APIC 2018
Infection Prevention Gaps Found Across Critical Access Hospitals

Significant gaps exist in infection prevention across critical access hospitals (CAHs) and more support is needed to ensure proper staffing, according to research presented at the 45th Annual Conference of the Association for Professionals in Infection Control and Epidemiology (APIC).

The infection prevention field is broad, and as such, a hospital infection preventionist (IP) covers everything from communicable disease surveillance to health care–associated infection (HAI) investigations to construction risk assessments and isolation rounding everyday. This practice is critical for identifying gaps in infection prevention processes that result in infections and should be considered (continued on page 22)

Markers, Erasers in Patient Rooms May Harbor Dangerous Bacteria

Terminal cleaning of hospital rooms between patients is essential to eliminating contamination. Checklists are used as standard guides for staff in most hospitals. A presentation at the 45th Annual Conference of the Association for Professionals in Infection Control and Epidemiology (APIC) suggests that the checklist is more important than originally thought.

At a Summit Health hospital in rural Pennsylvania, the environmental services team was provided with a 175-item checklist, in use since 2012, for terminal room cleaning. Upon reviewing the checklist, infection (continued on page 23)

ASM Microbe 2018
Colistin-Resistant E coli Found in Most Residents of Vietnam Village

Investigators from Vietnam have found that the majority of the residents in the rural village of Nguyen Xa harbor a multidrug-resistant (MDR) strain of *Escherichia coli* that is resistant to a last-resort antibiotic, colistin. Study results were presented at the 2018 ASM Microbe Meeting in Atlanta, Georgia.

Colistin resistance has been emerging largely due *MCR* genes, discovered in 2015 The genes are found on plasmids, which is concerning because these small pieces of DNA can confer the *MCR* genes from (continued on page 24)

Biodefense World Summit 2018
Better Mass Casualty Management Through Radiation Biodosimetry

Media attention around the potential for nuclear and radiological threats has increased more in the past year than in the past decade; but, what does this increased attention mean for clinicians? Mary Sproull, a biologist at the National Institutes of Health (NIH) and biodefense doctoral student at George Mason University, and Kevin Camphausen, MD, the radiation oncology branch chief at the NIH, gave a presentation1 to answer that question at the Biodefense World Summit 2018.

Ms. Sproull and Dr. Camphausen are working to make the medical management process more efficient and effective in the event of a mass casualty radiation exposure. They are developing a dosimetry dose prediction model to determine how radiation biodosimetry diagnostics can (continued on page 26)

Biodefense World Summit 2018
Early Diagnostic, POC Testing for Emergent Biological Events

From the hospital to an emergency treatment center at the epicenter of an outbreak, point-of-care (POC) testing is critical for rapid diagnoses and medical interventions. Such efforts can be life-saving, which makes their presence in biodefense efforts critical. Two such presentations from the Biodefense World Summit 2018, held June 27-29, 2018, in Bethesda, Maryland, discussed the potential for early diagnostic testing for certain infectious diseases and the application of POC testing for more emergent biological-event situations. The first presentation, “Far-Forward Early Diagnosis of Biothreat Agents,” by Charles Young, PhD, principal professional staff and chief scientist of the Applied Biology Group at The Johns (continued on page 27)
Antibiograms for Optimizing Empiric Therapy: Use Them Wisely

Although antibiograms can be important tools for stewardship programs to optimize empiric therapy, an understanding of the limitations in their functionality and strategies for more appropriate applications are necessary for clinicians.

BY JASON M. POGUE, PHARMD
Antibiotic Development—We Gave It a Push, Now It Needs a Pull

After years of sounding the alarm about the dangers of limited antibiotic development, infectious diseases clinicians have been rewarded with multiple new antibiotics in the 2010s. To my shock, the Infectious Diseases Society of America’s “10x20” goal (10 new antibiotics before 2020) may actually be achieved. Changed regulatory pathways and “push” incentives that assist antibiotic development are partially responsible for the increased antibiotic throughput that we are benefitting from now.

However, the number of major pharmaceutical companies that invest in antibiotic development continues to decline, with AstraZeneca, Novartis, and Allergan recently announcing that they are leaving the anti-infective space. Allergan’s exit is particularly notable as the company markets several recently approved antibacterial agents that address critical needs. Antibiotics are a societal good that rely on private industry for production and the message that even selling approved, useful antibiotics that save patient lives is not enough to attract major drug developers to stay in the market is disheartening to say the least.

What is going on? There are many issues, however, the main issue is that because private industry is for-profit, it gravitates toward therapeutic areas that make the most money. Antibiotics, which fulfill an acute need that most people do not have, are not one of those areas. Inexpensive generic antibiotics are currently effective for the majority of infections in the world, while branded, expensive antibiotics that fulfill a need, such as infections caused by carbapenem-resistant Enterobacteriaceae (CRE), are used in a very small number of patients. To put that in another context, 100% of the CRE market is smaller than 1% of the diabetes market.

And what happens when a new antibiotic is approved? We try not to use it to preserve its use for the patients who really need it, and shorten durations of therapy to decrease resistance, laudable goals that clearly do not incentivize further development. Life can be painfully ironic.

We need to hit the reset button on how antibiotics are developed and admit that our current model does not work. Push incentives are not enough. Although smaller pharmaceutical companies have picked up the pace of antibiotic development, without larger companies to partner with they may be headed for difficult futures, and new antibiotics that make it to the market and then fail are not helpful. “Push” incentives are needed to encourage companies to get back in the game. Because antibiotics are not profitable, it is necessary to reward companies who develop these needed agents in ways that serve their interests.

The pull incentive that I like the most is that of an awarded patent extension for an agent of the company’s choosing. A company that develops an antibiotic that offers a true advantage in the treatment of a resistant infection, such as CRE, is rewarded with a 12-month patent extension for another product that they market. If you wonder if this will work, just think for a minute: What would it have been worth to Pfizer to extend the patent for Lipitor (atorvastatin)? Billions.

Congress is considering a bill, the Re-Valuing Antimicrobial Products Act, that suggests this pathway as a solution. In today’s challenging political environment, the bill faces an uphill battle, but it is an example of the type of out-of-the-box thinking we need to change the current paradigm of antimicrobial drug development. If the incentive is strong enough, it could be used to encourage many positive outcomes, such as deeply discounted anti-infectives, funding for antimicrobial stewardship, and developments in susceptibility testing that keep pace with approvals.

Whatever form our incentives take, it is clear that something radical is needed. Our unique system that relies on private companies to produce a public good is failing.

Note: We have combined coverage on viral hepatitis into other sections in this publication. Continue to look for the latest infectious disease news on our website (contagionlive.com) and social media channels (Contagion_Live on Twitter and ContagionLive on Facebook).

Jason C. Gallagher, PharmD, FCCP, FIDSA, BCPS
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FMT Proves to Be Effective and Acceptable Treatment for rCDI
By Maureen Taylor, CCPA, BHSc

Fecal microbiota transplantation (FMT) is a widely accepted, safe, and effective treatment for recurrent Clostridium difficile infection (rCDI) that has made its way into the latest Infectious Diseases Society of America guidelines.1 But does the cure endure? A recent study in Clinical Infectious Diseases by Mamo et al evaluated the durability and long-term outcomes associated with FMT.2 This was a telephone follow-up survey and chart review of 137 patients who received FMT predominately via colonoscopy at Emory University for rCDI between 2012 and 2016. The median age of the patients was 66 years (range, 19-91). All patients had failed at least 1 course (median 4 courses) of C difficile treatment before they were offered FMT. The majority had been treated with oral vancomycin either alone or in combination with fidaxomicin, metronidazole, or rifaximin. Eighty-five percent of participants had completed 1 FMT at survey time and a small percentage had received between 2 and 4 procedures. The primary outcome of the study was absence of rCDI post FMT at survey time, defined as diarrhea after FMT that was positive for C difficile by polymerase chain reaction (PCR). The median time from the last FMT to follow up was 22 months (range, 3-51).

Overall, 82% of patients had a durable cure of CDI after FMT. Although almost half experienced recurrent diarrhea after FMT, 64% was either self-limited or C difficile PCR negative and not attributed to rCDI. Post-FMT antibiotic exposure was more common in the RCDI group (75% vs 38%), and treatment with a cephalosporin, clindamycin, or fluoroquinolone after FMT was associated with an estimated odds ratio of 3.78 (95% CI, 1.16-12.30) for CDI recurrence compared with other antibiotics.

Previous studies have looked at post-FMT relapse rates,3 but the Mamo study stretches that and adds to the growing evidence that FMT is a safe procedure without significant adverse events in an extended follow-up period. Additionally, this study’s findings reaffirm the importance of antibiotic avoidance post FMT, especially in those known to carry a higher risk of CDI. Obviously, 100% avoidance is unrealistic, and the authors call for more research into strategies that can preserve microbiome diversity in patients who require antibiotics post FMT. Prophylactic FMT, as the authors suggest, may be one such strategy, although this has not yet been evaluated. ▲

References available at ContagionLive.com.

Coffee, Donuts, and Antimicrobial Stewardship
By Payal K. Patel, MD, MPH

A few years ago, researchers in Israel decided to test the hypothesis, “Justice is what the judge ate for breakfast.” More than 1000 parole decisions by 8 judges were reviewed and categorized according to whether they happened at the beginning of the day, near a snack or meal, or at the end of the day.1 For each judge, the pattern held true: Prisoners were more likely to be granted parole after a snack or lunch break than just before a meal. The authors wrote that this indicated judicial rulings may be swayed by “extraneous” variables. There is evidence in health care, as well, that time of day, time of week, whether a national cardiology conference is happening, and many other extraneous factors can influence quality of care.2,3

A recent Journal of Antimicrobial Chemotherapy article by Sikkens and colleagues describes a single-center prospective study done with repeated point prevalence surveys to measure how factors such as gender, professional experience, and time of day (not all extraneous) can affect antimicrobial appropriateness.4 The investigators performed 7 point-prevalence surveys in their 700-bed tertiary care hospital in Amsterdam, The Netherlands. The study comprised 351 antimicrobial prescriptions by 150 physicians. The authors also mention that during the time this study was happening, there were no ongoing antimicrobial stewardship interventions, except preauthorization for restricted antimicrobials and that pharmacists tend to have limited roles in antimicrobial stewardship in Dutch hospitals.

The primary outcome was appropriateness of the antimicrobial prescription, which was defined as either following relevant guidelines, deviating from guidelines with a rational documented reason, or there was no relevant guideline but the prescription was considered a rational choice. Appropriateness was determined by an adult or pediatric infectious diseases physician. The team found that, overall, appropriateness of antimicrobial prescriptions per the definition used in this study was 65% and that it was lower in the morning versus afternoon and night (43% vs 68% vs 70%, respectively; crude odds ratio [OR] afternoon vs morning, 3.00 [95% CI, 1.60-5.48]; crude OR evening vs morning, 3.40 [95% CI, 1.64-6.69]). They also found interns had less appropriate prescribing behavior versus more experienced colleagues and that an infectious disease consultation was associated with improved appropriateness. There was no difference in prescribing noted between the genders.

Although certainly an interesting paper, readers must take a few things into consideration when reflecting upon this work. First, this is a single-center study and tells us only about this center. These results are not generalizable to other health care systems that may have different workflows, stewardship programs, ways of rounding, and culture. Second, defining appropriateness is tough and is one of the barriers to describing research in the antimicrobial stewardship field. The authors used a very broad interpretation of appropriateness here but did not note any inter-rater reliability, which decreases internal validity of the study. Third, factors that could influence prescriptions are countless and it would be difficult to make a reliable model for this work. However, the study was strengthened by a qualitative post hoc analysis that gave some potential reasons this “morning dip” in appropriateness may be seen at this hospital. Factors included the morning rush, reduced support from consultants, and lag time of diagnostic results in the morning.

One aspect of the study to take away is that it could be worth doing a similar study at your own center, particularly the combination of the quantitative and qualitative parts of this study to best target stewardship interventions. By doing that, one would be using several of the US Centers for Disease Control and Prevention core elements of hospital antibiotic stewardship programs (Tracking, Reporting, Action, and Education).5 If you see results like those found in this study, targeting stewardship interventions to the morning hours may have a greater impact than afternoons and nights. The authors also suggest that more education about stewardship could benefit housestaff. For now, this steward says avoid the morning dip by dipping into a coffee with an optional donut, and be mindful before you prescribe antibiotics. ▲

References available at ContagionLive.com.
E coli Outbreak Linked With Romaine Lettuce Teaches Important Lesson in Food Safety

By Kristi Rosa

The US Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration (FDA) recently announced that the deadly multistate outbreak of Escherichia coli O157:H7 infections linked with romaine lettuce is over. The outbreak has been referred to as the largest E coli outbreak since 2006.

The final case count released on June 28, 2018, indicated there were 210 cases spanning 36 states. Five individuals died from their infections, 96 required hospitalization, and 27 developed hemolytic uremic syndrome.

In a statement, FDA Commissioner Scott Gottlieb, MD, stressed that although the outbreak is over, there is more work to be done to further understand what happened. "The FDA, CDC, and Arizona state officials continue to analyze samples from [the farm in the] Yuma region collected in early June, and initial results are starting to become available," he wrote. "Several environmental samples of canal water in the area have been found to contain E coli O157:H7 that genetically match the strain of bacteria that caused the outbreak."

He added that there are still many questions, such as how the outbreak strain got into the water and how this led to the contamination of romaine lettuce growing in multiple farms. "We, along with our partners, will continue to assess these findings [and] their meanings, and determine what additional efforts may help us better understand this outbreak," he stressed. "We are committed to continuing to share updates on our progress."

The CDC estimates that a staggering 50 million individuals are affected by foodborne illnesses each year. Of those, 128,000 will require hospitalization and about 3,000 will die.

"These numbers are tragically high," Dr. Gottlieb stressed. "While we know we can’t stop foodborne illness completely, these numbers underscore the need for us to do much more. We need to take additional steps, and do it faster, to improve the safety of our food supply. We must never settle for just a small number of outbreaks or grow comfortable with foodborne illness as a fact of life. We may not stop every outbreak from occurring, but our goal should be to try."

### Administration Errors Involving Shingrix Vaccine

By Laurie Saloman, MS

Shingles is a painful disease. Originating from the same virus that causes chickenpox, infection results in a blistering rash on one side of the body. A mild case may clear up within a few weeks and cause no complications, while a more severe case can result in lasting postherpetic neuralgia or pain at the rash site.

