Fever of Unknown Origin: What Do We Know and Where Do We Go?

As the number of potential etiologies for fever of unknown origin dramatically increases, we must ground our application of new diagnostic modalities with appropriate initial assessments.

By Christina H. Mallarino-Haeger, MD; and Gavin H. Harris, MD

This fall and winter promise to bring about another unusual respiratory viral season in the United States. Adult vaccination will (hopefully) continue to drive COVID-19 cases down—if we can overcome... (continued on page 10)

HIV/AIDS

Examining the HIV Treatment Pipeline
By Ian Cook, PharmD, AAHIVP, BCACP

Since the start of the HIV epidemic 40 years ago, the FDA has approved over 40 medications and medication combinations to treat HIV. For years, people living with HIV (PLWH) and providers have been asking for long-acting therapy options with the hope that these would increase patient adherence, achieve a durable... (continued on page 14)

Multidrug-Resistant Infections

Daptomycin as Frontline Therapy for MRSA Bacteremia: Has the Time Come?
By Michael Trisler, PharmD, MPH, BCIDP; Fidelia Bernice, PharmD, BCIDP; and Louise-Marie Oleksiuk, PharmD, BCPS

Daptomycin (Cubicin) is a cyclic lipopeptide antibiotic with broad-spectrum gram-positive activity, including methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci (VRE). The drug... (continued on page 16)

Stewardship & Prevention

Children, COVID-19, and Another Crazy Respiratory Viral Season
By Conan MacDougall, PharmD, MAS, BCPS, BCIDP

This fall and winter promise to bring about another unusual respiratory viral season in the United States. Adult vaccination will (hopefully) continue to drive COVID-19 cases down—if we can overcome... (continued on page 18)
Questions Linger Around COVID-19’s Origin

**WAS IT NATURAL ZOONOTIC** spillover that catapulted SARS-CoV-2 from an emerging virus into a pandemic pathogen, or was it something much more sinister? Is it at all possible that a lab leak in Wuhan, China, was the spark that lit the fuse?

Debate and discussion about the origin of the virus that causes COVID-19 have been at the forefront of the global consciousness since the first cases were reported in December 2019. Early on, whispers of a potentially engineered virus quickly grew to a roar and fueled speculation that China was behind the pandemic. This narrative was so pervasive that, in February 2020, a group of 27 public health scientists published a letter in The Lancet disputing the lab leak theory and announcing their support of their counterparts in China: the scientists, public health officials, and medical professionals combating the pandemic.

“The rapid, open, and transparent sharing of data on this outbreak is now being threatened by rumors and misinformation around its origins,” wrote the authors, who all declared no competing interests in their disclosures as recommended by the International Committee of Medical Journal Editors. “We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin.”

And although it’s true that analyses of the genomic sequence of the virus subsequently pointed to natural origins, the questions regarding China’s role persisted, led by pesky discrepancies and conflicting reports.

Fast forward to June 2021 and new evidence that has breathed new life into those origin questions. In an update to the February 2020 letter, the Lancet has published an addendum with revised disclosure statements from virologist and investigator Peter Daszak, 1 of the 27 authors. In the revised document, Daszak noted that his remuneration is paid solely in the form of a salary from EcoHealth Alliance, a New York–based nonprofit research foundation of which he is president. The company has reportedly worked directly with Wuhan laboratories and funded gain-of-function research at China’s Wuhan Institute of Virology.

Consider, too, other odd associations. Recent reports have uncovered financial ties between Google and EcoHealth Alliance. This comes after accusations that the tech giant was censoring lab leak “conspiracy theory” stories in its search results. Google’s health lead, David Feinberg, has dismissed those reports, insisting that the company is simply taking steps to protect users from unverified information.

Are these coincidences or “where there’s smoke, there’s fire” situations? It’s unclear. But they add to the bank of troublesome questions standing in the way of the truth about COVID-19.

The questions extend beyond origin theory, though. With the FDA’s green lighting of vaccines for adolescents and young adults comes hesitation over long-term effects: What is the effect on fertility? Do the vaccines cause heart inflammation? Robert Malone, MD, the inventor of the messenger RNA (mRNA) technology, appeared on television recently, expressing strong concern over the risk-benefit analysis of vaccination for young adults, and the CDC’s Advisory Committee on Immunization Practices recently met to discuss instances of myocarditis or pericarditis in people 30 years and younger who have received an mRNA COVID-19 vaccine.

Of course, the answer to our ultimate question is that we may never know.

We may never know where this virus came from. We may never know what triggered the global pandemic that has claimed more than 4.3 million lives. And we won’t know the long-term effects until enough time has elapsed. What we do know for certain is that the incredible strength and collaboration of the scientific community have allowed us to regain some semblance of normalcy. The development and rollout of multiple effective vaccine options have been the medical miracle of our lifetime.

That, right now, will have to be the only answer that matters.

Mike Hennessy Sr
Chairman and founder
MJH Life Sciences™

Delta Means Change

I CANNOT TELL YOU HOW MUCH I was hoping to write about something other than COVID-19 this issue. In June, things were very different. In the US, cases, hospitalizations, and deaths were the lowest they had been in 2021. Vaccinations drove this change, and while they never reached an ideal number of Americans, over 69% of adults have received at least one dose.1 The CDC responded by changing guidance to state that fully vaccinated people did not need to wear face masks. I went on vacation (to Florida, no less!). Things were looking grand.

In July, a pivot occurred. The delta variant of concern that had already become dominant in other parts of the world did the same in the US at a pace that is hard to grasp. At the end of May, the delta variant was responsible for 3.1% of infections, while the alpha variant was 69.1%; at the midpoint of July, delta had caused 83.2% of infections and alpha was 8.3%.2 That is an enormous swing in under 2 months. In the competitive world of viral mutations, the delta variant has won.

With this rapid shift to this hypertransmissible variant, our approach needs to change as well. The paths that we have charted for the rest of the year need to be adjusted. As I write this, it has been reported that CDC is moving to recommend masking indoors again for many vaccinated people.3 The American Academy of Pediatrics already recommends masks for all school-aged children.4 These represent changes from policies at many places that were established when cases were diminishing this spring.

Another organization that needs to react to change is the FDA. The full approval of the vaccines granted emergency use authorizations (EUAs) needs to be FDA’s No. 1 priority. It may not seem obvious because they have been available by EUA since December 2020, but a lack of full approval has kept many other organizations, including those in higher education and health care, from mandating vaccination for their employees and students. It seems that after a few months of lotteries and free beer that we have run out of carrots. One of the common tropes of unvaccinated people is that the vaccines are “experimental” and “unapproved.” After 8 months, hundreds of millions of doses administered, and an impressive safety record, what more is there to learn about them? It is time for FDA to complete the job.

Humans dislike change, especially when it is rapid, unexpected, or negative. Delta is all 3. We need to shift our own course to catch up with it.

Jason C. Gallagher, PharmD, FCCP, FIDP, FIDSA, BCPS

References are available at ContagionLive.com.

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CHAIRMAN’S LETTER

EDITOR-IN-CHIEF’S LETTER

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Fever of Unknown Origin: What Do We Know and Where Do We Go?

As the number of etiologies increases, we must ground our application of new diagnostic modalities with appropriate assessments.

BY CHRISTINA H. MALLARINO-HAEGER, MD; AND GAVIN H. HARRIS, MD
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Eagerly Awaited Trial on Periprosthetic Joint Infections Reinforces Practice

BY DON BAMBINO GENO TAI, MD; CHRISTINA G. RIVERA, PHARM.D; AND OMAR M. ABU SALEH, MBBS

The duration of antibiotic therapy for periprosthetic joint infections (PJIs) has been a perennial question among infectious diseases experts. Orthopedic surgeons have standardized debridement, antibiotics, and implant retention (DAIR); 1-stage exchange arthroplasty; and 2-stage exchange arthroplasty throughout the years. However, there is an evidence gap regarding antimicrobial strategy after surgery. The literature on this topic has been of low quality and primarily retrospective in nature. International and national organizations have published treatment guidelines recommending different treatment durations (Table).1,4

Bernard et al’s study on the duration of antibiotic therapy for PJI sought to address this knowledge gap. The DATIPO trial (NCT01816009) was an open-label, randomized, controlled, noninferiority trial of patients 18 years or older with PJI. The study was conducted in 28 trial sites across France from November 29, 2011, to January 22, 2015. Investigators randomized 410 patients into 2 treatment groups of 6 weeks vs 12 weeks of antibiotics after surgery. The randomization was based on infected joint (hip vs knee), surgical procedure (DAIR, 1-stage, 2-stage), and episode of infection (first vs subsequent). Outcomes of interest were treatment failure microbiologically confirmed with similar or different bacteria and clinical diagnosis of infection. An adjudication committee, which was blinded to the randomization, assessed these outcomes. Noninferiority was defined as less than 10% in risk difference using the upper limit of the 95% CI.

The investigators found that 6 weeks of antibiotics was not noninferior to 12 weeks of antibiotics for all patients (18.1% vs 9.4%, respectively). In addition, they found a 10.6% difference between the 2 groups regarding persistent infection within 2 years with per-protocol analysis (95% CI, 3.7-17.5). This difference was driven by the subgroup of patients treated with DAIR, who accounted for 41.3% of the study sample. The failures in this subgroup represented 64% of all failures (n = 34). Among patients with knee PJIs treated with DAIR, failure was 38.2% for 6 weeks and 13.5% for 12 weeks for a risk difference of 24.7% (95% CI, 4.4-43.1). These findings reinforced previous knowledge that prolonged antibiotic treatment is needed for PJI treated with DAIR, particularly knee PJIs.

For 2-stage exchange arthroplasty, there was a 10.1% difference (95% CI, –3.1 to 23.3) which meant that it also did not meet noninferiority. Note that this does not mean that 12 weeks is superior. Interestingly, for patients treated with 1-stage exchange arthroplasty, the difference between 6 and 12 weeks of therapy met the noninferiority criterion (1.2; 95% CI, –4.8 to 7.1). However, since this subgroup was smaller and the events were fewer, it would not have enough power. Nevertheless, this is another area for future research.

The most significant limitation of this study is the heterogeneity of surgical management, as pointed out by the study authors. DAIR and exchange arthroplasties are vastly different surgical procedures. Thus, antimicrobial strategies are also vastly different. It was also unclear whether randomization was performed according to institution. As PJI is a surgical disease, it would be imperative that differences in surgical expertise were taken into account during randomization, as these would affect outcomes. There was also an imbalance in the distribution of Staphylococcus aureus complex and coagulase-negative staphylococci between groups. Some evidence exists that infection with S aureus complex is a risk factor for failure of DAIR or exchange arthroplasties, although this was not uniformly seen across all studies.13 It is unclear whether the results would be generalizable to gram-negative infections, as these were less well represented. Further, it is worth noting that the study relied on oral antibiotics for most of the treatment course. The median duration of parenteral antibiotics was only 9 days, an uncommon practice in the United States.

DATIPO is an excellent foundation for more randomized, controlled trials. Future trials should focus on a more homogeneous group, such as patients treated with DAIR separately from those treated by 1-stage or 2-stage exchange. The current study strongly supports the need for a longer duration of antibiotics for DAIR. What is unknown is the ideal duration past 3 to 6 months after debridement. Dedicated studies for the exchange arthroplasties are also needed to settle the adequate duration of antibiotics after resection. In practice, the duration of therapy is nuanced and influenced by nonsurgical factors such as patient, history of treatment failures, and feasibility of future surgical interventions. Although this trial had a good representation of various patient presentations, we should still note individual variations seen in the clinics. At present, practices that follow the Infectious Diseases Society of America clinical practice guidelines on PJI treatment duration are reinforced by the findings of this study.

### TABLE. Recommendations for Treatment Duration of PJI According to Surgical Management

<table>
<thead>
<tr>
<th>IDSA</th>
<th>ICMMI</th>
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</thead>
<tbody>
<tr>
<td>DAIR</td>
<td>3 months for hips* 6 months for knees* Minimum of 6 weeks</td>
</tr>
<tr>
<td>1-stage exchange</td>
<td>6 weeks* 2-6 weeks</td>
</tr>
<tr>
<td>2-stage exchange</td>
<td>6 weeks 4-6 weeks</td>
</tr>
</tbody>
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DAIR, debridement, antibiotics, and implant retention; ICMMI, International Consensus Meeting on Musculoskeletal Infection; IDSA, Infectious Diseases Society of America.

*with option for chronic oral antibiotic suppression

References are available at ContagionLive.com.

