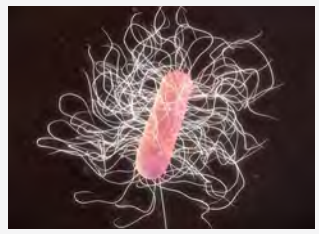
Medical World News®

FDA Approves the Therapy Cabotegravir for PrEP

(continued on page 8)



C. diff. Conference

Investigational Vaccine, Therapeutics Headline Conference

(continued on page 26)

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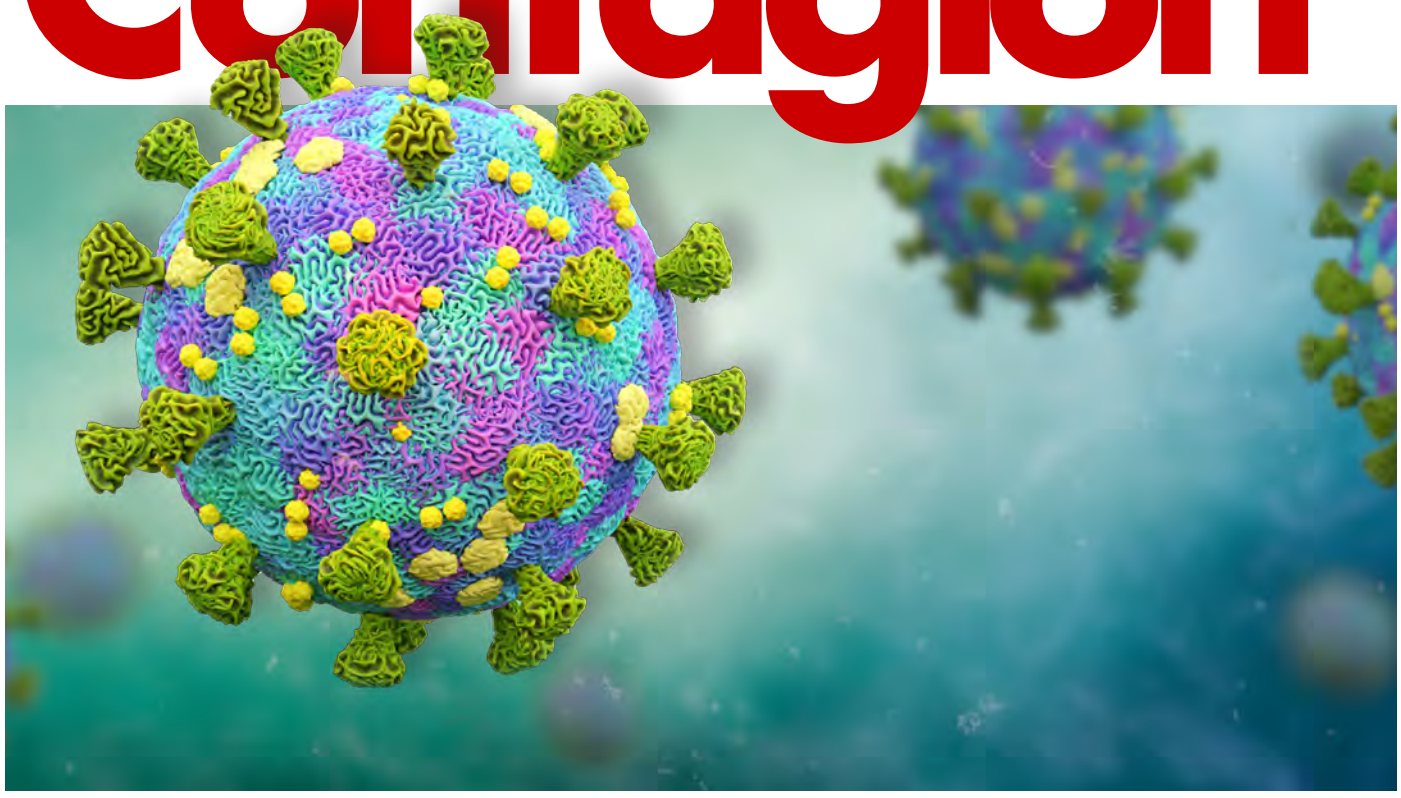


Understanding COVID-19 infection offers value in how to live with the virus.

Emerging & Re-Emerging Infections

From Pandemic to Endemic

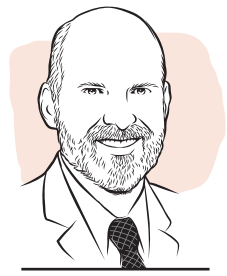
A research agenda focusing on breakthrough infections, reinfections, severity, and sequelae is needed to inform clinical practice when COVID-19 emphasis shifts from eradication to living with the disease.

by Paul A. Monach, MD, PhD; *and* Westyn Branch-Elliman, MD, MMSc

Vaccination is the preferred mechanism for developing immunity against SARS-CoV-2 infection, but evidence is now conclusive that natural infection, which has become common around the world,[1,2] also provides protection. Research on reinfection (ie, a second, independent infection) and breakthrough infection (ie, despite vaccination) has only recently started to emerge, simply because the phenomena are new. In countries where the majority of adults have been either vaccinated or infected (eg, 89% in the United States)[1] and where vaccination of children has been approved, reinfection and breakthrough infection will soon represent most cases. Lessons learned in countries with early widespread access to and distribution of vaccines and detailed clinical data should be of great value worldwide as COVID-19 knowledge evolves.

COVID-19 is a worldwide crisis only because the disease is often severe and life-threatening or has long-term sequelae (postacute sequelae of COVID-19 [PASC]).[3] High-priority public health topics, including transmission and development of viral variants, always come back to the fundamental questions of severity and sequelae. Risk factors for severe disease in unvaccinated patients are known, and those for PASC will soon be known. Risk factors for severe breakthrough or reinfection will

(continued on page 14)



Paul A. Monach, MD, PhD

Westyn Branch-Elliman, MD, MMSc

HIV/AIDS

Optimizing ART for Patients With a History of Treatment Failure and Resistance

by John Faragon, PharmD, BCPS, AAHIVP

The treatment of HIV infection for newly-diagnosed patients has been simplified in recent years with the advent of highly active antiretroviral therapy and the use of single-tablet regimens (STRs)—tablets that contain 2 or more medications in 1 pill,

(continued on page 18)

Multidrug-Resistant Infections

Updates to Multidrug Resistance Guidance

by Sam Aitken, PharmD, MPH, BCIDP

Antimicrobial-resistant (AMR) bacteria continue to be a significant cause of morbidity in the United States and worldwide. Recognizing this, the Infectious Diseases Society of America (IDSA) issued an evidence-informed guidance document for the treatment of AMR gram-negative bacteria in

(continued on page 20)

Stewardship & Prevention

What's New With Non–COVID-19 Vaccines

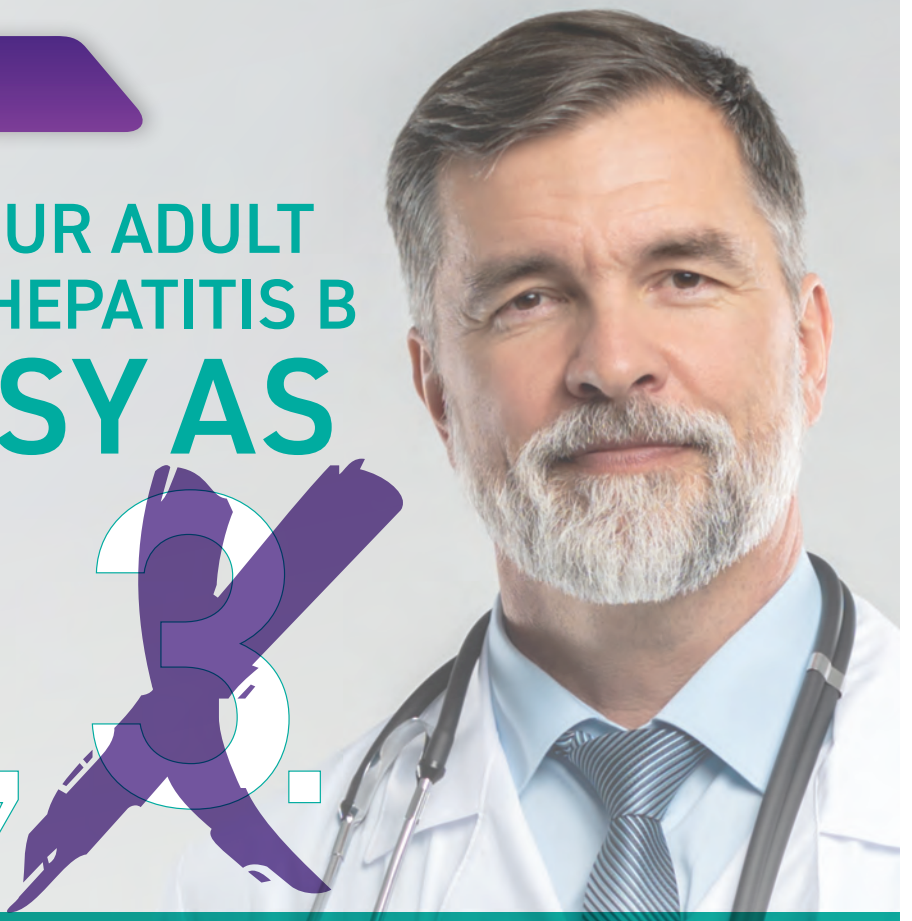
by Albert Bach, PharmD; Heidi Lee, PharmD; *and* Jelena Lewis, PharmD, BCACP

As the COVID-19 pandemic took center stage around the globe, it also shifted much of our focus to the vaccines and efforts to immunize populations against this disease. Although our successes in developing, distributing, and administering the COVID-19 vaccines deserve merit, we must not forget the fight against other vaccine-preventable diseases. Data

(continued on page 22)

UNANIMOUSLY RECOMMENDED BY THE ACIP[1]

PROTECTING YOUR ADULT PATIENTS FROM HEPATITIS B IS AS EASY AS 1, 2, 3.



HEPLISAV-B IS **THE ONLY 2-DOSE, 1-MONTH** HEPATITIS B VACCINE FOR ADULTS[2,3]

INDICATION

HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.

IMPORTANT SAFETY INFORMATION

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (e.g., anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast.

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B.

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B.

Hepatitis B has a long incubation period. HEPLISAV-B may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration.

The most common patient-reported adverse reactions reported within 7 days of vaccination were injection site pain (23%-39%), fatigue (11%-17%), and headache (8%-17%).

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

heplisavb.com

HEPLISAV-B®
Hepatitis B Vaccine (Recombinant), Adjuvanted

2 DOSES. 1 MONTH. DONE.[2]

Abbreviation: ACIP, Advisory Committee on Immunization Practices.

REFERENCES: 1. Schillie S, Harris A, Link-Gelles R, Romero J, Ward J, Nelson N. Recommendations of the Advisory Committee on Immunization Practices for use of a hepatitis B vaccine with a novel adjuvant. *MMWR Morb Mortal Wkly Rep.* 2018;67(15):455-458. **2.** HEPLISAV-B [package insert]. Emeryville, CA: Dynavax Technologies Corporation; 2020. **3.** Freedman M, Kroger A, Hunter P, Ault KA. Recommended Adult Immunization Schedule, United States, 2020. *Ann Intern Med.* 2020;172(5):337-347.

DYNAVAX

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

HEPLISAV-B [Hepatitis B Vaccine (Recombinant), Adjuvanted] Solution for Intramuscular Injection

1 INDICATIONS AND USAGE

HEPLISAV-B is indicated for prevention of infection caused by all known subtypes of hepatitis B virus. HEPLISAV-B is approved for use in adults 18 years of age and older.

2 DOSAGE AND ADMINISTRATION

For intramuscular administration.

2.1 Dose and Regimen

Administer two doses (0.5 mL each) of HEPLISAV-B one month apart.

2.2 Administration

HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Administer HEPLISAV-B by intramuscular injection in the deltoid region using a sterile needle and syringe.

3 DOSAGE FORMS AND STRENGTHS

HEPLISAV-B is a sterile solution for injection available in 0.5 mL single-dose prefilled syringes. [see *How Supplied/Storage and Handling* (16.1)].

4 CONTRAINDICATIONS

Do not administer HEPLISAV-B to individuals with a history of severe allergic reaction (e.g. anaphylaxis) after a previous dose of any hepatitis B vaccine or to any component of HEPLISAV-B, including yeast [see *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Managing Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of HEPLISAV-B.

5.2 Immunocompromised Individuals

Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to HEPLISAV-B.

5.3 Limitations of Vaccine Effectiveness

Hepatitis B has a long incubation period. HEPLISAV-B may not prevent hepatitis B infection in individuals who have an unrecognized hepatitis B infection at the time of vaccine administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice.

A total of 9597 individuals 18 through 70 years of age received at least 1 dose of HEPLISAV-B in 5 clinical trials conducted in the United States, Canada, and Germany. Data from 3 of these trials are provided below.

Study 1 in Subjects 18 through 55 Years of Age

Study 1 was a randomized, observer-blind, active-controlled, multicenter study in Canada and Germany in which 1810 subjects received at least 1 dose of HEPLISAV-B and 605 subjects received at least 1 dose of Engerix-B® [Hepatitis B Vaccine (Recombinant)]. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 40 years; 46% of the subjects were men; 93% were white, 2% black, 3% Asian and 3% Hispanic; 26% were obese, 10% had hypertension, 8% had dyslipidemia, and 2% had diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Solicited Local and Systemic Adverse Reactions

Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who reported local and systemic reactions are shown in Table 1.

Table 1
Study 1: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination

	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
Reaction	**1**	**2**	**1**	**2**	**3**
Local	N=1810	N=1798	N=605	N=603	N=598
Injection Site Pain	38.5	34.8	33.6	24.7	20.2
Injection Site Redness†	4.1	2.9	0.5	1.0	0.7
Injection Site Swelling†	2.3	1.5	0.7	0.5	0.5
Systemic					
Fatigue	17.4	13.8	16.7	11.9	10.0
Headache	16.9	12.8	19.2	12.3	9.5
Malaise	9.2	7.6	8.9	6.5	6.4
	N=1784	N=1764	N=596	N=590	N=561
Fever‡	1.1	1.5	1.8	1.7	1.8

Note: only subjects having data are included. Clinical trial number: NCT00435812
*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months
† Redness and swelling ≥ 2.5 cm.
‡ Oral temperature ≥ 100.4°F (38.0°C).

Unsolicited Adverse Events:

Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 42.0% of HEPLISAV-B recipients and 41.3% of Engerix-B recipients.

Serious Adverse Events (SAEs)

Subjects were monitored for serious adverse events for 7 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 1.5% in the HEPLISAV-B group and 2.1% in the Engerix-B group. No acute myocardial infarctions were reported. No deaths were reported.

Potentially Immune-mediated Adverse Events

Potentially immune-mediated adverse events that occurred within 7 months of the first dose of vaccine were reported in 0.2% (n = 4) of HEPLISAV-B recipients and 0.7% (n = 4) of Engerix-B recipients. The following events were reported in the HEPLISAV-B group in one subject each: granulomatosis with polyangiitis, lichen planus, Guillain-Barré syndrome, and Grave's disease. The following events were reported in the Engerix-B group in one subject each: Bell's palsy, Raynaud's phenomenon, and Grave's disease. One additional Engerix-B recipient with a history of mixed connective tissue disease had p-ANCA-positive vasculitis.

Study 2 in Subjects 40 through 70 Years of Age

Study 2 was a randomized, observer-blind, active-controlled, multicenter study in Canada and the United States in which 1968 subjects received at least 1 dose of HEPLISAV-B and 481 subjects received at least 1 dose of Engerix-B. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Enrolled subjects had no history of hepatitis B vaccination or infection. Engerix-B was given at 0, 1, and 6 months. In the total population, the mean age was 54 years; 48% of subjects were men; 82% were white, 15% black, 1% Asian and 6% Hispanic; 44% were obese, 30% had hypertension, 30% had dyslipidemia, and 8% had diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Solicited Local and Systemic Adverse Reactions

Subjects were monitored for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The percentages of subjects who experienced local and systemic reactions are shown in Table 2.

Table 2
Study 2: Percent of Subjects Who Reported Local or Systemic Reactions Within 7 Days of Vaccination

	HEPLISAV-B %		Engerix-B %		
	Post-Dose*		Post-Dose*		
Reaction	**1**	**2**	**1**	**2**	**3**
Local	N=1952	N=1905	N=477	N=464	N=448
Injection Site Pain	23.7	22.8	18.4	15.9	13.8
Injection Site Redness†	0.9	0.7	0.6	0.2	0.2
Injection Site Swelling†	0.9	0.6	0.6	0.6	0.2
Systemic					
Fatigue	12.6	10.8	12.8	12.1	9.4
Headache	11.8	8.1	11.9	9.5	8.5
Malaise	7.7	7.0	8.6	7.1	5.1
Myalgia	8.5	6.4	9.6	8.0	4.5
	N=1923	N=1887	N=472	N=459	N=438
Fever‡	0.6	0.6	0.6	0.9	0.7

Note: only subjects having data are included. Clinical Trial Number: NCT01005407
*HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months
† Redness and swelling ≥2.5 cm.
‡ Oral temperature ≥ 100.4°F (38.0°C).