Zoster vaccine live (ZVL, Zostavax) to prevent shingles was introduced more than a decade ago and was approved by the Advisory Committee on Immunization Practices (ACIP) for use in adults aged 60 and older. Last year, a more effective vaccine, recombinant zoster vaccine (RZV, Shingrix) became available. ACIP now recommends this vaccine for all adults aged 50 and older who are at risk of shingles—basically, anyone who had chickenpox—and are not immunocompromised. Shingrix differs from Zostavax in that it’s an intramuscular injection, rather than a subcutaneous one, and it’s given in 2 doses, from 2 to 6 months apart.

The Vaccine Adverse Event Reporting System (VAERS), part of the US Centers for Disease Control and Prevention (CDC), began monitoring Shingrix in October 2017. Over 4 months, VAERS looked at 155 reports about Shingrix, 13 of which involved at least 1 error in the administration of the vaccine. Nine of the reports involved Shingrix being administered subcutaneously rather than intramuscularly, with 8 of these administrations causing reactions such as pain, redness, and itching at the injection site; 1 patient was 48 years, younger than the minimum recommended age; and 2 of the 9 patients were given the Zostavax vaccine information statement rather than the Shingrix statement. The other 4 of 13 error reports involved 1 person of unknown age receiving the vaccine, 1 person aged 39 receiving the vaccine, 1 person receiving the vaccine after it had been incorrectly stored, and 1 person receiving only part of the vaccine without the accompanying antigen necessary for reconstitution of the vaccine. Nine of the errors took place in a pharmacy, 2 occurred in a health care provider’s office, and 2 occurred at unknown sites.

It’s possible that these errors occurred because providers were used to storing, handling, and administering Zostavax, which has different requirements than Shingrix. Can such administration errors affect the efficacy of the vaccine or, even worse, pose dangers to recipients?

"The impact of an administration error on [the] effectiveness of giving the new shingles vaccine depend[s] on the error," Tom Shimabukuro, MD, MPH, MBA, deputy director of the CDC’s Immunization Safety Office, told Contagion®. "There is no evidence to suggest incorrectly giving Shingrix subcutaneously reduces the effectiveness of the vaccine; however, this may worsen side effects."

Because Shingrix is meant to be administered in the deltoid muscle of the shoulder, injecting it underneath the skin could raise the risk of reactions at the injection site and possibly increase severity, according to Dr. Shimabukuro. "These reactions could include pain, redness, swelling, induration, etc. However, in this case, despite the adverse reaction, the vaccine would still be effective," he said. "Other errors, like those related to improper storage and handling or giving the second Shingrix dose too soon, may affect the effectiveness of the vaccine and require someone to get revaccinated."

Because VAERS and CDC-INFO, the national contact center and publication fulfillment system, receive reports and information spontaneously, it’s difficult to make definitive pronouncements about whether pharmacies, doctor’s offices, hospitals, or other settings are more prone than others to vaccine errors.

"The limitations of spontaneous reporting, also known as passive monitoring, constrain our ability to draw conclusions about how often these errors occur in different types of settings, so we are unable to say definitively that they occur more frequently in any particular health care setting versus another," said Shimabukuro. "The important thing to note is that vaccine administration errors are preventable, regardless of the health care setting, with proper training and adherence to established guidelines and protocols for administering vaccines."
Two-Drug HIV Regimen May Control Virus in Treatment-Naïve Patients
By Michaela Fleming

V HIV Healthcare recently reported positive results from 2 phase 3 studies that were designed to evaluate the safety and efficacy of a 2-drug regimen of dolutegravir and lamivudine compared with a 3-drug regimen for treatment-naïve patients with HIV.

GEMINI 1 and GEMINI 2 are duplicate phase 3 randomized double-blind multicenter parallel group noninferiority studies. They are part of ViiV Healthcare’s innovative clinical trial program for 2-drug regimens that seeks to reduce the number of medications used in HIV treatment in order to address long-term toxicity concerns.

Approximately 1400 treatment-naïve adults with HIV-1 with baseline viral loads less than 500,000 copies/mL were enrolled in the studies, which were conducted at research centers in Europe, Central and South America, North America, South Africa, and the Asia Pacific regions.

During the course of the study, participants either received dolutegravir/lamivudine or dolutegravir and tenofovir disoproxil fumarate/emtricitabine. According to ViiV Healthcare, the studies met their primary endpoint for noninferiority based on plasma HIV-1 RNA <50 copies/mL, a standard measure of HIV control at week 48. According to the investigators, those participants who experienced virologic failure did not develop treatment-emergent resistance.

“The GEMINI studies demonstrate the potency, safety, and tolerability of the dolutegravir plus lamivudine combination. They affirm our 2-drug regimen strategy and reinforce our belief that many patients can control their disease with 2 drugs instead of 3 or more,” said John C. Pottage, Jr, MD, chief scientific and medical officer of ViiV, in a statement. “Importantly, the study results show that this 2-drug regimen could be an option for treatment-naïve patients and can support a broad range of patients living with HIV around the world.”

ViiV Healthcare plans to apply for regulatory approval for the 2-drug regimen of dolutegravir and lamivudine later this year.

Tuberculosis, HAZMAT Suits, and Tons of Confusion
By Saskia v. Popescu, MPH, MA, CIC

Most members of hospital infection prevention and control programs have a handful of stories regarding an incident involving an infectious disease that resulted in a lot of hysteria and not a lot of critical thinking. As an infection preventionist in both adult and pediatric acute care, I’ve seen health care workers brazenly walk into the room of a patient who is under isolation precautions for horribly resistant infections such as carbapenem-resistant Enterobacteriaceae without wearing 1 piece of personal protective equipment (PPE); however, they will wear every scrap of protection they can find (including a coverall suit, shoe covers, etc) when caring for a patient with bed bugs. Threat perception and understanding is a serious issue when it comes to infectious diseases.

The latest example of this occurred at Johns Hopkins Hospital in Baltimore, Maryland. On July 6, 2018, 2 buildings were evacuated and employees within a certain area were isolated and medically evaluated because of a potential infectious-disease–related incident. HAZMAT suits were involved and, of course, a lot of press coverage.

So, what happened? Perhaps a rule-out patient with Ebola or a patient with measles? No. The alarm was caused by potential exposure to Mycobacterium tuberculosis that occurred when an employee inadvertently dropped a test tube containing a frozen sample of the bacteria on an internal bridge between 2 oncology research buildings. Although the lid came off, the frozen sample stayed inside the tube.

The ensuing reaction to this incident left many of my infectious disease colleagues a bit confused. Why the evacuation? Sadly, this incident has drawn attention to what many of us in infection prevention already know: Despite health care worker education on tuberculosis, which is required in new employee orientations, when faced with the airborne transmission associated with infectious patients, people tend to throw logic out the window and induce worry.

The dropping of a sample tube can be worrisome, to be sure, and perhaps we are hypersensitive to such incidents because of biosafety breaches that have occurred with more dangerous select agents. What is most concerning, though, is that this event induced such a large and overzealous response.

HAZMAT suits are not necessary for tuberculosis. The only PPE needed is an N95 or higher respirator. The use of HAZMAT suits or powered air purifying respirators in a situation like this has the potential to create confusion and hysteria. Moreover, the dropping of a frozen vile of a pathogen does not translate to an immediate threat. Tuberculosis is an airborne-spread organism; health care worker exposures require spending time near someone with the disease who is coughing, sneezing, etc. Aerosolization occurs from those aerosol-generating actions or procedures. To this end, when speaking about the incident, Landon King, MD, executive vice dean at the Johns Hopkins School of Medicine, stated, “[W]e have determined that there is actually no risk, meaning zero risk, to anybody involved. So, there is no preventive measure or testing that’s required for anyone in the buildings or on the campus as a result of this event.”

This incident reveals 2 issues: (1) gaps in infectious disease understanding and (2) communication failures during a potential outbreak response. Johns Hopkins Hospital infection control, emergency preparedness, and laboratory officials are likely reviewing the incident to understand why such a massive response was triggered.

My guess would be that the initial messages about the incident had limited information and, based on my experiences, infection prevention and control was probably not consulted until later in the event. Communication is a major weakness in health care, and it goes beyond the bedside, encompassing all partners in a hospital.

We know that communication during an emergency is flawed, but the truth is that communication leading up to a response is just as critical and just as imperfect. Helping health care workers and hospital employees understand the infectious disease risks of their jobs and who to contact if they have concerns is one of the hardest aspects of infection control, and this event shines a glaring spotlight on these issues.
What’s New From the CLSI Subcommittee on Antimicrobial Susceptibility Testing?
Updates you need to know from the June 2018 meeting.

BY ELIZABETH HIRSCH, PHARMD, RPH

The latest Clinical and Laboratory Standards Institute’s Subcommittee on Antimicrobial Susceptibility Testing meeting was held June 3-5, 2018, in San Diego, California. Although new and revised breakpoints included in this article are approved by the subcommittee, they are subject to change prior to official approval of the meeting minutes at the January 2019 meeting.

REVISED BREAKPOINTS

Ceftaroline

Ceftaroline is a cephalosporin with a broad spectrum of activity, including methicillin-resistant *Staphylococcus aureus* (MRSA). Its high affinity for penicillin-binding proteins (PBPs), including PBP2a in MRSA, contributes to its activity against MRSA.\(^1\) Ceftaroline is US Food and Drug Administration (FDA)-approved as a 600-mg dose every 12 hours (given over 5 to 60 minutes), while a high-dose regimen of 600 mg every 8 hours (given over 2 hours) has been approved for select indications in many countries outside the United States since 2017.

The in vitro activity of ceftaroline varies widely by geographic region, fueled by pandemic MRSA clones.\(^2\) Data from the SENTRY Antimicrobial Surveillance Program presented by Helio S. Sader, MD, from JMI Laboratories show that ceftaroline minimal inhibitory concentrations (MICs) for MRSA rarely exceed 1 mg/L within the United States, while the proportion of MICs greater than or equal to 2 mg/L is near 30% in some Latin American countries. In regions with greater than 15% ceftaroline-nonsusceptible MRSA isolates, correlation between disk diffusion and broth microdilution MICs are poor, with elevated error rates. Although the current CLSI breakpoints appeared appropriate to reduce these discrepancy errors in the United States, CLSI breakpoints are often used outside the United States. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has developed indication-specific breakpoints, with guidance surrounding dosing, but logistical implementation of these is often difficult.\(^3\) In light of all of the data presented, the Antimicrobial Susceptibility Testing (AST) Subcommittee approved revised breakpoints with a new susceptible-dose dependent (SDD) category based on the high-dose regimen (Table 1).

Daptomycin

Although daptomycin is approved for the treatment of vancomycin-susceptible *Enterococcus faecalis*, it is often a workhorse agent for the treatment of vancomycin-resistant *Enterococcus faecium* where treatment options are limited. The FDA-approved dose of 6 mg/kg was primarily based on results from clinical trials for staphylococci whereas daptomycin MICs against *E faecium* are reportedly 2- to 4-fold higher than for staphylococci. Several studies’ findings have demonstrated worse clinical outcomes when daptomycin MICs are 3 to 4 mg/L versus less than or equal to 2 mg/L for patients with vancomycin-resistant *Enterococcus faecium* bacte remia treated with daptomycin.\(^5,6\) Additionally, several studies have reported improved outcomes for VRE bacteremia when using high-dose (≥8 mg/kg) therapy compared with the 6-mg/kg dose that is FDA approved for MRSA bloodstream infections.\(^7,8\) In addition to published data, unpublished modeling data generated by Avery et al from Hartford Hospital, Hartford, Connecticut, were reviewed. Their modeling suggested that with 6-mg/kg dosing, a susceptible breakpoint should be 1 to 2 mg/L, while 10- to 12-mg/kg dosing suggested a susceptible
breakpoint of 2 to 4 mg/L. The revised breakpoints approved by the AST Subcommittee are detailed in Table 1. Verbiage to be included with the SDD category includes "the SDD category is based on a dosage regimen of 8 to 12 mg/kg in adults and is intended for serious infections due to Enterococcus spp. Consultation with an infectious diseases specialist is recommended."

**Fluoroquinolones: Ciprofloxacin and Levofloxacin**

Discussion of revised ciprofloxacin and levofloxacin breakpoints for Enterobacteriaceae and Pseudomonas aeruginosa has been ongoing at CLSI for several years. The AST Subcommittee voted to accept the revision of MIC breakpoints in 2017/2018 pending disk diffusion correlates data. New data were presented and are now sufficient to meet M23 criteria. Revised breakpoints for both ciprofloxacin and levofloxacin, projected for the 29th edition of the M100, were approved, as detailed in Table 1.

**NEW BREAKPOINTS**

*Cefiderocol*

Cefiderocol is a novel siderophore cephalosporin undergoing clinical development; it is not yet approved by the FDA for use. Although its chemical structure is similar to cepofime, it is unique in that it forms chelating complexes with ferric iron and is transported across the outer membrane of gram-negative bacteria via the active bacterial iron transport system. Once in the periplasmic space, the structure confers stability to both serine- and metallo-carbapenemases. It has shown in vitro activity against a broad range of problematic gram-negative bacteria, including carbapenem-resistant Enterobacteriaceae, P aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia. Over the last 30 years, several attempts to develop siderophore β-lactam compounds have been fruitless due to demonstration of adaptive resistance against some P aeruginosa strains.

Navigating uncharted territory under the 21st Century Cures Act, sponsors can now approach CLSI as a standards development organization for guidance on clinical breakpoints prior to FDA approval. Cefiderocol is one of the first agents to be reviewed by CLSI prior to FDA approval. Detailed microbiology, pharmacokinetic/pharmacodynamic, and clinical data from a phase 3 complicated urinary tract infection study comparing cefiderocol to imipenem supplied by the sponsor were reviewed. Following extensive discussion, provisional breakpoints were approved for 4 organism groups: Enterobacteriaceae, P aeruginosa, A baumannii, and S maltophilia (Table 2). As provisional breakpoints, ongoing data review will take place as more clinical trial data become available.

**Meropenem-Vaborbactam**

Meropenem-vaborbactam, the latest β-lactam/β-lactamase inhibitor (BLI) combination, was approved for use in the United States in 2017. Meropenem combined with vaborbactam, a novel cyclic boronate BLI, was designed to inhibit for which response rates may be lower than for susceptible isolates.” Also noted in the definition is that “this category also includes a buffer zone, which should prevent small uncontrolled technical factors from causing major discrepancies in interpretations.”

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<th>Table 1. Notable Revised CLSI Interpretive Categories and MIC Breakpoints Approved at the June 2018 Meeting</th>
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<td><strong>AGENT</strong></td>
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- Indicates absence of MIC breakpoint; CLSI, Clinical and Laboratory Standards Institute; MIC, minimal inhibitory concentration.
*All previous breakpoints are cited from the 28th edition (January 2018) of the CLSI M100 document.