Highlighted Study


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IN THE LITERATURE
Mono or Combo? Exploring Antimicrobial Therapies for Invasive Carbapenem-Resistant Gram-Negative Infections

BY SEAN S. M. BULLIS, MD; AND ANDREW J. HALE, MD

New agents to combat multidrug-resistant gram-negative (MDRGN) organisms are sorely needed. Some new compounds have been developed in recent years and incorporated into updated Infectious Diseases Society of America guidelines, including novel β-lactam–β-lactamase inhibitors, tetracyclines, and a first-in-class siderophore antimicrobials, cefiderocol. Although a precise niche for each remains to be determined, combination therapies continue to be employed for MDRGN organisms, based on a theoretical advantage of augmented bacterial killing and preservation of susceptibility to individual drug classes. Randomized trial data are limited and have shown improved microbiological eradication but similar clinical outcomes.

Carbapenem-resistant GN bacilli (CR-GNB), broadly including Enterobacteriales and certain lactose nonfermenters (Acinetobacter, Pseudomonas), are problematic and novel treatments have been prioritized by the World Health Organization. Scudeller and colleagues recently described in vitro data of bacterial killing and antibiotic synergism, part of the broader COHERENCE Project, a global collaboration examining combination therapies for CR-GNB. The study included various antibiotic combinations and dosages against CR-GNB from time kill (TK) and pharmacokinetic/pharmacodynamic (PK/PD) studies, chosen for their standardized methods and reproducibility, and their ability to recapitulate drug exposure in vivo, respectively.

Articles published through 2018 within PubMed and Scopus databases and Web of Science were eligible. Reviews, editorials, and protocol papers were excluded, as were publications examining single bacterial strains. Two investigators reviewed relevant studies for eligibility, with a third acting as a tie-breaker. Study quality was assessed on a 0 to 18 point scale. Studies with greater than 11 points were deemed high quality and warranting sensitivity analysis. Relevance was categorized as reliable without restrictions, reliable with restrictions, not reliable, or not assignable.

The primary outcome was in vitro synergy or antagonism (defined as a > 2-log reduction or increase, respectively, in colony-forming unit [CFU]/mL vs most active single agent) and was stratified by effect size (high, moderate, low, or absent). Secondary outcomes included bactericidal rates (a > 3-log reduction in CFU/mL from baseline) and regrowth rate (a ≥ 2-log CFU/mL decrease of initial colony count, followed by an increase of ≥ 1-log CFU/mL at 12 and 24 hours). Resistance was determined according to European Committee on Antimicrobial Susceptibility Testing 2019 break points.

From nearly 7000 publications, 797 were assessed for eligibility and 136 included in the meta-analysis. Of these, 31% (42 of 136) reported PK/PD data, 69% (94 of 136) reported TK data, and 7% (10 of 136) reported both. One-hundred eighty-two antimicrobial combinations were tested in TK studies and 41 in PK/PD studies. The vast majority involved 2-drug regimens, most commonly colistin (CST)- and carbapenem-based. Of 136 studies, 73 (54%) were deemed high quality.

For Acinetobacter baumannii, high synergy was observed with meropenem plus polymyxin (PMB)/CST, tigecycline plus CST, rifampicin (RIF) plus CST, and imipenem (IPM) plus tobramycin (TOB). On sensitivity analysis, 4 high-quality TK studies confirmed synergy with carbapenem plus PMB, and high synergy was observed with IPM plus TOB and TMP/SMX plus CST. With respect to secondary outcomes, of 29 PMB- and doripenem (DOR)-based combinations, the authors observed no significant differences in bactericidal activity or regrowth rates vs monotherapy.

For Pseudomonas aeruginosa, moderate synergy was seen with combinations of ceftolozane/tazobactam plus CST, IPM plus CST, meropenem (MEM) plus amikacin (AMK), MEM plus CST, IPM plus TOB, and DOR plus CST; high synergy was seen with IPM plus AMK. Sensitivity analysis revealed moderate synergy with combinations involving DOR/IPM plus CST from 2 PK/PD studies and 1 TK study. For secondary outcomes, 6 combinations showed significantly higher bactericidal rates with combinations of MEM plus AMK, or IPM plus AMK/TOB vs monotherapy, and significantly less regrowth at 24 hours with IPM plus AMK/TOB vs monotherapy.

For Klebsiella pneumoniae, high synergy was observed with combinations of RIF plus CST, IPM/DOR plus PMB, IPM/MEM plus AMK, ceftriaxone/avibactam plus aztreonam, and fosfomycin (FOF) plus PMB. Sensitivity analysis revealed moderate to high synergy for combinations of FOF plus PMB, RIF plus PMB, and a carbapenem plus PMB. In 39 combination regimens from TK and PK/PD studies that were examined for secondary outcomes, investigators found that PMB-based combinations (with RIF or gentamicin) had significantly higher bactericidal rates vs monotherapy, and significantly lower regrowth at 12 and 24 hours vs monotherapy.

This was the largest analysis of in vitro combination therapy vs monotherapy for CR-GNB that examined multiple pathogens and a prolific number of regimens (> 180). Compared with monotherapy, the authors found high synergy and increased bactericidal activity for A baumannii; high synergy, increased bactericidal activity, and lower regrowth for K pneumoniae with PMB-based regimens; and high synergy, high bactericidal activity, and lower regrowth for P aeruginosa with a carbapenem and an aminoglycoside. Limitations included scant high-quality data for combinations involving novel compounds, heterogeneity in the combinations studied, regrowth assessment limited to 24 hours, and limited generalizability due to the variability of bacterial strains and resistance patterns. Additionally, the lack of in vivo correlates limits one’s ability to translate into clinical practice.

Although the results do not address who should be treated with combination therapy, the authors should be commended on their appraisal of the literature. Despite their findings, it is incumbent upon infectious diseases practitioners to exercise caution with PMB-based regimens, which is underscored by the updated Clinical and Laboratory Standards Institute breakpoints listing only intermediate and resistant categories for Enterobacteriales. These data, though intriguing, perhaps best serve to stimulate subsequent human trials of the most promising regimens identified to combat the rising tide of MDRGN infections.
Novel Malaria Vaccine Shows Strong, Lasting Protection in Phase 1 Trials

BY KILLIAN MEARA

Findings from 2 recent phase 1 clinical trials conducted by the National Institutes of Health (NIH), in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), have shown that a novel malaria vaccine candidate confers high levels of durable protection against the disease. Results from the trials were published in the journal Nature.

“We are encouraged by the significant findings reported in this seminal paper, which justify our investment in Sanaria and its systematic, scientifically sound approach to developing the highly protective, cost-effective vaccines required to eliminate malaria. [The disease is] a scourge of humanity, particularly for the most underserved on our planet,” said Holm Keller, comanaging director of the EU Malaria Fund.

The vaccine, known as PfSPZ, was developed by the biotechnology company Sanaria. The therapy is composed of sporozoites, the form of the malaria parasite transmitted to people by mosquito bites.

In the trials, healthy adult volunteers received PfSPZ along with either pyrimethamine, a drug that kills liver-stage parasites, or chloroquine, which kills blood-stage parasites.

After 3 months, the participants were then exposed to either an African malaria parasite strain that was the same as that in the vaccine (homologous challenge) or a variant South American parasite (heterologous challenge) that was more genetically distant from the vaccine strain than hundreds of African parasites.

Findings from the trials showed that at the lowest dosage the vaccine gave only modest protection. However, at the highest dosage, 7 of 8 participants were protected from homologous challenge, and 7 of 9 were protected from heterologous challenge.

Additionally, in the chloroquine combination, all 6 participants who received the higher dosage were completely protected from the heterologous challenge. Protection with the higher dosage was also seen to last for 3 months.

“These results represent extremely important progress, unanticipated by most malaria experts,” said Martin P. Grobusch, MD, PhD, MSc, chair of tropical medicine and travel medicine and head of the Center of Tropical Medicine and Travel Medicine at the Academic Medical Center of the University of Amsterdam.

“Until recently, malaria vaccine developers sought to achieve high-level protection against nonvariant malaria parasites, often only 2 to 3 weeks after vaccination, with immunity waning thereafter.

“The finding of 100% protection against variant parasites that are so divergent from the vaccine parasites at 3 months is unprecedented. This vaccine approach should be advanced now as a potential tool to protect travelers to Africa and further developed for the prevention of malaria in African populations.”

Flu Vaccination Could Lessen Impact of COVID-19

BY JEFFREY BENDIX

Influenza vaccines may protect against some of the worst effects of COVID-19, results from a new study suggest.

A retrospective analysis of data from more than 37,000 patients with COVID-19 worldwide suggests that annual flu shots reduced the risk of stroke, sepsis, and deep vein thrombosis (DVT), according to a press release from the European Society of Clinical Microbiology and Infectious Diseases.

The study authors also found that patients with COVID-19 who had received a flu vaccination were less likely to be admitted to emergency departments or intensive care units than those who had not.

Investigators from the University of Miami Leonard M. Miller School of Medicine divided patients in the study into 2 groups. One group had received a flu shot between 2 weeks and 6 months before receiving a COVID-19 diagnosis, whereas the second group had not received a flu vaccination.

Both groups were matched for factors that could affect their risk of severe COVID-19, including age, gender, smoking, diabetes, and obesity, among others. According to the analysis, those in the nonvaccinated group were up to 20% more likely to have been admitted to an ICU, up to 58% more likely to have visited an emergency department or experienced a stroke, and 40% more likely to have had a DVT than the vaccinated group. However, there was no difference in the risk of death between the 2 groups.

The fact that flu vaccines could protect against many of COVID-19’s worst outcomes “is particularly significant because the pandemic is straining resources in many parts of the world,” said Devinder Singh, MD, the study’s lead author, in the press release. “Therefore our research—if validated by prospective randomized clinical trials—has the potential to reduce the worldwide burden of disease.”

“Influenza vaccination may even benefit individuals hesitant to receive a COVID-19 vaccination due to the newness of the technology,” said Susan Taghioff, a member of the research team. “Continued promotion of the influenza vaccine also has the potential to help the global population avoid a possible ‘twindemic’—a simultaneous outbreak of both influenza and coronavirus,” she added.

Worldwide, there have been approximately 187,000,000 cases of COVID-19 and 4,000,000 deaths from the disease as of July 12 2021, according to the Johns Hopkins Coronavirus Resource Center.
Single Dose of Pfizer, AstraZeneca Vaccine Protects Older Adults

BY KILLIAN MEARA

According to a recent study by investigators from the University College London Institute of Health Informatics, a single dose of the Pfizer or AstraZeneca COVID-19 vaccine provided significant protection in older adults. The study results were published in the *Lancet Infectious Diseases* journal.

“The protective effect of a single dose of vaccination is evident from 4 weeks to at least 7 weeks after vaccination, which provides some evidence to support extension of the dose interval beyond 3 weeks, in line with UK policy,” the authors wrote. “However, even beyond 4 weeks, a single vaccine dose does not eliminate infection risk, highlighting the continued importance of nonpharmaceutical measures to control transmission within long-term care facilities.”

For the study, the team of investigators analyzed data from the VIVALDI study, which investigated SARS-CoV-2 transmission, infection outcomes, and immunity in residents and staff in long-term care facilities in England.

The study included 10,412 participants who were 65 years or older from 210 long-term care facilities. Of the participants, 9160 received at least 1 dose of vaccine, with 6138 receiving the AstraZeneca vaccine and 3022 receiving the Pfizer vaccine.

Findings from the study showed that between December 8, 2020, and March 15, 2021, there were 1335 polymerase chain reaction (PCR)-positive infections, of which 713 were in unvaccinated residents and 622 in vaccinated residents.

From 28 days after the first vaccine dose, adjusted hazard ratios for PCR-positive infection relative to unvaccinated residents declined to 0.44 at 28 to 34 days, and to 0.38 at 35 to 48 days. Both vaccines showed a similar effect size at 35 to 48 days.

“Further work is required to evaluate the effectiveness of the second dose of the vaccine, and the effect of vaccination on transmission,” the authors wrote. “This knowledge will be critical to inform policy decisions regarding revaccination schedules in this vulnerable population and the disease control measures needed in the short, medium, and long term to protect long-term care facilities from future waves of SARS-CoV-2 infection.”

Has Progress Against the Pandemic Also Improved Antibiotic Prescribing?

BY KENNETH BENDER, PHARMD, MA

Fewer antibiotic prescriptions were prescribed for respiratory symptoms during the pandemic than in the comparable prepandemic period. The findings were from a study of ambulatory clinic patients of the University of Wisconsin (UW) Health system in southern Wisconsin.

Alexander Lepak, MD, and colleagues found that although antibiotic prescribing rates had increased during the prepandemic winter respiratory viral season, they decreased in the short term and remained low throughout the corresponding pandemic period.