Unsolicited Adverse Events
Unsolicited adverse events within 28 days following any injection, including placebo, were reported by 35.4% of HEPLISAV-B recipients and 36.2% of Engerix-B recipients.

Serious Adverse Events
Subjects were monitored for serious adverse events for 12 months after the first dose of vaccine. The percentage of subjects reporting serious adverse events was 3.9% in the HEPLISAV-B group and 4.8% in the Engerix-B group. Acute myocardial infarction occurred in 0.1% (n=2) of HEPLISAV-B recipients and 0.2% (n=1) of Engerix-B recipients.

Autoimmune Adverse Events
Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 12 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.2% (n=3) of HEPLISAV-B recipients: two subjects with hypothyroidism and one subject with vitiligo. None of these events was considered related to vaccination by the expert group. No new-onset autoimmune adverse events were reported in the Engerix-B group. Although not referred to the external group of experts, one HEPLISAV-B recipient was determined to have Tolosa-Hunt syndrome which is presumed to have an immune-mediated etiology. This event was not considered related to vaccination.

Deaths
One subject (0.05%) died of a pulmonary embolism in the HEPLISAV-B group and 1 subject (0.2%) died of heart failure in the Engerix-B group. Neither death was considered related to vaccination.

Study 3 in Subjects 18 through 70 Years of Age

Study 3 was a randomized, observer-blind, active-controlled, multicenter study in the United States in which 5587 subjects received at least 1 dose of HEPLISAV-B and 2781 subjects received at least 1 dose of Engerix-B. Enrolled subjects had no history of hepatitis B vaccination or infection. HEPLISAV-B was given as a 2-dose regimen at 0 and 1 month followed by saline placebo at 6 months. Engerix-B was given at 0, 1, and 6 months. In the total study population, the mean age was 50 years; 51% were men; 71% were white, 26% black, 1% Asian, and 9% Hispanic; 48% were obese, 36% had hypertension, 32% had dyslipidemia, and 14% had type 2 diabetes mellitus. These demographic and baseline characteristics were similar in both vaccine groups.

Unsolicited Medically-Attended Adverse Events
Subjects were monitored for unsolicited medically-attended adverse events, those for which a subject sought medical care, for 13 months after the first dose of vaccine. Overall, medically-attended adverse events were reported in 46.0% of HEPLISAV-B recipients and 46.2% of Engerix-B recipients. Herpes zoster was reported in 0.7% of HEPLISAV-B recipients and 0.3% of Engerix-B recipients. Unsolicited medically-attended adverse events within 28 days following any injection, including placebo, were reported by 20.1% of both HEPLISAV-B and Engerix-B recipients.

Serious Adverse Events
Subjects were monitored for serious adverse events for 13 months after the first dose of vaccine. The percentage of subjects who reported serious adverse events was 6.2% in the HEPLISAV-B group and 5.3% in the Engerix-B group. Acute myocardial infarction (AMI) was reported in 0.25% (n=14) of HEPLISAV B recipients and 0.04% (n=1) of Engerix-B recipients. An analysis of serious adverse events likely representing myocardial infarction (MI) was conducted using the standard Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for MI. This analysis identified a total of 19 HEPLISAV-B subjects (0.3%) and 3 Engerix-B subjects (0.1%) with events included in the SMQ for MI (these events include the 15 reports of AMI). Additional evidence, including information on temporal relationship and baseline risk factors, does not support a causal relationship between HEPLISAV-B administration and AMI. Among the 19 events identified as MI in HEPLISAV-B recipients, three occurred within 14 days, nine occurred within 53-180 days, and seven occurred more than 180 days following any dose of HEPLISAV-B. Among the three events identified as MI in Engerix-B recipients, one each occurred 13, 115, and 203 days following any dose. All 19 HEPLISAV-B recipients and 3 Engerix-B recipients reported one or more baseline risk factors for cardiovascular disease.

Autoimmune Adverse Events
Subjects were monitored for the occurrence of new-onset potentially immune-mediated adverse events for 13 months after the first dose of vaccine. Events were adjudicated as to whether they were autoimmune by an external group of experts who were blinded to treatment assignment. As determined by the adjudicators, new-onset autoimmune adverse events were reported in 0.1% (n=4) of HEPLISAV-B recipients [one each of: alopecia areata, polymyalgia rheumatica, ulcerative colitis, and autoimmune thyroiditis (with concurrent diagnosis of papillary thyroid carcinoma)]. None of these events was considered to be related to vaccination by the external experts. No new-onset autoimmune adverse events were reported in the Engerix-B group.

Deaths
During the study death was reported in 25 subjects (0.4%) in the HEPLISAV-B group and 7 subjects (0.3%) in the Engerix-B group. No death was considered related to vaccination.

7 DRUG INTERACTIONS

7.1 Use with Immune Globulin
There are no data to assess the concomitant use of HEPLISAV-B with immune globulin. When concomitant administration of HEPLISAV-B and immune globulin is required, they should be given with different syringes at different injection sites.

7.2 Interference with Laboratory Tests
Hepatitis B surface antigen (HBsAg) derived from hepatitis B vaccines has been transiently detected in blood samples following vaccination. Serum HBsAg detection may not have diagnostic value within 28 days after receipt of HEPLISAV-B.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to HEPLISAV-B during pregnancy. Women who receive HEPLISAV-B during pregnancy are encouraged to contact 1-844-443-7734.

Risk Summary
All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In clinically recognized pregnancies in the US general population, the estimated background risk of major birth defects is 2% to 4% and of miscarriage is 15% to 20%.

There are no clinical studies of HEPLISAV-B in pregnant women. Available human data on HEPLISAV-B administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.

In a developmental toxicity study, 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg cytosine phosphoguanine (CpG) 1018 adjuvant was administered to female rats prior to mating and during gestation. These animal studies revealed no evidence of harm to the fetus due to this vaccine formulation *[see Data]*.

Data
Animal data
Developmental toxicity studies were conducted in female rats. Animals were administered 0.3 mL of a vaccine formulation containing 2.5 mcg HBsAg and 3000 mcg CpG 1018 adjuvant twice prior to mating, and on gestation days 6 and 18 (a single human dose of HEPLISAV-B contains 20 mcg HBsAg and 3000 mcg CpG 1018 adjuvant). No adverse effects on pre-natal and post-natal development up to the time of weaning were observed. There were no vaccine-related fetal malformations or variations observed.

8.2 Lactation
Risk Summary
It is not known whether HEPLISAV-B is excreted in human milk. Data are not available to assess the effects of HEPLISAV-B on the breastfed infant or on milk production/excretion.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HEPLISAV-B and any potential adverse effects on the breastfed child from HEPLISAV-B or from the underlying maternal condition. For preventive vaccines, the underlying condition is susceptibility to disease prevented by the vaccine.

8.4 Pediatric Use
Safety and effectiveness of HEPLISAV-B have not been established in individuals less than 18 years of age.

8.5 Geriatric Use
Clinical trials included 909 adults 65 through 70 years of age who received HEPLISAV-B.

Among subjects who received HEPLISAV-B, a seroprotective level of antibody to HBsAg was achieved in 90% of those 65 through 70 years of age compared to 96% of those aged 18 through 64 years of age.

Safety and effectiveness of HEPLISAV-B in adults older than 70 years of age were extrapolated from findings in subjects younger than 70 years of age.

8.6 Adults on Hemodialysis
Safety and effectiveness of HEPLISAV-B have not been established in adults on hemodialysis.

17. PATIENT COUNSELING INFORMATION

- Inform vaccine recipient of the potential benefits and risks associated with vaccination, as well as the importance of completing the immunization series.
- Emphasize that HEPLISAV-B contains non-infectious purified HBsAg and cannot cause hepatitis B infection.
- Advise vaccine recipient to report any adverse events to their healthcare provider or to the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967 and www.vaers.hhs.gov.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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Health Care Industry Mourns Passing of Publishing Giant

Michael J. Hennessy Sr

The beloved founder of MJH Life Sciences™ left a legacy of medical publishing brands and a well-accomplished company

Visionary businessman

Michael J. Hennessy Sr, the beloved chairman and founder of MJH Life Sciences™, passed away on November 21, 2021. Hennessy spent his career turning his passion for building businesses and creating jobs into a run of successful ventures and brands. He built MJH Life Sciences™ into the largest privately held medical media company in North America.

Following his graduation from Rider College (now Rider University) in Lawrence, New Jersey, in 1982, he started his career in medical publishing as a sales trainee, eventually advancing to the position of chief operating officer. In 1986, Hennessy became chief operating officer of Medical World Business Press, which was part of the launch of medical newspapers and other media products. The company prospered and was eventually sold to a Boston, Massachusetts–based venture capital firm.

Hennessy launched Multimedia Healthcare, LLC, in 1993 and built a portfolio of award-winning clinical journals. In 2001, Freedom Communications, Inc, acquired Multimedia HealthCare, about the time that Hennessy was pioneering a new approach to print and digital publishing with Intellisphere® LLC (now part of MJH Life Sciences™). Guided by the principles of innovation and entrepreneurial spirit and reflecting its founder's dedication to improving quality of life through health care research and education, Intellisphere® publishes a variety of integrated print and digital products focusing on a range of topics in research and clinical medicine.

To build a comprehensive multimedia and education platform, Hennessy added more companies and capabilities to the MJH Life Sciences™ portfolio. In 2004, he acquired Healthcare Research Analytics (HRA®), which has been the leader in health care market research for over 30 years. In 2005, Hennessy acquired ArcMesa Educators LLC, leaders in online certification for physicians, pharmacists, nurses, and other health care professionals. Reflecting his lifelong interest in politics, Hennessy acquired *Campaigns & Elections* magazine in 2005, publishing the journal through Political World Communications LLC. He sold the publication to Biteback Media Ltd in 2011. In February 2008, Hennessy acquired the rights to the journals *Pharmacy Times*® and *The American Journal of Managed Care*®, both recognized in their respective markets as authoritative, trusted media platforms that provide essential information to a large audience of health care professionals.

In April 2011, MJH Life Sciences™ acquired Physicians' Education Resource® LLC (PER®), an accredited continuing medical education company that is an industry leader in producing high-quality, first-rate oncology and hematology meetings and conferences. The PER® acquisition included a variety of multichannel enduring educational activities, as well as the rights to legacy medical meetings, such as the annual Miami Breast Cancer Conference®.

Hennessy's commitment to improving the lives of patients with cancer is deeply rooted within the halls of MJH Life Sciences™. As a complement to the industry-leading OncLive® platform, he developed the Giants of Cancer Care® awards to recognize the leaders and pioneers who often go unrecognized for their contributions to advancing oncology care. He further strengthened his commitment to education by acquiring CURE Media Group in 2014, followed by the purchase of the Chemotherapy Foundation Symposium, in his quest to provide oncology professionals with focused education on innovative cancer therapy.

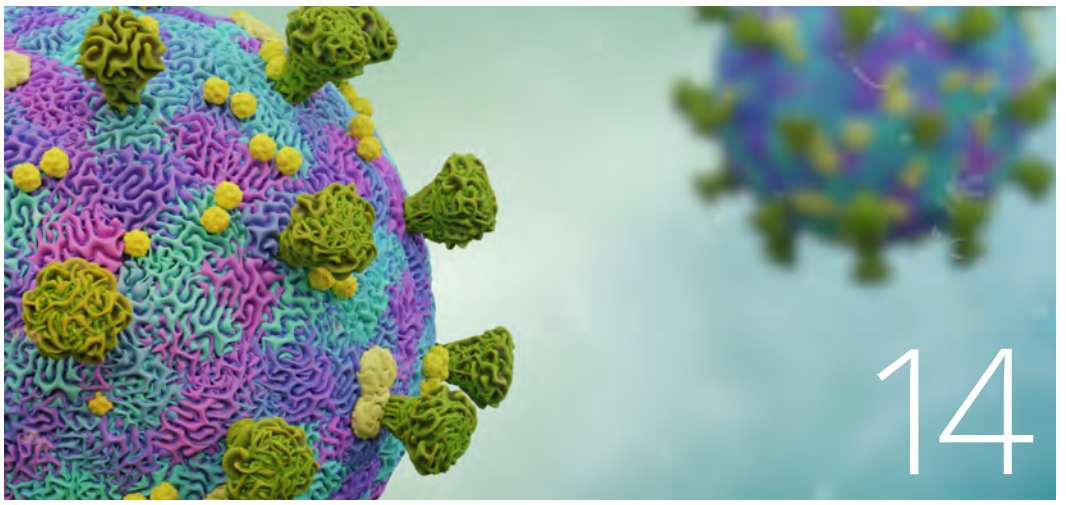
In 2019, MJH Life Sciences™ made its largest acquisition to date when it acquired the Healthcare and Industry Sciences divisions of UBM Medica, nearly doubling the size of the organization and adding legacy titles such as *Medical Economics*® to its already impressive portfolio. This acquisition made the organization the largest independently owned medical communications company in North America. In addition to acquisitions, Hennessy organically developed ancillary in-house agency divisions with Proximyl Health®, Truth Serum NTWK, and MJH Global Medical Affairs.

Later in 2019, Hennessy elevated his own role to chairman while naming his son Mike Hennessy Jr to assume the leadership role of the organization and carry on the family legacy. Under Mike Jr's leadership, the company enhanced its global potential by entering a long-term partnership with BDT Capital Partners LLC in November 2021.

Because of his broad business and educational experience and understanding of the challenges facing New Jersey, Hennessy's counsel and insight had been sought by several organizations, including his alma mater Rider University, where he served on the board of trustees and was elected to the executive committee. In addition to being active in state and national politics, Hennessy also had a long record of service at the local level, where he was a strong advocate for veterans and environmental issues.

Hennessy's true passion was his relationship with his wife, Patrice "Patti" Hennessey. After they met in college, Hennessy devoted his life to Patti and his family, raising 4 wonderful children, Shannon, Ashley, Mike Jr, and Chris. Hennessy was Patti's rock as she bravely battled cancer for almost 10 years until her death in January 2020. Hennessy recently honored Patti by making a donation to Rider University to expand the Science and Technology Center at their alma mater. The Mike & Patti Hennessy Science and Technology Center is set to be completed in 2022.

Hennessy's legacy and "family first" mantra will live on through his children; their spouses, Matt, Phil, Rachel, and Jordan; and his 10 grandchildren. He will be greatly missed by his family, friends, and MJH Life Sciences™ family. ▲



EMERGING & RE-EMERGING INFECTIONS

From Pandemic *to* Endemic

A research agenda focusing on breakthrough infections, reinfections, severity, and sequelae is needed to inform clinical practice when COVID-19 emphasis shifts from eradication to living with the disease.

by **Paul A. Monarch, MD, PhD;** ***and*** **Westyn Branch-Elliman, MD, MMSc**

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DOTTEDYETI, GAETAN, CALIN/ ADOBE STOCK

ILLUSTRATION BY PATRICK WELSH
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A Future of Living With COVID-19:

As 2022 begins, the world again finds itself wrapped in a heavy blanket of COVID-19, driven by the remarkably infectious Omicron variant. How many times can we go through the same pattern? Individuals are fatigued and confused as overpromises and misunderstandings about the degree of protection from vaccines do not live up to their understandably inaccurate expectations. Acceptance of a future with COVID-19 is settling in. Building strategies that improve quality of life as we live with this viral disease requires addressing the unknowns that still exist after 2 years of COVID-19. It is unclear what a future with endemic SARS-CoV-2 will look like. Will it be seasonal, like many other respiratory viruses? This seems likely, although so far changes in dominant variants have affected infection incidence at least as much as the weather has, so it is difficult to measure. Will SARS-CoV-2 be circulating at the same time as influenza and respiratory syncytial virus?

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

Variants

Future variants are inevitable, but their impact on society is difficult to predict. The combination of increased transmissibility and immune evasion led to the rapid dominance of Omicron. The plan to vaccinate the world and decrease the amount of mutable circulating virus needs to be scaled rapidly to protect us all.

Long COVID-19

"Long COVID-19" is an enormous unknown. Our diminished ability to control Omicron infection means most individuals will likely be exposed to it, with significant proportions of them becoming infected. Will the somewhat milder course of infection with Omicron, whether innate to the virus or due to partial immunity, attenuate cases of long COVID-19? What is the mechanism of long COVID-19, and can we come to a consensus on its definition? This problem may require resources for many years to come.

Antiviral benefits and pathways to access

A significant step forward in 2022 is the availability of oral antivirals. These therapies, highlighted in this issue of *Contagion*®, have prevented progression to hospitalization in clinical trials, with nirmatrelvir/ritonavir (Paxlovid) looking particularly promising. However, we know that starting antiviral therapy early in the course of infection is key to its success. How useful will these therapies be in real-world use? When availability improves, will test-to-treat protocols be established that shorten time from symptom development to clinician assessment to prescription to dispensing? Because at-home antigen tests are (intermittently) available, can patients utilize them in clinician-aided self-diagnosis to expedite this process?

Vaccine durability and improvement

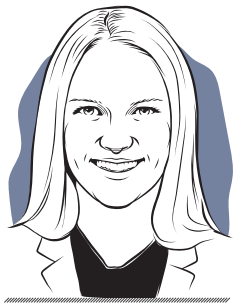
Our vaccines had been a home run before Delta and Omicron each took some of the shine from their luster. They are still proving highly effective in preventing hospitalization, but can we improve their ability to prevent transmission? Will changing variants require constantly updated vaccines or can a pan–COVID-19 vaccine be created? And how long are they protective? We have learned much in these 2 years, but understanding COVID-19 is a work in progress. Filling the remaining knowledge deficits starts with identification.