<table>
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<th>Table 2. New CLSI Interpretive Categories and MIC Breakpoints Approved for Agents Without Existing CLSI Breakpoints</th>
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<td><strong>AGENT</strong></td>
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<td>Meropenem-vaborbactam</td>
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- Indicates absence of MIC breakpoint; CLSI, Clinical and Laboratory Standards Institute; MIC, minimal inhibitory concentration.

Class A serine carbapenemases, specifically the Klebsiella pneumoniae carbapenemase (KPC) enzyme. Although the drug has shown potent in vitro activity against KPC-producing isolates, including some resistant to ceftazidime-avibactam, the drug lacks activity against Class B metallo-β-lactamases and Class D β-lactamases. Data supporting the previously FDA-identified MIC interpretive criteria for Enterobacteriaceae (Table 2) were presented and subsequently approved for publication in the M100 document, with the FDA-approved dosage regimen of 4 g (2 g meropenem + 2 g vaborbactam) every 8 hours over a 3-hour infusion.

**NOTEWORTHY NONBREAKPOINT NEWS**

An ad hoc intermediate working group was charged with determining the fate of the intermediate CLSI category. The definition of this category is that it is "defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels and

Both EUCAST and the National Antimicrobial Susceptibility Testing Committee for the United States are currently operating under a majority 2-category breakpoint system (eg, susceptible and resistant) while CLSI has mostly 3-category breakpoints (eg, susceptible, intermediate, and resistant [S/I/R] or susceptible, SDD, and resistant [S/SDD/R]). The working group achieved consensus that all drugs should have a 3-category system to account for variability. Two options were presented for discussion. The first was S/I/R, eliminating the SDD category and revising the intermediate category. The second option was use of either S/I/R or S/SDD/R, with revision to the intermediate definition that no longer includes drugs for which a higher dose or exposure can be used (to be SDD only). The committee was in favor of the second (eg, S/I/R or S/SDD/R) option, but no consensus was reached. The topic of intermediate categories has also been in discussion at EUCAST, and it appears that more dialogue is on the horizon for CLSI. References available at ContagionLive.com.
Antibiograms for Optimizing Empiric Therapy: Use Them Wisely

An understanding of the limitations in their functionality and strategies for more appropriate applications are necessary for clinicians.

BY JASON M. POGUE, PHARMD

(continued from cover)

pathogen and can subsequently drive empiric therapy recommendations for infections caused by those organisms. For example, in urinary tract infections (UTIs), empiric therapy primarily targets *Escherichia coli*. If an antibiogram shows that, at your institution, 70% of *E coli* are susceptible to ciprofloxacin but 93% are susceptible to nitrofurantoin, then nitrofurantoin makes much more sense as an empiric therapy recommendation for a UTI than a fluoroquinolone. Although it is true that this example suggests that nitrofurantoin is a better option than ciprofloxacin at targeting *E coli*, it is critical that clinicians appreciate the limitations of traditional antibiograms and, perhaps more importantly, strategies to improve their utility. The purpose of this review is to discuss strategies for improving the functionality of antibiograms and ultimately providing more appropriate empiric therapy.

HOW TO IDENTIFY ISOLATES FOR ANTIBIOGRAMS TO IMPROVE THEIR UTILITY FOR A GIVEN DISEASE STATE

One strategy that many institutions use to improve the functionality of their antibiograms is to analyze isolates from the hospital floor and the intensive care unit (ICU) separately. The logic is simple: Patients in ICUs represent a different population, having multiple risk factors for drug-resistant organisms, and are the population in whom the appropriateness of empiric therapy is most critical. Therefore, separating ICU isolates from floor isolates and directing empiric therapy for ICU infections, such as pneumonia, against the ICU isolates is pragmatic. Institutions most commonly do this for *Pseudomonas aeruginosa* and report their institutional antibiograms for this pathogen dichotomized into “ICU” and “floor” isolates. Institutions then often choose their empiric ICU pneumonia regimen to be the 2 agents with the best activity against this pathogen in isolates...
recovered from ICU patients. Although this approach is certainly preferred to the hospital-wide antibiogram, it is not without its own significant limitations. It assumes that for the treatment of pneumonia in the ICU, the only gram-negative pathogen of concern is *P. aeruginosa*, and it fails to consider that the purpose of the second empiric agent is to provide activity when there is resistance to the first agent. Traditional antibiograms cannot address this issue because they do not assess cross resistance (ie, activity of the second agent in the setting of resistance to the first.)

**INFECTION SITE–SPECIFIC ANTIBIGRAMS, PART 1: COMBINATION ANTIBIOMGRAMS FOR ICU PNEUMONIA**

Antimicrobial stewardship programs can overcome the limitations of traditional antibiograms through the development of an infection site-specific antibiogram to help determine the optimal empiric therapeutic regimen for a given disease state. The most common application of this is a combination antibiogram for the treatment of pneumonia in ICU patients. Instead of developing organism-specific antibiograms and using these to develop targeted empiric therapy recommendations based on the most likely pathogens, antibiograms are developed by including all isolates for a given site of infection over a time frame and assessing both the activity of monotherapy options and the likelihood of combinations having at least 1 active agent. Table 1 displays a sample site-specific antibiogram for all gram-negative respiratory isolates in an ICU over a given time frame. The first column consists of potential 1-drug options. As demonstrated in the table, different β-lactams were found to be active against 68% to 76% of gram-negative isolates in the ICU, making them unacceptable as empiric monotherapy regimens. As alluded to previously, in order to increase the likelihood of active empiric therapy, clinicians need to know what other drug is most likely to be active against a β-lactam–resistant isolate.

This is what makes combination antibiograms unique: They assess the activity of potential second agents (ie, fluoroquinolones or aminoglycosides) against β-lactam–resistant isolates. For example, of the 100 cefepime-resistant isolates listed in Table 1, 20 are susceptible to ciprofloxacin. Therefore 230 (210 cefepime susceptible and 20 cefepime resistant, ciprofloxacin susceptible) isolates are susceptible to at least 1 agent in the cefepime/ciprofloxacin combination. Repeating this process for all logical 2-drug combinations demonstrates that a β-lactam plus amikacin is the optimal gram-negative empiric regimen for hospital-acquired/ventilator-associated pneumonia in this ICU.

Although these data can provide critically important information for optimizing empiric therapy for pneumonia in ICU patients, it is also crucial for stewards to appreciate that what is good for one ICU might not be for another. For example, published data from the University of Michigan demonstrated that the optimal regimens, as determined by combination antibiograms, for the medical ICU (MICU) and surgical ICU were different.1

**INFECTION SITE–SPECIFIC ANTIBIGRAMS, PART 2: OPTIMIZING THERAPY FOR DIFFERENT COMMUNITY-ACQUIRED INFECTIONS**

At the beginning of this article, we discussed how traditional antibiograms might be used to develop empiric therapy guidelines. The example provided indicated that an *E. coli* antibiogram could be utilized to determine the optimal empiric regimen for UTIs given that up to 80% or more of UTIs are caused by *E. coli*. Theoretically the same principle could apply to intra-abdominal infections (IAIs) given the frequency that *E. coli* is isolated from these infections when aerobic organisms are present; however, there are 2 faults to this logic. First, *E. coli*, although predominating, are not the only pathogens in these disease states. Secondly, the assumption that *E. coli* in patients with UTIs and patients with IAIs are identical is inappropriate given that different patient populations present with these disease states and they have different risk factors for drug-resistant isolates.

To circumvent these issues, clinicians can develop syndrome-specific antibiograms, similar in many ways to the site-specific combination antibiogram described above. The syndrome-specific antibiogram takes all causative microbiology for a given disease state (eg, UTI or IAI) for a given time frame (eg, within ~48 hours of admission to ensure that only community pathogens are included) and assesses what regimens will provide optimal coverage. Hebert and colleagues utilized this methodology to develop optimal empiric regimens for UTIs and IAIs at their institution.7 In their analysis, the investigators demonstrated that a one-size-fits-all method attacking *E. coli* is insufficient for these 2 disease states and that the optimal empiric regimen, even from a purely aerobic coverage standpoint, differed between UTIs and IAIs. For example, ciprofloxacin was active against 62% of pathogens causing UTIs, whereas even when adding anaerobic coverage with metronidazole, it was only active against 37% of isolates in IAIs (P < .001). The authors described that the major driver of the difference was that the proportion of *E. coli* in these disease states differed (~4-fold higher in UTIs), although differing susceptibilities of the *E. coli* present in UTIs and IAIs could also play a potential role.

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Table 1: Example Combination Antibiogram

<table>
<thead>
<tr>
<th></th>
<th>N (%) SUSCEPTIBLE</th>
<th>CIPROFLOXACIN N (%) SUSCEPTIBLE</th>
<th>TOBRAMYCIN N (%) SUSCEPTIBLE</th>
<th>AMIKACIN N (%) SUSCEPTIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>210 (68)</td>
<td>230 (74)</td>
<td>254 (82)</td>
<td>270 (87)</td>
</tr>
<tr>
<td>Piperacillin/ Tazobactam</td>
<td>236 (76)</td>
<td>245 (79)</td>
<td>264 (85)</td>
<td>272 (88)</td>
</tr>
<tr>
<td>Meropenem</td>
<td>228 (74)</td>
<td>243 (78)</td>
<td>267 (86)</td>
<td>275 (89)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>215 (69)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>262 (85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>275 (89)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**SYNDROME-SPECIFIC ANTIBIOGRAMS: BE CAREFUL!**

**COMBINATION ANTIBIGRAMS** and syndrome-specific antibiograms offer significant advancements over traditional antibiograms that can be used by stewardship programs and clinicians to optimize empiric therapy. Furthermore, given that empiric therapy is syndrome based and not pathogen based, they are also more logical. However, clinicians should be aware that they still have significant limitations.

For example, if we were to create a community-acquired UTI-specific antibiogram, as described in the above example, we might include all urine cultures obtained in the emergency department (ED) and within the first 48 hours of admission and develop an antibiogram to guide empiric recommendations. In reality, this is an overly simplistic grouping of isolates as doing so assumes that all of these cultures are created equally and that it is appropriate to group otherwise healthy community dwellers with those who have risk factors for resistant pathogens (eg, previous antibiotic exposure, recent hospitalization, presentation from a nursing home/long-term acute care facility). In fact, this is an inaccurate and inappropriate assumption and can lead to suboptimal empiric therapy recommendations.

To illustrate the concerns with this approach, **Table 2** represents an internal analysis that was performed at Sinai-Grace Hospital in Detroit, Michigan, on all gram-negative UTIs presenting from the community over a 6-month period. The antibiogram was assessed first as all gram-negative organisms isolated over the time frame, similar to the above described methodology, and then divided into those who presented from the community without risk factors for resistant pathogens, those classified as health care associated (risk factors present for resistance such as recent hospitalization and previous antibiotic use), and those who came from nursing homes. The data indicate that if all isolates are grouped together, then multiple oral options (nitrofurantoin, ciprofloxacin) and more narrow-spectrum intravenous options (ceftriaxone and gentamicin) appear to have unacceptably high resistance rates that do not allow for routine empiric use. However, when split into different patient populations, the susceptibility differences—and, ultimately, the optimal empiric therapy recommendations as a function of patient type—become clearer. For example, even though nitrofurantoin and ceftriaxone appear to only be active against 80% and 85% of community isolates, respectively, when assessing the antibiogram as a whole, this is not the case when the antibiogram is stratified as a function of patient type. Once true community acquired UTI patients (ie those without risk factors for resistance) are separated out it becomes apparent that these agents are much more active (90% to 97%) and appropriate first-line therapies. Conversely, although tobramycin appears to be an appropriate first-line therapy, with activity against 90% of community isolates, a deeper dive demonstrates that if only assessing patients in nursing home, susceptibility is much worse (60%) and thus tobramycin is an inappropriate empiric option for these patients.

**TABLE 2:** Community-Onset UTI Antibiogram

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>PERCENT SUSCEPTIBLE</th>
<th>FEP</th>
<th>CRO</th>
<th>CIP</th>
<th>ETP</th>
<th>MEM</th>
<th>GEN</th>
<th>NIT</th>
<th>TOB</th>
<th>TMP/SMX</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n = 279)</td>
<td>AMK</td>
<td>85</td>
<td>80</td>
<td>96</td>
<td>98</td>
<td>86</td>
<td>80</td>
<td>90</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Comm (n = 154)</td>
<td>CRO</td>
<td>97</td>
<td>89</td>
<td>99</td>
<td>99</td>
<td>91</td>
<td>91</td>
<td>92</td>
<td>92</td>
<td>75</td>
</tr>
<tr>
<td>HCA (n = 90)</td>
<td>CIP</td>
<td>94</td>
<td>82</td>
<td>79</td>
<td>74</td>
<td>96</td>
<td>99</td>
<td>84</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>NH (n = 35)</td>
<td>ETP</td>
<td>94</td>
<td>54</td>
<td>46</td>
<td>54</td>
<td>83</td>
<td>94</td>
<td>71</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

AMK indicates amikacin; CIP, ciprofloxacin; Comm, community acquired; CRO, ceftriaxone; ETP, ertapenem; FEP, ceftazidime; GEN, gentamicin; HCA, health care associated; MEM, meropenem; NH, nursing home; NIT, nitrofurantoin; TOB, tobramycin; TMP/SMX, trimethoprim/sulfamethoxazole.

**CONCLUSIONS**

The purpose of this article was to demonstrate the limitations of conventional antibiograms and suggest potential improvements that antibiotic stewards can make to further refine empiric therapy recommendations at their institutions. Clinicians should shy away from a one-size-fits-all mentality and incorporate flexibility into their guidelines. For example, a combination antibiogram of respiratory isolates from the MICU might mandate the empiric use of cefepime plus tobramycin for grammegative coverage in septic patients with a suspected pulmonary source in that unit. However, when developing hospital-wide HAP guidelines, these MICU-based recommendations should not apply to non-ICU patients. Patients on the general ward often have less-resistant pathogens, are more hemodynamically stable, and usually have pneumonia as part of a differential diagnosis that includes both infectious and noninfectious etiologies. Although it is prudent to provide empiric antipseudomonal therapy to the right pneumonia patient, the risk/benefit ratio, of both toxicity and collateral damage, likely warrants avoidance of a second empiric gram-negative agent (ie, an aminoglycoside) in these more stable floor patients.