“One way to interpret the study is to draw a conclusion about how much inappropriate antibiotic use was occurring for respiratory viruses in the prepandemic period. But I think there is another side to this story and that this is a huge success story,” Lepak, an associate professor in the Infectious Disease Faculty at UW School of Medicine and Public Health in Madison, told *Contagion®*.

“We had massive COVID-19 surges, with unprecedented numbers of patients with respiratory complaints, especially in the fall between October and December. [However,] antibiotics were not prescribed, for the most part, in patients with respiratory complaints during this period—keeping in mind they had indistinguishable symptoms from other respiratory viruses [for which] antibiotics were previously prescribed.”

Lepak and colleagues—with whom, Lepak emphasized, the study was a “huge collaborative effort”—compared the number of antibiotic prescriptions given at UW Health’s 80-plus ambulatory clinic sites with 7 million annual ambulatory encounters in the prepandemic period of July 2018 to February 2020 and April 2020 to February 2021 during the pandemic. The numbers of ambulatory encounters during those periods were similar: 637,000 and 662,000 per month, respectively.

The winter seasonal viruses, including influenza, respiratory syncytial virus (RSV), and seasonal coronavirus, demonstrated seasonal variation during the prepandemic but not the pandemic period. The number of patients presenting with seasonal viruses decreased from approximately 4800 per month before the pandemic to 12 per month during the pandemic. Other respiratory virus detections also decreased, from 560 per month before the pandemic to 228 per month during the pandemic.

The investigators reported that, adjusting for seasonality, monthly antibiotic prescriptions for respiratory tract infections (the indication for antibiotic prescriptions is required by UW Health pharmacy) fell 79%, from 10.5 to 2.2 prescriptions per 1000 patient encounters.

“Antibiotic prescribing for respiratory complaints was best correlated with activity of seasonal coronaviruses, rhinoviruses, RSV, metapneumovirus, etc. It was not as well correlated with influenza and wasn’t correlated at all with COVID-19 activity,” Lepak commented. “The difference between these is that we have accessible and timely diagnostics for the latter 2 but not necessarily the former group[s], at least for ambulatory care patients.”

“Based on these findings, our hypothesis is that providing more comprehensive respiratory viral testing that is accessible and timely to ambulatory providers and patients may significantly [enable the curbing of] antibiotic prescribing for respiratory viruses,” Lepak said.

The investigators found results of other studies that showed relatively quick declines in rates of viral infections or antimicrobial prescribing. However, they characterize their study as “the first to combine respiratory virus activity and antibiotic prescriptions that were indexed to the number of encounters over a prolonged period that includes the typical respiratory virus season.”
Ibrexafungerp: A Novel Antifungal Agent That Is Easier to Pronounce Than Spell

BY GEENA KLUDJIAN, PHARMD; AND JASON C. GALLAGHER, PHARMD, FCCP, FIDP, FIDSA, BCPS

The first antifungal medication, amphotericin B deoxycholate, was approved in 1958 for the treatment of fungal infections. It wasn’t until 15 years later that fluconazole was introduced and 15 years after that when azole antifungals were brought to market in the 1990s.1 Echinocandins, introduced in the 2000s, provided broad-spectrum antifungal coverage with minimal toxicity compared with the preceding agents. Since that time, the FDA has approved no new classes of antifungal agents. Although the current antifungals used in clinical practice provide sufficient coverage against a plethora of fungal species, resistant species and strains are evolving rapidly. The multidrug-resistant fungus Candida auris is a specific species of Candida that is emerging as a serious global health threat; it has high rates of resistance to azoles and amphotericin B, correlating to poor clinical outcomes.2

Ibrexafungerp (Brexafemme) is a first-in-class triterpenoid approved by the FDA on June 1, 2021, for the treatment of vulvovaginal candidiasis (VVC) in adult and postmenarchal pediatric girls.3 In this article we review the agent’s mechanism of action, pharmacokinetic properties, safety and efficacy, and place in therapy.

ABOUT THAT NAME
Ibrexafungerp has a unique name that can be understood by breaking it down. “Ibrexa” is the fantasy prefix, “fung” refers to the mechanism of action targeting (1,3)-β-D-glucan synthase (similar to caspofungin), and “erp” is derived from triterpenoid. In 2019, the United States Adopted Names Council approved the use of the “-fungerp” stem for this new class of triterpenoid antifungals.4

PHARMACOLOGY AND MICROBIOLOGY
Similar to echinocandins, ibrexafungerp is an inhibitor of (1,3)-β-D-glucan synthase; however, it is structurally different and interacts with the enzyme in a different way. Because of this difference there is limited potential for cross-resistance with echinocandins, which has been confirmed by in vitro studies, as ibrexafungerp was shown to retain activity against echinocandin-resistant strains of Candida species (spp).5,6

Ibrexafungerp is active against Candida spp (including C. auris), Aspergillus spp, and Pneumocystis, and inactive against Cryptococcus spp, Mucorales, and Fusarium spp. It is also active against some other less common molds.7 Ibrexafungerp has demonstrated activity against biofilms produced by Candida spp, with similar activity to that of echinocandins but significantly higher than that of fluconazole (P < .001).8

PHARMACOKINETICS
Unlike the echinocandins, ibrexafungerp is highly bioavailable and can be given both intravenously and orally. Ibrexafungerp is available as 150-mg oral tablets and administered at 300 mg given 12 hours apart for 2 doses, which completes the regimen in a single day.3 Plasma concentrations peak around 4 to 6 hours after oral administration. Administration with a high-fat meal increased the maximum concentration and area under the curve by approximately 32% and 38% compared with fasting, respectively, but this is not considered clinically significant. Ibrexafungerp
can be taken with or without food.\(^3\) Protein binding is 99.6% to 99.8% and the mean steady state volume of distribution is approximately 600 L.\(^4\) Tissue to blood ratios for several organs have been estimated in a single-dose pharmacokinetic analysis in rats, which found extensive distribution in vaginal tissue; the lung, kidney, liver, and spleen; bone marrow; muscle; and skin, but minimal distribution in central nervous system tissue and the spinal cord.\(^5\) Ibrexafungerp is hepatically cleared and mainly eliminated in the feces and bile (\(~\)90%), with approximately 1.5% urinary elimination. Dose adjustments are not required for renal or hepatic impairment. The half-life is approximately 20 hours, supporting the single-day dosing.\(^3\) Currently, no data exist on crushing or breaking the oral tablets.

**DRUG-DRUG INTERACTIONS**

Ibrexafungerp is extensively metabolized by the cytochrome P450 (CYP) pathway and is affected by drugs that induce or inhibit this pathway. Because it is a substrate of cytochrome P3A4 (CYP3A4), coadministration of the drug with strong CYP3A4 inhibitors increases its concentration and a 50% dose reduction is recommended.\(^3\) Avoid coadministration with moderate to strong CYP3A4 inducers, such as rifampin, which may reduce concentrations of ibrexafungerp. Ibrexafungerp is also a CYP3A4, P-gp, and OATP1B3 transporter inhibitor, but the clinical significance of this is not of concern for the short duration of treatment for VVC.\(^3\) Concomitant use with pantoprazole for 5 days resulted in decreased ibrexafungerp exposure by 25%, though this was not considered clinically significant at the current approved dose.\(^3\)

**PHASE 3 CLINICAL TRIALS**

Two phase 3 clinical studies evaluated the safety and efficacy of ibrexafungerp compared with placebo for the treatment of VVC. VANISH 303 and VANISH 306 (NCT03734991 and NCT03987620) were multicenter, randomized, double-blind, placebo-controlled trials that included nonpregnant postmenarchal patients 12 years and older with a diagnosis of symptomatic acute VVC.\(^3\) More than 90% of patients with baseline cultures were culture positive with *C. albicans*. The investigators in both trials evaluated clinical cure, defined by the complete resolution of signs and symptoms, at test of cure at 8 to 14 days post treatment. According to the data, patients receiving ibrexafungerp showed complete response rates compared with those receiving placebo of 50% vs 28% (\(P = .001\) in VANISH 303, and 63.5% vs 44.9% (\(P = .009\)) in VANISH 306. Adverse effects among patients were minimal and mainly gastrointestinal in nature.\(^6\)

Several other ongoing phase 2 and 3 clinical trials are being conducted to evaluate the role of ibrexafungerp in patients with recurrent VVC (CANDLE, NCT04029116), invasive aspergillosis (SYNERGIA, NCT03672292), refractory invasive fungal infections (FURI, NCT02244606), and invasive infections due to *C. auris* (CARES, NCT03363841). Highlighting the CARES study in particular, investigators evaluated the safety and efficacy of ibrexafungerp 750 mg twice daily for 2 days, then 750 mg once daily for up to 90 days in hospitalized patients with documented candidiasis or candidemia caused by *C. auris*. Interim results have demonstrated a complete or partial response in 8 of 10 patients (80%).\(^7\) FURI has also shown positive results thus far, with investigators reporting that 46 of 74 patients (62%) experienced complete or partial responses and 18 of 74 (24%) had stable disease at the time of analysis.\(^8\)

**ADVERSE EFFECTS, WARNINGS, AND PRECAUTIONS**

Based on data from clinical trials in patients with VVC, the adverse effect profile of single-day ibrexafungerp is generally favorable. Gastrointestinal adverse effects were the most common, including diarrhea (16.7%), abdominal pain (11.4%), nausea (11.9%), dizziness (3.3%), and vomiting (2.0%).\(^7\) A press release for the FURI and CARES studies stated that ibrexafungerp was well tolerated overall and that investigators had identified no safety signals warranting changes to the studies.\(^9\) In contrast to many azole antifungals, ibrexafungerp does not cause QTc prolongation.\(^9\)

The use of ibrexafungerp is contraindicated in pregnancy, as data from animal studies have shown a potential for fetal harm. During treatment with the agent, the use of effective contraception is advised. Concentrations in breast milk are unknown.

**RESISTANCE DATA**

Investigators in in vitro studies have evaluated the potential for resistance to ibrexafungerp, finding an association with mutations in the *FKS2* gene. The clinical relevance of this is not yet known, but it has been established that ibrexafungerp retains activity against most echinocandin- and fluconazole-resistant strains of *Candida spp.*\(^3,10\)

**PLATE IN THERAPY**

Although fluconazole is an inexpensive, well-tolerated, single-dose agent that is effective in the majority of VVC cases, ibrexafungerp is an option for patients who either fail fluconazole therapy or may be unable to receive it. Ibrexafungerp is available orally and has a favorable adverse effect profile.

Beyond VVC, ibrexafungerp has the potential to advance the care of patients with invasive fungal infections, including those caused by resistant *Candida* spp. Clinical data evaluating inpatient use in more invasive and resistant infections are pending. There is currently insufficient data to support the use of ibrexafungerp in patients with these infections, and clinicians should note that the dosing regimen under study are different from the approved VVC regimen. The drug interactions that are not clinically relevant with a single-day dosing regimen may warrant caution or necessitate dose modification for other uses.\(^5,6\)

**SUMMARY OF KEY POINTS**

- Ibrexafungerp is a first-in-class triterpenoid antifungal approved for the treatment of vulvovaginal candidiasis (VVC) in adult and postmenarchal pediatric females.
- It has a similar mechanism of action to echinocandins in that it inhibits (1,3)-\(\beta\)-D-glucan synthase, but it is structurally different from echinocandins.
- Ibrexafungerp shows reliable activity against *Candida* species (pp) and *Aspergillus* spp.
- Its high bioavailability allows for oral administration, and its long half-life allows for single-dose dosing.
- Ibrexafungerp carries the risk of drug-drug interactions as it is a substrate of cytochrome P450 3A4 (CYP3A4), and dose adjustments may be warranted.
- Clinical trials have established the safety and efficacy of ibrexafungerp in patients with VVC. Interim analyses of data looking at indications for more invasive and resistant infections are promising.
- Ibrexafungerp is generally well tolerated with minimal adverse effects, with the most common being gastrointestinal effects.

References are available at ContagionLive.com.
Fever of Unknown Origin: What Do We Know and Where Do We Go?

As the number of potential etiologies for fever of unknown origin increases, we must ground our application of new diagnostic modalities with appropriate initial assessments.