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

Active member of the Society of Infectious Diseases Pharmacists Active member of MAD-ID (Making a Difference in Infectious Diseases)

Secnidazole Offers Hope as Option for Treating Trichomoniasis in Women

by MEGAN CHATOWSKY, PHARMD CANDIDATE; *and* CATHERINE LI, PHARMD, BCIDP ⁂



MEGAN CHATOWSKY, PHARMD CANDIDATE

Megan Chatowsky is a PharmD candidate, class of 2022 at University of Rhode Island. Her current interests include optimizing the role of pharmacists in public health.

CATHERINE LI, PHARMD, BCIDP ⁂

Catherine Li, PharmD, BCIDP, is an infectious diseases pharmacist and codirector of the Antimicrobial Stewardship Program at Women & Infants Hospital in Providence, Rhode Island.

Trichomonas vaginalis is a protozoan parasite estimated to affect 3.7 million individuals in the United States, including 2.1% of women aged 14 to 59 years. Black women are disproportionately affected, with an increased prevalence rate of 9.6%.[1,2] Potential complications of trichomoniasis include increased risk of other sexually transmitted infections (STIs) including HIV and adverse birth outcomes in pregnancy.[2,3] Previously, the recommended treatment for trichomoniasis in HIV-uninfected individuals was a single oral dose of metronidazole. However, a recent randomized controlled trial reported that a 7-day course of metronidazole resulted in 45% fewer treatment failures compared with the single dose (10.9% vs 18.6%; relative risk [RR], 0.55; 95% CI, 0.34-0.70).[4] In the 2021 US Centers for Disease Control and Prevention (CDC) STI guidelines, the recommended trichomoniasis treatment regimen was revised to 7 days of metronidazole for all women.

Secnidazole is a nitroimidazole antibiotic with a prolonged half-life of 17 hours, compared with 7 to 8 hours for metronidazole and 12 hours for tinidazole. It was initially approved by the FDA in 2017 for bacterial vaginosis (BV) and is included as an alternative agent and the only single-dose regimen for BV treatment.[2] Literature from other countries in the 1970s and 1980s described clinical efficacy of a single dose of secnidazole for treatment of trichomoniasis with parasite eradication rates greater than 90%.[5] In June 2021, with the results of this phase 3 trial (NCT03935217), secnidazole received FDA approval for the additional indication of trichomoniasis treatment.

Muzny et al conducted this randomized, double-blind, placebo-controlled, delayed treatment study in postmenarchal females (12 years and older) diagnosed with *T vaginalis* infection. Patients who were pregnant or lactating, had symptomatic vulvovaginal candidiasis, or received antimicrobial treatment in the previous 14 days were excluded. Patients were randomized 1:1 to receive a single dose of secnidazole 2 g oral granules or matching placebo that was taken under direct observation at visit 1. Visit 2 occurred 6 to 12 days later to assess test-of-cure and treatment-emergent adverse events (TEAEs). Patients also received the opposite treatment at this time. For patients not meeting test-of-cure criteria, third and fourth visits were scheduled for additional treatment.

Table. Microbiological Cure at Test-of-Cure Visit

Group	Secnidazole		Placebo		*P* value
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	
mITT	92.9% (52 of 56)	87.5% (7 of 8)	0% (0 of 55)	8.3% (1of 12)	< .001
BV coinfection	95.2% (20 of 21)	-	-	0% (0 of 17)	< .001
HIV infection	HIV infection	-	0% (0 of 4)	-	-

BV, bacterial vaginosis; mITT, modified intention to treat population

The primary efficacy end point was microbiological cure with the InPouch culture device at the test-of-cure visit in the modified intention-to-treat (mITT) population, defined as patients with a positive *T vaginalis* culture and negative chlamydia and gonorrhea testing at baseline. The analysis was adjusted for presence of trichomoniasis symptoms.

The study enrolled 147 women; 131 were included in the mITT population. More than 90% of patients included were Black/African American. Of note, 29% of patients had BV coinfection and 6.9% were HIV positive. Microbiological cure at test-of-cure was achieved in 92.2% (95% CI, 82.70%-97.41%) of the secnidazole group compared with 1.5% (95% CI, 0.04%-8.04%) of the placebo group ($P < .001$). Post hoc subgroup analyses in patients with symptoms, without symptoms, BV coinfection, and HIV infection suggested similar results (**Table**).

TEAEs were assessed in the safety population of all patients who received at least 1 dose of study medication. Overall, the rates of reported AEs were lower in the secnidazole group compared with placebo (14.9% vs 21.9%) and included nausea, diarrhea, headache, and vulvovaginal candidiasis. All reported events were mild and no serious events occurred.

Secnidazole was found to be efficacious for treatment of trichomoniasis in women and was generally well tolerated. Efficacy seemed to be maintained in patients with BV coinfection and in patients with HIV infection; however, larger confirmatory studies are needed for these populations. As an additional single-dose option for trichomoniasis treatment, secnidazole may be advantageous for patients with difficulty adhering to a 7-day metronidazole course. However, with tinidazole as a guideline-recommended single-dose treatment for trichomoniasis and the lack of head-to-head comparative trials, cost-effectiveness will impact secnidazole's place in therapy. Furthermore, although animal studies did not find adverse developmental outcomes with secnidazole use in pregnancy,[6] metronidazole remains the preferred treatment in pregnancy due to a paucity of clinical safety data with tinidazole and secnidazole. One notable advantage of secnidazole over the other nitroimidazoles is that it is the only single-dose treatment regimen for BV. The prevalence of trichomoniasis and BV coinfection was 29% in the present study and has been reported to be as high as 60% to 80% in the literature.[7] Prior to secnidazole's approval, treatment of these patients was limited to multidose regimens with either metronidazole or tinidazole, representing a group that may benefit most from a 2-for-1 single-dose treatment option. ▲

References are available at ContagionLive.com.

Highlighted Study

Muzny CA, Schwebke JR, Nyirjesy P, et al. Efficacy and safety of single oral dosing of secnidazole for trichomoniasis in women: results of a phase 3, randomized, double-blind, placebo-controlled, delayed-treatment study. *Clin Infect Dis*. 2021;73(6):e1282-1289. doi:10.1093/cid/ciab242

Section Editor:
MONICA V. MAHONEY, PHARMD, BCPS AQ-ID

Bacterial Resistance Drives Need for New Therapies in Treating cUTIs in Adult Patients

by JOY UZOMA, PHARMD; *and* TIFFANY LEE, PHARMD, BCIDP

Urinary tract infections represent one of the most common bacterial entities encountered throughout the world, comprising a spectrum of diseases including cystitis and pyelonephritis.[1] Complicated urinary tract infections (cUTIs) typically occur in patients with functional or structural abnormalities of the urinary tract.[1,2,3] These infections can also be characterized by the presence of unique host factors (ie, immunosuppression) or systemic involvement.[1,2,3] In view of this, patients presenting with cUTIs are more prone to deleterious complications including sepsis and septic shock.[4] β-Lactam antibiotics are considered mainstays of therapy. However, in an era of bacterial resistance, the utility of these agents has largely been hindered by the presence of extended-spectrum β-lactamase (ESBL)-producing bacteria.[1,2]

Carbapenems were considered last-line agents because of their broad spectrum of activity against gram-negative bacteria, including ESBL-producing organisms. However, use of these agents carries the risk of carbapenem resistance, leading to suboptimal clinical outcomes and thus warranting the need for alternative therapies.[2,3] Although newer, carbapenem-sparing agents have emerged within the past decade, the question of which agent to select for empiric cUTI management is unclear.[2,3] One systematic review comparing efficacy of carbapenems with noncarbapenem agents, including some novel antimicrobials, for cUTI produced inconclusive results limited by factors including heterogeneity of antibiotics used in the randomized controlled trials (RCTs) selected.[2] In this study, authors sought to tighten the lens of comparison and examine the efficacy and safety of carbapenems vs select novel antibiotics for treatment of cUTI.

METHODS

This meta-analysis included RCTs comparing the use of carbapenems vs novel antibiotics for the treatment of cUTI in adult patients. Novel antibiotics included agents approved by the FDA or the European Medicines Agency for cUTI indication between 2009 and 2019. Trials were notably excluded if the novel agent under investigation was a carbapenem, or if they included patients receiving other antibiotics for concomitant infections. Efficacy between the 2 treatment arms was assessed through individual and composite rates of clinical and microbiological response at the test-of-cure visit. Comparative safety was evaluated through the rates of adverse events during the treatment period.

Novel antibiotics appear to have clinical efficacy and safety comparable to carbapenems for treatment of cUTIs.

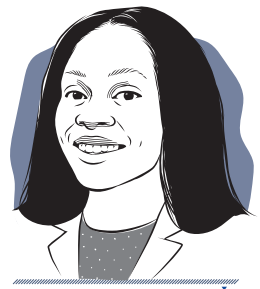
RESULTS

Six RCTs, encompassing 3343 subjects, were included for analysis. All RCTs were multicentered, multinational, noninferiority trials of adults with cUTIs. One RCT also included patients with intra-abdominal infections, although this study had separate outcomes available for cUTI. Duration of intravenous therapy ranged from 5 to 10 days. Baseline uropathogens were comparable between trials and inclusive of species of the Enterobacterales order and the *Pseudomonas* genus (see **Table** online). A higher rate of microbiological response was observed in the novel antibiotics group compared with the carbapenem group (relative risk [RR], 0.85; 95% CI, 0.79-0.91; $P < .01$). Meanwhile, no significant difference was observed in either individual or composite rates of clinical response (RR, 1.00; 95% CI, 0.98-1.04; $P = .83$ and RR, 0.91; 95% CI, 0.79-1.04; $P = .15$, respectively). Similarly, no difference in rates of adverse or serious adverse events (SAEs) was identified between groups (RR_{AEs}, 1.09; 95% CI, 0.93-1.29; $P = .297$ and RR_{SAEs}, 0.96; 95% CI, 0.53-1.76; $P = .896$).

DISCUSSION

Based on these results, the authors concluded that novel antibiotics appear to have clinical efficacy and safety comparable to carbapenems for treatment of cUTIs. The authors further suggest that novel antibiotics may demonstrate greater microbiological response compared with carbapenems. Although this outcome was statistically significant, the clinical significance of this finding is unclear. Moreover, although statistical significance was not demonstrated for the composite outcome, the favorable trend observed toward the novel antibiotic group may have been influenced largely by microbiological response.

Taken together, the applicability of these findings is limited by a few considerations. First, included studies did not publish rates of organisms resistant to multiple drugs, rendering it difficult to extrapolate these findings to that clinical context. Second, in 2 studies, patients received oral antibiotic therapy initially followed by intravenous antibiotic therapy, opening the possibility for confounding. Additionally, some of the therapies assessed (plazomicin, doripenem, and eravacycline) are not therapeutic options typically utilized for these infections. Last, there was a substantial degree of heterogeneity observed between studies, rendering it difficult to generalize findings. Despite these shortcomings, this article sheds light on an important issue: the evolving need for new therapies to overcome the burden of multidrug-resistant organisms. Ultimately, these findings suggest the need for more robust RCTs evaluating clinical outcomes between the carbapenems and novel agents within the context of bacterial resistance. ▲



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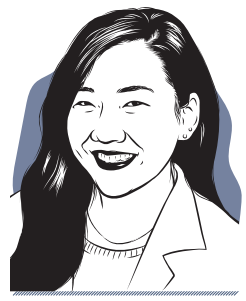

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FDA Approves Injectable Cabotegravir for PrEP

by JOHN PARKINSON *and* NINA COSDON

The US Food and Drug Administration (FDA) announced on December 20, 2021, that it had approved cabotegravir extended-release injectable suspension (Apretude) for pre-exposure prophylaxis (PrEP) for adults and adolescents to reduce the risk of HIV. Injectable cabotegravir is administered first as 2 injections a month apart, and then every 2 months indefinitely thereafter. Users can either start their treatment with injectable cabotegravir or take oral cabotegravir (Vocabria) for 4 weeks to decide how well they tolerate the drug.

This approval "adds an important tool in the effort to end the HIV epidemic by providing the first option to prevent HIV that does not involve taking a daily pill," Debra Birnkrant, MD, director of the Division of Antiviral Products in the FDA's Center for Drug Evaluation and Research, said in a statement. "This injection, given every 2 months, will be critical to addressing the HIV epidemic in the US, including helping high-risk individuals and certain groups where adherence to daily medication has been a major challenge or not a realistic option."

CLINICAL TRIALS

The safety and efficacy of injectable cabotegravir were evaluated in 2 trials that compared injectable cabotegravir with tenofovir disoproxil fumarate with emtricitabine (TDF/FTC; Truvada), a once-daily oral medication for PrEP. The trials were randomized, double-blind studies. Trial 1 (NCT02720094) included HIV-uninfected cisgender men and transgender women who have sex with men and have high-risk behavior for HIV infection. Trial 2 (NCT03164564) included uninfected cisgender women at risk of acquiring HIV.

Participants who took injectable cabotegravir started the trial with cabotegravir (oral, 30-mg tablet) and a placebo daily for up to 5 weeks followed by injectable cabotegravir 600-mg injection at months 1 and 2, then every 2 months thereafter and a daily placebo tablet. Participants who took TDF/FTC started the trial taking oral TDF/FTC and placebo daily for up to 5 weeks followed by oral TDF/FTC daily and placebo intramuscular injection at months 1 and 2 and every 2 months thereafter.

In Trial 1, 4566 cisgender men and transgender women who have sex with men received either injectable cabotegravir or TDF/FTC. The trial measured the rate of HIV infections among trial participants taking daily cabotegravir followed by injectable cabotegravir every 2 months compared with daily oral TDF/FTC. The trial showed participants who received injectable cabotegravir had 69% less risk of getting infected with HIV when compared with participants who took TDF/FTC orally.

In Trial 2, 3224 cisgender women received either injectable cabotegravir or TDF/FTC. The trial measured the rate of HIV infections in participants who took oral cabotegravir and injections of cabotegravir compared with those who took TDF/FTC orally. The trial showed participants who received injectable cabotegravir had 90% less risk of getting infected with HIV when compared with participants who had an oral TDF/FTC regimen.

"This potent new PrEP option…is a terrific development in HIV prevention," Douglas Krakower, MD, a faculty member with the Division of Infectious Diseases at Beth Israel Deaconess Medical Center, research scientist at The Fenway Institute, and assistant professor of medicine and population medicine at Harvard Medical School, all in Boston, Massachusetts, told *Contagion*®.

Adverse effects occurred more frequently in participants who received injectable cabotegravir compared with participants who received TDF/FTC, and included injection site reactions, headache, fever, fatigue, back pain, myalgia, and rash.

POSITIVE TREND, STILL GREATER INITIATION NEEDED

The past 5 years have seen significant strides toward greater PrEP initiation. According to the US Centers for Disease Control and Prevention (CDC), PrEP use in the United States is at approximately 25% of the 1.2 million individuals for whom it is recommended. This increase is up from about 3% usage in 2015.

Still, there is a long way to go for greater initiation and uptake in communities disproportionately affected by HIV, such as those who inject drugs, trans individuals, and Black Americans. Because of social inequities, these groups typically have lower initiation rates compared with White men who have sex with men, a statistic for which public health officials need to prioritize finding a solution.

"This approval adds an important tool in the effort to end the HIV epidemic by providing the first option to prevent HIV that does not involve taking a daily pill."

—Debra Birnkrant, MD, director of the Division of Antiviral Products

Krakower believes the approval of injectable cabotegravir can help reduce HIV rates in these populations, but change will hinge on how public health programs and individual providers reach them to disseminate messaging and the therapies. "If it is implemented in ways that are culturally sensitive, patient focused, and convenient.This could include mobile van units to meet [individuals] where they live; embedding PrEP in community-based organizations that can improve trust in populations that have experienced discrimination in health care settings, such as LGBTQIA+ populations, Black and Latinx [individuals], and [individuals] who inject drugs, among others," Krakower explained. ▲

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Moderna Provides Stronger, Durable Vaccine Efficacy Over 4 Months

by KEVIN KUNZMANN

The US Centers for Disease Control and Prevention (CDC) investigators have observed an approximate 10 percentage point difference in efficacy between the 2 available COVID-19 messenger RNA (mRNA) vaccines after 4 months, according to data from a military veteran cohort. The findings, published in the CDC's *Morbidity and Mortality Weekly Report* on December 10, 2021, also showed a reduced mean antibody count in the observed older veteran patients with underlying medical conditions compared with that of younger, healthier vaccine recipients—further emphasizing the need for continued COVID-19 vaccine monitoring and booster dose prioritization.

Led by Kristina L. Bajema, MD, of the CDC COVID-19 Response Team, investigators sought to compare the vaccine effectiveness of Moderna's mRNA-1273 and Pfizer-BioNTech's BNT162b2 at 2 different periods: 14 to 119 days and 120 days or more after receipt of the second vaccine dose. Their cohort included 1896 US veterans at 5 Veterans Affairs (VA) medical centers between February 1 and September 30, 2021.