Similarly, although the antibiogram for nursing home-associated UTIs presented in this article suggests a very high rate of extended-spectrum β-lactamase (ESBL)-producing organisms, this does not mean that every nursing home patient who presents to the ED with mental status changes and previous antibiotic use), and those who came from nursing homes. The data indicate that if all isolates are grouped together, then multiple oral options (nitrofurantoin, ciprofloxacin) and more narrow-spectrum intravenous options (ceftriaxone and gentamicin) appear to have unacceptably high resistance rates that do not allow for routine empiric use. However, when split into different patient populations, the susceptibility differences—and, ultimately, the optimal empiric therapy recommendations as a function of patient type—become clearer. For example, even though nitrofurantoin and ceftriaxone appear to only be active against 80% and 85% of community isolates, respectively, when assessing the antibiogram as a whole, this is not the case when the antibiogram is stratified as a function of patient type. Once true community acquired UTI patients (ie those without risk factors for resistance) are separated out it becomes apparent that these agents are much more active (90% to 97%) and appropriate first-line therapies. Conversely, although tobramycin appears to be an appropriate first-line therapy, with activity against 90% of community isolates, a deeper dive demonstrates that if only assessing patients in nursing home, susceptibility is much worse (60%) and thus tobramycin is an inappropriate empiric option for these patients.

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

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Controversies of Antimicrobial Transitions in Adults With Gram-Negative Bacteremia
Moving away from the standard course of IV antibiotics.

BY NICHOLAS J. MERCURO, PHARMD, AND SUSAN L. DAVIS, PHARMD

Inevitably, most clinicians and antimicrobial stewards will encounter a challenging clinical decision: Can a patient with transient gram-negative bacteremia be treated with something other than 14 days of intravenous (IV) antimicrobial therapy? The potential disadvantages of a 2-week course of IV antibiotics (line infections, adverse effects, monitoring outpatient parenteral antimicrobial therapy [OPAT], prolonged hospital stay) are enough to cause second thoughts. Recent literature suggests that shorter courses of antibiotics and oral agents are reasonable alternatives for many patients, given several key considerations (see Sidebar).

Bloodstream infections (BSIs) due to gram-negative bacilli are typically manifestations of complicated urinary tract (UTI) or intra-abdominal infections. Some of the most common stewardship strategies for these infections include rapid organism identification and pharmacokinetic/pharmacodynamic dose optimization of empiric and targeted therapy. However, practice guidelines offer little direction on the management of the bacteremic patient regarding antimicrobial transitions from IV therapy, selection of stepdown agents, and the duration of treatment.1,2 Until recently, management strategies for gram-negative BSIs have only been examined in observational studies or subgroups of randomized trials.3-5 Much of the available data are limited due to retrospective study designs, varying definitions of outcomes, differences in organisms studied, and a lack of complete antimicrobial administration information with follow-up.6-9 Given that each additional antimicrobial day/central-line day is associated with increased risk of Clostridium difficile infection, adverse effects, and reinfection, it is critical that antibiotic stewards critically evaluate each case individually.10

CAN ORAL ANTIBIOTICS BE USED?
More than 20 years of evidence from observational and randomized studies support the practice of using sequential IV-to-highly bioavailable oral agent when treating bacteremia.10-12-11 IV-to-oral conversion upon clinical stability is becoming the expected standard of care, in large part because of the benefits of reduced hospital stay, costs, and avoidance of the risks associated with OPAT. About 1 in 4 patients are readmitted by 30 days following

*Active members of the Society of Infectious Diseases Pharmacists (SIDP)
discharge with OPAT, with many of the reasons for readmission possibly related to the IV therapy. Clinical trials in disease states such as pyelonephritis, in which over 30% of patients can have a secondary BSI, can be helpful for directing therapy in gram-negative bacteremia. When comparing IV-only to oral ciprofloxacin for pyelonephritis/complicated UTI in a randomized study, the microbiologic and treatment failure rates were less than 5% in each group. In Enterobacteriaceae BSIs from urinary sources, a large retrospective study concluded there were no differences in clinical failure between IV-only and IV/ oral therapy. Patients with bacteremia secondary to cholangitis converting from IV to oral therapy also showed comparable outcomes to those only receiving IV therapy. For example, Park et al randomized 59 patients starting on IV therapy to either oral transition or all IV route and found no difference in microbiologic eradication or recurrence. However, length of stay was shorter in the oral conversation group.

Similarly, in a retrospective observational study of 263 patients with bacteremic cholangitis, 36.5% were converted to oral therapy. In the short- and long-course treatment arms, oral antibiotics were received for 3 and 7 days, respectively. Although the clinical impact of oral conversion was not described, there was no difference in mortality, recurrence, or composite outcome of failure between the arms. Reliable pharmacokinetic profiles and improvement in patient safety and quality of life, without increasing risk of treatment failure, justify IV to oral conversion for uncomplicated gram-negative BSIs.

**WHEN TO “GO PO”?**
Gram-negative BSIs do not typically advance to persistent infections such as endocarditis, where duration depends on surgical intervention and no growth in repeated blood cultures, at which point many experts begin counting antibiotic days. The first day of active antibiotic therapy seems to be the accepted “day 1” for uncomplicated gram-negative BSIs, and it is also likely unnecessary to confirm clearance of bacteremia. The results of single-center observational studies suggest that repeating blood cultures for gram-negative BSIs may be unlikely to alter management, while increasing resource utilization. Ongoing clinical trials may provide further insight on the significance of confirming microbiologic eradication in gram-negative BSI.

The median transition period to oral therapy was between 3 and 5 days in observational IV/oral gram-negative studies. One such study examined the impact of a short (<3 days) versus longer time to conversion, and there was no difference in clinical success, although it was a secondary outcome. Trending procalcitonin and C-reactive protein levels may also help predict early clinical improvement for patients with gram-negative BSI. Clinical trials often allow oral conversion at the discretion of the provider. This approach is appropriate, as oral conversion should be based on clinical stability, adequate control of infectious foci, and meeting criteria for enteral antibiotic administration.

**FIVE CLINICAL CONSIDERATIONS FOR ORAL CONVERSION IN GRAM-NEGATIVE BSI**

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Source control, source control, source control Most patients in the literature supporting IV/oral switch do not have complicated BSIs, undrained abscesses, or metastatic foci.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient specific attributes</td>
<td>Conditions such as cirrhosis, urinary abnormalities, and nonimmunocompetent status may predispose clinical failure, requiring careful attention. Oral therapy should be avoided in those with malabsorption or other contraindications to enteral medication administration.</td>
</tr>
<tr>
<td>Anticipating the oral switch</td>
<td>Oral options are often available when patients approach clinical stability (afebrile, normotensive, resolving leukocytosis, etc) after 3 to 5 days of IV therapy.</td>
</tr>
<tr>
<td>Bug and drug</td>
<td>Most literature pertaining to oral conversion focuses on susceptible Enterobacteriaceae; an assessment of antibiotic access, adherence, adverse events, drug interactions, and pharmacokinetics/pharmacodynamics are necessary to leverage efficacy and safety.</td>
</tr>
<tr>
<td>The shorter course</td>
<td>Limiting total antibiotic days reduces the risk of adverse drug events and longer time to return to baseline activity. Patients achieving clinical stability leading up to day 7 of therapy are likely candidates for a shorter antibiotic course.</td>
</tr>
</tbody>
</table>

BSI indicates bloodstream infection; IV, intravenous.
There is sufficient evidence to conclude that highly bioavailable agents are efficacious as stepdown therapy for gram-negative BSIs. Given widespread quinolone and SXT resistance and the risks associated with OPAT therapy, oral β-lactams could be considered for use in stable patients with minimal adherence barriers, source control, and organisms with low minimum inhibitory concentrations. Although reduced bioavailability is concerning, success rates remain high across studies. Data from large randomized trials are anticipated to confirm these findings.

HOW LONG TO TREAT?
Until recently, observational and pooled clinical trial data were the best available evidence for the duration of antibiotic therapy for gram-negative BSIs. A meta-analysis of randomized trials including only bacteremic subpopulations from urinary sources found no difference in clinical success between treatment with a fluoroquinolone that was less than or equal to 7 days and greater than 7 days. The trial that provided the most patients for this meta-analysis assigned 156 females with pyelonephritis (27% with E coli bacteremia) to either 7 or 14 days of ciprofloxacin. Only 16% received initial IV ciprofloxacin, yet 93% achieved clinical success, with 27% of the population having BSIs. Patients on longer courses of ciprofloxacin durations had more mucosal candida infections.

In a multicenter propensity-matched cohort of adults with Enterobacteriaceae BSIs, mortality at 30 days for short-course treatment (range, 6-10 days) was no different when compared with long-course treatment (range, 11-16 days). The largest observational study that did not support a shorter treatment duration for gram-negative bacteremia determined that predictors of treatment failure were cirrhosis, nonimmunocompetent status, and use of short-course therapy.

Doi et al concluded no difference in mortality or composite primary outcome in a propensity-scored retrospective cohort (n = 263) comparing short (<7 days) and long (>7 days) durations of therapy for bacteremic cholangitis, with source control. There were notable differences between the groups related to severity of illness, microbiology, appropriate empiric therapy, and utility of expert consultation. In a multicenter study, Daneman et al also found comparable mortality between short and long durations (27% vs 29%) in critically ill patients with uncomplicated bacteremia, although this was not specific to gram-negative organisms. Other observational studies have also determined no correlation between clinical success and longer durations of therapy, but they were underpowered to assess this specific endpoint.

Yahav et al recently presented the results of their randomized trial assessing noninferiority of 7 days versus 14 days of antibiotics for uncomplicated gram-negative BSIs (n = 602) at the 28th European Congress of Clinical Microbiology and Infectious Diseases. Enterobacteriaceae represented more than 90% of the organisms that were isolated. Most sources of bacteremia stemmed from the urinary tract, and patients were required to achieve clinical instability within 48 hours before randomization (day 7) and have source control of infection. Short-course therapy was noninferior to the 14-day course in the primary outcomes of mortality, failure, and readmission/extended hospitalization at 90 days. There were also only minor differences in 90-day mortality (11.8% vs 10.7%), treatment failure, adverse drug events, or development of resistant organisms. However, patients treated with a short course had improved “time to return to baseline activity” (14 vs 21 days; P<.001). Based on these observational and randomized data, patients who are clinically stable after several days of appropriate antibiotic therapy can safely receive a 7- to 10-day course for Enterobacteriaceae BSI.

IN SUMMARY
It appears that the dogma of a 2-week IV-antibiotic course for uncomplicated gram-negative BSIs has had its day. With similar treatment success, clinicians can reduce the risk of additional antibiotic-related harm by using shorter durations. Although not all from randomized trials, there are ample data to support the practice of oral stepdown to a highly bioavailable agent for BSIs due to Enterobacteriaceae from a urinary or intra-abdominal source and completing at least 7 days of active therapy. It is not yet clear which subsets of patients are poor candidates for shorter courses or agents with lower bioavailability. Stepdown is conditional on clinical stability and criteria for oral medication administration. β-lactams may be useful in cases involving resistance or intolerance to quinolone/SXT, although it is difficult to maintain optimal serum concentrations. Final results from ongoing clinical trials are highly anticipated.

References are available at ContagionLive.com.
Dimorphic Fungal Pathogen May Be Causing Fatal Infections in Western US and Canada

New geographical spread of the disease may warrant increased vigilance among labs and clinicians.

BY BRIAN P. DUNLEAVY

A new potentially fatal fungal infection may be on the rise in the western regions of North America, according to new research.\(^1\) *Blastomyces helicus*, a dimorphic fungal pathogen, has remained a mystery to researchers and clinicians alike. Although it was initially identified in samples taken from the brain and lungs of a man who died of encephalitis in Alberta, Canada—his initial diagnosis was blastomycosis—the geographic range, epidemiology, and clinical features of disease-causing *B helicus* remain unknown. The findings of the study, however, suggest that it may be the cause of fatal infections in the western United States and Canada.

"Fungi are important pathogens of humans, animals, and plants, and yet there is so much we do not yet understand about them," lead author Ilan Schwartz MD, PhD, FRCPC, assistant professor, division of infectious diseases, University of Alberta, Edmonton, Canada, told *Contagion*®. "A medically important but poorly understood group of fungi are the dimorphic fungi that cause the endemic mycoses. For many years, mycologists have noted differences in some strains of fungi that caused blastomycosis in different regions, but the availability of genetic analysis has now clarified the relationship of these fungi."

According to Dr. Schwartz, the newly isolated fungi is related to, but distinct from, *Blastomyces dermatitidis*, which he describes as “the classic cause of blastomycosis.” Historically, *B dermatitidis* has been endemic in areas around the St. Lawrence and northern Mississippi rivers in the United States and Canada. It is found most commonly in animals and, occasionally in humans. The US Centers for Disease Control and Prevention estimates that the annual incidence rate of blastomycosis, in humans, is roughly 1 to 2 per 100,000 individuals.\(^2\)

For their research, Dr. Schwartz and colleague analyzed human and veterinary isolates of *B helicus* identified from samples taken from blastomycoses and *Emmonsia* cases collected at the University of Alberta, the University of Texas Health Science Center at San Antonio’s Fungus Testing Laboratory, and the ARUP Institute for Clinical and Experimental Pathology Laboratory. Isolates were selected based on low *B dermatitidis* DNA probe values (<400,000 relative light units) and/or atypical morphology. Nine isolates were obtained from the first 2 institutions. The authors then searched for additional cases by reviewing human *emmonsia* isolates collected since 2008 at ARUP, a national reference lab at the University of Utah.

THE POWER OF A TWEET

The search was prompted by a tweet\(^3\) on Twitter showing an image of an *emmonsia* isolate cultured at ARUP (see tweet).
“This tweet led us to search the database of ARUP Laboratories in Utah, and we identified 2 additional cases that were confirmed with sequencing,” Dr. Schwartz recalled. “In the words of my co-author, Lynne Sigler, ‘Finding a case through Twitter opens up a whole new way of finding and identifying fungal pathogens.’”

The team confirmed the species identification for the collected isolates via DNA sequence analysis, assessing the morphological features of isolates by comparing them with the ex-type culture of *B helicus*, which they called UAMH 7101. The isolates studied were grown on potato dextrose agar at 30°C and 35°C and on cereal agar, oatmeal salts agar, and Takashio agar at 25°C or 30°C to assess colonial features and transition to yeast phase and sporulation, respectively. The investigators then compared the sequences to those found in their respective laboratories or in the NCBI GenBank, the latter of which includes sequences of 5 *Emmonsia* species isolates obtained in 2009 that have now been reclassified *B helicus*. Finally, they performed antifungal susceptibility testing on the mold phases of the isolates using either the Clinical and Laboratory Standards Institute (CLSI) M38-A2 broth macrodilution method or the CLSI M38-A2 broth microdilution method with Sensititre Custom Plates. They then analyzed epidemiological and clinical data for each of the isolates.