BY CHRISTINA H. MALLARINO-HAEGER, MD; AND GAVIN H. HARRIS, MD

(continued from cover page)

Table 1. Common and Uncommon Infectious Causes of FUO1,11

<table>
<thead>
<tr>
<th>COMMON</th>
<th>UNCOMMON</th>
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<tbody>
<tr>
<td>Complicated urinary tract infections</td>
<td>Acute HIV</td>
</tr>
<tr>
<td>Culture-negative IE</td>
<td>Anaplasmosis</td>
</tr>
<tr>
<td>Occult abscess*</td>
<td>Babesiosis</td>
</tr>
<tr>
<td></td>
<td>Bartonellosis</td>
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<tr>
<td></td>
<td>Blastomycosis</td>
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<td>Brucellosis</td>
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<td></td>
<td>Coccidioidomycosis</td>
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<td>Ehrlichiosis</td>
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<td></td>
<td>Hepatitis A</td>
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<td>Hepatitis B</td>
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<td>Hepatitis E</td>
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<td></td>
<td>Salmonellosis</td>
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<td></td>
<td>Bone and joint infections</td>
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<tr>
<td></td>
<td>Histoplasmosis</td>
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<tr>
<td></td>
<td>Human herpesvirus-6 Human herpesvirus-7</td>
</tr>
<tr>
<td></td>
<td>Leptospirosis, malaria, visceral leishmaniasis</td>
</tr>
<tr>
<td></td>
<td>Psittacosis</td>
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<tr>
<td></td>
<td>Q fever</td>
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<tr>
<td></td>
<td>Rat-bite fever, relapsing fever</td>
</tr>
<tr>
<td></td>
<td>Rocky Mountain spotted fever, tularemia</td>
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<tr>
<td></td>
<td>Occult abscess*</td>
</tr>
<tr>
<td></td>
<td>Whipple disease</td>
</tr>
</tbody>
</table>

FUO, fever of unknown origin; IE, infective endocarditis.

*There is disagreement in the literature as to whether occult or pyogenic abscesses are common or uncommon causes of FUO. Thus we have placed them in both columns to highlight not only this discordance, but also their ubiquity.

Table 2

| Table 2 |

Table 2

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Bone marrow</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Autoimmune</td>
</tr>
<tr>
<td></td>
<td>Immune</td>
</tr>
</tbody>
</table>

Although the causative agent may not be identified in 50% to 65% of cases, infectious agents are responsible for approximately 10% to 20% of FUO.2,13 Common and uncommon causes of FUO are listed in Table 1.1,11

The frequency of infectious diseases in some cohorts of patients older than 65 years with classic FUO is lower. Additionally, connective tissue diseases predominate particularly in developed countries.4 Infectious causes of classic FUO are listed in Table 1.1,11

FUO is generally less common in children, but infections still represent the most common etiology, including cytomegalovirus, Epstein-Barr virus, human herpesvirus (HHV)-6, HHV-7, osteomyelitis, bartonellosis, and urinary tract infections.1,12 Conversely, the frequency of infectious diseases in some cohorts of patients older than 65 years with classic FUO is lower. Additionally, connective tissue diseases predominate particularly in developed countries.4 Infectious causes of classic FUO are listed in Table 1.1,11

Fever in the returned traveler should always be taken seriously and the cause is usually identified before the illness becomes a FUO. However, malaria, typhoid fever, and acute HIV infection are the illnesses most likely to manifest as FUO in this setting.1 Neoplastic, inflammatory, and miscellaneous causes of classic FUO are listed in Table 2.2,13

Nosocomial

Nosocomial FUO manifests as fever during hospitalization for a different illness and requires at least 3 days of investigation and 2 days of culture incubation.4 The main causes of such FUO include drug fever, postoperative complications, septic thrombophlebitis, recurrent pulmonary emboli, myocardial infarction, blood transfusion, and Clostridioides difficile colitis.1 However, countless etiologies often exist in the setting of highly complex critical care. As Harold W. Horowitz, MD, points out in his perspective article “Fever of Unknown Origin or Fever of Too Many Origins?” the new FUO that infectious diseases consultants face is often found in critically ill patients who have multiple potential sources and relatively underwhelming or equivocal work-up. These patients are usually already receiving broad-spectrum antimicrobials, and decisions about expanding work-up or coverage are often challenging.5

Neutropenic

Neutropenic FUO is defined as a temperature greater than 38.3 °C recorded on several occasions in a patient whose neutrophil count is less than 500/μL or expected to fall to that level in 1 to 2 days. Importantly, an FUO can only be considered if 2 days or more of incubating cultures has not revealed a cause.1,4

Patients with neutropenia are at high risk of infection due to impaired

[10 | Contagion® • August 2021]
TABLE 2. Common and Uncommon Causes of Neoplastic, Inflammatory, and Miscellaneous FUO4,13

<table>
<thead>
<tr>
<th>NEOPLASIA</th>
<th>INFLAMMATORY</th>
<th>MISCELLANEOUS</th>
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<tbody>
<tr>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Leukemia</td>
<td>GCA* Adult-onset Still</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disease</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td></td>
<td>SLE</td>
</tr>
<tr>
<td>Castleman disease</td>
<td></td>
<td>PMR</td>
</tr>
<tr>
<td>Mesothelioma</td>
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<td>IBD</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer; CPE, chronic pulmonary embolism; FM, familial Mediterranean fever; FUO, fever of unknown origin; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; IBD, inflammatory bowel disease; MDS, myelodysplastic syndrome; MM, multiple myeloma; PAN, polyarteritis nodosa; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

*Accounts for 16%-17% of all causes of FUO in elderly patients.

HIV-ASSOCIATED

HIV-associated FUO is defined as a temperature greater than 38.3 °C that is found on several occasions over more than 4 weeks or more than 3 days in hospitalized patients with HIV infection. This diagnosis is considered if appropriate investigations over 3 days, including 2 days of culture incubation, reveal no source.4,4 As expected, the main risk factor for FUO in people living with HIV (PLWH) is a lack of antiretroviral therapy.17,18 In general, FUO in PLWH is due to opportunistic infections, and the specific etiology largely depends on the frequency of pathogens in a particular location.1 In a case-control study conducted over 6 years in Madrid, Spain, the main causes of FUO in PLWH were mycobacterial infections, including tuberculosis (21%) and Mycobacterium avium-intracellulare (25%), leishmaniasis (12%), and lymphoma (8%); 19% of cases were undiagnosed.17 Notably, noninfectious inflammatory conditions such as connective tissue diseases are very rare in this population.18,19 Similarly, a retrospective study conducted in Michigan and Boston revealed disseminated Mycobacterium avium complex as the most common etiology of HIV-associated FUO (31%), followed by Pneumocystis jirovecii pneumonia (13%), cytomegalovirus (11%), histoplasmosis (7%), lymphoma (7%), and tuberculosis (5%).20

FINDING A CAUSE

Even though the differential diagnosis of FUO is broad, a thorough history and detailed physical examination should provide key information to guide the work-up in a stepwise fashion. This will help physicians to avoid obtaining unnecessary studies that may be costly and difficult to interpret in the wrong clinical context.1 A history of present illness should include travel history, animal exposure, immunosuppressive history, and therapeutic and toxin history. The continued reassessment and revisiting of the history is crucial, especially as testing results for various pathogens return. Indeed, as evidenced by research performed during a time when laboratory testing and diagnostic imaging were still rudimentary, most patients who eventually received diagnoses were not suffering from rare conditions but rather atypical presentations of more common illnesses.21

As Wright and Auwaerter emphasized in their review, many algorithms that assist with the diagnostic work-up have often been indiscriminately applied, which has led to excessive testing. These authors point out that potentially diagnostic clues (PDCs) should guide further work-up.4 And without a thorough assessment, such PDCs may never be elucidated.

NUCLEAR MEDICINE TESTING

AND DIAGNOSTIC DILEMMAS

This has been a controversial area in the diagnosis of FUO, especially in cases in which the initial evaluation is unrevealing. Gallium 67 and indium 111-labeled studies (via leukocyte scanning) are highly sensitive but nonspecific tests that often lead to more focused testing. Newer modalities such as 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) and magnetic resonance imaging (specifically diffusion-weighted imaging) have also shown promise in identifying anatomic sites of inflammation or infection as well as malignancy.22,23 18FDG illuminates areas of increased cellular glucose metabolism, present in many conditions; it exposes patients to less radiation than conventional computed tomography (CT) and has not been associated with nephrotoxicity.24 This modality and PET/CT have reported sensitivities that approach 85% and are useful for localizing lesions and areas that may be of further interest. For example, authors of a meta-analysis reported that 18FDG-PET combined with CT localized an undiagnosed fever source in 58% of patients.25 A growing body of evidence suggests that early implementation increases diagnostic accuracy.26

But diagnosis via an empiric “response to therapy” rarely, if ever, provides a diagnosis. Antibiotics should never be initiated for the purposes of treating fever alone and will decrease the diagnostic yield of important culture and pathology data. Although unstable patients may require time-limited empirical therapy, the concept of “emergent FUO therapy” is not one that is grounded in science. In fact, focused diagnostic testing should be prioritized in the appropriate setting.

WHERE DO WE GO FROM HERE?

FUO continues to pose significant diagnostic challenges and can dramatically impact patients’ clinical courses. Advances in diagnostic and laboratory testing, although extraordinary, should not outweigh the continued reassessment of a patient’s history and physical examination to find diagnostic clues. It is to these roots of internal medicine that we should always seek to return. From this grounding, an appropriate application of technology can aid us in uncovering a diagnosis. ▲

*References are available at ContagionLive.com.*
The Variety of Variants in COVID-19

The evolution of the major variants, including the delta mutation.

BY RICK STARLIN, MD; AND KELLY CAWCUTT, MD, MS, FACP, FIDSA

Merriam-Webster defines variant as “manifesting variety, deviation, or disagreement.” Variant has become a normal part of our lexicon during the COVID-19 pandemic, but what does this actually mean for SARS-CoV-2? SARS-CoV-2 is the virus that causes COVID-19 infection. It is an enveloped, nonsegmented RNA virus with an error-prone RNA polymerase that leads to accumulated mutations during periods of high viral replication. Many of these mutations will not rise to a level of clinical significance but some will confer a fitness advantage on the virus. This advantage may lead to easier transmission, immunologic escape, less response to therapeutics, or more severe clinical disease. These fitter mutant viruses have been deemed variants. They had been expected to occur and will continue to become more diverse and potentially more challenging as the pandemic persists.

The scientific community has been monitoring and assessing the evolution of SARS-CoV-2 since January 2020 when information about the virus first became available. During late 2020, investigators identified the emergence of variants that posed an increased risk to global health. They have since developed a variant classification scheme that groups SARS-CoV-2 variants into 3 distinct groups based on viral and clinical characteristics: variant of interest (VOI), variant of concern (VOC), and variant of high consequence. A VOI has been defined as possessing specific genetic markers that are associated with changes to receptor binding, reduced neutralization by antibodies generated from previous infection or vaccination, reduced efficacy of treatments, potential diagnostic impact, or predicted increase in transmissibility or disease severity. A VOC is defined as showing evidence of increase in transmissibility, more severe disease, significant reduction in neutralization by antibodies, reduced effectiveness of treatment or vaccines, or diagnostic detection failures. A variant of high consequence shows clear evidence that prevention measures or medical countermeasures have significantly reduced its effectiveness relative to previously circulating variants. Currently no SARS-CoV-2 variants rise to the level of high consequence.

The variants were originally labeled with the location in which they were first detected. Those labels led to stigmatization and discrimination. Rambaut et al proposed a dynamic nomenclature for SARS-CoV-2 lineages that focuses on actively circulating virus lineages and those that spread to new locations. This became known as the Pango classification of SARS-CoV-2. However, these labels were confusing and difficult to remember as the number of variants grew. At the end of May 2021, the World Health Organization (WHO) assigned a simple label for key variants of SARS-CoV-2 using letters of the Greek alphabet. These labels have become widely accepted.