Eligible patients for the test-negative case-control assessment were adults 18 years or older hospitalized at the VA medical centers. Adults with COVID-19–like illness who received a positive SARS-CoV-2 nucleic acid amplification test result were included as case patients; those with COVID-19–like illness and a negative SARS-CoV-2 test results served as controls.

The trial cohort included 755 case patients and 1141 controls. A majority (92.7%) were male and approximately half (49.7%) were Black; another 8.5% were Hispanic. Median patient age was 67 years (IQR, 59-75).

With the Moderna vaccine, Bajema and colleagues observed an 89.6% vaccine efficacy at 14 to 119 days (95% CI, 80.1%-94.5%) and 86.1% efficacy at 120 days or more (95% CI, 77.7%-91.3%). With the Pfizer-BioNTech vaccine, investigators observed 86.0% efficacy at 14 to 119 days (95% CI, 77.6%-91.3%) and 75.1% vaccine efficacy at 120 days or more (95% CI, 64.6%-82.4%).

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In an assessment of antibody sera taken from 259 (40.6%) fully vaccinated controls, investigators observed greater antispike immunoglobulin G (IgG) levels at 14 to 119 days vs 120 days or more, irrespective of vaccine product. Younger vaccinated adults aged 18 to 64 years reported greater mean antispike IgG levels than those 65 years or older. "These findings from a cohort of older, hospitalized veterans with high prevalence of underlying conditions suggest the importance of booster doses to help maintain long-term protection against severe COVID-19," investigators wrote.

Previous research has shown correlations between binding antibody levels, neutralizing antibody levels, and COVID-19 vaccine efficacy in clinical trials—although no immune correlate of protection for COVID-19 vaccination has been established. Nonetheless, investigators noted that changes in humoral immunity as they relate to real-world COVID-19 protection can be informed by pairing antibody levels from the same population in which vaccine effectiveness is investigated, as with this cohort assessment.

"Although this analysis was not powered to detect small differences in vaccine effectiveness by mRNA product as seen in other hospitalized settings, significantly higher post–Moderna vaccination antibody levels compared with Pfizer-BioNTech were observed, which is consistent with findings from other studies," they concluded. "Potential reasons for this difference include higher antigen content and a longer interval between doses for the Moderna vaccine compared with the Pfizer-BioNTech vaccine." ▲

It's Getting Harder to Find a Doctor in the House

by JEFF BENDIX

The United States could lose nearly a quarter of its physicians and up to 40% of its nurses unless health care organizations mitigate the high levels of stress and burnout among clinical workers due to the COVID-19 pandemic. Those troubling results emerge from a recent study of the relationship between pandemic-related stress and work intentions among more than 20,000 clinical and nonclinical health care employees at 124 organizations around the country.

In the study, conducted between July 1 and December 31, 2020, 23.8% of doctors, 40% of nurses, and 33% of advanced practice providers (APPs) said chances were moderate, likely, or definite that they would leave their current practice in the next 2 years. In addition, 34% of nurses, 31% of physicians, and 29% of APPs reported moderate, likely, or definite plans to reduce their work hours in the next 12 months. Study respondents worked in both inpatient and outpatient settings.

The study found that higher levels of burnout, stress, workload, fear of infection, anxiety/depression due to COVID-19, and number of years in practice were each associated with a greater intention to reduce work hours or leave practice. High stress was most prevalent among nurses (37.4% of respondents), followed by those in other clinical roles (34.5%), doctors (33.7%), and APPs (32.6%). Nurses also reported the highest levels of burnout (63.1%), followed by those in other clinical roles (58.7%), APPs (53.7%), and physicians (47.9%).

The authors offer suggestions for addressing 2 of the key factors associated with intent to reduce hours or leave. The first is to reduce stress/burnout through steps such as providing adequate personal protective equipment, ensuring access to confidential mental health services, and reducing work overload by creating more opportunities for teamwork.

The second approach builds on the study's findings that workers are less likely to leave a job or reduce work hours if they feel valued. To demonstrate appreciation for workers, the authors recommend that health care organizations make communication transparent, support childcare, and provide rapid training for employees deployed to unfamiliar units.

The study, "COVID-Related Stress and Work Intentions in a Sample of US Health Care Workers," appeared in the December 2021 *Mayo Clinic Proceedings: Innovations, Quality & Outcomes*. ▲

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Oral Therapeutic Options to Prevent Disease Progression From COVID-19 in an Ambulatory Setting

As the number of COVID-19 cases continues to rise, oral treatment options for at-home use are in demand to provide early intervention and reduce the progression to severe disease, hospitalization, and death.

by KRISTIN L. FEICK, PHARMD, BCPS; *and* CHRISTINA ROSE, PHARMD, BCCCP

KRISTIN L. FEICK, PHARMD, BCPS

Kristin Feick, PharmD, BCPS, is a PGY2 critical care pharmacy resident at Temple University School of Pharmacy in Philadelphia, Pennsylvania.

COVID-19, caused by SARS-CoV-2, has been declared a global pandemic; cases have exceeded 352 million and 5.61 million deaths worldwide.[1-3] Three vaccines have become available in the United States that demonstrate effectiveness against development of disease, hospitalization, and death.[4-9] Despite vaccine effectiveness, only 74% of the US population has received at least 1 vaccine dose.[10] Unvaccinated individuals and populations at high risk of severe disease continue to require hospitalization for COVID-19.[11] Emergency use authorization (EUA) has been granted for various ambulatory COVID-19 treatment options; all require administration in a hospital or observational setting and parenteral administration. Monoclonal antibodies represent a treatment option for outpatients and have been shown to reduce the risk of hospitalization and death in high-risk patient populations.[12-15]

Early treatment of COVID-19 with orally available agents could be a game changer in preventing hospitalization and reducing death in high-risk patients.

However, with the emergence of new variants, the efficacy of current vaccines and treatment options has waned, leaving vulnerable populations at higher risk of developing disease progression.[9,13] There is a need for safe, effective oral treatment options that can be easily distributed in the outpatient setting, prevent progression or death, and retain effectiveness despite newly emergent variants. There are currently 3 oral treatment options that may be considered for the management of outpatient COVID-19 infection.

FLUVOXAMINE

Fluvoxamine is an oral selective serotonin reuptake inhibitor indicated for the treatment of obsessive-compulsive disorder and off-label for other psychiatric disorders (**Table**). Although not a true antiviral medication, fluvoxamine has multiple proposed mechanisms in COVID-19. Fluvoxamine has a high affinity for the σ-1 receptor (S1R) that regulates cytokine production and reduces inflammatory events associated with COVID-19 via decreased cytokine production, an effect similar to other COVID-19 treatment options.[16,17] Fluvoxamine's other proposed mechanism to combat COVID-19 include decreased platelet aggregation, mast cell degranulation, and interference with viral entry into cells.[16] Three randomized controlled trials (RCTs) have evaluated the use of fluvoxamine for COVID-19. Lenze et al conducted a randomized, double-blind, placebo-controlled trial (NCT04342663) in nonhospitalized patients with confirmed COVID-19. The dose of fluvoxamine in the trial was increased on day 3 to 100 mg 3 times daily, to maximize affinity for S1R, and continued for a total of 15 days. The primary end point of clinical deterioration—defined as shortness of breath (SOB) or hospitalization for SOB or pneumonia and oxygen saturation less than 92% or requirement of supplemental oxygen to maintain saturation equal to a greater than 92%—was collected via phone from participants and a review of hospital records. Clinical deterioration occurred in 0 of 80 patients who received fluvoxamine compared with 6 of 72 (8.3%) patients who received placebo.[18] The TOGETHER randomized, placebo-controlled trial (NCT04727424) evaluated the use of fluvoxamine in nonhospitalized patients at high risk for severe disease. A total of 1497 patients received fluvoxamine or matching placebo at a dose of 100 mg twice daily for 10 days. The primary outcome of referral for hospitalization or retention in a COVID-19 emergency setting for 6 hours or more up to 28 days after randomization was lower in the fluvoxamine group at 11% compared with 16% in the placebo group. Patients with more than 80% adherence to fluvoxamine were included in a per-protocol analysis and demonstrated a larger treatment benefit compared with placebo regarding the primary outcome and mortality.[19] The rate of adverse effects (AEs) was similar in the fluvoxamine group compared to placebo in both trials with the most common being headache, nausea, and vomiting.[18, 19]

Overall, between the 2 RCTs there was a trend toward lower all-cause hospitalizations with fluvoxamine (9.3%) compared with placebo (12.4%), (RR, 0.75; 95% CI, 0.57-0.99).[17] The STOP COVID 2 (NCT04668950) RCT aimed to assess unvaccinated adults at risk for clinical deterioration. The study enrolled more than 700 patients but was stopped for futility by the data safety monitoring board.[20] Although guidelines currently give a recommendation for fluvoxamine to be used in a clinical trial and the third RCT was stopped for futility, the familiarity, safety, and low cost make it a possible option for nonhospitalized patients in areas without other treatment options.[13,17]

NOVEL ANTIVIRALS FOR COVID-19

As of December 2021, the FDA has issued EUAs for 2 oral antiviral agents [21,22] that demonstrate a benefit for the treatment of outpatient COVID-19 (**Table**). Molnupiravir (MOV), developed by Merck and Ridgeback Biotherapeutics, is a ribonucleoside analogue that targets RNA-dependent RNA-polymerase, an enzyme responsible for replication of viral RNA. MOV is a prodrug converted by esterases to *N* [4]-hydroxycytidine (NHC). NHC is phosphorylated inside cells, leading to mutation and impairment of viral replication. In vitro, NHC has a broad activity targeting multiple RNA viruses including MERS-CoV, SARS-CoV, and SARS-CoV-2. MOV activity in animal

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TABLE. Comparison of Oral Agents[31-37]

Drug	Emergency use authorization indication	Dosing	Dose adjustment	Reproductive risk	Drug interactions
Fluvoxamine[31]	N/A	Clinical trials used 200-300 mg/d in divided doses[18-20]	Consider decreased dose in hepatic cirrhosis to max 150 mg/d	Limited data in first trimester but low risk of congenital malformations; third-trimester exposure may increase risk of persistent pulmonary hypertension and adverse effects in neonates[32-34]	Contraindicated: MAOIs, antipsychotics, serotonergic agents Others: inhibitors or substrates of CYP1A2, CYP2C9, CYP2C19, or CYP3A4[31]
(MOV)[35]	Treatment of mild to moderate COVID-19 in ambulatory adults at high risk for progression to severe disease with no other treatment options within 5 days of symptom onset[35,36] *# NIR/RTV approved for patients ≥ 12 years of age weighing ≥ 40 kg[36]*	800 mg (four 200-mg capsules) orally twice daily for 5 days	None	Animal studies demonstrated the potential for fetal harm and should be avoided during pregnancy and recommendation to use contraception for duration of treatment and 4 days after the last dose[35] Men: Men [RP1] [CR2]: theoretical concern for mutagenic effects on sperm cells, studies ongoing, recommendation to use contraception during treatment and for at least 3 months after the last dose[35]	None identified
(NIR/RTV)[36]		300 mg NIR (two 150-mg tablets) with 100 mg RTV (one 100-mg tablet), taken together twice daily for 5 days	CrCl 30-60 ml/min: 150 mg NIR (one 150-mg tablet) with 100 mg RTV (one 100-mg tablet), taken together twice daily for 5 days CrCl < 30 ml/min and severe hepatic impairment: not recommended	NIR: No demonstration of developmental toxicities observed in animal studies[36] RTV: No increased risk of teratogenicity[36,37]	Contraindicated: Strong CYP3A4 substrates for which high concentrations are associated with serious or life-threatening effects* Others: substrates, inhibitors, or inducers of CYP3A4

CrCl, creatinine clearance; CYP, cytochrome P450; MAOIs, monoamine oxidase inhibitors; MOV, molnupiravir; NIR, Nirmatrelvir; RTV, ritonavir;
Only NIR/RTV is approved for patients ≥ 12 and ≥ 40 kg; MOV is associated with the potential for issues associated with bone growth and should not be used in individuals < 18 years.
*For a detailed list see facts sheet for health care providers: emergency use authorization for Paxlovid.[36]

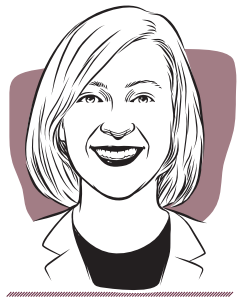
studies demonstrates a reduction in viral load, viral replication, and transmission of the virus.[23-25] A phase 2A trial (NCT04405570) evaluating escalating doses of MOV in nonhospitalized patients exhibited a significant reduction in viral RNA isolation and increased clearance in the high dose compared with placebo.[26]

MOV was assessed in a randomized, double-blind, phase 3 trial (NCT04575597) in high-risk, nonhospitalized, and unvaccinated adults with mild to moderate COVID-19 using MOV or placebo for 5 days. The primary efficacy end points of hospitalization or death were significantly lower with MOV compared with placebo by day 29. Signs and symptoms of COVID-19 were more likely to resolve and less likely to progress in the MOV group. AEs were similar between MOV and placebo; most reported were diarrhea, nausea, and dizziness.[27]

Nirmatrelvir and ritonavir (NIR/RTV; Paxlovid), developed by Pfizer, was studied in adult patients with COVID-19 at high risk for disease progression.[28] NIR inhibits the main protease in SARS-CoV-2 that is responsible for viral replication. It is designed to work before viral replication occurs. NIR is coadministered with RTV, an HIV-1 protease inhibitor and CYP3A4 inhibitor, which allows for an increased concentration of the drug.[29] In December 2021, Pfizer announced final results from its phase 2/3 EPIC-HR (NCT04960202) study. NIR/RTV was compared to placebo in a randomized, double-blind study of nonhospitalized, unvaccinated adults with at least 1 risk factor for progression to severe illness from COVID-19 or who were older than 60 years. When compared with placebo, patients who received NIR/RTV within 5 days of symptom onset had an 88% reduced risk of hospitalization or death through day 28. The rate of hospitalization or death was 8 of 1039 (0.8%) in NIR/RTV compared with 66 of 1046 (6.3%) placebo. No deaths occurred in the NIR/RTV group and 12 occurred in placebo. NIR/RTV demonstrated a 10-fold reduction in viral load compared with placebo by day 5 in 499 patients. The most common AEs were nausea, vomiting, diarrhea, and dizziness and were similar between treatment and placebo groups.[28] RTV has the potential to cause significant drug-drug interactions and caution must be given to patients prescribed concurrent CYP3A4 substrates or inhibitors.[30] NIR/RTV is being studied to evaluate the benefit in patients with standard risk and post exposure to COVID-19.[28]

Early treatment of COVID-19 with available agents could be a game changer in preventing hospitalization and reducing death in high-risk patients. These oral agents are intended to be used early in the course of infection, optimally within the first 5 days. Prompt testing at the first sign of symptoms or following exposure and administration of oral medications as soon as possible would provide patients with the greatest potential benefit. Although not a replacement for vaccination, the ease of distribution and short course make them a favorable option. ▲

References are available at ContagionLive.com.



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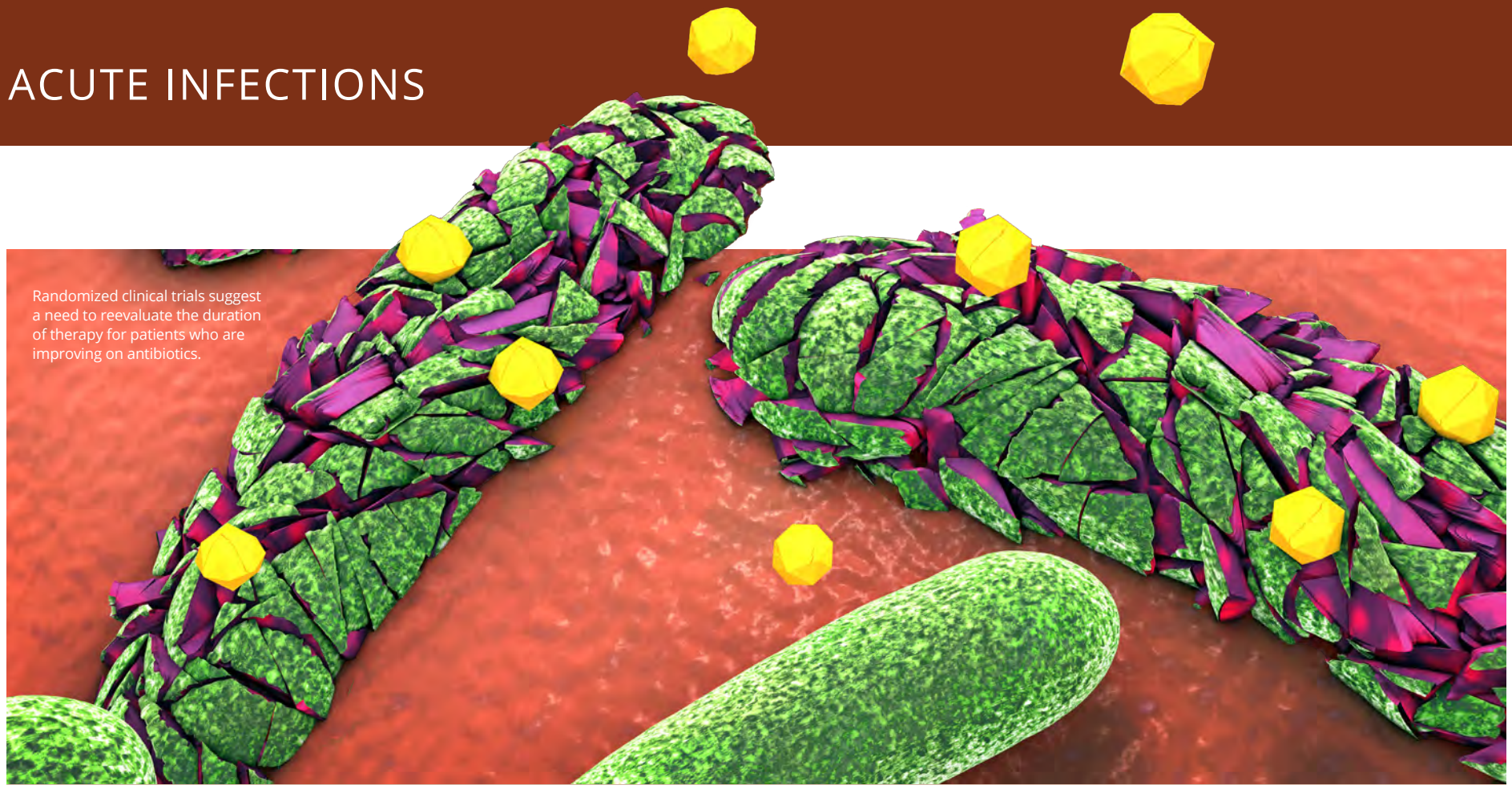

Randomized clinical trials suggest a need to reevaluate the duration of therapy for patients who are improving on antibiotics.