**FINDINGS**

In all, Dr. Schwartz and his colleagues identified isolates from 10 human and 5 veterinary cases of *B helicus* infection, all of which originated in the western regions of Canada and the United States. These isolates were most frequently cultured from blood and bronchoalveolar lavage in humans and from the lungs of the animal cases included in the study. They noted that the isolates remained “sterile in culture, producing neither conidia nor sexual spores in the mycelial phase.” However, the isolates frequently produced coiled hyphae. Their histopathological findings included pleomorphic, small or variably sized yeast-like cells, with single or multiple budding. These cells occasionally proliferated “to form short, branching, hyphal-like elements.” Within the sample population, the disease caused by *B helicus* carried a high fatality rate, although 6 of 7 of the human cases in the study were immunocompromised.

“We observed that the infection occurs primarily among immunocompromised hosts, and it is uncommon,” Dr. Schwartz said. “The threat posed by this fungus is relatively low. Although it is certainly underdiagnosed or misdiagnosed, reports of dimorphic fungal infections in the western parts of North America are rare. However, clinicians should be aware that dimorphic fungal infections can occur in patients who lack a history of residence in or travel to areas typically considered endemic.”

As a follow-up to their research, Dr. Schwartz added that he and his colleagues plan to reexamine local collections of fungi implicated in cases of blastomycosis in regions where *B helicus* is endemic and sample environmental sources for the fungus (eg, soils) in endemic areas to “identify the environmental reservoir.”

**NOTE TO CLINICIANS AND LABS**

Shaun Morris, MD, MPH, FRCP, FAAP, clinician-scientist, Division of Infectious Diseases, Hospital for Sick Children and associate professor, Department of Pediatrics, University of Toronto, Canada, who has treated patients with blastomycosis and written about it in several peer-reviewed journal articles on the infection and *B dermatitidis*, told *Contagion* that the findings of Schwartz et al are notable because of the differences between *B helicus* and the more well-known species of the fungus.

*“B dermatitidis is fairly well described and probably the most important of the dimorphic fungi,” said Dr. Morris, who was not part of the *B helicus* team. “But this is a newly recognized species, and it has some pretty significant differences from the species that are more understood, such as the geographic region where it’s found, the types of humans and animals it affects, how it presents, and, in the case of humans, the mortality associated with it.”*

Although Dr. Morris was quick to emphasize that the *B helicus* research still needs to be confirmed and expanded upon, through the analysis of more isolates, it raises some alarm bells because “blastomycosis is a notoriously late diagnosis even in highly endemic areas.”

Given the “new geography” of *B helicus*, the western United States and Canada, physicians and labs should be more vigilant for the new species going forward, particularly until more is learned about the fungi.

“Historically, at least, *B dermatitidis* has generally infected people with intact functioning immune systems,” he added. “However, in this study, 6 of the 7 humans were immunocompromised. These organisms exist in nature. In the case of *B helicus*, it seems, in the environment of small mammals. So the risk factors for infections caused by *B helicus* may be different as well, and that’s very significant.”

References are available at ContagionLive.com.
The burden of pediatric HIV infection in the United States has decreased in the recent years. The number of patients 19 years and younger at their HIV diagnosis declined from 4250 in 2011 to 3813 in 2016.1 Among children who received the diagnosis when they were younger than 13 years, the number of perinatal infections fell to below 100 in the United States in 2016.1 This drop may be attributed to efforts focused on the prevention of HIV transmission from mother to child. Examples of such efforts include universal prenatal HIV screening, combination antiretroviral therapies (ARTs) to maximally suppress the maternal viral load, elective cesarean delivery, provision of neonatal antiretroviral (ARV) prophylaxis, and neonatal replacement feeding.2

In the current era of ART, treatment options are more potent but have fewer toxicities and better adverse effect profiles. Lower pill burdens and dosing frequencies and more combination drug formulations, including single-tablet regimen (STR) options, provide multiple options to complement patients’ preferences and lifestyles. Specifically, for pediatric patients who have difficulty swallowing pills, the availability of chewable formulations, such as chewable raltegravir (Isentress), provides patients a better chance of improved adherence to achieve viral suppression and preservation of immune function.2

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Selecting an ARV regimen for pediatric patients living with HIV follows the same principles as treating adolescents and adults living with HIV. An ARV regimen for a treatment-naïve patient typically includes 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus another ARV agent, which can be either an integrase strand transfer inhibitor, a boosted protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor.3,4 Other considerations include the presence of comorbidities, such as hepatitis B or C virus infection; resistance testing results; and potential for drug–drug interactions.3,4 Special considerations for pediatric patients include the child’s age and weight when determining appropriate dosing requirements; the palatability of the drug formulations; most commonly an issue with liquid ARVs; and the potential for long-term toxicities.3

When selecting a regimen for pediatric patients living with HIV, “Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection,” which are updated regularly, should be consulted for the most up-to-date evidence-based recommendations.3 In May 2018, the guidelines were updated to increase the strength of the recommendations from moderate to strong to reflect new data that all children should receive ART, regardless of symptoms or CD4 count.

Baseline plasma viral load, CD4 count, resistance testing, complete blood count with differential, chemistries, lipid panel, urinalysis, and hepatitis B screening should be completed prior to ART initiation.3 Raltegravir plus 2 NRTIs is recommended for HIV treatment in infants at birth until age 6 years. Other recommended regimens for children aged at least 3 to 6 years included atazanavir (Reyataz)/ritonavir (Norvir) plus 2 NRTIs or darunavir (Prezista)/ritonavir twice daily plus 2 NRTIs. In addition to raltegravir plus 2 NRTIs, for children older than 14 days up until 3 years, the guidelines...
recommend lopinavir/ritonavir and 2 NRTIs. For infants after birth to <14 days, the guidelines recommend raltegravir in combination with 2 NRTIs or nevirapine (Viramune) plus 2 NRTIs. For children 6 years to 12 years, the guidelines recommend a regimen of 2 NRTIs plus atazanavir/ritonavir or dolutegravir (Tivicay). For adolescents older than 12 years, if they have a sexual maturity rating (SMR) of 4 or 5, they can be treated according to the adult and adolescent guidelines. In adolescents older than 12 years with an SMR of 1 to 3, 2 NRTIs plus atazanavir/ritonavir, dolutegravir, darunavir/ritonavir, or elvitegravir/cobicistat (Tybost) can be used (Figure).

Preferred dual-NRTI regimens differ between age groups. For children from birth to <3 months, zidovudine (Retrovir) plus lamivudine (Epivir) or emtricitabine (Emtriva) is recommended. Abacavir (Ziagen) or zidovudine plus lamivudine or emtricitabine is recommended for children 3 to <6 years. For children ≥6 years with an SMR of 1 to 3, abacavir plus lamivudine or emtricitabine or emtricitabine/tenofovir alafenamide (Descovy) is recommended. Finally, for adolescents ≥12 years with an SMR of 4 or 5, the guidelines recommend referring to the adult and adolescent guidelines.3-4

The guidelines recommend once-daily regimens and STRs whenever feasible, especially in the current era of simplified regimen options.3 The Table outlines the pediatric age and weight requirements for using all US Food and Drug Administration–approved STRs. For pediatric patients who struggle with adherence due to pill swallowing difficulties, alternative formulations should be considered. Many recommended ARVs are also available as liquids: abacavir, lamivudine, emtricitabine, zidovudine, nevirapine, lopinavir/ritonavir, darunavir, and ritonavir. A limitation to liquid formulations, however, is their palatability. Volume is also a concern for pediatric patients in higher weight groups who require higher doses, which results in larger volumes. Other formulations are available as highlighted in the guidelines.3

The guidelines have updated the ritonavir section to include information about a new pediatric oral powder formulation that can be administered in 100-mg increments. This formulation can only be used for doses of 100 mg or greater, which is recommended in children weighing at least 30 kg when used with darunavir or in children weighing at least 15 kg when used with atazanavir capsules. The guidelines prefer the oral powder formulation of ritonavir over the oral solution for children who have difficulty swallowing because the powder does not contain propylene glycol or ethanol, which can cause a range of central nervous system, respiratory, cardiac, renal, and gastrointestinal toxicities in children.5

Other alternative formulations include efavirenz (Sustiva) capsules, which can be opened and sprinkled onto 1 to 2 teaspoons of age-appropriate soft foods for children who are unable to swallow capsules or tablets. Atazanavir and tenofovir disoproxil fumarate are also available in an oral powder formulation that can be mixed with 1 tablespoon of food. Raltegravir is also formulated as granules for oral suspension, which is recommended to be mixed with 10 mL of water. What may be most useful in transitioning from alternative formulations to swallowing tablets are chewable raltegravir tablets. These can be used in children weighing at least 11 kg. For all formulations of ARVs, refer to Appendix A in the guidelines.3 The guidelines also recommend pill-swallowing training, as it has been shown to improve adherence at 6 months post training.6

In the current era of HIV ART, there are more formulations available for pediatric patients living with HIV. With new drug developments, therapies are easier to take with fewer toxicities. One formulation that was not discussed in the current update to the guidelines is efavirenz/lamivudine/tenofovir disoproxil fumarate (Symfi Lo), which contains a lower dose of efavirenz (400 mg). This formulation may be useful in patients who are CYP2B6 slow metabolizers but recommendations for use will be included with the next guideline update. With time, as STR formulations are being studied in pediatric patients, more options will become available that will help facilitate better adherence in pediatric patients living with HIV. Finally, when treating these patients, the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, which are updated 6 months post training,6 should be consulted. ▲

References are available at ContagionLive.com.
Hospital-acquired and ventilator-associated pneumonias (HAPs/VAPs) are common infections linked with significant morbidity and mortality, particularly when caused by multidrug-resistant gram-negative bacilli (MDR GNB) such as Pseudomonas aeruginosa, Acinetobacter baumannii, and carbapenem-resistant Enterobacterales. The increasing prevalence of pneumonia caused by these organisms, which often exhibit reduced susceptibility to β-lactam antibiotics, has led to a resurgence of the use of aminoglycoside or polymyxin therapies in certain applications. However, the utility of these systemic agents in pneumonia is limited by low lung concentrations and narrow or poorly understood therapeutic indices. These treatment barriers may ultimately contribute to inferior outcomes in critically ill patients with pneumonia. From a pharmacokinetic and pharmacodynamic perspective, aerosolized antibiotic formulations have several perceived advantages over conventional systemic therapy for treatment of MDR gram-negative pneumonia, but data remain limited. Still, aerosolized antibiotics are prescribed for nosocomial pneumonias in up to 67% of intensive care units worldwide, with tobramycin, amikacin, and colistin most frequently used.

BACKGROUND
Unlike in systemic administration, aerosolized antibiotics avoid the need for drug diffusion across the blood-alveolar barrier into the epithelial lining fluid, a process dependent on antibiotic physicochemical properties (eg, lipophilicity, molecular weight, protein binding) and patient-specific characteristics (eg, tissue permeability, renal function) that may complicate target-site penetration. Aminoglycosides and polymyxins have been found to poorly concentrate in lung tissue of humans and large animals due to compound hydrophilicity and/or poor lung tissue binding properties. Direct antibiotic administration through inhalation allows for higher parenchymal concentrations and maximal antibiotic exposures needed for pharmacokinetic/pharmacodynamic optimization, with limited systemic drug exposure and risk for toxicity. Aerosolization technique (eg, nebulization, metered or dry powder inhaler) and availability of inhalation powder formulations have also been shown to impact the efficiency of aerosolization.

Elevated minimum inhibitory concentrations (MICs) of MDR GNB and poor lung concentrations achieved by systemic aminoglycosides and polymyxins require aggressive dosing...
strategies to effectively treat severe pneumonia.5,6,9 Prolonged high-dose exposures of these antibiotics may ultimately potentiate the risks of toxicities; some literature suggests the prevalence of nephrotoxicity to be 43% to 58% with either antibiotic class.11,12 To avoid these issues related to systemic use, some clinicians have used aerosolized aminoglycosides and polymyxins as adjunctive treatment in MDR GNB pneumonia with some success.

CLINICAL DATA
The majority of published aerosolized antibiotic data in nosocomial pneumonia are limited by comparisons of heterogeneous antibiotic and dosing regimens, questionable pneumonia diagnostic criteria, nonstandard endpoint definitions, and small patient samples.10,13 Furthermore, many studies used variable aerosolization techniques and were not designed to assess differences in efficacy for patients receiving adjunct inhaled antibiotics. These concerns ultimately make study results difficult to extrapolate to the general population, although the theoretical benefits of inhaled antibiotic administration remain valid. Most studies to date have assessed aerosolized tobramycin or colistin, both available as powdered formulations for inhalation, as adjunct therapy to systemic therapy (ie, inhaled drug combined with the intravenous [IV] drug formulation), and typically in combination with a β-lactam, although a few trials describe an inhaled antibiotic as a single agent used in combination with another antibiotic class. Although some data suggest no difference in outcomes,10,14,13 a number of recent studies have found treatment success with aerosolized antibiotics in MDR gram-negative pneumonia.15-17

Tumbarello et al performed a matched retrospective analysis of patients receiving aerosolized colistin plus IV colistin (n = 104) to IV colistin alone (n = 104) in microbiologically confirmed MDR GNB VAP and found significant improvement in clinical cure at the end of therapy (P = .03) and decreased duration of mechanical ventilation (P = .001) in the adjunct aerosolized colistin group.15 Similarly, a retrospective study performed by Doshi et al found significant improvement in clinical cure at the end of therapy (P = .033) when adding aerosolized colistin to IV colistin (n = 35) compared with IV colistin alone (n = 33) for MDR GNB pneumonia with high-quality cultures.16

Hassan and colleagues performed a randomized trial comparing the efficacy of nebulized amikacin with piperacillin/tazobactam (n = 86) to IV amikacin with piperacillin/tazobactam (n = 47) in post–cardiac surgery patients with HAP or VAP caused by microbiologically confirmed MDR GNB.17 Efficacy was defined as clinical cure evaluated on day 7 of amikacin initiation: normalized body temperature, total leukocyte count less than 10,000/mL, absence of purulent secretions, and improvement of radiological findings, in addition to PaO2/FiO2 greater than 250 in patients with VAP. Clinical cure was significantly higher in the nebulized group (P = .002), and this association was retained in a stratified analysis by isolated organism. Patients receiving IV amikacin also developed acute kidney injury more frequently than the nebulized group (P = .0232). Although these data are interesting, another recent randomized trial by Kollef et al found no differences (P = .70) in the clinical pulmonary infection score for patients with GNB VAP receiving an amikacin/fosfomycin inhalation system (n = 71) in addition to standard antibiotics compared with a control group (n = 72).14

SAFETY AND ADVERSE EFFECTS
Aerosolized antibiotics are generally well tolerated and display a good safety profile, with the most common adverse effects identified as bronchospasm and wheezing.10,15 The limited systemic antibiotic exposure achieved with aerosolization has resulted in no data identifying associations with nephrotoxicity in humans. Hypotension and fatal respiratory distress have been documented in patient cases where parenteral powder formulations were used for inhalation and thus should be avoided.16,17 Prior to the development of inhalation formulations, antibiotics were extemporaneously compounded from IV powder or solution and subsequently aerosolized, which was found to induce bronchospasm and pneumonitis potentially related to the presence of preservatives in the IV powder or solution.20 Inhaled antibiotic formulations do not contain preservatives.13

FUTURE DIRECTIONS AND CONCLUSIONS
The optimal patient population for aerosolized antibiotic therapy remains controversial. The 2016 Infectious Diseases Society of America and the American Thoracic Society guidelines on the management of HAP and VAP provide narrow recommendations for aerosolized antibiotic use in patients with documented MDR gram-negative infections susceptible to only aminoglycosides and colistin (weak recommendation, low-quality evidence) and in combination with systemic therapy.21 Although the use of concomitant systemic aminoglycoside or colistin therapy may negate the main advantages of aerosolized antibiotics (ie, high lung drug exposure and minimal risk of toxicity), the low systemic antibiotic concentrations achieved after inhalation suggest use as monotherapy is likely not appropriate in critically ill patients with MDR GNB pneumonia in the case of necessitating extrapulmonary foci.