The Centers for Disease Control and Prevention (CDC) and WHO’ lists of VOIs and VOCs vary slightly, with the CDC listing epsilon (Pango B.1.427/B.1.429) as a VOC but the WHO listing it as a VOI. Otherwise the VOCs are similar across both agencies. Looking deeper into the...
VOCs on both lists shows essentially 4 main variants being closely monitored and studied. The alpha variant (Pango B.1.1.7) was first identified in the United Kingdom and designated a VOC by the WHO in December 2020, with the first samples dating back to September 2020. Alpha shows a 43% to 90% increased transmissibility rate, potentially increased severity based on hospitalization and fatality rates, but no reduced response to monoclonal antibody treatments and only minimal impact on neutralization by convalescent and postvaccination sera. The beta variant (Pango B.1.351), first identified in South Africa, was designated a VOC by the WHO in December 2020. The first samples date to May 2020. Beta shows an increased transmissibility rate of approximately 50% but also shows significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment; other emergency use authorization (EUA) monoclonal antibody treatments also are available. Beta also shows notable reduced neutralization by convalescent and postvaccination sera. The gamma variant (Pango P.1) dates back to samples identified in Brazil in November 2020, and was designated a VOC by the WHO in January 2021. Gamma shows significantly increased transmissibility, with a rate possibly as high as 100%. It also has been shown to possess significantly reduced susceptibility to the bamlanivimab and etesevimab combination but retains susceptibility to other EUA monoclonal antibody treatments. Gamma displays reduced neutralization by convalescent and postvaccination sera. As a result, this variant (P1 or gamma) may cause severe disease even in persons who have been previously infected by another variant. The delta variant is the last VOC designated by the WHO on May 11, 2021, and is rapidly becoming the most problematic variant in the United States and worldwide. The earliest sample dates back to October 2020 in India. Delta shows an increased transmissibility rate (26%-113%) relative to alpha and potential reduction in neutralization by some monoclonal antibody treatments. It also demonstrates reduced neutralization by postvaccination sera, resulting in higher risks of infection and clinical progression of disease, even among those who have received vaccinations. Hospitalization rates as high as 85% above that seen with alpha have been reported. A variant deemed delta plus is also being monitored in England and India. It should be noted that to date none of the above variants have shown any changes in testing efficacy.

Where does this leave us? Clearly, SARS-CoV-2 will continue to evolve. Variants of concern will continue to develop, with selective advantage generally favoring those that are more transmissible. We now know more about delta per the CDC. Delta is no longer becoming the predominant strain, but in fact it has become the predominant strain. CDC data and updated guidance suggest that vaccine efficacy is no longer the same with this strain. Vaccinated persons are more likely to develop asymptomatic or mild infection. In addition, with infection, the viral loads remain elevated, therefore increasing the risk of transmission from vaccinated persons to others. The transmissibility of delta is markedly higher than alpha. For these reasons, the CDC has updated its guidance for mask use indoors in public areas amongst vaccinated persons in areas with substantial or high community transmission. We also have ongoing variant evolution with delta plus and lambda. Not much is known at this point, but with new variants comes concerns about the unknown. Vigilance in preventing transmission of infection and in monitoring for newer variants is critical, as a new VOC could evolve with even higher rates of immune evasion from vaccination or prior infection, prompting continued spread and risks of ongoing reinfection. However, such a variant would also require increased transmissibility to become the predominant circulating strain. The available vaccines continue to provide significant protection from the development of severe infection, aiding in the prevention of further variations emerging. Widespread, rapid vaccination is of paramount importance to avoid further surges. However, this does not negate the continued need for mask use, hand hygiene, distancing, and testing for those who are unvaccinated or may have a blunted immune response (immunocompromised patients). We may be entering a new phase of the pandemic regarding vaccines and variants, but the pandemic is not over

References are available at ContagionLive.com.
Examining the HIV Treatment Pipeline

A review of select investigational long-active treatment options for HIV

BY IAN COOK, PHARMD, AAHIVP, BCACP

(continued from cover page)

undetectable viral load, decrease HIV transmission, and improve quality of life.2 Earlier this year their request was answered with the US approval of long-acting cabotegravir/rilpivirine (CAB-LA/ RPV-LA; Cabenuva). This regimen is a monthly set of dual injections for the treatment of HIV in PLWH who are virally suppressed.3 Although this is the first approved long-acting HIV treatment, there are numerous other long-acting HIV therapies under investigation by a wide array of pharmaceutical and biotechnology companies. Two of the treatments furthest along in development are islatravir and lenacapavir. Both options are also first-in-class medications and their approvals would bring 2 new classes of medications to the fight against HIV.

ISLATRAVIR

Islatravir (ISL; MK-8591) is the first nucleoside reverse transcriptase translocation inhibitor and works with a dual mechanism of action. The agent rapidly undergoes phosphorylation intracellularly to its active form of islatravir triphosphate (ISL-TP).4 The active form then binds to reverse transcriptase and prevents the incorporation of nucleotides into the viral DNA, leading to immediate chain termination (Figure 1).6 If translation occurs, the active form also terminates the viral DNA chain by being added to the end of the viral DNA; this causes primer mismatch, leading to delayed chain termination (Figure 1).6 This secondary mechanism of action, delayed chain termination, is not seen in nucleoside reverse transcriptase inhibitors (NRTIs).7 ISL-TP is slowly metabolized back to islatravir intracellularly, can exit the cell in a usable form, be taken up by another cell, and undergo phosphorylation again to ISL-TP.6

Islatravir was designed to have a higher binding affinity for reverse transcriptase than current NRTIs. The higher affinity is the result of the addition of a 3’ hydroxyl group that is not found in other NRTIs but is found in natural nucleotides.5 A 2-fluoro group that is found in islatravir inhibits the metabolism of the drug and leads to a long half-life. The half-life of ISL-TP is estimated to be approximately 79 to 214 hours.7 Study findings have shown islatravir to have a high barrier to resistance and a potency 10 times greater than any therapy currently on the market.5,8 Islatravir has resistance to common NRTI mutations in vitro and “no single amino-acid substitution was shown to significantly decrease its potency.”8 Even though M184I and M184V did decrease the potency of islatravir, these mutations were still susceptible.8 Based on these properties, investigators are studying islatravir for a wide variety of clinical situations. The Illuminate trials are currently investigating islatravir in combination with doravirine for the treatment of HIV. In these trials, patient are receiving oral islatravir 0.75 mg and oral doravirine (Pifeltro) 100 mg daily.9 Investigators are studying the combination as switch therapy in virally suppressed patients and as initial therapy in treatment-naive patients. In one of the treatment-naive trials, islatravir plus doravirine was compared with doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF; Delstrigo).9 At 48 weeks, 90% of patients in the 0.75-mg islatravir arm had achieved an HIV-1 RNA level of less than 50 copies/mL compared with 83.9% of patients in the DOR/3TC/TDF arm.9 The most common adverse events in the islatravir arm compared with the DOR/3TC/TDF arm were headache (11.1% vs 6.5%), nausea (8.9% vs 9.7%), and diarrhea (6.7% vs 16.1%).9 In this trial, 37.8% of participants in the islatravir arm had a weight gain greater than 5% (compared with 22.6% in the DOR/3TC/TDF arm),9 mostly seen in the first 24 weeks. The authors hypothesized that this may be the result of a “return-to-health-effect” but more research is needed to determine the cause.9

The Illuminate series of trials is also evaluating the use of this combination in highly treatment-experienced patients and adolescents.4 Due to islatravir’s long half-life, investigators are examining extended dosing options. The

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FIGURE 1. Translocation Inhibition and Delayed Chain Termination

<table>
<thead>
<tr>
<th>Translocation Inhibition</th>
<th>Delayed Chain Termination</th>
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<tbody>
<tr>
<td>vRNA</td>
<td>ISL</td>
</tr>
<tr>
<td>Translocation</td>
<td>ISL changes</td>
</tr>
<tr>
<td>Nucle</td>
<td>As ISL</td>
</tr>
<tr>
<td>Viral</td>
<td>Viral</td>
</tr>
</tbody>
</table>

ISL, islatravir; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.
combination of MK-8507 with islatravir is under investigation as a once-weekly oral HIV treatment option. MK-8507 is a non-nucleoside reverse transcriptase inhibitor that itself is also under development. It has a "similar resistance profile to doravirine" but extended dosing. Islatravir is not only being investigated for treatment, but it is also being evaluated for pre-exposure prophylaxis (PrEP) in an array of formulations, including a once-monthly oral tablet and a yearly implant.

LENACAPAVIR
Lenacapavir (GS-6207) is the first capsid inhibitor. It works by "interfering with capsid-protein-mediated interactions between proteins that are essential" for capsid stability and transport. Specifically, lenacapavir inhibits "HIV replication as it interferes with the disassembly of the HIV capsid core, inhibits the role of capsid proteins during viral RNA/DNA translocation to the nucleus, and disrupts assembly of the capsid core" (Figure 2).

Both oral and subcutaneous formulations of lenacapavir are currently in development. Oral lenacapavir has a half-life of approximately 12 days and accumulates significantly with multiple doses. This allows for extended dosing intervals, with the oral formulation being dosed once weekly and the subcutaneous formulation being dosed every 6 months. Lenacapavir has been shown in vitro to be fully active against major resistance mutations including K65R, M184V, K103N, Q148R, and N155H. Based on data from ongoing trials the most common adverse events with lenacapavir, not including injection site reactions, are headache (11.1%), nausea (11.1%), and diarrhea (9.7%). Injection site reactions (swelling, erythema, nodule, and pain) were common with lenacapavir (46%) but were mostly grade 1 (82%) and resolved within a few days. Injection site reactions did not cause any patient to discontinue participating in the CAPELLA trial (NCT04150068). The CAPELLA trial is currently investigating lenacapavir for use in highly treatment-experienced patients, in combination with an optimized background regimen. The CALIBRATE trial (NCT04143594) is investigating the combinations of lenacapavir withbictegravir (BIC), lenacapavir with FTC/TDF, and lenacapavir with TDF compared with the standard of care (BIC/F/TAF). In both trials, patients will start on a loading dose of oral lenacapavir at 600 mg on day 1, 600 mg on day 2, and 300 mg on day 8. On day 15, patients will receive their first subcutaneous dose of lenacapavir 927 mg, then a subcutaneous dose of lenacapavir 927 mg every 6 months. The oral loading dose of lenacapavir is required to optimize therapeutic concentrations, unlike the oral load used with CAB-LA/RPV-LA, which is for safety only. Lenacapavir is also being investigated as a twice-yearly subcutaneous injection for PrEP.

COMBINATION
Earlier this year, the companies developing islatravir and lenacapavir announced a codevelopment partnership. They plan to study the combination of these medications as a complete 2-drug regimen for the treatment of HIV. Under the partnership, the companies will develop both an oral and an injectable formulation of the combination. The first trials for the oral formulation are slated to begin later this year. Neither company has confirmed the extended dosing strategy that will be investigated in these trials.

CONCLUSIONS
Islatravir and lenacapavir are both promising HIV treatments currently in development. The array of formulations and extended dosing options of these treatments will enable providers to better tailor a patient’s treatment to their needs. The addition of 2 new classes of medications for HIV treatment provides new treatment options for those patients who have been living with HIV for decades and who are highly treatment experienced. These patients usually have few treatment options and are on multiple, partially active medications. Although long-acting therapy alone will not solve adherence issues, it will be interesting to see the impact these therapies have on patients. As with any new medications, cost, insurance coverage, and implementation barriers will all be considerations for these treatments if they are approved by the FDA.
Daptomycin as Frontline Therapy for MRSA Bacteremia: Has the Time Come?

Findings increasingly suggest the mortality risk may be reduced by initiating daptomycin within 3 days of infection.

BY MICHAEL TRISLER, PHARMD, MPH, BCIDP; FIDELIA BERNICE, PHARMD, BCIDP; AND LOUISE-MARIE OLEKSIUK, PHARMD, BCPS

received additional FDA labeling for patients with *S aureus* bacteremia, including those with right-sided infective endocarditis, following the completion of a phase 3, randomized, double-blind clinical trial that found daptomycin to be noninferior to the standard of care.1

*S aureus* bacteremia is a heterogeneous entity. Treatment of methicillin-susceptible *S aureus* (MSSA) bacteremia with antistaphylococcal penicillin is associated with superior outcomes when compared with vancomycin.2,3 On balance, daptomycin is noninferior to the standard of care for *S aureus* bacteremia, which was defined as treatment with an antistaphylococcal penicillin or vancomycin.4 Notably, however, only 89 of 235 patients (38%) with *S aureus* bacteremia enrolled in the trial had bacteremia due to MRSA.4 The large number of patients with MSSA and the known superiority of antistaphylococcal penicillins make it difficult to extrapolate these conclusions to the efficacy of daptomycin vs vancomycin for MRSA bacteremia. Post hoc analyses further evaluated patient outcomes according to pathogen-specific therapy, and the efficacy of daptomycin was similar to both antistaphylococcal penicillin and vancomycin; however, the power to detect a significant difference was limited.5

Since these data were published in 2007, additional studies have been conducted whose results suggest a benefit to early daptomycin initiation in patients with MRSA bacteremia. Data from 2 matched, retrospective cohort studies found significantly lower 30-day mortality rates when daptomycin was initiated within 72 hours of MRSA bacteremia.6,7 Most recently, investigators from the Iowa City VA Health Care System also found that switching to daptomycin within 3 days of the initial receipt of vancomycin was associated with a lower 30-day mortality rate among patients with MRSA bacteremia. This benefit was not observed if patients were switched to daptomycin after 3 days.8 The retrospective review, published in *Clinical Infectious Diseases*, included 7411 patients from 124 VA hospitals with MRSA bacteremia who had initially received vancomycin. The investigators excluded patients who had died within the first 3 days of antibiotic treatment, had been treated with another anti-MRSA antibiotic for at least 3 days prior to receiving vancomycin, had received vancomycin and daptomycin concomitantly for more (continued from cover page)
than 24 hours, or received daptomycin before vancomycin. Six hundred and six (8.2%) patients had been switched to daptomycin at any time during their first hospitalization. The median time to the switch was 6 days (interquartile range, 3-10 days), and 108 (1.5%) patients were switched within the first 3 days of the initial receipt of vancomycin. The authors elected to use a 3-day period for switching because of prior clinical trial recommendations which suggest that fewer than 3 days of alternative therapy is unlikely to impair the ability to attribute patient outcomes to the antibiotic of interest.