Optimizing Antibiotic Use by Limiting Total Antibiotic Exposure

Shorter durations of antibiotic therapy demonstrate similar efficacy and may improve safety compared with longer courses for certain infections.

by Megan E. Klatt, PharmD ⁂; *and* Erin K. McCreary, PharmD, BCPS, BCIDP ⁂ M

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Antimicrobial stewardship is a coordinated program to optimize antimicrobial use, which includes evaluating duration of therapy. Infectious diseases organizations encourage strategies to reduce antimicrobial therapy to "the shortest effective duration."[1] Indeed, each additional day of antibiotic therapy has been associated with development of antimicrobial resistance and adverse drug events, including *Clostridioides difficile* infection.[2,3] However, until recently, the most effective and safe durations of therapy for several common indications were not well defined, and historical recommendations were largely based on expert opinion (**Table**).

COMMUNITY-ACQUIRED PNEUMONIA

The 2019 American Thoracic Society and Infectious Diseases Society of America (IDSA) guidelines endorse 5 days of antibiotics for patients with community-acquired pneumonia (CAP) who are improving on therapy.[4] The authors reference a randomized controlled trial (RCT) by el Moussaoui and colleagues that found 3 days of therapy with amoxicillin was noninferior to 8 days as part of the justification for a short course of treatment.[5] However, study limitations including small sample size and broad exclusion criteria prevented widespread application of this approach—and even 5-day courses are not adhered to, especially at hospital discharge.[6,7] In March 2021, another 3-day vs 8-day duration RCT (NCT01963442) for CAP was published, challenging the status quo.

This randomized, double-blind, noninferiority study included 303 adults with moderately severe CAP who were admitted to a medical ward and were clinically stable after 72 hours of empiric treatment.[8] Stability was defined as temperature at or below 37.8 °C, heart rate less than 100 beats/min, respiratory rate less than 24 breaths/min, oxygen saturation at or greater than 90%, systolic blood pressure at or greater than 90 mm Hg, and normal mental status. Patients with severe or complicated CAP, known immunosuppression, possible aspiration pneumonia, or with health care–associated pneumonia were excluded. Baseline demographics were well balanced between groups, with most patients having an age greater than 65 years, 24% with at least 2 comorbidities, and median pneumonia severity index (PSI) score in class III (median 80.5 in short course vs 83.0 in long course). Three days was noninferior to 8 days in the primary outcome of clinical cure 15 days after start of treatment (77.0% vs 67.5%, respectively; 95% CI, −0.38 to 20.04). Furthermore, short courses remained noninferior regardless of age and PSI score in post hoc subgroup analyses.

The results of these 2 RCTs suggest a need to reevaluate the duration of therapy for patients with CAP who are improving on antibiotics. In patients with uncomplicated CAP who are clinically stable after 72 hours of effective therapy, further antibiotics may provide no additional benefit. The role of excessive antibiotic use and patient outcomes, specifically among patients with CAP, was explored by Vaughn et al in their retrospective cohort study conducted across 43 hospitals in Michigan.[6] Among the study population, approximately two-thirds (67.8%) received a longer course of antibiotics compared with guideline-recommended durations (ie, 5 days), with a median excess duration of 2 days (IQR, 0-4 days). Each additional day of excessive antibiotic treatment was associated with 5% increased odds of a patient-reported adverse drug event.

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TABLE. Studies Supporting Shorter Antibiotic Durations Published From 2019-2021

INDICATION	RESULTS	REFERENCE
Community-acquired pneumonia (adults)	3 days noninferior to 8 days	Dinh et al. *Lancet*. 2021
Community-acquired pneumonia (pediatrics)	3 days noninferior to 7 days 5 days noninferior to 10 days	Bielicki et al. *JAMA*. 2021 Pernica et al. *JAMA Pediatr*. 2021
Uncomplicated gram-negative bacteremia	7 days noninferior to 14 days	Yahav et al. *CID*. 2019 van Dach et al. *JAMA*. 2020 Molina et al. *Clin Microbiol Infect*. 2021
Complicated urinary tract infection	7 days noninferior to 14 days	Drekonja et al. *JAMA*. 2021
Diabetic foot osteomyelitis	3 weeks noninferior to 6 weeks	Gariani et al. *CID*. 2021

Importantly, the Vaughn et al study also revealed over 90% of excessive antibiotic use occurred at the time of discharge. In fact, antibiotic overuse occurs frequently at discharge for pneumonia and other common infections.[9] It is clear more attention should be focused on the interventions within the transitions of care space to reduce antibiotic misuse. However, implementing shorter antibiotic courses, such as 3 days for CAP, may allow for antibiotic discontinuation during hospital admission, thereby reducing the potential for excessive durations at the time of hospital discharge by eliminating the need for a discharge prescription.

UNCOMPLICATED GRAM-NEGATIVE BACTEREMIA

In 2019, Yahav et al conducted an RCT (NCT01737320) that demonstrated 7 days was noninferior to 14 days for treatment of uncomplicated gram-negative bloodstream infections.[10] This landmark study was followed by another RCT (NCT03101072) in 2020 that compared 7-day, 14-day, and C-reactive protein (CRP)-guided treatment durations. In this study, a 7-day duration was noninferior to 14 days of therapy in the primary outcome of clinical failure at 30 days (6.6% vs 5.5%, respectively; 1-sided 97.5% CI, –infinity to 6.3; $P < .001$). CRP-guided treatment duration also had similar outcomes; median duration of therapy in this cohort was 7 days (IQR, 6-10 days).[11] In September 2021, Molina et al also demonstrated similar outcomes in patients treated with 7 vs 14 days of therapy for uncomplicated Enterobacterales bloodstream infections.[12] It is important to note that these data are primarily representative of patients with uncomplicated, monomicrobial Enterobacterales bacteremia from a urinary source. Patients with *Pseudomonas aeruginosa* bacteremia and/or immune compromise are a minority of cases in these studies, thus limiting extrapolation of the findings. However, results from recent retrospective studies suggest short courses (ie, 7-9 days) may be appropriate for uncomplicated bacteremia due to *P aeruginosa*, as well.[13,14]

COMPLICATED URINARY TRACT INFECTION

Short courses of certain antibiotics (eg, 3-5 days) are standard care for patients with uncomplicated cystitis, whereas complicated urinary tract infections (UTIs) typically result in longer durations, although data are limited. UTIs in men are considered complicated by nature of the male anatomy and thus are commonly treated with a course between 7 and 14 days. In 2021, Drekonja et al challenged this practice with an RCT (NCT01994538) comparing 7 vs 14 days of antibiotics for afebrile men with clinical symptoms consistent with a UTI.[15] Participants received either trimethoprim/sulfamethoxazole or ciprofloxacin at standard treatment dosing. Overall, 254 patients were included in the primary as-treated analysis (patients who missed ≥ 3 doses or > 2 consecutive doses were excluded). Among the as-treated population, 7 days was noninferior to 14 days in the primary outcome of resolution of UTI symptoms at day 14 post completion of treatment (93.1% vs 90.2%, respectively; 1-sided 97.5% CI, –5.2 to infinity). Additionally, recurrence of UTI symptoms was not significantly different between groups and rates of adverse effects were lower in the 7-day cohort (20.6%) compared with the 14-day group (24.3%). This study has several limitations including small sample size, inclusion of only 2 antibiotics for treatment option, and most importantly inclusion of patients without confirmed microbiological evidence of UTI and for whom antibiotics may have been inappropriately prescribed. These results should not be extrapolated to patients who meet other criteria for complicated UTI (eg, presence of urinary catheter, anatomic abnormality, etc), given a lack of data. However, it is advisable to implement shorter, 7-day courses in male patients who present without signs and symptoms of systemic infection.

DIABETIC FOOT OSTEOMYELITIS

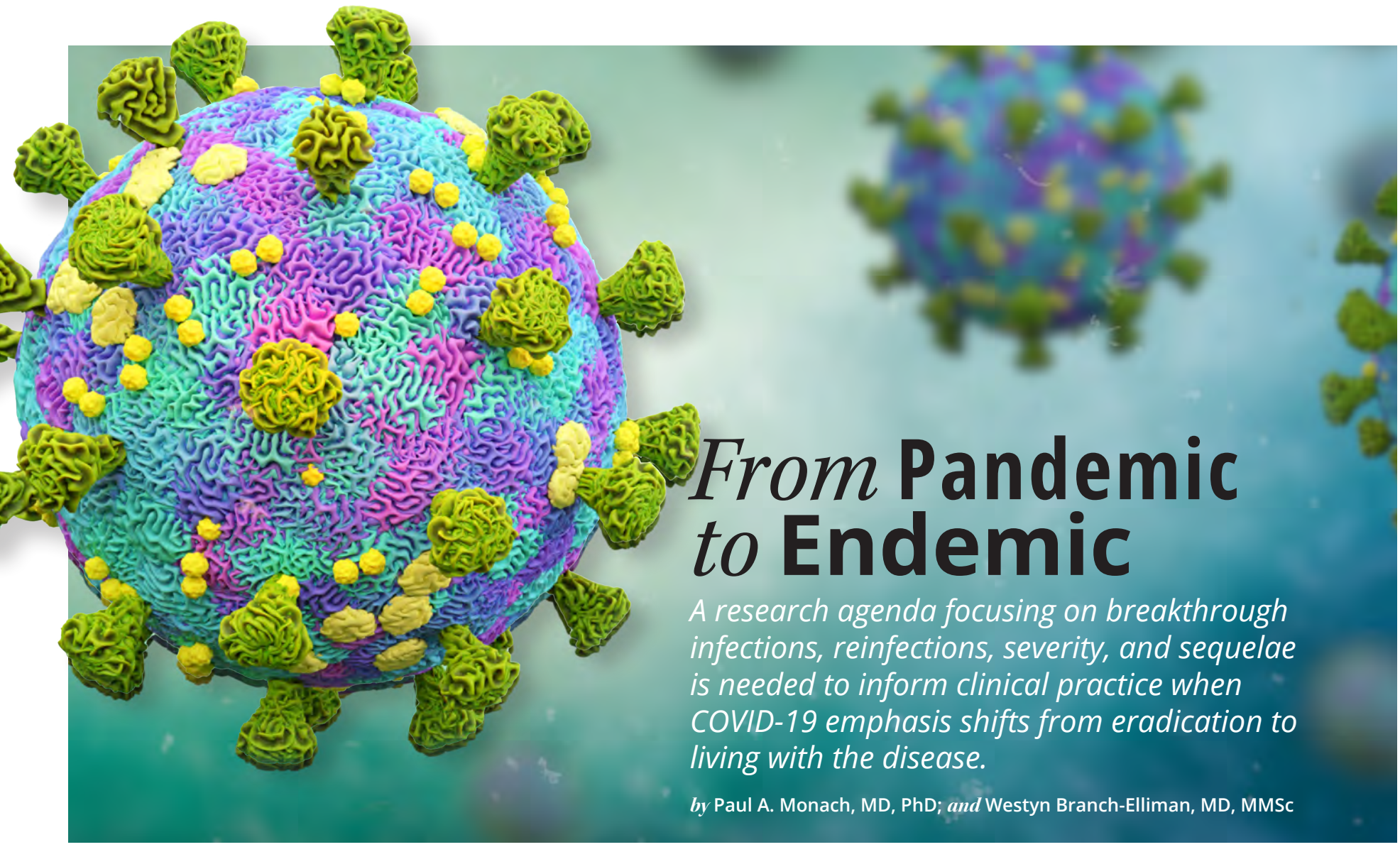
Diabetic foot infections with bone and/or joint involvement are usually treated with 4 to 6 weeks of antibiotics, per the IDSA guidelines.[16] Gariani et al compared 3 vs 6 weeks of antibiotic therapy for patients with diabetic foot osteomyelitis after surgical debridement in a recent RCT (NCT03615807).[17] Ninety-three patients were included in the study. Most were male (82%), 57% had osteomyelitis involving toe(s), and 37% had received partial amputation. Rates of remission were similar between 3-week vs 6-week groups in the intention-to-treat (ITT) population (84% vs 73% respectively, $P = .21$). Additionally, shorter courses were not associated with increased remission in multivariate analysis (ITT population, HR, 1.1; 95% CI, 0.6-1.7). Given the positive results of this trial, the study authors plan to proceed with an additional RCT with a larger cohort, and it is reasonable for clinicians to consider shorter courses of therapy in similar patients with surgical source control.

> As more trials are conducted regarding duration of therapy, evidence guides us toward shorter courses.

CONCLUSION

Historical recommendations for duration of therapy are largely based on expert opinion. As more RCTs are conducted in the infectious disease space regarding duration of therapy, high-quality evidence consistently guides us toward shorter courses. Limiting antibiotic exposure has a multitude of benefits for patients including similar efficacy, improved safety, optimized transitions of care, and decreased health care costs. Clinicians should make every effort to apply these studies' findings in their routine practice to curb unnecessary antibiotic use and improve patient care. ▲

References are available at ContagionLive.com.



From Pandemic *to* Endemic

A research agenda focusing on breakthrough infections, reinfections, severity, and sequelae is needed to inform clinical practice when COVID-19 emphasis shifts from eradication to living with the disease.

by Paul A. Monach, MD, PhD; *and* Westyn Branch-Elliman, MD, MMSc

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(continued from cover page)

undoubtedly overlap to some degree, but we already know the immune status of the individual will play a major role. This article will discuss how the current evidence about immunity acquired through infection and/or vaccination points to urgent areas of research that would not just serve public health but could be used to tailor clinical treatment for individuals as society moves away from eradication and toward living with SARS-CoV-2.

NATURAL INFECTION AND VACCINATION: SUMMARY OF CURRENT EVIDENCE

The literature on immunity conferred by infection or vaccination was recently reviewed comprehensively by the US Centers for Disease Control and Prevention (CDC), and we refer the reader to that document[4] for most references. We will focus on areas where ongoing uncertainties point to urgent research priorities. The following statements can be made with confidence as a starting point for identifying clinically relevant research gaps:

- One dose of messenger RNA (mRNA) vaccine confers moderate and temporary protection to an individual with no history of infection, in adults and adolescents.
- Infection confers protection from severe disease.
- A complete vaccine course confers protection against infection and strong protection against severe disease for well over 6 months in many adults, but not in all.
- The optimal initial dosing interval is not known, but an 8-to-12-week period between the first and second doses confers a stronger antibody response than shorter intervals.[5,6]
- Individuals previously infected and subsequently vaccinated are better protected than those who have only been vaccinated[7] or infected.[8] One dose of mRNA vaccine in individuals with a history of infection is sufficient when antibody levels are used for that assessment.[4-9]
- It is not clear whether previous infection or 1 course of vaccine confers better long-term protection, nor how long the protection against severe disease lasts.
- Immunity against any infection wanes over time, and an additional dose of vaccine increases protection.[10] Durability of the protection conferred by a third dose is unknown.
- Neutralizing antibody titers are correlated with resistance to infection but are not a perfect surrogate marker, and antibody/immunoglobulin (IgG) titers to the spike protein are correlated imperfectly with neutralizing antibodies.
- T-cell responses are detectable after vaccination or infection and are presumed to be highly relevant to clinical protection,[9] but correlation with protection has not been studied to the same degree as correlation with antibodies.
- Antibody and T-cell responses and their decay after vaccination or infection vary widely, even within the general population.[4,9,11,12]
- Cross-protection against different viral variants occurs, but is often attenuated, at the antibody and T-cell levels.
- Cross-protection against any infection vs severe disease varies depending upon the specifics of the variant in question.