Controversy also remains in regard to the utility of, or warranted duration of, combination therapy in MDR GNB infections.1 However, in select populations with HAP/VAP (eg, critically ill patients, high institutional prevalence of MDR GNB), it would seem reasonable to utilize at least 1 dose of systemic antibiotics in combination with inhaled formulations until respiratory culture susceptibilities have resulted, as aminoglycoside- or colistin-associated nephrotoxicity develops after roughly 6 days of therapy.11,12

The lack of therapeutic options for lower respiratory tract infections caused by emerging bacterial pathogens represents a major threat to humanity.2 Fortunately, the landscape for new antibiotics targeted toward MDR GNB is promising.22 New data surrounding recently developed antibiotics suggest they achieve adequate pulmonary concentrations and are effective compared with conventional regimens.23,24 As more efficacious and less toxic antibiotics are developed, the role for aminoglycoside and polymyxin therapies, including aerosolized formulations, may be regulated for use in other populations, such as patients with cystic fibrosis. ▲

References are available at ContagionLive.com.
Management of Gram-Positive Multidrug-Resistant Infections: The Role of Long-Acting Lipoglycopeptides

According to Sandy J. Estrada-Lopez, PharmD, the long-acting lipoglycopeptides oritavancin and dalbavancin have been game-changing for the treatment of MRSA skin and soft tissue infections because they provide an option for patients to receive intravenous (IV) antibiotics as an outpatient or after early discharge from the hospital. She added that using these antibiotics in the outpatient setting, most commonly the ED, allows the patient and health care system to avoid the high costs associated with hospitalization.

“The target is that patient who needs an IV antibiotic either due to the severity of the infection, having failed previous oral antibiotics, [having] resistance to oral antibiotics, or perhaps where there’s significant concerns for adherence,” she said.

Dr. Estrada-Lopez also pointed out that past attempts to administer daily doses of a shorter-acting antibiotic, such as vancomycin or daptomycin, in the outpatient setting in her health care system often led to greater financial and societal costs when the patient stopped showing up for infusions and had to be readmitted to the hospital.

“There’s a big cost associated with that [choice of treatment], if they get readmitted a week later, and now maybe...
we don’t want to give them that antibiotic again when moving further down the line,” said Estrada-Lopez.

Debra Goff, PharmD, FCCP, also pointed out that the single-dose long-acting antibiotics are useful for IV drug users because they do not require insertion of a peripherally inserted central catheter (PICC) line, which they could use for illicit purposes. However, she cautioned that assessing the individual and their home scenario is important for deciding whether to use this single-dose strategy. “Sometimes it’s almost an emotional decision of how you want to approach that IV drug user,” said Dr. Goff. “It’s very complex, [and] there are pros and cons of each decision.”

Dr. Estrada-Lopez also pointed out that the logistical convenience of a single dose could be useful for elderly patients who may travel frequently. “If they are saying, ‘I’m getting on a plane in 3 days, I can’t come for these infusions, I definitely don’t want to be in the hospital,’” we want to treat them with something that’s one-and-done, so to speak,” she said.

**NUANCING LIPOGLYCOPETIDE THERAPY**

Although long-acting lipoglycopeptides are convenient and may reduce the need for hospital admission in selected patients, Dr. Estrada-Lopez cautioned that they could be problematic for complex cases or those in whom bacteremia is missed.

“Let’s say that perhaps the patient is bacteremic and we didn’t realize that because they came into the ED. They looked like they just had an abscess, we drained it, but it was significant,” she said. “We felt like they needed antibiotics, but on day 3, their culture comes back positive and we can’t find the patient. They still have 7 days of antibiotics on board but maybe now we’re thinking they need 14 days or we need repeat blood cultures and we don’t have that patient in front of us.”

She also pointed out that even if they are able to get the patient to return, the strategy for additional treatment is unclear. “Would we consider that antibiotic active for 7 days and then give another dose, which would be off label, and switch to another antibiotic? At what point would you add another gram-positive agent that perhaps has a similar mechanism of action when this one is still active? There’s a lot of uncharted territory because we don’t have the clinical work to tell us.”

She added that providers should inform patients that it may take 48 to 72 hours to start seeing improvements and at least 7 days to see total improvement with long-acting lipoglycopeptides. “Just because you’re only going to get 1 dose does not mean you’re going to wake up tomorrow and [see a complete resolution of symptoms],” she said.

Dr. Shorr pointed out that providers also need to consider whether the long-acting glycopeptides are suitable for a given patient’s situation. “The novel long-acting glycopeptides are not better than the currently available therapies,” he said. “They have a different profile that may or may not offer a benefit to your patient or institution, but they’re not better in vitro [or] in clinical trials. They’re just different, and you have to decide if that distinction is a difference that matters to you or not.”

**CONSIDERING THE COSTS OF LIPOGLYCOPETIDE THERAPY**

Judicious patient selection for lipoglycopeptide therapy is especially important given their exponentially higher costs relative to other antibiotics. “You have to be fiscally responsible in how you decide to use them,” said Dr. Goff. “They can be the best spent money if they prevent a hospital admission or they could be a total waste of money.”

The panelists agreed that avoiding hospital admission and readmission within 30 days, as well as guaranteeing compliance, are the primary factors in cost savings. “If you can show that [the patient] didn’t get readmitted at 30 days because they either didn’t overdose on [illicit drugs] or they didn’t get a secondary complication from the PICC line, that’s cash in someone’s pocket at the hospital administrator level,” said Dr. Shorr.

Although estimating the costs of noncompliance is complicated, Dr. Estrada-Lopez stated that the basic cost is equivalent to that of a hospital admission that would have otherwise been unnecessary. Similarly, Dr. Goff noted that “the most expensive antibiotic is the one that doesn’t work,” and the costs from a lack of response can be estimated by the cost of the increase in length of hospital stay. However, she also pointed out that the associated societal costs are substantial and difficult to quantify.

“If you’re working for a living and you’re sitting in the hospital and you have children at home, [the costs to the patient start] escalating and snowballing,” she said.

The panelists concluded that the compartmentalization of the different hospital budgets remains a major challenge for justifying the overall cost-effectiveness of using long-acting lipoglycopeptides. “When we talk about antibiotics, it’s the pharmacy budget that’s getting hit for using more expensive antibiotics, and it’s the overall hospital budget that benefits from not having [an] extended length of stay,” said Dr. Estrada-Lopez.

Dr. Shorr added that breaking down this compartmentalization of the different budgets may introduce an opportunity to reassess the institutional protocols for treating these infections. “But you have to have a well-thought-out argument that shows it from a systems level [and present it] to the right person in the C-suite.”

References are available at ContagionLive.com.
A CAH is a specific designation given by the Centers for Medicare & Medicaid Services (CMS) aimed at "reducing the financial vulnerability of rural hospitals and improving access to health care by keeping essential services in rural communities." CAHs are small and often have fewer than 25 inpatient beds. To meet CMS guidelines, these hospitals must be farther than a 35-mile drive from another hospital or more than a 15-mile drive from another hospital in a land area that has mountainous terrain or secondary roads. These hospitals provide vital health care to small communities that struggle to gain access to hospitals.

The role and presence of infection prevention and control within CAHs, like long-term health care facilities, has become a growing topic of concern. How do such small hospitals, ensure adequate infection prevention staffing or monitoring?

Bearing these concerns, a new study from investigators in Nebraska, and presented at APIC 2018, sought to identify the role of infection prevention in CAHs and potential gaps in their practices. Coordinated by public health officials, the investigators reviewed infection prevention practices at 36 Nebraska hospitals utilizing assessment tools from the US Centers for Disease Control and Prevention (CDC) to identify gaps in processes.

According to the study results, CAHs lacked competency-based training programs and the ability to perform audits and provide feedback regarding infection prevention process failures. The hospitals in the study participated on a voluntary basis; however, they were able to receive visits from a team of certified IPs and public health officials to both audit their processes and provide summaries of their findings and recommendations for fixing such failures.

The most significant gaps were found to be in injection safety, central-line–associated bloodstream infection prevention, and catheter-associated urinary tract infection prevention. Although these were the hotspots for infection prevention gaps, the investigators ultimately found failures across the full domain of infection control practices.

Contagion® spoke with the lead study author Margaret Drake, MT (ASCP), CIC, on the team’s findings to learn if they found issues in IP knowledge or training (ie, identifying HAIs, surveillance, etc) or establishing infection prevention programs and the role of administrative support. Ms. Drake noted that there weren’t “issues with identifying HAIs, but instead realizing or understanding how to do a risk assessment to set goals. Administrative support is there, but IPs need to know what and how to ask for it.”

She emphasized that IPs need to be “given the time and training to focus on infection control duties.” When asked what immediate infection prevention support should be given to these hospitals if resources are limited, Ms. Drake stated that “education and training” would be the most valuable.

Following the study work, the investigators developed a resource website where IPs could find valuable training information. They also underscored the importance of having a trained IP at the CAH and ensuring that the IP has the time to focus on activities such as rounding and promoting CDC-based practices. The study findings underscored the importance of adequate IP staffing and training, and that even the most rural hospitals benefit from the presence of an experienced IP.

Staffing issues are problematic across the country in all types of hospital systems. The importance of having IPs within health care and ensuring they have access to training and the ability to focus on infection control activities, not just reporting tied to CMS reimbursement, is critical. IPs need time for activities such as education, rounding, antibiotic stewardship, and more.

This study's results support the notion that hospitals should be ensuring proper staffing and support for infection prevention programs and that significant gaps exist across CAHs. In the areas where CAHs are the only health care resource patients may access, it is vital that infection prevention processes be supported and followed. Ensuring adequate IP staffing and time is imperative for patient and health care worker safety. ▲

References are available at ContagionLive.com.
Marketers, Erasers in Patient Rooms May Harbor Dangerous Bacteria

BY MICHAELA FLEMING

(continued from cover)

prevention specialists found that although whiteboards were on the cleaning checklist, markers and erasers were not included. The investigators wanted to know if the omission of these items meant they were not being cleaned.

“Markers and erasers are obviously high-touch, yet they were not included on the checklist for routine cleaning, which was surprising. We hypothesized that the concept of ‘out of sight, out of mind’ may come into play. If the visual reminder is absent from the checklist, the cleaning may not occur,” Ericka Kalp, PhD, MPH, CIC, FAPIC, lead study author and director of epidemiology and infection prevention at Summit Health, Chambersburg, Pennsylvania, told Contagion®.

In an inspection of 55 rooms that had been cleaned and set up for new patients, 39 markers and 52 erasers were tested for the presence of adenosine triphosphate (ATP), which is an indicator for the presence of biological residue. All of the markers tested positive for ATP, although only 2 erasers tested positive. Conversely, 95% of the items on the checklist tested negative for ATP.

“Although they are just small writing instruments, both the markers and erasers tested at 40 times the threshold [for ATP],” said Dr. Kalp in a statement. “Because these are a main communication tool for nurses, cleaning them properly is of great significance to improving infection prevention.”

The testing was conducted in the presence of environmental services staff. If an object tested positive for ATP, the infection preventionist conducting the test demonstrated how to properly clean the object, prior to retesting.

“Environmental cleaning is essential to preventing the spread of infection,” said 2018 APIC President Janet Haas, PhD, RN, CIC, FSHEA, FAPIC, in a statement. "This study emphasizes the importance of not only using a checklist as a reminder of what needs to be cleaned, but also making sure the list includes all frequently touched items.”

Since conducting this study, markers and erasers have been added to the terminal cleaning checklist. ▲

More Information Comes to Light on Burkholderia cepacia Outbreak at Johns Hopkins Health System

BY SASKIA V. POPESCU, MPH, MA, CIC

The presence of Burkholderia cepacia is growing in the United States. These bacteria are a common cause of infections in patients with compromised immune systems or certain medical conditions such as cystic fibrosis (CF). Typically soil and water bacteria, B cepacia commonly carry resistance to several antibiotics and have an alarming capacity to contaminate medical supplies and medicines. Within the past 15 years, there have been outbreak clusters associated with contaminated mouthwash, nasal spray, and more.1 Contaminated medical supplies and medicines have been associated with health care–associated infections and pose a serious health risk for patients in intensive care units and those who are immunocompromised.

A presentation at the 45th Annual Conference of the Association for Professionals in Infection Control and Epidemiology (APIC) underscored the challenges of identifying sources for outbreaks, especially in patients without weakened immune systems or CF. The presenters detailed the plight of the infection prevention team from the Johns Hopkins Health System and their unique experience identifying and investigating a B cepacia outbreak among patients in their pediatric intensive care unit (PICU). The affected patients in this case did not have CF.

The Johns Hopkins team noted that in May 2017, 3 infants in the PICU tested positive for B cepacia. The positive isolates were from tracheal aspirates and blood. After the identification, the patients were placed in contact isolation, as B cepacia can spread among susceptible individuals. All 3 infants were on mechanical ventilation, and so the team started their investigation by looking at their respiratory medications and equipment.