When compared with patients who remained on vancomycin, those who switched to daptomycin were significantly more likely to have a vancomycin minimum inhibitory concentration (MIC) of 2 μg/mL or greater; experience acute kidney injury (AKI), osteomyelitis, or endovascular infection; have an infectious diseases physician consult; and have a higher mean body mass index. Patients who switched to daptomycin early in treatment were also younger and more likely to receive therapy with a concomitant anti-MRSA antibiotic, particularly linezolid (2.5% vs 0.2%; P < .001) but not ceftaroline (1.7% vs 0.9%; P = .48). After adjusting for these findings and other potential confounders, patients who switched to daptomycin within 3 days were less likely to die within 30 days (HR, 0.48; 95% CI, 0.25-0.92). Importantly, the mortality risk reduction was only observed for those who switched to daptomycin within 3 days. There was no significant difference after adjustment when comparing patients who remained on vancomycin with those who switched to daptomycin at any point during their initial hospitalization (HR, 0.87; 95% CI, 0.69-1.09). Since its FDA approval in 1958, vancomycin has been widely prescribed and is recommended as first-line therapy for patients with MRSA bacteremia. The use of vancomycin requires therapeutic drug monitoring to both maximize efficacy and reduce the risk of AKI. The clinical and economic impact of AKI is significant, as noted in the vancomycin dosing guidelines, which state: “many patients, especially those who are critically ill, do not fully recover renal function after AKI, and even mild AKI can significantly decrease long-term survival rates, increase morbidity, prolong hospitalizations, and escalate healthcare costs.”

Additional studies have been conducted, and their results suggest a benefit to early daptomycin initiation in patients with MRSA bacteremia. A meta-analyses by van Hal and colleagues reported the prevalence of vancomycin-associated AKI to range between 5% and 43%. Vancomycin trough concentrations of 15 mg/L or greater were associated with significantly increased odds of AKI compared with trough concentrations below 15 mg/L (odds ratio, 2.67; 95% CI, 1.95-3.65). Accordingly, updated vancomycin dosing guidelines now recommend that area under the curve (AUC)-guided dosing be performed, which is associated with a lower risk of vancomycin-associated AKI. Although transitioning to AUC-guided dosing may lower AKI rates, it requires additional laboratory and clinical resources to implement.

Daptomycin’s once-daily dosing, lack of required therapeutic drug monitoring, and favorable tolerability profile make it a desirable candidate for patients with MRSA bacteremia, who often require prolonged courses of therapy. The potential advantages of daptomycin have been historically offset by its high cost; however, the FDA approved the generic formulation in 2019 and the acquisition costs have decreased significantly. These factors, coupled with a mortality benefit when initiated early, should prompt clinicians to reconsider vancomycin as first-line therapy for MRSA bacteremia and shift practice toward the early initiation of daptomycin.

The preferential use of daptomycin warrants consideration of potential collateral effects. Most notably, VRE has a paucity of treatment options, and increased use of daptomycin could potentially result in greater selective pressure for daptomycin-resistant VRE. Switching to daptomycin may have many potential benefits, but current data suggest the mortality benefit for MRSA bacteremia is predicated on the drug’s early use, rather than waiting for persistent disease, treatment failure, or toxicity with vancomycin. Furthermore, concerns related to vancomycin-associated AKI may not be as prudent if utilizing an early switch approach in these patients, as most episodes develop after at least day 4 of therapy. To this end, we favor daptomycin initiation once MRSA bacteremia has been identified rather than as empiric therapy or based on Gram stain results.

In light of the current evidence, antimicrobial stewardship programs (ASPs) should consider developing criteria targeting the early switch to daptomycin in specific patient populations with MRSA bacteremia. Patients who may benefit the most include those who lack pulmonary involvement and are critically ill (eg, septic shock), those who have complicated infections (eg, endocarditis), or those who are at greater risk for vancomycin-associated AKI (eg, elderly patients, those with baseline chronic kidney disease).

Daptomycin may also be preferred in patients with MRSA isolates possessing reduced susceptibility to vancomycin, those with limited intravenous access, and patients who have difficulty obtaining therapeutic vancomycin concentrations or have fluctuating renal function. Real-time alerts via the electronic health record, third-party software, or the microbiology laboratory may assist ASPs with the timely identification of these patients. Additionally, ASP collaboration with the microbiology laboratory can be used to promote the implementation of rapid diagnostics that allow for earlier identification of the organism and resistance patterns.

References are available at ContagionLive.com.
Children, COVID-19, and Another Crazy Respiratory Viral Season

Kevin J. Downes, MD; and Contagion® section editor Conan MacDougall, PharmD, MAS, BCPS, BCIDP, discuss these important topics as another season approaches.

BY CONAN MACDOUGALL, PHARMD, MAS, BCPS, BCIDP

(continued from cover page) vaccine hesitancy. Vaccinated people will be triumphantly ditching their masks, except immunosuppressed patients who may not mount as robust of an antibody response. Children will likely be returning to in-person school under varying masking and distancing conditions and before the availability of vaccination for younger children. Assuming a COVID-19 vaccine is approved for younger children, parents will have to make risk-benefit decisions about vaccinations for those children during a time when the levels of circulating virus may be low. Additionally, other respiratory viruses such as influenza that were near absent in the 2020-2021 season will return, whether with a vengeance or a whimper. Conan MacDougall, PharmD, MAS, BCPS, BCIDP, Contagion’s section editor for Antimicrobial Stewardship & Infection Prevention, discusses these and other questions with Kevin J. Downes, MD, an attending physician in the Division of Infectious Diseases at Children’s Hospital of Philadelphia in Pennsylvania.

CONAN MACDOUGALL (CM): You help take care of sick and vulnerable children in the hospital, some of whom have had COVID-19 or are at risk of severe COVID-19. What do you wish people who may be hesitant to get vaccinated, or who downplay the disease, knew about your experience?

KEVIN J. DOWNES (KD): Since the pandemic began, death has been the focal point of discussions about COVID-19. Understandably, early vaccination efforts were focused on those who were most vulnerable: older adults, immunocompromised individuals, and health care workers. In turn, people have viewed their own vaccine decisions in light of their personal risk of death from COVID-19. While reducing one’s risk of death is certainly a goal of vaccination, it’s not the only reason to get vaccinated. COVID-19 vaccines protect you and those around you. So it frustrates me when I hear people say they don’t want to get vaccinated because they feel that their risk of dying from [the disease] is low. While that may or may not be true, that argument ignores the risk that being unvaccinated poses to others who can’t get vaccinated, such as children, or who may not be fully protected with vaccines, such as immunocompromised individuals.

Along these lines, there has been an argument against vaccinating children because they are at low risk for severe disease. But kids can get sick and die from COVID-19. They can be hospitalized with it, get complications from it, and develop long-term effects following it. While it’s true that kids are at a lower risk of dying from COVID-19 than older adults, vaccination will keep kids safe too. For now, while young children remain ineligible for vaccination, the best way for us to protect them is to get everyone around them vaccinated.

CM: We’ve seen the rapid study and deployment of a variety of experimental therapeutics for COVID-19. Most of those studies were performed in adults. What were the challenges in adapting those data for use in pediatrics?

KD: What’s been most consistently challenging [in terms of] COVID-19 therapeutics has been figuring out the risk-benefit ratio for children. This is primarily because age has been such an important factor influencing COVID-19 severity and outcomes. As a result, it’s been really hard to extrapolate how the treatment effects [shown in results] from adult studies apply to kids. For example, many COVID-19 therapeutics have focused on preventing death in hospitalized patients with severe disease. But the risk of dying from COVID-19 is higher for a hospitalized adult than it is for a child. So even if [the results of] a study find that there’s a significant mortality benefit in hospitalized adults, that doesn’t mean the same benefit would be present in children. We’ve really had to look carefully at the data, at the population studied, and the setting in which these therapeutics were used to try to estimate the risk-benefit ratio in children. Even now, after a year, we still don’t have strong pediatric-specific data for most COVID-19 therapeutics.

Another challenge has been identifying which children are at highest risk for severe [illness]. Drugs that have been studied for the prevention of progression from mild to severe COVID-19, such as monoclonal antibodies, have largely focused on patients at high risk for poor outcomes from COVID-19. However, since fewer children develop severe COVID-19, it has not been readily apparent which pediatric populations these are. We have relied largely on our experience with other respiratory viruses to know who is most vulnerable.

CM: Looking ahead to the fall and to influenza vaccination season, have the COVID-19 vaccination experiences taught us lessons we could apply toward other vaccine campaigns, such...
as the flu, or are the COVID-19 vaccinations just too different?

**KD:** One of the rallying cries for COVID-19 vaccination has been to bring about a return to normalcy. I don’t think that theme will promote uptake of the influenza vaccination this fall. Flu has been a part of people’s normal lives for a long time, and many people have already decided if being protected against flu is something that’s important to them. However, I do think there will be an opportunity to build on the messaging surrounding staying healthy. If COVID-19 remains circulating in communities this fall and winter, which is likely, it will continue to be important to identify and isolate cases quickly. That means testing people who have febrile or respiratory illnesses for COVID-19 to know what’s COVID-19 vs flu or another virus. One way to stay healthy this winter will be for people to get their flu shots. So even if people are not worried enough about the flu specifically, we may be able to build on the idea that it will be important to be protected against all viruses.

**CM:** At my hospital we are taking advantage of hospital admission to vaccinate many adult inpatients against COVID-19, regardless of their reason for admission, as we do with influenza. As vaccines are approved for a greater spectrum of pediatrics, do you foresee a similar approach for children admitted to your hospital?

**KD:** This is the ‘vaccinate em’ while you ‘got em’ strategy, which is a good way to vaccinate as many people as possible. This can be an effective method to combat some of the access issues that have prevented adults from getting vaccinated against COVID-19, and [it helps them] avoid the need for a separate...visit for a COVID-19 vaccination. But I am not sure how this will play out in pediatrics. Certainly, there could be an appeal for some families as it’s 1 less health care visit. However, the COVID-19 vaccines that are currently approved for children 12 and older are 2-dose series, and I don’t know when single-dose vaccines will be available for them. As a result, if a pediatric hospital were to implement this approach, it would also be important for that hospital to ensure that the child will have access to a second dose to complete the series.

Additionally, a number of communities have been able to successfully administer COVID-19 vaccination programs in older children through schools. This is probably a better and more efficient approach to ensure access to COVID-19 vaccines for children than through the hospital setting.

**CM:** We basically went without a flu season last year, and the incidence of other respiratory viral infections was significantly decreased or shifted in seasonality. Did we learn anything from this experience that might alter practice once those viruses come back?

**KD:** Masks and social distancing work. This has been reiterated time and time again during this pandemic. Despite the naysayers, the epidemiology of non–COVID-19 respiratory viral infections this past year has clearly borne this out. As you mention, we saw essentially no influenza transmission last year—I believe the CDC reported just a single pediatric death from flu all of last season—which is a testimony to the effectiveness of the public health measures put in place. While this may not change how most people behave, I would not be surprised to see masks being worn more routinely when people cannot maintain social distancing, such as on planes, on public transportation, etc. Hopefully we can all embrace this. That’s not to say everyone should be wearing masks. But if a person feels more comfortable wearing one because they know it keeps them safer, then that should be accepted and even encouraged. Certainly, for immunocompromised individuals, who are at higher risk for severe infections not only from SARS-CoV-2 but other respiratory viruses, I believe that the effectiveness of masks and distancing will have longer lasting implications on general infection prevention guidance…And we hopefully will see more routine mask wearing in health care settings, especially during winter months.

**CM:** A lot of attention has been given recently to transplant patients, who appear to have decreased antibody responses to COVID-19 vaccines. Should transplant recipients or other immunocompromised patients routinely get extra doses of COVID-19 vaccines? Should they get a booster dose if their COVID-19 antibodies are low after completing the vaccine series?