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- Immune-suppressed patients, who are more susceptible to severe COVID-19 in the absence of vaccination,[13] often make weak antibody responses to a standard course of vaccine; some but not all achieve better responses after an additional dose.[14-17]

We will provide a more detailed discussion of several topics before proceeding to suggestions about priorities for future research.

Comparison of immunity conferred by vaccination vs prior infection. Few studies so far, one not yet peer-reviewed, have compared risks of severe reinfection vs severe breakthrough infection. All can be criticized based on high risk of confounding. They have reached different conclusions about whether the protection provided by vaccination is better, worse, or no different from that provided by infection, but all support the notion that both vaccination and infection provide substantial immunity.[4,18,19]

Optimal initial dosing intervals and booster doses. In clinical trials, the 2 doses of Pfizer/BioNTech vaccine BNT162b2 were spaced 3 weeks apart, and the 2 doses of Moderna vaccine mRNA-1273 were spaced 4 weeks apart. With these intervals, waning of immunity against any infection is clinically apparent in many individuals by 6 months, and even shorter against Omicron; duration of protection against severe disease is less clear. Some countries, including the United Kingdom and Canada, adopted a longer interval between the 2 doses of the initial vaccination series as a means of accelerating delivery of a first dose, but that strategy may also have improved the duration of response.[5,6] In countries where booster shots can be widely administered, the timing of the initial regimen may be less important, but the optimal timing and frequency of booster shots in the general population, high-risk populations, and previously infected patients remains an important consideration, especially with the spread of variants.

Vaccination in immune-suppressed patients. IgG titers are lower after a standard course of vaccination in patients on immune-suppressive drugs, and immune-suppressed states are probably a major risk factor for breakthrough infection requiring hospitalization: In one US study, 40% of hospitalized breakthrough cases (including 8 of 17 fatal breakthrough cases) were immune-suppressed, whereas 15% of unvaccinated patients were immune-suppressed.[20] The degree of reduction varies widely among different drugs and underlying conditions, with results overall being consistent with known mechanisms of action.[16,17] A third dose of mRNA vaccine increases IgG levels substantially in some but not all immune-suppressed patients, and there is particular concern that patients with profound deficits in humoral immunity, either due to disease states or B-cell–depleting therapy, cannot be effectively immunized.[16,21]

Immune responses. Standard vaccine regimens produce well over 90% protection against severe disease for at least 6 months in most individuals; thus, extremely high IgG titers are not necessary for protection against severe disease. However, multiple studies confirm a correlation between IgG levels (whether tested for neutralizing activity or simply binding the spike protein) and protection against infection of any severity.[4] Because IgG titers also vary widely after infection or vaccination and decay over time to variable degrees,[9,11,12,14,15,22,23] time since vaccination or infection might not be the best predictor for risk of breakthrough or reinfection if IgG titers were available on an individual basis. Higher titers, as measured against the ancestral spike protein, may be needed to provide cross-protection against different variants.

Implications of the gaps in evidence. Toward the goal of devising policy and clinical guidance to protect individuals and the overall population as effectively and efficiently as possible, urgent questions are:

- Who is at risk for reinfection or breakthrough infection, and in particular infection that is severe or has prolonged sequelae?
- Why do these patients remain at risk? Can IgG titers be used along with other health factors to make more precise risk-stratification for individual patients?
- When do these infections occur (ie, what is the contribution of time since infection or vaccination in determining risk, independent of other measurable factors)?

Answers to these questions could be used to refine recommendations about revaccination strategies and public policy about mitigation measures and vaccine mandates, to the benefit of society as a whole and to individual patients. Identification of who is at risk and when could be used to inform preexposure and postexposure prophylaxis strategies with monoclonal antibodies, especially those that can be self-administered, and/or antiviral drugs, especially if available orally (**Figure**). Prophylaxis and early antivirals in high-risk patients would not only reduce individual risk but also protect society by limiting spread and prolonged infections in immunocompromised patients, which may contribute to the development of problematic new variants.[24]

STEPS TOWARD CLOSING THE INFORMATION GAP

A proposed research agenda for studying reinfection and breakthrough infection is shown in **Box**. Clinical scenarios that are important to study are shown in **Table**. Additional steps to facilitate the usefulness of these studies are as follows.

Definitions of severe infection. Infection with SARS-CoV-2 is only clinically significant if it is severe or has PASC. In May 2021, the CDC started focusing on the subset of breakthrough infections that lead to hospitalization, and a recent study aimed at estimating vaccine effectiveness used a rigorous case definition.[20] However, use of the metric "hospitalization contemporaneous with a positive test" to identify severe cases in hospitals that screen all inpatients for SARS-CoV-2 will magnify risk of hospitalization due to COVID-19 and make it more difficult to answer clinically important questions.[25] More precise—but still simple and objective—definitions of moderate to severe COVID-19 are needed, as is research to determine whether concomitant SARS-CoV-2 infection worsens >>

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BOX. Proposed Research Agenda for Study of Reinfection and Breakthrough Infection

- Study reinfection, with or without vaccination after the first episode, including outcomes of severity and sequelae (postacute sequelae of COVID-19).
- Use rigorous, objective, and reproducible definitions of severity, with gradations, and determine risk factors for severe breakthrough and severe reinfection.
- Study the clinical characteristics of severe breakthrough and severe reinfection and compare to the findings in immunologically naïve patients.
- Study the predictive value of clinically available IgG tests in assessing protection, especially in groups at higher risk of breakthrough or reinfection, to determine clinical usefulness of measuring antibody titers in individual patients.
- Include cross-reaction of neutralizing antibodies and T cells to variants in lab-based studies of vaccinated patients, breakthrough infections, and reinfections known or suspected to have been caused by variants.
- Incorporate negative testing for antibodies into definition of control groups used to determine vaccine effectiveness, to avoid the problem that immunity among controls will reduce the calculated effectiveness of initial or booster vaccination.

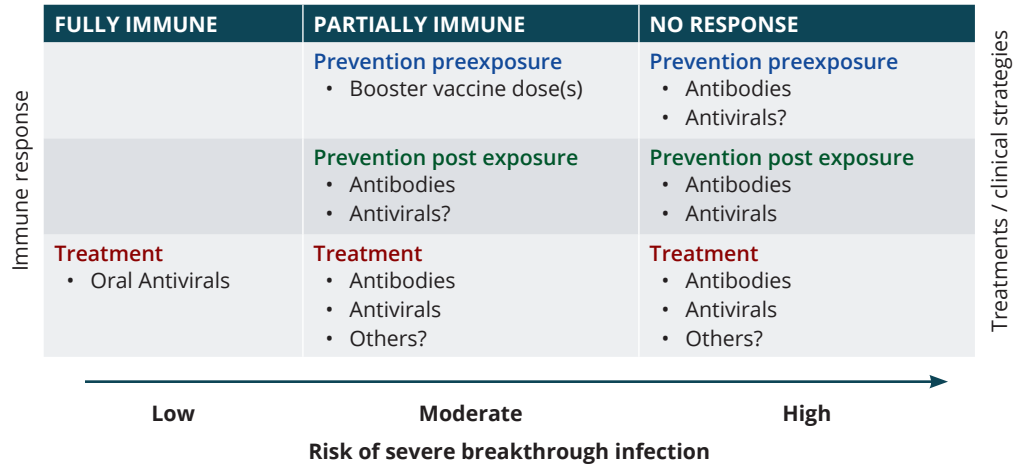
TABLE. Patient Groups of Interest for Breakthrough and Reinfections.

EXPOSURES			OUTCOMES
Vaccination			Infection, Ab[b], B[c]+T[d] cells
Vaccination	Vaccination (booster)		Infection, Ab, B+T cells
Infection[a]			Infection, Ab, B+T cells
Infection	Vaccination		Infection, Ab, B+T cells
Infection		Infection	Ab, B+T cells
Infection	Vaccination	Infection	Ab, B+T cells
Vaccination	Vaccination (booster)	Infection	Ab, B+T cells
Vaccination		Infection	Ab, B+T cells
		Infection	Ab, B+T cells

Clinical outcomes including severity should be easily defined and extractable from electronic health records. Studies of antibody specificities and neutralizing activity against variants, as with study of B and T cells, will continue to be performed in research labs, but widespread testing of antispike-protein antibodies in clinical practice would enable study on a larger scale through electronic health records. "Vaccination," referring to an initial course of vaccine, should continue to be an area of study, comparing different vaccines and different intervals of administration of multidose vaccines.

[a]Infection, includes severity, postacute sequelae of COVID-19, and assessment of risk factors for those adverse outcomes.
[b]Ab, antibodies, including antibodies against variants, and use of IgG titers as predictors of risk.
[c]B, B cells, including subsets such as memory B cells and plasmablasts, in research labs.
[d]T, T cells, including subsets and recognition of variants, in research labs.

FIGURE. Framework for Developing Evidence-Informed Clinical Treatment Pathways.



Following prior SARS-CoV-2 infection or vaccination, patients may develop different degrees of protection against severe disease: fully immune, partially immune, or little to no response. As different therapeutics become available, identifying patients who fall into these categories could be used to inform a clinical guidance framework that incorporates preexposure prophylaxis for very high-risk patients, postexposure prophylaxis for those at intermediate risk, and early treatment for those at low risk. "Antibodies" indicates monoclonal antibody products. "Antivirals?" indicates uncertainty about appropriateness. "Others?" indicates treatments not yet identified that might be helpful through mechanisms other than antiviral effects.

outcomes of other serious medical conditions.[26] Finally, to determine risk factors for severe breakthrough or reinfection, comparator groups must include patients with nonsevere infection. Data collection from only hospitalized patients will not allow such analysis.[20]

Vaccination strategies for individuals previously infected or previously vaccinated. Multiple studies demonstrate that IgG titers are higher after 1 dose of mRNA vaccine in previously infected patients than they are after 2 doses in patients with no history of infection.[4,9,27-30] This evidence should be sufficient to determine policy, but clinical protection against severe disease and PASC will also need to be evaluated. Study of clinical protection in individuals who have been vaccinated without prior or subsequent infection should also include time between the initial doses in 2-dose regimens, time until and after an extra dose, and the specific vaccines used. Over time, the known or likely variant responsible for infection will become another important variable.

Moving toward clinical use of antibody testing in high-risk groups. Determining IgG titers that correlate with different levels of protection against any infection and specifically severe disease would inform clinical decision-making. After additional study, IgG titers could be used to predict those at risk of severe reinfection or breakthrough infection, particularly among populations at high risk of limited vaccine response based on age, immune suppression, or other factors. Rather than only providing odds ratios comparing populations, studies of IgG should include metrics for classification, with the most useful being positive and negative likelihood ratios at cutoff values using commercially available assays. Even a moderately helpful correlate of immunity would be preferable to making a guess based on a patient's age, comorbidities, and time since vaccination or infection. Relevance to viral variants will need to be assessed, either by using existing assays or variant-specific assays.

Developing new methods to calculate vaccine effectiveness. Many of the vaccine effectiveness trials use "test-negative designs," which means vaccinated cases are compared with controls with negative test results for current SARS-CoV-2 infection. However, over time, the control arms increasingly include a higher proportion of individuals with natural immunity, and the calculated protection conferred by vaccination will be artificially reduced simply due to naturally acquired immunity in the control arm. These challenges are compounded when measures of disease severity are not considered. Developing new strategies for estimating effectiveness, or incorporating antibody testing when defining the control group, would help mitigate this challenge.

Identification of nonresponders and suboptimal responders to vaccination. As more individuals become immune to SARS-CoV-2, a progressively higher proportion of infections will be in those who either never developed immunity to the vaccine or had relatively early waning of protection. This phenomenon is again likely to inappropriately deflate calculations of vaccine effectiveness for the general population. Research is needed to classify individuals as (1) nonresponders (many immunocompromised patients), (2) those with waning immunity (likely older and chronically ill patients), or (3) those with longer-term protection against severe disease. Patients identified as being at high risk of vaccine nonresponse could be targeted for preexposure or postexposure prophylaxis with antiviral treatments, and those with waning immunity could be prioritized for additional vaccine doses (Figure).

CONCLUSION

Provided health care workforce shortages caused by even mild infections do not strain the health care system beyond capacity, the percentage of adults in many higher-income countries who have at least partial immunity to SARS-CoV-2 is likely approaching what is needed to prevent hospitals from becoming overwhelmed with severely ill patients, provided new variants that are both vaccine resistant and highly virulent do not emerge. Substantial uncertainty continues regarding the potential for additional pandemic waves, but some individuals will remain at risk of severe disease or long-term sequelae when SARS-CoV-2 becomes an endemic disease. Answering research questions about breakthrough and reinfection with a focus on severity and long-term sequelae promises to greatly improve the care received by the vast number of individuals worldwide who want to minimize their risks of severe COVID-19 and PASC. Relatively minor but useful changes in policy on vaccination could be made now based on existing data, and more sweeping changes should be considered to move the approaches to prevention of severe COVID-19 and PASC from the realm of population-based guidelines to decision-making about individual patients. ▲

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Optimizing ART *for Patients With a History of* Treatment Failure and Resistance

A review of treatment modalities for this patient population.

by John Faragon, PharmD, BCPS, AAHIVP

(continued from cover page)

providing a complete daily regimen. STR data demonstrate excellent efficacy with virologic suppression rates over 90%.[1-5] Current guidelines from the International Antiviral Society–USA panel (IAS–USA) and the US Department of Health & Human Services (HHS) guidelines recommend use of an integrase strand transfer inhibitor (INSTI) in combination with 1 to 2 nucleoside reverse transcriptase inhibitors (NRTIs) for initial therapy.[6,7] INSTI-based regimens are preferred for treatment-naïve patients because of their advantages over older regimens relating to efficacy, tolerability, and risk of drug-drug interactions.[6,7]

For patients with HIV treatment failure associated with prior regimens, suboptimal medication adherence, or significant HIV resistance, optimal therapy that leads to an undetectable HIV viral load can be challenging. Patients with prior HIV treatment failure and significant resistance often have regimens involving medications requiring more than once daily dosing, relatively large pill burdens, potential increased risk of drug-drug interactions, and tolerability concerns. The reasons for why patients fail previous regimens are multifactorial but can be placed into 3 broad categories: patient related, HIV related, and regimen related.[6, 8-10]

Patient-related factors related to adherence are common, especially with those requiring multiple tablets taken several times a day for their HIV regimen. Comorbidities—especially active substance abuse, mental health disorders and other neurocognitive impairment—can lead to missed doses and adherence challenges. Other psychosocial issues such as unstable housing, lack of transportation, and communication difficulties (ie, unpaid phone bills or lack of cell phones) can lead to missed clinic appointments. HIV medication and insurance issues related to formulary restrictions can also be a challenge.

HIV-related factors such as the presence of transmitted or acquired drug resistance, prior treatment failures, innate resistance to certain HIV medications, and high pretreatment viral loads can contribute to virologic failure.

HIV regimen–related factors such as suboptimal pharmacokinetics or viral potency, low barriers to HIV resistance, food requirements, drug-drug interactions, and medication/dispensing errors may lead to virologic failure. When optimizing a patient's treatment regimen, it is crucial that providers consider all these factors—a new regimen is not going to work in someone unwilling to take it, so open patient and provider communication is encouraged when making a regimen change.