Pharmacy personnel confirmed that the hospital was not utilizing any of the liquid docusate that was involved in the 2016 recall.2 By July 2017, 4 additional cases were identified and the infection prevention team began working with the US Centers for Disease Control and Prevention (CDC) and other medical facilities to identify additional cases and potential sources. During the investigation, the team found that all cases had received 1 medication with the same National Drug Code of the previously implicated liquid docusate. This medication was sent to the CDC for additional testing. By August 2017, the manufacturer had issued a voluntary recall of liquid docusate and the CDC laboratory testing had confirmed it to be the source of the B cepacia. Interestingly, the strain implicated in this outbreak was different than that of the 2016 B cepacia outbreak.

Although this outbreak will likely not be the last involving B cepacia in medical supplies, it gives insight into the importance of considering medications as a source of infection. B cepacia are hardy organisms that can easily live on surfaces and in water, and they are often resistant to preservatives, which makes them particularly worrisome. The presentation underscored the importance of utilizing and working with outside sources, like the CDC and other health care facilities, to help identify potential sources. Health care can easily be siloed, and this study is a good reminder that no matter what part of patient care we are responsible for, the universal goal is patient safety, and this can be better achieved through collaboration. ▲

References are available at ContagionLive.com.
ASM Microbe 2018

Plasmids Found to Confer Antibiotic Resistance Among Unrelated Bacteria at US Hospital

BY CONTAGION® EDITORIAL STAFF

The results of a new study have revealed that carbapenem resistance conferred by plasmids can be transferred among unrelated bacteria in the health care setting, underscoring the need for more granular laboratory testing methods in public health institutions to investigate outbreaks of antibiotic-resistant pathogens. The study was presented at the 2018 ASM Microbe meeting in Atlanta, Georgia, on June 10, 2018.

According to the US Centers for Disease Control and Prevention (CDC), carbapenem-resistant Enterobacteriaceae (CRE) are responsible for more than 9000 health care-associated infections and 600 deaths each year in the United States, making them an urgent public health threat.

In 2017, a team of investigators, including Richard Stanton, PhD, a health scientist in the CDC’s Division of Healthcare Quality Promotion, investigated an outbreak of CRE in 18 patients at a primary care hospital in Kentucky using whole-genome sequencing as a means of identifying the carbapenemases and their potential source. The team analyzed 20 carbapenemase-producing isolates (18 Klebsiella pneumoniae, 2 Escherichia coli) and found that 9 of the isolates had 1 β-lactamase (bla) gene variant (blaKPC-2), 8 had blaKPC-3, and 1 had blaNDM1.

Further analysis revealed that the K pneumoniae were not clonal, varying between 0 and <1100 SNPs. Indeed, they had 4 different sequence types. The E coli isolates were determined to be related. According to the study abstract, “Long-read sequencing determined that the blaKPC-2 and blaKPC-3 genes were harbored on 2 distinct plasmids, sharing only 48% homology. The blaKPC-2 gene was found on a 128kb plasmid with IncFIB and IncFII replicons that also included a blaTEM-1A gene. The plasmid harboring the blaKPC-3 gene was 164kb, with IncFIA and IncFIB replicons, as well as blaoXA-9, blaTEM-1A, and 6 additional antimicrobial resistance genes.”

Perhaps most alarming is that the investigators found that homologous sequences to 164kb were “found in K pneumoniae isolates from 4 different STs (including ST258) and both of the E coli, suggesting horizontal transfer between unrelated bacteria.

Speaking about these results in a news release, Dr. Stanton is quoted as saying, “This outbreak shows us how drug resistance genes can be shared among other unrelated bacteria co-existing in a patient’s microbial community or in the environment.”

This finding may suggest that infection control and detection efforts at health care institutions may want to look for multiple strains in order to quell outbreaks. Typical outbreak response efforts focus on 1 strain of the bacteria. Because of the propensity for these bacteria to be found in the environment as well, infection control efforts should be shored up to focus on environmental areas such as sinks and drains where plasmid sharing may occur.

(continued from cover)

One country that is taking colistin usage in livestock around local villages into account is South Africa. As Contagion® previously reported on its website,1 researchers and public health officials in the country created the South Africa Colistin Working Group in 2016 as a direct response to the identification of MCR-1 in E coli in poultry and, subsequently, some patients in South Africa. To stave off the spread of further resistance, the group recommended interventions such as preventing the compounding of medicines containing antibiotics and colistin for food-producing animals and phasing out the use of all antibiotics for growth promotion in food-producing animals. The South African Veterinary Council took their recommendations a step further, issuing a letter to all veterinarians stating, “It is recommended that colistin not be used in food-producing animals at all unless the veterinarian can justify its use at the hand of a sensitivity test and as a very last resort to treat an animal. Any conduct to the contrary would be regarded by Council as unprofessional conduct.”

An aspect of antimicrobial resistance that is continually underrepresented in research is the study of the presence of these genes in the environment. The South Africa Colistin Working Group found antibiotic-resistant bacteria in water from 3 drinking water production facilities they tested, highlighting the need to establish an antimicrobial monitoring and evaluation program of the environment to include colistin.

As more colistin-resistant bacteria are found in humans and the environment, a OneHealth approach in which all health professionals are involved—including those who ensure the health of humans, animals, and the environment—may be needed to halt their growth.

References are available at ContagionLive.com.

ASM Microbe 2018

Colistin-Resistant E coli Found in Most Residents of Vietnam Village

BY DANIELLE MROZ, MA

1 bacterium to another, creating the potential for colistin-resistant forms of the most egregious of bacteria, carbapenem-resistant Enterobacteriaceae (CRE). The MCR gene was found to be responsible for the resistance in Nguyen Xa as well.

For the study, the team of investigators collected stool samples from 98 healthy participants from 36 households in the rural village between November 2017 and February 2018 to test for colistin-resistant E coli. Of the residents tested, 71.4% were found to be harboring the resistant bacteria, all of which were identified as E coli. Furthermore, 69 of 70 “colistin-resistant E coli isolates possessed either MCR-1 and/or MCR-3 genes,” according to a news release on the research.

Yoshimasa Yamamoto, PhD, Osaka University, Japan, presenting author on the study, explained in the release that “these results revealed the dissemination of MDR colistin-resistant E coli, harboring the colistin-resistant mobile gene MCR among commensal bacteria of [the] residents.”

Further information gleaned from the study included minimum inhibitory concentrations of MCR-positive isolates at 28 µg/ml. No clonal expansion of any of the strains was found using pulse-field gel electrophoresis, and the rate of multidrug resistance of the colistin-resistant E coli isolates was found to be 91.4%. These results indicate that the isolates have resistance to “at least 1 antibiotic drug in 3 or more antibiotic classes,” according to the statement. Furthermore, investigators are concerned that harboring mobile resistance genes opens these residents up to acquiring intractable infections.

“This requires urgent public health attention,” Dr. Yamamoto stated. “The susceptibility and exposure of local residents living in the areas of frequent usage of colistin in livestock to the colistin-resistant bacteria remains to be studied [in most areas].”
ASM Microbe 2018

First ‘Triple Threat’ Strain of K pneumoniae Found in the US

BY BRIAN HOYLE, PHD

(continued from cover)

who presented the findings at the 2018 ASM Microbe Meeting and spoke with Contagion®.

The isolate that was the source of an outbreak in 2017 at a hospital in Hangzhou, China, killed 5 individuals despite the aggressive use of antibiotics. The isolate found by the Emory University investigators can withstand the polymyxin antibiotics. The isolate found by the Emory University investigators can withstand the polymyxin antibiotics, which is used as a last resort to thwart hospital-acquired infections in the era of multidrug resistance.

The investigators were able to show that the isolate was heteroresistant to colistin. Heteroresistance is a phenomenon where only a small number of cells in the total population possess the resistance, which makes them hard to detect. But given the right selection pressure—in this case, the use of colistin—the small number of cells can burgeon into an infection.

“K pneumoniae may be inching toward prevalence in an already very drug-resistant background of K pneumoniae,” speculates Ms. Wozniak. “So, with time, what has transpired in China is conceivable here.”

Adding to the concern, the results of experiments in mice conducted by the Emory University researchers indicate that colistin heteroresistance could be setting the stage for the failure of antibiotic treatment when the infection is finally recognized.

Ms. Wozniak was part of the team that examined 265 isolates of carbapenem-resistant K pneumoniae collected by the US Centers for Disease Control and Prevention as part of its Emerging Infections Program’s Multi-site Gram-negative Surveillance Initiative. Carbapenem is one of the last-resort antibiotics. If it proves ineffective, few treatment options are left.

The detection strategy was decidedly low tech, but effective. By touching an inoculating loop to a colony and withdrawing the loop, hypermucoviscous colonies can be revealed, much like the thread of a triple-cheese pizza as a slice is retrieved, according to the investigators. “All the work is done in a fume hood since the capsule can be up to a foot long,” said Ms. Wozniak.

More in-depth analyses of the isolate detected by this “string test” revealed it to be markedly more virulent in mice than its K pneumonia brethren. Whole-genome sequencing ferreted out several antibiotic-resistant genes, including a new arrangement of virulence genes that differ from the K pneumoniae isolates from Asian countries. A key to the virulence appears to be the expression of genes that control the ability of the bacteria to acquire iron. This capability is very important in governing the severity of infection. The isolate also contains an armada of genes that, when expressed, bestow resistance to silver, copper, β-lactamases, fluoroquinolones, and aminoglycoside antibiotics.

The antibiotic resistance of the isolate is broad and includes amikacin, ampicillin/sulbactam, aztreonam, cefazolin, cefepime, cefazidime, ceftriaxone, gentamicin, ertapenem, levofloxacin, meropenem, piperacillin/tazobactam, tetracycline, tigecycline, tobramycin, nitrofurantoin, and trimethoprim/sulfamethoxazole.

“Taken together, our research supports the conclusion that the emergence of hypermucoviscous, carbapenem-resistant K pneumoniae, could be a concern that necessitates further study and surveillance,” the investigators wrote in the poster. ▲

ASM Microbe 2018

Antifungal Proves Potent Against New Strains of Candida and Aspergillus

BY MICHAELA FLEMING

Data on SCYNEXIS’ antifungal candidate, SCY-078, which is currently in phase 2 trials, revealed that the antifungal remains active against organisms that are resistant to caspofungin (CAS) and it demonstrated “a profound effect on cellular morphology in CAS-resistant organisms, which may be indicative of a difference in target engagement from the echinocandins,” according to a statement on the research.

The results were presented at the 2018 ASM Microbe Meeting in Atlanta, Georgia.

SCY-078 is the first representative of a novel oral and intravenous (IV) triterpenoid antifungal family and has shown activity against Aspergillus and Candida pathogens. In addition to being a potential new treatment option for multiple fungal infections including vulvovaginal candidiasis (VVC), invasive candidiasis (IC), and invasive aspergillosis (IA), the antifungal may provide benefits for prophylaxis use and the treatment of chronic or refractory fungal infections.

“SCY-078 would be the only class of antifungals, other than the azoles, with an oral formulation. This is a critical feature, because currently patients undergoing treatment for invasive fungal infections receive that treatment for 14 to 82 days,” David Angulo, MD, chief medical officer of SCYNEXIS explained to Contagion®. “Given the high and growing number of pathogens resistant to theazole class, there are currently patients who must return to the hospital each day to get IV therapy.”

SCY-078 inhibits the synthesis of β-(1,3)-β-D-glucan, a critical component of the fungal cell wall, thereby compromising its ability to survive. “The cell wall of fungi is a unique target not encountered in mammalian cells, which provides for the good safety profile of SCY-078 and other glucan synthase inhibitors,” as it limits the risk for an “off-target” effect such as human cell toxicity, according to Dr. Angulo.

In a poster presentation at ASM Microbe, representatives from SCYNEXIS explained that SCY-078 was found to be synergistic in vitro against many Aspergillus spp when used in combination with isavuconazole.

The drug’s mechanism of action allows for retention of activity against azole- and polypene-resistant strains, and has the potential for a more favorable safety profile, a lower risk for drug-drug interactions compared with azoles, enhanced activity at acidic vaginal pH, and synergistic antifungal activity in combination with azoles and polyenes, which is critical for the treatment of IA.

The US Food and Drug Administration has granted qualified infectious disease product and Fast Track designations for the formulations of SCY-078 for the indications of IC, IA, and VVC, and an orphan drug designation was given for the IC and IA indications. ▲
Biodefense World Summit 2018
Better Mass Casualty Management Through Radiation Biodosimetry

BY SASKIA V. POPESCU, MPH, MA, CIC

(continued from cover)

help physician estimate how much radiation exposure a patient has experienced. Radiation biodosimetry diagnostics measure changes in biological markers that include cytogenetic assays like the dicentric chromosome assay.

Research into medical countermeasures for chemical, biological, radiological, and nuclear (CBRN) attacks has increased since the Project BioShield Act of 2004, which supports the Biomedical Advanced Research and Development Authority and the NIH to work with the Public Health Emergency Medical Countermeasures Enterprise to develop and procure medical countermeasures for radiation exposure. The radiation biodosimetry test measures changes in biological markers and works to move beyond the current methods (cytogenetic assays, lymphocyte depletion kinetics, etc) toward proteomic, genomic, metabolomic, and transcriptomic diagnostics.

Although the scenarios in which the radiation biodosimetry tests would need to be used seem unlikely, in the case of a nuclear radiological event, testing a large group of people is exceedingly difficult. Ms. Sproull and Dr. Camphausen discussed an example of an incident in Goiania, Brazil, in 1987, in which a radiological incident required testing 125,000 individuals. Of those, 250 were contaminated, 46 received medical countermeasures, and 14 developed acute radiation syndrome. The lack of point-of-care (POC) biodosimetry diagnostic tests and limited testing in a mass triage situation makes medical response efforts more stressful and challenging. Their work focuses on developing prediction models and identifying new proteomic biomarkers of radiation exposure that could be utilized between 24 and 72 hours post exposure and possibly extended to 1 to 3 weeks.

NUCLEAR POWER IN THE UNITED STATES

Nuclear power is still being used within the United States. There are 61 commercially operating nuclear power plants with 99 nuclear reactors across 30 states. Imagine an incident like the second worst nuclear accident in the history of nuclear power, that at Fukushima, Japan, in 2011—which is considered the 99 nuclear reactors across 30 states. Imagine an incident like the second worst nuclear accident in the history of nuclear power, that at Fukushima, Japan, in 2011—which is considered the second worst nuclear accident in the history of nuclear power, when over 100,000 residents were forced to leave their homes and the government established an 18-mile no-fly zone around the area—happening in the United States.