**KD:** No, based on current information I would not administer extra doses of COVID-19 vaccine to transplant patients. It is not entirely surprising that transplant recipients would have decreased production of antibodies to COVID-19 vaccines compared with the general population. We know this to be true for influenza and some other vaccines as well. But having low-binding antibodies doesn’t necessarily mean that someone isn’t protected against COVID-19, particularly severe COVID-19. Cellular responses also contribute to immunity, and some transplant recipients may mount effective cellular responses without producing high antibodies. Furthermore, neutralizing antibodies, which are a better marker of protection than binding antibodies, are not measured by commercial antibody tests. While COVID-19 vaccines may be less immunogenic in transplant recipients, these data don’t tell us the extent to which the vaccines are clinically effective in this population. Until we know that, and we have tests that are true correlates of protection, I don’t think we should be recommending extra doses of vaccines, early boosters, or the routine performance of serologic tests. Instead we should be encouraging transplant recipients to get their vaccines and remain vigilant in their infection prevention practices. With continued research, we will know how effective these vaccines are against mild, moderate, and severe COVID-19 in the transplant population, which can inform recommendations about COVID-19 vaccine schedules and booster dosing.
Paradigm Shift in the Management of Clostridioides difficile Infections

GINA BATTAGLIA, PHD

Management of Clostridioides difficile infection (CDI) has shifted toward more targeted, microbiome-sparing approaches to decrease recurrence and improve clinical outcomes. Demonstrating the return on investment will be important to increase the uptake of these new, more expensive agents, according to panelists who participated in a Contagion® Peer Exchange panel moderated by Peter L. Salgo, MD.

UPDATES TO CLINICAL GUIDELINES

Thomas Lodise, PharmD, PhD, noted that an update to the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines prioritized fidaxomicin as the primary agent recommended for patients with initial and recurrent episodes of CDI. The update was based on data showing lower rates of recurrence with fidaxomicin than with vancomycin, including results from the initial phase 3 trial (NCT00314951) in patients with clinically diagnosed CDI (initial or recurrent) and the phase 3b/4 EXTEND trial (NCT02254967) that used an extended-pulsed fidaxomicin in hospitalized patients 60 years or older.

The update was delivered as provisional recommendations at IDWeek 2020.

"Fidaxomicin seems to come to the forefront for treatments with the initial episode," said Joseph Reilly, PharmD, BCGP. "When fidaxomicin came out, I don't think many people were familiar with the term sustained clinical response. That seems to be the advantage of using [fidaxomicin] in many patients, that they are less likely to have recurrences."

Lodise added that the provisional IDSA/SHEA recommendations included an additional recommendation for bezlotoxumab, a human monoclonal antibody that targets toxin B, in individuals who are at high risk for recurrence, are 65 years or older, are immunosuppressed, have a history of CDI, or have severe CDI. The MODIFY I and MODIFY II trials (NCT01241552 and NCT01513239) showed that bezlotoxumab was associated with lower rates of recurrence in multiple prespecified subgroups, including patients who were 65 years or older, had immunocompromised status or severe CDI, or had a CDI episode within the past 6 months.

SELECTING THERAPY TO TREAT C DIFFICILE

Adequate treatment of CDI is particularly challenging, because it requires eradicating the C difficile organism while attempting to restore the microbiota, according to Paul Feuerstadt, MD. He added that optimally effective treatment involves antimicrobial therapy (such as vancomycin or fidaxomicin) followed by modulation of the immune system with bezlotoxumab or microbiota restoration therapy to "give C difficile that knockout punch."

"Most patients who receive either fidaxomicin or vancomycin will respond and will get better," said Feuerstadt. "What we're talking about with other therapies are those subgroups that are at greater risk: age over 65, history of immune suppression, history of C difficile, the NAP1/B1/027 strain, severe infection, patients on PPIs [proton pump inhibitors], [and] patients who received concomitant antimicrobials. Those are the individuals [who] we're really focusing on [to gain] a better understanding of how we get rid of this."

"I think we need to stop talking about drugs in terms of dollars and cents, which we're never going to get away from, and rather say, 'If I do this, these are the adverse events I'm going to prevent.' "

-Thomas Lodise, PharmD, PhD

Feuerstadt added that the "entire clinical gestalt" of a patient should be considered in the approach to therapy. Factors that may affect management decisions include source of infection (community or health care setting) and presence of multiple risk factors for recurrence, severe disease, and high white blood cell count and creatinine level.

"Deciding between vancomycin and fidaxomicin to me really boiled down to those factors and risk factors for recurrence," said Feuerstadt. "Fidaxomicin's sweet spot is that it is associated with statistically significant reduction in rates of recurrence. Patients who have multiple high-risk factors for recurrence would benefit from that product."

C DIFFICILE TREATMENT: FIDAXOMICIN

Fidaxomicin is a macroline-like antibiotic that inhibits RNA synthesis by binding to bacterial RNA polymerase and has potent activity against CDI, according to Lodise. He added that the more targeted approach, less disruption of the gut microbiota, and lower minimum inhibitory concentration.
with fidaxomicin likely contribute to the lower rates of recurrence compared with vancomycin. "It’s that prolonged disruption of the microbiota [with vancomycin] that drives a lot of the adverse outcomes we see in some of our CDI patients," he said.

"When we think about treating CDI from a stewardship standpoint, our thought [is], ‘How do we stop that event from moving forward?’" Lodise said. "Although we appreciate the similar clinical response, we were very impressed with a lot of the lower recurrence data and particularly with some of the altered dosing with fidaxomicin in one of their 2 trials." Lodise noted that the tapered and pulsed regimen of fidaxomicin may be beneficial for treating a recurrent episode while facilitating recovery of the microbiota, but that developing additional methods to replenish the microbiota will be important moving forward.

Reilly noted that although the data appear to support the use of fidaxomicin in the first-line setting, the high acquisition cost of the drug relative to vancomycin remains a concern. However, Salgo and he agreed that using the more expensive fidaxomicin could reduce overall costs of care in the long run and improve patient outcomes by reducing readmission rates and other comorbidities.

"It’s that silo budget mentality, just looking at how much we’re spending and not looking at the outcomes," said Reilly. "If I spend more money and it’s saved somewhere else by decreasing admissions that might lose money...people often don’t take that into consideration."

Teena Chopra, MD, MPH, said that patient-centered outcome research could help demonstrate the overall improvement in clinical outcomes and cost savings with fidaxomicin. Chopra and her colleagues performed an analysis of a patient discharge database that showed that the 30-day readmission rate was higher for patients with CDI than for those without CDI (30.1% vs 14.4%, respectively). In addition, results from a single-center retrospective study demonstrated that, on average, treatment with fidaxomicin saved the hospital $3207 per patient compared with vancomycin treatment (even though the drug costs were higher with fidaxomicin). This was largely attributable to the lower readmission costs associated with fidaxomicin.

Lodise noted that the financial penalties associated with high rates of CDI and readmission and the escalating costs associated with multiple recurrences should encourage the shift toward fidaxomicin. He added that the 2020 IDSA/SHEA provisional recommendations were an important step forward in the acknowledgment of return on investment by including the number needed to treat.

"I think we need to stop talking about drugs in terms of dollars and cents, which we’re never going to get away from, and rather say, ‘If I do this, these are the adverse events I’m going to prevent,’” said Lodise. “We must change the script a bit. Cost is always going to be the common denominator, but we need to talk about how, with this investment, this is going to be [the] return, and we must make that return in terms of dollars and cents as well.”

CHOOSING BETWEEN THERAPIES

Feuerstadt highlighted the fact that the lower recurrence rates observed in multiple trials comparing fidaxomicin with vancomycin were also observed in real-world data from the United Kingdom. This study, which assessed recurrence rates during the years before and after local introduction of fidaxomicin in 7 UK hospitals, showed that 2 hospitals that used fidaxomicin in the first-line setting for all primary and recurrent infections had a decrease in recurrence rate (10.6% to 3.1% and 16.3% to 3.1% for hospitals “A” and “B,” respectively). Feuerstadt noted that even the hospital that used fidaxomicin only for first recurrences (hospital “D”) had a decrease in recurrence rate (12.5% vs 21.1%, prior to fidaxomicin), suggesting that the real-world data reflect the results observed in phase 3 clinical trials.

“What we’re seeing is no matter how fidaxomicin is being used, if a health care system commits to it, it seems to remarkably reduce those rates of recurrence,” concluded Feuerstadt. ▲

References are available at ContagionLive.com.
Tracking a Rare Postinfectious Complication of COVID-19 in Children

BY JOHN PARKINSON

Multisystem inflammatory syndrome in children (MIS-C), is rare and mysterious in its presentation, effects on young patients, and related immune responses. The condition, also known as pediatric multisystem inflammatory syndrome—temporarily associated with SARS-CoV-2 (PIMS-TS), is a unique complication related to COVID-19 infection and can have a broad presentation spectrum that may overlap with Kawasaki disease.

Investigators from the United Kingdom wanted to discover the long-term physical and psychological outcomes in children with the syndrome and used a multidisciplinary team to review their cases at a 6-month follow-up. This retrospective cohort study involved 46 children who met the criteria and had been admitted to a hospital in London, between April 4 and September 1, 2020.

A 6-month follow-up showed some common conditions. “Common sequelae included muscular fatigue; neurological sequelae, such as proximal myopathy, dysmetria, and abnormal saccades; and anxiety and emotional lability,” the investigators wrote.

From a physiological standpoint, there was a reduced ability to exercise among the children. “The notable reduction in functional exercise capacity in this cohort could be attributed to various factors: the underlying inflammatory nature of PIMS-TS; the high proportion of patients requiring PICU [pediatric intensive care unit] admission, resulting in the possibility of critical illness myopathy; [nonadherence to] home-based exercise programs; a pre-illness sedentary lifestyle; and side-effects of high-dose corticosteroid use, which might have contributed to proximal myopathy and increased BMI [body mass index] at the initial 6-week follow-up,” said the investigators.

They noted that residual neurological effects have been witnessed in other studies looking at PIMS-TS, but that not many were observed in this study.

“In our cohort, persistence of subtle findings, which were only noticeable on detailed neurological exams, did not correlate with neurological functional impairment (median Expanded Disability Status Scale score, 0 at 6 months),” the investigators reported. “Although 98% of patients had resumed full-time education by 6 months, formal neuropsychology testing was not done and the long-term cognitive effects of PIMS-TS require attention, given the high frequency of neurological involvement at presentation.”

They stressed the importance of continued follow-up in these patients.

“Whether other longer-term sequelae will manifest beyond 6 months (eg, inflammatory gastrointestinal pathology or renal disease from acute kidney injury) is yet to be determined, stressing the importance of ongoing multidisciplinary follow-up of patients with PIMS-TS,” the investigators concluded.

Second COVID-19 Wave Is Linked to Greater Mortality, Hospitalization

BY KILLIAN MEARA

Results from a recent study by investigators from South Africa’s National Institute for Communicable Diseases show that the second wave of COVID-19 in that country was associated with a higher incidence of disease, a rapid increase of hospital admissions, and an increase in in-hospital mortality.

“This 13-month study of 2 waves driven by 2 different viral lineages is both interesting and instructive,” Linda-Gail Bekker, PhD, MChB, and Ntobeko A. B. Ntusi, MChB, DPhil, said in an attached commentary. “We can take several salient lessons away from this South African COVID-19 case study.”

For the study, the team of investigators analyzed data from DATCOV, a national active surveillance system for COVID-19 hospital admissions, between March 5, 2020, and March 27, 2021.

The team determined 5 wave periods—prewave 1, wave 1, postwave 1, wave 2, and postwave 2—and compared the characteristics of patients with COVID-19 admitted to hospital in both waves. Using a random-effect multivariable logistic regression, they determined the risk factors for in-hospital mortality in each wave period.

Findings from the study showed that peak rates of cases, admissions, and deaths occurred in the second wave. In wave 1, the average growth rate in hospital admissions was 20%, compared with 43% in wave 2.

Additionally, the second wave was associated with a 31% increase in in-hospital mortality. In-hospital case-fatality risk increased from 17.7% in weeks of low admission to 26.9% in weeks of very high admission.

“Globally, we have witnessed reduced access and retention in care for patients with HIV, tuberculosis, and noncommunicable diseases, such as diabetes and cancer, in the past 18 months,” Bekker and Ntusi said. “Strengthening of health systems to ensure continuing care for chronic conditions will be crucial to limit new variants of concern.”
Do Socioeconomics Play a Role in Testing Positive, Mortality for SARS-CoV-2?