A critical component in successfully optimizing an HIV regimen is to gather and review all previous resistance tests to obtain an accurate, complete assessment of prior HIV resistance. A complete history of prior HIV regimens is also important—use of preprinted charts with medication names and pictures can help the patient remember prior regimens. When resistance tests are compiled and evaluated, print and online databases such as the IAS–USA 2019 HIV Drug Resistance Mutations Update and the Stanford University HIV Drug Resistance Database can assist in selecting the new regimen.[11,12] Although the application of these databases to patient care can be complex, they are crucial in making appropriate decisions when selecting the next regimen; expert consultation is recommended with more complex cases and the National Clinician Consultation Center (800-933-3413) can be helpful in making decisions.[13] Once resistance testing is reviewed and analyzed, it is typical to construct a new HIV regimen that ideally contains 3 fully active drugs; however, this is not always possible.[6] If only 2 active drugs can be used in the new regimen, the HHS guidelines recommend use of at least 1 with a high barrier to resistance—these include a second-generation INSTI such as dolutegravir or bictegravir; or a regimen containing boosted darunavir.[6] Regimens that may be selected for patients with significant resistance usually have acceptable pharmacokinetic data (ie, the drugs combined have acceptable blood levels); however, clinical data on their efficacy may be lacking. For example, to minimize pill burden in patients, providers may select an STR and add an additional medication to it to construct a fully active regimen with the smallest pill burden possible. In doing so, providers combine medications for treatment-experienced patients outside of United States Food and Drug Administration (FDA) labeling to provide the smallest pill burden for the patient to maximize success in attaining an undetectable viral load (see **Table**[6] for examples). Print or online databases should also be consulted to ensure drug-drug interactions with the new regimen are evaluated—not just among the new HIV medications but also in combination with other primary care, psychiatric, and recreational therapies or substances the patient may be using. University of Liverpool (www.hiv-druginteractions.org) and the HHS HIV Guidelines Drug-Drug Interaction Tables are excellent recourses.[6,14]

NEW TREATMENT OPTIONS

Recent approval of medications designed for patients with treatment experience also provides new options that offer new tools to attain virologic suppression. Fostemsavir is a newer medication in a novel class of medications known as attachment inhibitors. A prodrug of temsavir, fostemsavir is approved by the FDA for use in combination with other antiretrovirals for treatment-experienced adults with resistant HIV who are failing their current antiretroviral regimen. Data supporting its approval were from the BRIGHTE study (NCT02362503) demonstrating that in patients with extensive prior HIV treatment (some with zero fully active medications), 60% of subjects who received fostemsavir with other medications attained an undetectable viral load through 96 weeks of treatment.[15,16]

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TABLE. Select Examples of HIV STR Combinations Used in Heavily Pretreated Subjects[6]

STR	IN COMBINATION WITH	CLINICAL COMMENT/RECOMMENDATION
Bictegravir/tenofovir alafenamide/ emtricitabine (INSTI with 2 NRTIs)	Darunavir/cobicistat (boosted PI)	Bictegravir AUC increases 74%; no dose adjustment needed
	Doravirine (NNRTI)	No significant change in levels expected for doravirine or bictegravir; no dose adjustment needed
	Fostemsavir (attachment inhibitor)	No significant change in levels expected for bictegravir or fostemsavir; no dose adjustment needed
	Rilpivirine (NNRTI)	No significant change in levels expected for doravirine or bictegravir; no dose adjustment needed
Darunavir/cobicistat/ tenofovir alafenamide/emtricitabine (boosted PI/2 NRTIs)	Dolutegravir (INSTI)	No significant change in levels for dolutegravir, darunavir, or cobicistat; no dose adjustment needed
	Doravirine (NNRTI)	Increased doravirine levels expected; no change in darunavir; no dose adjustment needed
	Fostemsavir (attachment inhibitor)	No significant change in levels for darunavir or fostemsavir; no dose adjustment needed
	Rilpivirine (NNRTI)	Increased rilpivirine levels expected; no change in darunavir; no dose adjustment needed
Rilpivirine/tenofovir alafenamide/ emtricitabine (NNRTI/2 NRTIs)	Darunavir/cobicistat (boosted PI)	No change in darunavir levels expected; increased rilpivirine possible; no dose adjustment needed
	Dolutegravir (INSTI)	No significant change in dolutegravir AUC, C_{min} increases 22%; no change in rilpivirine AUC, rilpivirine C_{min} increases 21%; no dose adjustment needed
	Fostemsavir (attachment inhibitor)	No significant change in levels for rilpivirine or fostemsavir; no dose adjustment needed
Dolutegravir/abacavir/lamivudine or dolutegravir/lamivudine (INSTI/1-2 NRTIs)	Darunavir/cobicistat (boosted PI)	No significant change in levels for dolutegravir, darunavir, or cobicistat; no dose adjustment needed
	Doravirine (NNRTI)	No significant change in doravirine; dolutegravir AUC increases 36%, C_{min} increases 27%; no dose adjustment needed
	Fostemsavir (attachment inhibitor)	No significant change in levels for dolutegravir or fostemsavir; no dose adjustment needed

AUC, area under the curve; Cmin, minimum concentration; INSTI, integrase strand transfer inhibitor; NNRTI, non- nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease Inhibitor; .

Increases in CD4 count were also significant; subjects with initial CD4 counts of less than 20 cells/mm^3 gained on average 240 additional T cells through 96 weeks.[15,16] Fostemsavir was also found to be well tolerated with nausea being the most common adverse event. Although drug interactions are minimal with fostemsavir, concurrent use of cytochrome P450 3A4 inducers may decrease fostemsavir levels. Therefore, medications such as carbamazepine, phenytoin, St John's wort (*Hypericum perforatum*), and rifampin should be avoided.[6] HMG-CoA reductase inhibitors (statins) may be increased so lowest statin dose should be used. Please consult additional references for more extensive drug interaction information on fostemsavir.[6,14] Based on its metabolism, fostemsavir can be combined with common HIV medications such as darunavir/cobicistat; dolutegravir and bictegravir; rilpivirine and doravirine; and tenofovir-containing regimens (Table[6]).

Ibalizumab, a CD4-directed postattachment HIV-1 inhibitor, is also indicated for use in heavily treatment-experienced patients with multidrug-resistant HIV. Ibalizumab is administered via intravenous infusion, dosed as a 2000-mg load and followed by a maintenance dose of 800 mg every 2 weeks.[17] Some patients may experience infusion-related reactions during the infusion, although this is rare. It also is important that patients not miss their maintenance dose beyond 3 days; when this occurs, it requires reloading with the 2000-mg dose and may require insurance approval. Data supporting the approval of ibalizumab came from the TMB-301 trial (NCT02475629) in which heavily pretreated patients were given ibalizumab combined with an optimized background regimen. At 25 weeks, 43% of patients attained an undetectable viral load. Although ibalizumab can be useful in this patient population, the need for a monitored infusion and medication costs are factors that may hinder its use. The average wholesale acquisition cost is approximately $9900 per month, which requires prior authorization with insurance for coverage.[6] Despite these challenges, ibalizumab can play an important role for patients with minimal options when optimizing therapy and trying to configure a regimen with active medications.

In addition to the FDA-approved options, an additional promising treatment for heavily pretreated patients is lenacapavir, one of a novel class of medications known as capsid inhibitors. Recent data from the CAPELLA study (NCT04150068) were presented demonstrating its efficacy in highly treatment-experienced patients. At study entry, patients had to have HIV resistance to at least 2 drugs from 3 of 4 commonly used drug classes (NRTIs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and INSTIs) with no more than 2 fully active agents from any of those 4 classes.[18] After adding lenacapavir to an optimized background regimen, 81% of subjects attained a viral load below 50 copies/mL and 89% were below 400 copies/mL at 26 weeks. In addition to its efficacy, lenacapavir is unique in that it is given as a long-acting subcutaneous injection that lasts 6 months.[18] Although injection site reactions such as redness, swelling, and pain can occur, these reactions had resolved within 2 weeks in the study for most subjects.

Optimizing HIV treatment in heavily pretreated patients can be challenging and complex. Despite excellent efficacy of newer medications in treating HIV, success rates in more complex cases are not as robust. Despite these challenges, attaining and maintaining an undetectable HIV viral load and improving CD4 cell counts are still our goals of therapy. The use of HIV resistance tests is critical to constructing an appropriate regimen, and the use of the Stanford database and other resources can be helpful. Use of newer medications such as fostemsavir and ibalizumab (and potentially lenacapavir, if granted FDA approval) provides novel mechanisms of action to combine with older medications to construct regimens sufficient to provide a virologic response. Providers are encouraged to work closely with patients to ensure that the optimized HIV regimen is one they are open to taking, especially if it involves infusion or injectable medications. ▲

References are available at ContagionLive.com.

Key components of the 2019 IDSA Strategic Plan call for dissemination of timely practice recommendations.

Updates to Multidrug Resistance Guidance

The 2019 Strategic Plan of the Infectious Diseases Society of America lays the groundwork for understanding prescribing practices.

by Sam Aitken, PharmD, MPH, BCIDP ⁑

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2020, containing recommendations for extended-spectrum β-lactamase(ESBL)-producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and difficult-to-treat resistance (DTR) *Pseudomonas aeruginosa.*[1] In December 2021, the second iteration of this guidance was released, offering treatment recommendations and suggestions for AmpC β-lactamase producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Stenotrophomonas maltophilia.*[2]

These documents, key components of the 2019 IDSA Strategic Plan, call for dissemination of timely practice recommendations. Unlike traditional guidelines, the IDSA guidance documents take a different path and do not rely on a formal systematic review of the literature or use of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria. Instead, the documents focus narrowly on specific clinical questions, which generally lack strong data and are the product of evidence-informed expert opinion.

The primary intent of the guidance documents is to provide recommendations for clinicians who have limited clinical experience in managing infections caused by these organisms. Through social media engagement, however, it quickly became apparent that infectious diseases specialists were key consumers of the IDSA guidance documents and able to provide essential input. This feedback actively informed development of the second guidance document and forthcoming revisions to the first document.

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The development of the second guidance document also revealed a unique challenge that was not seen during the development process for the initial guidance. In contrast to that of ESBL-E, CRE, and DTR *Pseudomonas*, the evidence base for treatment of AmpC-producing Enterobacterales, CRAB, and *S maltophilia* is very limited. In the case of CRAB, randomized controlled trials (RCTs) provide evidence for what *not* to do from a treatment perspective, but very little for what might be considered optimal treatment. For *S maltophilia*, no quality evidence supporting preferred treatment could be identified. For that reason, both the CRAB and *S maltophilia* sections have "suggestions" rather than "recommendations" as the primary form of guidance.

GUIDANCE HIGHLIGHTS

Several key points in the guidance document deserve specific mention. First, the AmpC-producing Enterobacterales section provides recommendations on what organisms should be considered high risk for inducible selection of AmpC hyperexpressing mutants during therapy with third-generation cephalosporins. For many years, clinicians have learned the mnemonics "SPACE" and "SPICE" to identify such organisms and inform treatment recommendations. The specific organisms included in SPACE and SPICE are not always clear (particularly the "P" component), but generally include *Serratia* species, *Pseudomonas* (or *Providencia*) species, *A baumannii, Citrobacter* species, indole-positive *Proteus* species, and *Enterobacter* species. While easy to remember, these mnemonics oversimplify complex issues, include organisms that don't produce AmpC, and fail to address recent taxonomic changes. As examples, many organisms in the *Citrobacter* genus, other than *Citrobacter freundii* and *Citrobacter youngae*, lack a chromosomal AmpC gene altogether.[3] In the past, indole-positive *Proteus* described *Proteus morganii* and *Proteus rettgeri*, but they have been reassigned to the genera *Morganella* and *Providencia*, respectively (both are at low risk for inducible AmpC expression). The newly created *Klebsiella aerogenes* (formerly *Enterobacter aerogenes*) is omitted entirely from these mnemonics, as is the uncommonly encountered *Hafnia alvei*, which appears to have a risk profile similar to the classic AmpC producer *Enterobacter cloacae*. The guidance document suggests treating only *E cloacae*, *C freundii*, *K aerogenes*, and *H alvei* as clinically significant AmpC producers and avoiding definitive therapy with third-generation cephalosporins and piperacillin-tazobactam, and instead favoring cefepime or carbapenems as the preferred β-lactam agents.[4] *Serratia marcescens,* which does have a chromosomal AmpC gene, is specifically excluded from this list, as significant risk for inducible expression does not appear to be present in most infection types.

Second, the lack of a specific, definitive treatment recommendation for CRAB must be mentioned. Currently available RCT data suggest that carbapenem, rifampin, and cefiderocol are not superior to monotherapy with colistin. Unfortunately, however, the published literature does not provide any guidance on what the optimal therapy might be. The panel consensus was that colistin or polymyxin therapy was likely suboptimal (contrary to the RCTs as described) and so combination therapy was recommended. In vitro models suggest that triple combination therapy of ampicillin-sulbactam, meropenem, and either minocycline or polymyxin demonstrate bactericidal killing, but it is impossible to make recommendations solely on the basis of in vitro pharmacodynamic assays.[5,6] Thus, these combinations are mentioned as possibilities, but are not specifically prioritized. Largely on the basis of small, uncontrolled studies suggesting that high-dose ampicillin-sulbactam might be beneficial even in ampicillin-sulbactam–resistant isolates, ampicillin-sulbactam is a suggested as a primary component of combination therapy.

Lastly, the lack of recommendations that could be made for *S maltophilia* was surprising. The body of evidence supporting the use of trimethoprim-sulfamethoxazole as primary therapy is nearly nonexistent, although trimethoprim-sulfamethoxazole remains the preferred therapy for serious infections in the absence of any evidence reasonably supporting an alternative therapy. A major reason for this is that *S maltophilia* causes a spectrum of illness, ranging from simple colonization of the respiratory tract or intravenous catheters to rapidly fatal pneumonia and disseminated infection. Objectively distinguishing these infections in patients with acute-on-chronic illness can be nearly impossible, making observational research incredibly challenging. Both fluoroquinolones and minocycline have been studied in an observational fashion as alternatives to trimethoprim-sulfamethoxazole; however, all studies are nearly hopelessly confounded by selection bias and are largely uninformative for clinical decision-making. Thus, no firm recommendations beyond maintaining the status quo of trimethoprim-sulfamethoxazole as the treatment of choice for *S maltophilia* could be madec.

> Randomized clinical trial data suggest that carbapenem, rifampin, and cefiderocol are not superior to monotherapy with colistin.

CONCLUSIONS

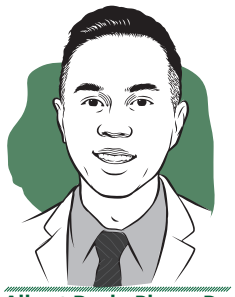
Unlike the first iteration of the IDSA guidance, clear recommendations were difficult to identify for the treatment of infections caused by AmpC-producing Enterobacterales, CRAB, and *S maltophilia*. However, the guidance documents do offer a summary of the available literature and evidence-informed suggestions (or recommendations) from a panel of clinicians with clinical and research expertise in these infections. As with the first IDSA guidance for the treatment of infections caused by drug-resistant gram-negative bacteria, any suggestions or recommendations, whether provided as formal letters to the editor, informal direct communication with the authors, or posts on social media, will be routinely assessed and updated as new evidence becomes available. ▲

References are available at ContagionLive.com.

What's New *With* Non–COVID-19 Vaccines

Although COVID-19 vaccination remains the primary focus for health care, other paramount vaccines need to be recognized. Here is a review.

by Albert Bach, PharmD; Heidi Lee, PharmD; *and* Jelena Lewis, PharmD, BCACP



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from the Centers for Disease Control and Prevention (CDC) demonstrate that there was a notable decline in global coverage for most child vaccines from 2019 to 2020, as well as low current adult vaccination coverage in all age groups across most vaccines.[1,2] The CDC reports that a substantial improvement in adult vaccination uptake is needed to reduce the burden of vaccine-preventable diseases. One of the biggest predictors of whether patients get vaccinated is if they receive a strong recommendation from their health care provider.[3,4] Keeping abreast of new vaccine products and recommendations will help in making the best evidence-based practice recommendation for your patients. This article will provide an update on non–COVID-19 adult vaccine recommendations and newly approved non–COVID-19 vaccines.

PNEUMOCOCCAL

Current routine pneumococcal vaccine recommendation is that all adults age 65 years or older receive the pneumococcal polysaccharide vaccine (PPSV23). PPSV23 is also indicated for adults aged 19 to 64 years with certain underlying medical conditions and risk factors. In November 2019, the CDC's Advisory Committee on Immunization Practice (ACIP) removed the recommendation for routine pneumococcal conjugate vaccination (PCV13) for all adults 65 years or older. PCV13 vaccination is now based on shared clinical decision-making for adults 65 years or older who do not have an immunocompromising condition, cerebrospinal fluid leak, or cochlear implant and have never received a dose of PCV13.[5] To assist in determining individualized pneumococcal vaccination recommendations for your patients under current guidelines, the CDC has a mobile app called PneumoRecs VaxAdvisor that providers can use. These recommendations will change in 2022 based on the introduction of 2 new pneumococcal vaccines.

Two new pneumococcal vaccines were approved in 2021, leading to upcoming changes in recommendations for pneumococcal vaccination. The first vaccine is Vaxneuvance (PCV15), a conjugate vaccine from Merck that was approved by the United States Food and Drug Administration (FDA) on July 16, 2021. PCV15 protects against 15 different *Streptococcus pneumoniae* serotypes in adults 18 years and older: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F. Vaxneuvance is a single 0.5-mL intramuscular (IM) injection.[6] The second vaccine is Prevnar 20 (PCV20), a conjugate vaccine from Pfizer that was approved by the FDA on June 8, 2021. PCV20 protects against the 15 *S pneumoniae* serotypes covered by Vaxneuvance and 5 additional serotypes: 8, 10A, 11A, 12F, and 15B. PCV20 is a single 0.5-mL IM injection.[7] Contraindications for both new pneumococcal vaccines include severe allergic reactions to any component of each respective vaccine or diphtheria toxoid. Common adverse effects (AEs) for both vaccines include injection site pain, fatigue, myalgia, headache, and arthralgia.[6,7]

To simplify the current pneumococcal vaccine recommendations and account for the 2 new vaccines, the updated pneumococcal vaccination recommendations below were approved by the ACIP in October 2021 and adopted by the CDC director and will become official once published in the CDC's *Morbidity and Mortality Weekly Report (MMWR)* in 2022. The updated recommendations for pneumococcal vaccination will be based on age and risk factors. Simplifying the pneumococcal vaccination recommendations could help improve vaccine uptake, equity, and overall health.

- Adults 65 years or older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive either the PCV20 or PCV15 vaccine.[8]
- Adults aged 19 to 64 years with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive either the PCV20 or PCV15 vaccine. Underlying medical conditions and risk factors indicated for pneumococcal vaccination prior to age 65 years include alcoholism, chronic heart/liver/lung disease, cigarette smoking, diabetes, chronic renal failure, nephrotic syndrome, immunodeficiency, iatrogenic immunosuppression, generalized malignancy, HIV, Hodgkin disease, leukemia, lymphoma, multiple myeloma, solid organ transplants, congenital or acquired asplenia, sickle cell disease or other hemoglobinopathies, cerebrospinal fluid leak, or cochlear implant.
- If PCV15 is used for either of the indications above, it should be followed by a dose of PPSV23.[8]

Detailed recommendations on spacing of PCV15 and PPSV23 and possible need for additional pneumococcal vaccinations after the primary dose have not been provided. Be sure to check the final recommendations from the CDC when published in *MMWR* (https://www.cdc.gov/mmwr/index.html).