Thankfully, there have been no deaths or incidents of radiation sickness from that nuclear accident, but what if this happened in the United States and medical providers needed to establish a radiation exposure protocol quickly and efficiently? Do you think that emergency departments in US hospitals would have the capacity to perform diagnostics to establish exposure? Even if the answer is yes, it’s doubtful that it would be possible in large volumes and to also determine just how much radiation the patient had been exposed to. Fundamentally, the gaps in preparedness are not just about how ready we are to respond to an event, but also whether we have the diagnostic skills to manage it. Ms. Sproull’s and Dr. Camphausen’s work seeks to close these gaps. Knowing if a patient has been exposed to radiation is one piece of the puzzle, and radiation dosimetry answers that, providing critical information regarding a patient’s degree of radiation exposure.

Even if you think radiological events are unlikely, here is a gentle reminder. On July 3, a drone decked out to resemble Superman crashed into a French nuclear plant to highlight security failures around the facility. Although the drone was intentionally crashed by an environmental group, such an incident highlights that accidents and failures are an unfortunate reality. Attention regarding advancing diagnostics typically focuses on their capabilities during an infectious disease outbreak, which is important, but it’s critical that medical management of mass exposures or casualties extends to all CBRN avenues. This work on radiation biodosimetry is a clear example of our efforts to close these gaps, but it is critical that medical providers, whether they are in a large hospital system or critical-access hospital, have knowledge of these advancements and access to them.

I was fortunate to chat with Ms. Sproull about her research, its application to medical providers, and why we would be having these conversations during health care preparedness exercises. She noted that, “The most critical gap in emergency preparedness and response for medical management of radiological/nuclear events is the lack of a screening tool to determine whether a radiation exposure has occurred. It is expected that following a radiological/nuclear event, a large number of the uninjured population or ‘worried well’ will self-mobilize and overwhelm triage systems wanting to know if they have received radiation exposure. Current efforts in research and late-stage development of new POC radiation biodosimetry diagnostics are aimed at meeting this critical need. Biodosimetry diagnostics are arguably the most critical countermeasure for radiation exposure as they are needed, firstly, to confirm that an exposure has occurred and, secondly, to estimate the severity of the radiation exposure and which organ systems will be affected.”

Although there’s more work to be done, the expression levels of radiation in their work reveal a greater need for diagnostic methods to have a wider range of expression values for dose prediction. Further studies will look to selected biomarkers such as the FMS-like tyrosine kinase 3 ligand, Pentraxin 3, and Matrix metallopeptidase 9, but the investigators already found that a single Fit3 ligand biomass was most efficient at the prediction of a dose at 24 hours post body irradiation. Ms. Sproull further noted, “Future operational challenges for POC biodosimetry diagnostics include translating these biological assays from animal models to application in a more heterogeneous human population. Development of the technology for use under field conditions by first responders and their integration into existing triage systems are some of the final hurdles that are being addressed to make this diagnostic fully deployable.”

Their research will continue to establish such relevant biomarkers for radiation biodosimetry and how testing can be improved for those on the ground during an event.

References are available at ContagionLive.com.

* Editor’s note: Mary Sproull’s statements are her personal opinion and not on behalf of the National Institutes of Health.
(continued from cover)

Hopkins University’s Applied Physics Lab, raised a question among many of us in health care have been asking: How can we improve the diagnosis of an infectious disease through early detection? Current diagnostics pose a problem as they only diagnose a disease after symptoms have begun or are near the invasive stage. To circumvent this, Dr. Young is working to reduce the delay between exposure, infection, and diagnosis by focusing on far-forward diagnostics, which would diagnose a potential infection before symptoms occur.

Rapid detection would be a game-changer for outbreak response. To explain this, Dr. Young highlighted the limited availability of diagnostics—particularly in military settings or for a rural outbreak response—when diagnostics tend to become available and utilized later in outbreak response and in designated care centers, instead of at the time when they are most immediately needed, at the beginning.

Furthermore, although we have been fortunate not to experience a large-scale biological weapons attack on US soil, the concern for one underscores the benefit of far-forward testing, which would allow medical providers and public health officials to get a head start on response measures before mass fear and anxiety sets in, and would translate to more improved hospital response measures, such as more efficient staffing, isolation practices, medical management, etc. Additionally, identifying patients who were exposed by using far-forward tests would allow for a faster approach to treatment and isolation should symptoms occur. Infectious disease response, both in medical management and infection control, in many ways could then become proactive. Only those patients who are truly infected would be evaluated for admission and monitoring, instead of potentially exposing and quarantining a large number of individuals who may have been exposed. A real-world example of when this would have been helpful was during the SARS outbreak in Toronto, Canada, in 2003, when the city implemented large-scale quarantine efforts to manage the individuals who had been exposed. Such practices have mixed efficacy and result in significant emotional stress and financial burden to those quarantined. If far-forward diagnostics were available at that time, the panic may have been avoided.

Unfortunately, a far-forward molecular diagnostic instrument has not been created yet, and there are still many hurdles to overcome before one is developed. In his presentations, Dr. Young pointed to several early exposure markers that are promising for immunoassay detection, such as the viral glycoprotein GPI in Lassa fever virus and the dimeric glycoprotein in Ebola. Both pointed to several early exposure markers that are promising for immunoassay detection, such as the viral glycoprotein GPI in Lassa fever virus and the dimeric glycoprotein in Ebola. Both indicated that there might be a point during the early stages of infection that viral glycoproteins can be detected before the whole virions are rampant in the bloodstream. These markers would give medical providers a window of opportunity during the early stage of infection to provide earlier treatment and move patients into isolation. The exploitation of this window could truly make a difference in future outbreaks or in the event of a bioterrorism attack.

The potential for future tests to identify an exposure before a full-blown infection is exciting, but what about our current tests? Moreover, what about the use of POC testing during an outbreak or during a public-health crisis, such as a biological attack? In their presentation, “Application of Point-of-Care Testing for Pathogen Detection and Patient Management,” Kent Lewandrowski, MD, and Elizabeth Lee-Lewandrowski, PhD, MPH, from Harvard Medical School and Massachusetts General Hospital, addressed this very issue.

POC testing helps reduce the turnaround time for results and the chances of a delay or a mix-up in the lab. Such tests are also more expensive and carry with them more operator errors and regulatory requirements to consider.

In their presentation, Drs Lewandrowski highlighted the expanding menu of POC testing: from dipstick urinalysis, to metabolic panels, HIV and hepatitis C testing, influenza A/B testing, complete blood counts, coagulation testing, and more. Such efforts are available for hospitals during a bioterror event, for bio-surveillance efforts, disasters settings, biothreats in a remote environment, or in the event of bioterrorism. During emergent situations, health care systems are stressed with an overabundance of patients and personnel are desperate to ensure proper medical management and patient safety. Time is of the essence. POC testing reduces the time to receive many critical results, which can mean the difference between life and death during an outbreak. At that time, it is critical to be able to rule out other diseases, especially if laboratory resources are limited. For example, the rapid malaria test was beneficial during the Ebola virus outbreak in West Africa to help rule out malaria as a potential cause of the, then-unknown disease. Such POC tests should be utilized and expanded upon for future health crises and public health events.

The speakers also discussed the challenges labs face during such events or during outbreaks of highly infectious diseases. From costliness to limited space, personal protective equipment requirements, and user knowledge required, the availability of such tests and the labs able to analyze them can be limited. For example, during the 2013-2016 Ebola outbreak, laboratory confirmation became an increasingly complex part of hospital preparedness and response. Patient labs tests had to be sent to designated laboratories, usually state labs or the CDC, for confirmation due to the biosafety level requirements for handling the Ebola virus.

Although there has been much focus on increasing the availability of diagnostics for high-consequence pathogens, there is also the inherent risk of biosafety failures and biosecurity incidents. Improving laboratory capacity presents a mixed bag of pros and cons, but that does not make it any less necessary. ▲

References are available at ContagionLive.com.
An Unexpected Meningitis Culprit
A team of physicians encounter surprising findings in an elderly patient.

BY EKAMJEET RANDHAWA, MD; KEDESHA SIBLISS, MD; AND JOHN WOYTANOWSKI, MD

HISTORY OF THE PRESENT ILLNESS:
An 81-year-old female presented to the emergency department (ED) with altered mental status and was found to be unresponsive, with shaking of her extremities. At baseline, she was ambulatory and verbal, but dependent on family for all activities of daily living. Per her family, the patient was found in her bed, laying on her left side, unresponsive, with mild shaking of the extremities. Her eyes were open but without movement. The family denies any bowel or bladder incontinence. They also reported she had no sick contacts, recent illness, fever, chills, or cough. She had no recent surgeries or health care contacts. The patient was last seen normal 2 hours prior.

PAST MEDICAL HISTORY:
Dementia, transient ischemic attacks, type 2 diabetes, hypertension, descending thoracic aortic aneurysm status post stent placement in 2008, chronic hepatitis C (untreated), and hyperlipidemia.

KEY MEDICATIONS:
Amlodipine (Norvasc), aspirin 81 mg, atorvastatin (Lipitor), and chlorthalidone (Thalitone).

EPIDEMIOLOGICAL HISTORY:
Lives with 1 of her granddaughters, not sexually active, nonsmoker, nondrinker, and no illicit drug use. Pet-free home, no recent travel.

PHYSICAL EXAMINATION:
Vital signs: 97.4°F rectally, heart rate 110 bpm, respiratory rate 25, blood pressure 143/85 mm Hg, oxygen saturation 100% on 40% FiO2. The patient was unresponsive, with left-sided neck deviation, shaking movements of right hand and foot, and a left gaze deviation with nystagmus. Her eyes were open but without movement. The family denies any bowel or bladder incontinence. They also reported she had no sick contacts, recent illness, fever, chills, or cough. She had no recent surgeries or health care contacts. The patient was last seen normal 2 hours prior.

LABS:
Complete blood count: white blood cells (WBC), 22.5 with 86.4% neutrophils. Cerebrospinal fluid (CSF) was cloudy, yellow. Red blood cells, 70. WBC (in CSF), 3400, with 12% neutrophils, 8% eosinophils, 28% lymphocytes, and...
52% monocytes, CSF glucose <10, and protein was elevated to >600 and opening pressure of 22 cmH2O. The CSF gram stain showed gram-positive cocci in chains. Head CT done in the ED for possible stroke revealed a left mastoid effusion and an interval development of right mastoid air cell effusion (FIGURE 1).

**CLINICAL COURSE:**
The patient was intubated in the ED and started on sedation and anti-epileptic medication for presumed status epilepticus. She was admitted to the medical intensive care unit as she was requiring vasopressor therapy for septic shock. The patient was initially given dexamethasone and started on broad-spectrum antibiotic coverage with ampicillin, ceftriaxone, and vancomycin for presumed bacterial meningitis, given the CSF findings. Twelve hours after admission, blood and CSF cultures were positive for gram-positive cocci in chains (FIGURE 2). Once final culture results came back as *Streptococcus pyogenes*, antibiotics were narrowed to penicillin G (TABLE).

Other pertinent events during the hospitalization included the patient being in septic shock requiring vasopressor therapy, acute renal injury, hepatic dysfunction, and an iatrogenic pneumothorax from a central line placement. Given the mastoid effusion on the head CT, otitis was presumed to be the primary source of the invasive central nervous system (CNS) infection. An electroencephalogram was also performed, which revealed intermittent spike and wave discharges seen from the left temporal region. She also had frequent seizures arising from the left hemisphere occurring every 2 to 3 seconds, suggestive of focal electrographic status epilepticus. Unfortunately, the patient failed to recover from the infection, her neurological status remained grave, and her family eventually changed her medical status to “Do not resuscitate.” The patient succumbed to multiorgan failure from septic shock.

**DISCUSSION:**
*S. pyogenes* is a gram-positive beta-hemolytic bacterium, also known as group A *streptococci* (GAS), which causes a wide variety of diseases. The spectrum of potential infections—in addition to the most common, acute pharyngitis—caused by *S. pyogenes* include integumentary infections, bacteremia, osteomyelitis, pneumonia, otitis media, sinusitis, and toxic shock syndrome. According to the US Centers for Disease Control and Prevention, in 2015, there were 15,540 cases of invasive GAS disease, with the most common etiology being cellulitis (39%), primary bacteremia (19.6%), pneumonia (14.1%), necrotizing fasciitis (7.5%), and Streptococcal toxic shock syndrome (2.7%).1 In addition, GAS can lead to nonsuppurative complications, such as rheumatic fever and glomerulonephritis.2 Rarely, meningitis and brain abscesses, as a direct extension of ear or sinus infections or hematogenous spread, can occur; CNS infections, such as meningitis, are rarely caused by GAS.3

Invasion of the CNS by microorganisms is a severe and often morbid event. A total of 1.2 million cases of bacterial meningitis occur annually worldwide.4 The major causes of community-acquired bacterial meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria monocytogenes*, with health care–associated meningitis being largely caused by *Staphylococci* and aerobic gram-negative bacilli.4 *S. pyogenes* is a rare cause of meningitis. GAS meningitis has a prevalence of 0.06 cases in 100,000 children per year, with a case mortality rate of 43%; GAS CNS infections remain rare and account for less than 0.2% of all bacterial meningitis.20

GAS meningitis is a community-acquired disease. In 2002, van de Beek published that of 41 patients with GAS meningitis, 60% had prior otitis or sinusitis; the fulminate disease had a mortality rate of 27%.7 Another case series by Sommer revealed that of 9 cases, 8 were community acquired, 6 had prior neurosurgical conditions, and 5 had upper respiratory tract infections.6 Epidemiological data from our hospital showed that from 2013 to 2017, there were 41 cultures positive for GAS, of which 40 were blood cultures and 1 was the case described above with a CSF culture. Resistance patterns showed that 1 culture was resistant to clindamycin, erythromycin, and tetracyclines; 4 cultures were resistant to erythromycin and tetracyclines; and 3 cultures were resistant to tetracyclines. From 2013 to 2017, there were no resistance to penicillins by GAS at our inner-city hospital (unpublished raw data).

In conclusion, GAS, or *S. pyogenes*, is a rare cause of bacterial meningitis after the neonatal period but must be considered as a potential pathogen. Early recognition and treatment are critical, as diagnostic failure can result in sepsis and death.

References available at ContagionLive.com.
This global Outbreak Monitor allows users to visualize occurrences of infectious diseases, such as Cyclospora and Salmonella on a local, regional, national, and international level. The monitor also tracks trends and details on confirmed cases and deaths, matched with recent coverage related to each outbreak. Use the Contagion® Outbreak Monitor to learn about infectious disease outbreaks in your geographical region, and manipulate the map to find out the latest information on global outbreaks.

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