, cases such as these can be particularly difficult to identify and seldom raise clinical suspicions. Our patient developed acute kidney injury 2 weeks after beginning treatment, which was attributed to intravenous amikacin. He was not a surgical candidate for valve replacement and was eventually discharged to home hospice.

*M. chimaera* endocarditis presents a diagnostic and management challenge for clinicians. Its indolent nature and slow growth on acid-fast cultures can delay diagnosis. Infection-control consultation is recommended to identify the source and prevent further cases. When diagnosed, treatment requires extended courses of multiple antibiotics. Surgical valve replacement may be required. Even with optimal treatment, the mortality rate of *M. chimaera* endocarditis is high.

As of 2017, approximately 120 cases of *M. chimaera* have been associated with heater-cooler units.

As a member of the mycobacteria genus, *M. chimaera* is intrinsically resistant to many classes of antibiotics. Treatment involves extended courses of multiple antibiotics that may include macrolides, rifamycins, ethambutol, quinolones, and parenteral aminoglycosides. Our patient developed acute kidney injury 2 weeks after beginning treatment, which was attributed to intravenous amikacin. He was not a surgical candidate for valve replacement and was eventually discharged to home hospice.

*M. chimaera* endocarditis presents a diagnostic and management challenge for clinicians. Its indolent nature and slow growth on acid-fast cultures can delay diagnosis. Infection-control consultation is recommended to identify the source and prevent further cases. When diagnosed, treatment requires extended courses of multiple antibiotics. Surgical valve replacement may be required. Even with optimal treatment, the mortality rate of *M. chimaera* endocarditis is high.

References are available at ContagionLive.com.
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