BY JOHN PARKINSON

Results from numerous studies have shown that populations who are challenged socioeconomically have been disproportionately affected by the COVID-19 pandemic. In a very large population study done in Switzerland, investigators found that people in a higher socioeconomic position (SEP) were more likely to be tested for COVID-19, but had lower incidence rates, less hospitalizations, and lower mortality rates than those in a lower SEP.

"Among tested people, test positivity was lower (0.75 [0.69-0.81]) in neighborhoods of highest SEP than of lowest SEP," the investigators reported. "Among people testing positive, the adjusted IRR [incidence rate ratio] was 0.68 (0.62-0.74) for hospitalization, 0.54 (0.43-0.70) for ICU [intensive care unit] admission, and 0.86 (0.76-0.99) for death."

In addition, the investigators found the "associations between neighborhood SEP and outcomes were stronger in younger age groups and we found heterogeneity between areas."

They reviewed surveillance data reported to the Swiss Federal Office of Public Health from March 2020 to April 2021, and 2018 population data.

"We geocoded residential addresses of notifications to identify the Swiss neighborhood index of socioeconomic position (Swiss-SEP). The index describes 1.27 million small neighborhoods of approximately 50 households each on the basis of rent per m², education and occupation of household heads, and crowding," the investigators wrote.

"We used negative binomial regression models to calculate incidence rate ratios (IRRs) with 95% credible intervals (CrIs) of the association between 10 groups of the Swiss-SEP index defined by deciles (1 = lowest, 10 = highest) and outcomes." They adjusted models for sex, age, canton, and epidemic wave (before or after June 8, 2020). They used the general population, number of tests, and number of positive tests as the different denominators.

Analyses were based on 4,129,636 tests, 609,782 positive tests, 26,143 hospitalizations, 2432 ICU admissions, 9383 deaths, and 8,221,406 residents.

"The higher incidence of SARS-CoV-2 infections, combined with a higher prevalence of comorbidities in neighborhoods of lower SEP compared with higher SEP, is likely to have contributed to worse outcomes, including the higher risk of hospitalization and death," the investigators wrote.

They did note that by June 2021, 40% of the Swiss population had received 1 dose of the COVID-19 vaccine and that a gradual reduction of preventive measures was taking place.

They also said that the information provided from these types of studies needs to be applied to help reduce the inequities related to socioeconomics. "Governments and health care systems should address this pandemic of inequality by taking measures to reduce health inequalities in their response to the SARS-CoV-2 pandemic."
A Case of *Candida albicans* Ventriculitis Secondary to *Escherichia Coli* Ventriculoperitoneal Shunt Infection

Rare cases of health care–associated meningitis and ventriculitis in adults caused by *Candida* species are associated with recent bacterial meningitis and broad-spectrum antibiotic use.

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FINAL DIAGNOSIS: *Candida albicans* ventriculitis

HISTORY OF PRESENT ILLNESS

A 52-year-old man initially presented to the hospital with a diagnosis of cerebellar tumor without associated hydrocephalus. One month later he returned to the hospital with worsening neurologic symptoms and was found to have hydrocephalus. At that time, he underwent extraventricular drain (EVD) placement; however, the hydrocephalus continued to worsen, prompting removal of the EVD and placement of a ventriculoperitoneal (VP) shunt. Nine days after placement, he returned to the hospital once again with a chief complaint of severe headache that had worsened over the 3 hours prior to admission with no alleviating or exacerbating factors. He also reported abdominal pain underlying the incision site from the VP shunt placement. He denied fever, chills, nausea, vomiting, and diarrhea.

MEDICAL HISTORY

The patient’s medical history included type 2 diabetes mellitus, hypertension, and cerebellar tumor. His surgical history included a craniotomy for cerebellar tumor, followed by a ventriculostomy and EVD placement the month prior to admission, as well as the VP shunt placement 9 days prior to admission.

KEY MEDICATIONS

Before admission, the patient was taking aspirin 81 mg, atorvastatin 80 mg, lisinopril 5 mg, pantoprazole 40 mg, and dexamethasone 2 mg, all daily.

EPIDEMIOLOGICAL HISTORY

The patient resided at a subacute rehabilitation facility. He had previously worked for an engineering firm but denied any chemical or toxin exposure. He also denied the use of tobacco, illicit drugs, and alcohol, and his family history was noncontributory.

PHYSICAL EXAMINATION

Upon presenting to the hospital, the patient was awake and alert but in moderate pain. He was tachycardic, with a heart rate of 110 beats per minute, but all other vital signs were within normal limits. Staples were in place on the left side (lateral occipital) and posterior occipital sites from the VP shunt placement. His physical exam was remarkable for mild neck stiffness and diffuse abdominal tenderness, which was worse at the incision site where the shunt had been placed. His neurologic exam was normal.

TESTING, TREATMENT, AND FOLLOW-UP

Initial labs were significant for leukocytosis with a white blood cell (WBC) count of 18.1 cells/mm³ (4.5-11.0 cells/mm³). The remainder of the complete blood count and basic metabolic panel was unremarkable. Inflammatory markers were elevated, with a C-reactive protein level of 11.70 mg/dL (< 0.99 mg/dL) and an erythrocyte sedimentation rate of 40 mm/h (0-10 mm/h). A CT scan of the abdomen revealed no acute pathology, and a shunt x-ray series revealed no abnormalities. A CT scan (Figure A) of the head revealed an extradural collection crossing the midline, resolving blood products, and a crowding of the cistern. MRI of the head showed white matter changes surrounding the posterior right ventriculostomy catheter. Blood cultures were drawn and finalized with no growth. A lumbar puncture (LP) was not attempted at the time of presentation.

Physicians in the departments of neurosurgery, surgery, gastroenterology, and infectious diseases were consulted. Vancomycin and cefepime were initiated for empiric therapy of a central nervous system (CNS) bacterial infection. Improvements in leukocytosis, headache, and abdominal pain were noted after 4 days of empiric antibiotic therapy; however, the patient complained of persistent fatigue that had begun prior to hospitalization. On hospital day 5, he reported occasional chills and became febrile to 38.3 °C. On hospital day 6, an LP was performed for suspected VP shunt infection. A cerebrospinal fluid (CSF) analysis revealed a WBC count of 65 cells/mm³ (segmented neutrophils, 70%; lymphocytes, 9%; monocytes, 21%), a red blood cell (RBC) count of 29 cells/mm³, a glucose level of 63 mg/dL (serum glucose 122 mg/dL), and a protein level of 53 mg/dL. Additionally, the Gram stain revealed gram-negative rods. The following day, vancomycin was discontinued, and cefepime was escalated to meropenem due to concern for resistant
organisms. On hospital day 8, the CSF culture result was finalized, with growth of pansensitive *Escherichia coli*; the cerebellar abscess seen on CT imaging was drained. On hospital day 10 cultures from the abscess were also finalized, with pansensitive *E coli*, and meropenem was then de-escalated to ceftriaxone.

After therapy for *E coli*, VP shunt infection with ventriculitis occurred; the shunt was removed and an EVD was placed on hospital day 8. A repeat LP was performed on hospital day 14 to evaluate the CSF for pleocytosis and culture clearance. A CSF analysis revealed a WBC count of 10 cells/mm³ (differential, not reported), an RBC count of 223 cells/mm³, a glucose level of 58 mg/dL (serum glucose, 100 mg/dL), and a protein level of 38 mg/dL; a Gram stain revealed no organisms. The EVD was removed the following day.

Cultures from both the CSF and EVD catheter tip grew *Candida albicans*. CSF culture susceptibilities were reported for caspofungin, fluconazole, and voriconazole, all of which were susceptible with minimum inhibitory concentrations of 0.12 µg/mL, 0.5 µg/mL, and 0.12 µg/mL, respectively.

Liposomal amphotericin B 400 mg (4 mg/kg) intravenously every 24 hours and fluycytosine 2 g (30 mg/kg) orally every 6 hours were initiated on hospital day 16 for treatment of *C albicans* ventriculitis. The patient refused fluycytosine doses intermittently. After 7 days of this regimen, he was transitioned to fluconazole 1200 mg (12 mg/kg) intravenously every 24 hours. On hospital day 42, 16 days after antifungal therapy initiation, he was transitioned to oral fluconazole 800 mg every 24 hours. The fluconazole dose was further reduced to 400 mg every 24 hours on hospital day 57 due to QTc prolongation. Fluconazole was discontinued on hospital day 64, completing 38 days of antifungal therapy. Ceftriaxone for the *E coli* shunt infection was also discontinued at this time.

The patient experienced various complications throughout his hospital stay, including a 4-day admission to the medical intensive care unit (MICU) for intubation for airway protection, and bilateral pulmonary emboli for which he was treated with enoxaparin.

Upon returning to the neurology floor from the MICU, he received physical therapy, occupational therapy, and speech therapy. He was discharged to a rehabilitation facility on hospital day 69 in stable condition.

**DISCUSSION**

The reported incidence of infections involving CNS drainage devices varies from 5% to 41%. Fungi account for only 2.7% of such infections in the United States, with a mortality rate of 11% to 33%. Newborns and children are most commonly affected, although adults may also develop these infections as postoperative neurosurgical complications or as disseminated disease. Neurosurgical procedures directly disrupt the blood-brain barrier, increasing its permeability and causing a reduction in immunity. This facilitates the fungus’s penetration into the CNS. In addition to neurosurgery, recent bacterial meningitis and the use of broad-spectrum antibiotics were risk factors that may have contributed to infection in the patient discussed in this case. Other risk factors for CNS candidiasis include abdominal complications and immunosuppression. Patients with these infections often present with headache, lethargy, fever, abdominal tenderness, and a change in mental status. Diagnosis is heavily dependent on CSF cultures. A CSF analysis may not accurately detect infection, as abnormalities could also be related to neurosurgery or the underlying indication for catheter placement. Normal values also may not rule out infection, as a study by Conen et al reported that 20% of adults with shunt-associated infections presented with normal CSF WBC counts and lactate concentrations.

Although the Infectious Diseases Society of America developed a clinical practice guideline for the treatment of CNS candidiasis, there is limited high-quality supporting evidence. Guidelines currently recommend initial treatment with liposomal amphotericin B, with or without fluconazole. This combination works synergistically to increase fungal cell uptake of fluycytosine. Therapy is subsequently transitioned to oral fluconazole after patients exhibit clinical improvement. Fluconazole achieves higher CSF concentrations and CSF-to-plasma ratios compared with other azole agents; however, it is not recommended in the first line as monotherapy because therapeutic failure has been documented. Avoiding the use of itraconazole and posaconazole for CNS candidiasis is recommended due to inadequate CNS penetration. Echinocandins also are not recommended because of findings from a pharmacokinetic study in a rabbit model demonstrating low CSF concentrations of micafungin. Results of animal studies may not translate to clinical outcomes in humans, but data on the use of echinocandins for CNS infections in humans are lacking.

Current literature describing CNS fungal infections reports varying results without a clearly defined treatment duration. Notably, this patient received 1 week of amphotericin B plus fluycytosine prior to stepping down to fluconazole, which is inconsistent with the guideline recommendation suggesting that several weeks of initial amphotericin B plus fluycytosine may be necessary. Based on the evidence available, the impact of early step-down to an azole is unclear. Additionally, it is not clear whether the approximate 6-week total of antifungals the patient received is adequate for cure. In a case series describing therapy for *C albicans* CNS infections in 10 patients, 8 were treated with various combinations of amphotericin B, fluconazole, and fluycytosine, with treatment durations ranging from 14 days to 2 months. At the time the patient in this case completed therapy and was discharged, his neurologic status had improved, his WBC count was within normal limits, and he denied headache, fever, abdominal pain, nausea, and vomiting. Although it is prudent to evaluate the pharmacokinetic literature and case studies in addition to guideline recommendations to direct therapy for patients with CNS candidiasis, further clinical data will assist in optimizing treatment regimens and defining an adequate duration. ▲

**FIGURE A:** CT scan of the brain/head without contrast revealed a small amount of epidural fluid crossing the midline in the inferior cerebellum, a hypodense area in the right inferior cerebellum that may represent an infarction, and increased crowding of the cisterns when compared with results of prior studies.

**TABLE 1**

| Antifungal | Duration | Recommended
| --- | --- | --- |
| Amphotericin B | 1 week | Not recommended
| Fluconazole | 6 weeks | Recommended
| Caspofungin | 1 week | Recommended |

**REFERENCES**

Available at ContagionLive.com.
Ferring is shedding light on the link between disease and disruptions in the gut microbiome, exploring the potential for repopulating its diversity and restoring hope to patients. Watch as this scientific animation explores the underlying mechanism of C. difficile infection, risk factors for recurrence, and how it can affect your patients.

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