ZOSTER

Shingrix, a recombinant, adjuvanted zoster vaccine indicated for prevention of herpes zoster in adults 50 years and older, received a new FDA indication. In summer 2021, the FDA approved this vaccine for use in patients 18 years or older who are or will be at increased risk for shingles due to immunodeficiency or immunosuppression caused by disease or therapy.[9] In line with this recommendation, in October 2021 ACIP unanimously approved Shingrix for adults 19 years and older who are immunodeficient or immunocompromised.[8,10] This approval was based on studies of the vaccine in adults with hematologic malignancies or who have received an autologous hematopoietic stem cell transplant.[10] Shingrix is administered as a 2-dose series by the IM route with the second dose administered 2 to 6 months after the first.[9] Individuals who are immunosuppressed

or immunocompromised may receive the second dose 1 to 2 months after the first dose.[10] Shingrix was initially approved in 2017 and has replaced the live attenuated virus vaccine Zostavax due to better effectiveness, among other advantages.[11] The US Zostavax manufacturer has discontinued its production and there are no remaining doses of this vaccine on the US market.

INFLUENZA

Influenza vaccine is recommended yearly for all individuals 6 months and older. The CDC continues to recommend that nonpregnant adults receive it after the month of August, whereas for pregnant adults in their third trimester the most current recommendation is to receive the influenza vaccine as soon as it is available.[12] Other notable changes for the influenza vaccines are that all are quadrivalent and any influenza vaccine may be administered on the same day as a COVID-19 vaccine.[12] Flucelvax, the cell-based inactivated influenza vaccine (IIV), has also received FDA approval for an expanded age indication for children 6 months and older.[13] Additionally, use of Flucelvax is a precaution for individuals with a history of severe allergic reaction to any egg-based IIV, live attenuated influenza vaccine (LAIV), or recombinant influenza vaccine of any valency, whereas the use of recombinant influenza vaccine (RIV4) is a precaution for individuals with a history of severe allergic reaction to a previous dose of any egg-based IIV, LAIV, or Flucelvax vaccine of any valency.[12] If Flucelvax or recombinant influenza vaccine are used in these situations, they should be administered under medical supervision and possible consultation with an allergist. For patients with an egg allergy that manifests as more than hives, influenza vaccines other than Flucelvax or Flublok should be administered while under medical supervision.[12] Because severe allergic reactions to vaccines can occur with any dose of the vaccine regardless of history, it is recommended that all vaccination providers understand the office emergency plan and be certified in cardiopulmonary resuscitation.[14] Lastly, consideration should be given to spacing of the LAIV4 administration and certain antiviral medications. LAIV4 should not be given to patients who received oseltamivir or zanamivir 48 hours prior, peramivir 5 days prior, or baloxavir 17 days prior to the vaccine.[14]

HEPATITIS B

There are 2 major changes regarding hepatitis B virus (HBV) vaccinations. A new recombinant vaccine called PreHevbrio has been approved, adding to the list of traditional options Engerix-B, Heplisav-B, and Recombivax HB. PreHevbrio is the only 3-antigen HBV vaccine approved in the United States and is indicated for prevention of HBV infections in adults 18 years and older. This vaccine follows a 3-dose schedule consisting of 1-mL IM doses administered at 0, 1, and 6 months. Contraindications include severe allergic reactions to any component of PreHevbrio or after a dose of another HBV vaccination. Common AEs include injection site pain, tenderness, headache, fatigue, and myalgia.[15,16] Although PreHevbrio gained FDA approval on November 30, 2021, it has not been incorporated into CDC's recommended adult immunization schedule.

In addition to the new vaccine, on November 3, 2021, the ACIP Hepatitis Vaccines Work Group posted an updated recommendation that all adults in the United States aged 19 to 59 years should receive HBV vaccination. Adults 60 years and older are advised to receive vaccination following a risk-based guideline that may include considerations for sexual and occupational exposures, history of injection drug use, chronic liver disease, HIV infections, and international travel.[17,18] Simplifying and consolidating adult HBV vaccination recommendations may help to not only reduce health disparities created by risk-based guidelines that often favor patients with health literacy, awareness of infection risks, and access to preventive health services but also may address the increasing rates of acute HBV infections within this age group.[19]

MENINGOCOCCAL

Preexisting meningococcal conjugate (MenACWY) vaccines Menactra and Menveo are indicated for those aged 2 months to 55 years depending on the vaccine. MenQuadfi (MenACWY-TT) is a new conjugate vaccine used for the prevention of invasive meningococcal disease caused by *Neisseria meningitidi*s in individuals beyond the traditional cutoff at age 55 years. This new vaccine was approved by the FDA on April 23, 2020, for use in individuals 2 years and older and is a single 0.5-mL IM injection followed by an optional booster dose 4 years after the primary vaccination for those 15 years and older, depending on the individual's continued risk. This vaccine is contraindicated in individuals who have had severe allergic reactions to MenQuadfi or another tetanus toxoid–containing vaccine, and AEs include injection site pain, tenderness, headache, fatigue, and myalgia.[20]

MenQuadfi not only presents a novel design as the first and only quadrivalent meningococcal vaccine to use tetanus toxoid as its protein carrier but also is appealing for its expanded target age group with the addition of adults 55 years and older.[21] MenACWY vaccines including MenQuadfi are interchangeable, although administration of vaccines made from the same manufacturer is still recommended. In addition, although MenQuadfi uses a tetanus toxoid as its protein carrier, it should not replace or affect other routinely recommended tetanus toxoid–containing vaccines because MenQuadfi is only indicated for prevention of invasive meningococcal disease.[22] This new vaccine only protects against *N meningitidis* serogroups A, C, W, and Y, meaning a separate vaccine will be required for serogroup B meningococcal (MenB) protection. Bexsero and Trumenba are the existing MenB vaccines and recommendations have not changed. MenB vaccination should be considered for those 10 years or older at increased risk of meningococcal disease.[23]

> Simplifying the current pneumococcal vaccination recommendations could help improve vaccine uptake, equity, and overall health.

CONCLUSION

The pandemic has reshifted our focus to the COVID-19 vaccines. However, other vaccine-preventable diseases remain prevalent. It is important to stay updated about these other non–COVID-19–related vaccine-preventable diseases to provide the best evidence-based practice recommendation for your patients. ▲

References are available at ContagionLive.com.

Jelena Lewis, PharmD, BCACP

Jelena Lewis, PharmD, BCACP, is an assistant professor at Chapman University School of Pharmacy in the Department of Pharmacy Practice. She is also a faculty-in-residence at Providence Medical Foundation, which provides chronic disease and population health management.

Watch more of the panel's discussion at **ContagionLive.com.**

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PANELISTS

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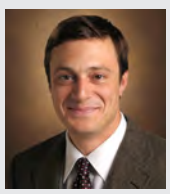

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Access the videos

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Age-Related Comorbidities and Quality-of-Life Issues in Patients Living With HIV

by GINA BATTAGLIA, PHD

Although treatment options and life expectancy of patients living with HIV have increased in recent years, age-related comorbidities (particularly obesity and diabetes) and quality-of-life issues continue to be of concern, according to panelists in a *Contagion® Peer Exchange* panel moderated by **Grace McComsey, MD FIDSA**. The panelists discussed approaches for screening and management of comorbidities, optimizing antiretroviral therapy (ART) regimens based on viral genotype and patient factors, discussing quality-of-life issues with patients, and addressing the relationship between HIV, obesity, and diabetes.

COMORBIDITIES IN PATIENTS WITH HIV

Comorbid diseases and clinical events associated with aging often occur at a younger age in patients living with HIV compared with the general population, and educating patients on screenings and intervals is imperative to ensure these comorbidities are diagnosed early, said **Todd Brown, MD, PhD**. He added that the higher burden of comorbidities in patients with HIV is in part related to the persistent effects of previous ART, noting that stavudine (Zerit) is commonly associated with lipoatrophy that can persist for several years after discontinuing the medication. Even if HIV infection is well treated, the HIV disease process itself results in increased systemic inflammation that can drive comorbidities, said Brown. "We have this confluence of inflammation related to HIV and inflammation related to aging, which is important in these aging-related comorbidities," he said.

Brown emphasized the importance of a long-term approach for screening and management of comorbidities and said preventing major clinical events is crucial for aging well. "Over the long term, you think about a patient who's middle-aged…you're trying to prevent events so the person can age well, so they can maintain their physical function, their cognitive function, their quality of life," he said. "What we know is that these events that happen—whether it be myocardial infarction, a stroke, or a fracture—can have major effects on these trajectories. Trying to be proactive and prevent these events is critical in the overall aging process."

HIV: TREATMENT OPTIMIZATION

John Koethe, MD, said that although viral suppression is the easiest measure of treatment success with HIV infection, durable suppression of the virus that is refractory to breakthrough and resistance using a regimen that fits the patient's comorbidities and other personal factors is likely a better gauge of success.

> "The principal goal of ART has always been the same…to maintain viral suppression or a level of plasma virus below 50 copies/mL, and thus allow CD4 reconstitution and ideally protect us from opportunistic infections within the environment."
>
> –John Koethe, MD

"The principal goal of ART has always been the same…to maintain viral suppression or a level of plasma virus below 50 copies/mL, and thus allow CD4 reconstitution and ideally protect us from opportunistic infections within the environment," said Koethe. "There [are] several routes to getting there, and the 2 things that we need to separate when we think about how we're going to approach this is, [first], matching the regimen to the preexisting patterns of viral resistance, and then also matching the regimen within that same idea to the likelihood that this [individual] is not going to take it sufficiently and is going to develop viral resistance."

Koethe said selection of a treatment regimen is guided by the viral genotype and often uses concatenated databases (such as the International AIDS Society) to identify the optimal agent(s) among protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors, and nucleoside reverse

transcriptase inhibitors. Even if a regimen appears appropriate for a patient's genotype, he said he may adjust it if he predicts that barriers will prevent the patient from adhering to once-per-day or twice-per-day dosing.

"We may select something with a higher barrier to resistance…for example, a boosted protease inhibitor such as darunavir…or it could be a newer-generation integrase inhibitor," he said. "For somebody who might be extremely adherent, that would probably be less [of] a question."

Koethe added that tailoring the regimen to minimize adverse or unwanted effects is important and involves considering the patient's neuropsychiatric profile (including depression), underlying comorbidities (eg, cardiovascular disease, insulin resistance, diabetes or hyperlipidemia, and current overweight or obesity status), and patient preferences for dosing, and Brown emphasized the importance of awareness of potential drug-drug interactions, notably between boosted PIs and statins and those between dolutegravir and metformin.

HIV: ADDRESSING QUALITY-OF-LIFE ISSUES

Issues related to quality of life are important to address and can prevent patients from continuing with care, according to **Tavell Kindall, PhD, DNP, APRN, FNP**. "In my experience here in New Orleans, there have been some individuals who have been out of care because they felt as though they weren't treated well," he said. "When they come to see me, they now have an opportunity to be on the newer medications that weren't available to them at the time when they [received their diagnosis]. It's amazing because they say things like, 'I can't believe [it]. If they would've had this 10, 15 years ago, I would've never fallen out of care, because the whole thing was, I don't want to take anything that will have me sick and making me feel bad.'"

Kindall added that conversations about quality of life should start at the first meeting with the patient, but the provider should expect to take time to get the patient's full story.

"You must be patient and allow the journey to have patients share things with you, and then that way you can address different things," he said. "One of the things right now that I have been talking a lot about with patients is, they tell you things like, 'Look, I'm afraid to tell [individuals] because I don't know how they're going to treat me,' or, 'What does this mean? Am I going to go to jail if somebody finds out that I have HIV and I didn't share my status with them?' Certainly anxiety, depression, if they were present before the diagnosis, [are] likely exacerbated on the other side of it, so that's always a concern."

Kindall added that employment, education, and finances are common concerns among patients, and many still believe a diagnosis of HIV infection means imminent death. "I try to address it along the journey, and I share with them right up front, 'This is a journey. This is a partnership that you and I have together, and we'll be talking about a lot of things,'" such as housing, transportation, employment, ability to care for oneself, and internalized stigma. "Because of the history of HIV and how [individuals] have been treated, some of those quality-of-life things are challenging," said Kindall.

RELATIONSHIP BETWEEN HIV, OBESITY, AND DIABETES

According to **Osama Hamdy, MD, PhD**, individuals living with HIV are 4 to 5 times more likely to develop type 2 diabetes compared with the general population. "When we see any patient with HIV, we must think of diabetes," he said.

Hamdy said that from a pathophysiologic perspective, the disease process as well as some HIV treatments are responsible for this increase in risk. "Our research, many years ago, showed that once you introduce inflammation in the adipose tissue and you have provocation from TNF-α [tumor necrosis factor α], IL-6, MCP-1 [monocyte chemoattractant protein 1], and all those provocative inflammatory cytokines, you will see all kinds of metabolic problems, including insulin resistance, endothelial dysfunction, and then atherosclerosis," he said.

Hamdy said medications, particularly older medications, may also contribute to diabetes. He added that patients who started treatment with protease inhibitors between 1997 and 2014 have an approximately 50-fold increase in risk for type 2 diabetes, and patients who used these drugs, even for a short time, are still presenting today because of the longer life span of patients living with HIV.

"Diabetes is something that you should think of all the time when you have anyone with HIV," he concluded, adding that weight gain and related health issues, such as obstructive sleep apnea, arthritis, and worsening of diabetes, cardiovascular disease, and pulmonary issues introduce a major health burden for patients with HIV and diabetes. ▲

WORLD ANTI-MICROBIAL RESISTANCE (AMR) CONGRESS

Prevention Is the Best Treatment: Vaccines and Antimicrobial Resistance

by NINA COSDON

As pathogens develop resistance to antibiotics and other therapies, new solutions are crucial—or, as Leonard Friedland, MD, puts it, old solutions: vaccines. "The best treatment of a disease is to actually not have to treat it at all but to prevent it, and that's the role of vaccines. Vaccines are, after clean water, the most effective public health tool that's ever been introduced," Friedland said.

Friedland is vice president of scientific affairs and public health vaccines at GlaxoSmithKline (GSK). At the 2021 World Anti-Microbial Resistance (AMR) Congress, Friedland gave a presentation entitled "Vaccines as an Essential Tool in the Fight Against AMR."

Friedland said both he and GSK are passionate about the development of vaccines to fulfill unmet medical need, describing AMR as "a global health security problem" and "the silent pandemic." Friedland expressed concerns that if AMR continues, the practice of medicine will be under threat: "If we don't have ways to treat infections, we won't be able to do many of the things that are part of modern medicine, such as organ transplants, safe cesarean deliveries, the ability to treat common infections."

Vaccines save lives, but Friedland says they are underappreciated. To ensure they remain at the forefront of preventive health care, Friedland follows the development of vaccines at GSK and beyond, encouraging the extension of bacterial and viral vaccines to drive down the use of antibiotics.

Friedland stressed that low-income and middle-income countries will be most affected by continued AMR. "We all recognize through the COVID-19 pandemic now how important it is to address access to care, equitably, for people all around the world...as we address this issue, we need to make sure we're thinking globally, not just locally." ▲

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Moving Forward: Investigational *C Difficile* Vaccine, Therapeutics Headline Conference

by JOHN PARKINSON

The 9th Annual International *C. Diff.* Live-Online Conference & Health EXPO saw a number of investigational therapies and modalities. After the program introductions, oral sessions were presented.

In the session titled "Development of a Vaccine With the Potential to Prevent *Clostridioides difficile* Infection (CDI)," Jennifer Moisi, PhD, vice president, global tick-borne diseases and enteric vaccines medical lead, Pfizer, presented on the company's investigational *C difficile* vaccine. Moisi said the vaccine is a bivalent toxoid vaccine candidate that aims to preserve important antigenic epitopes to induce broadly neutralizing antibodies.

In the company's first randomized study, there was a 3:1 ratio of patients receiving the QS-21 adjuvanted toxoid vaccine to 100 µg QS-21–containing *C difficile* vaccine or placebo. The vaccine was given in shortened month (0, 1, 3) or day (1, 8, 30) regimens. The second study involved patients randomized 3:3:1 to receive either 100 µg or 200 µg unadjuvanted *C difficile* vaccine formulation or placebo in stages 1 and 2 (sentinel cohorts of different age groups), and 3:1 to receive the selected dose of unadjuvanted *C difficile* vaccine formulation or placebo in stage 3 (days 1, 8, 30).

The investigators sought primary outcomes of safety for both studies. They also determined immunogenicity by measuring serum toxin A—specific and B—specific neutralizing antibodies.

The vaccine is being evaluated in its CLOVER phase 3 trial (NCT03090191). This is an international study across 397 sites in 23 countries. The subject enrollment is 17,536, and investigators expect results in the coming months.

In the session titled "The Burden of *Clostridioides difficile* Infection in the COVID-19 Era," Nicola Petrosillo, MD, head, Infection Control and Infectious Disease Service, University Hospital Campus Bio-Medico, Rome, Italy, discussed the incidence rates in hospitals before and since COVID-19. There were no significant increases in the national quarterly standardized infection ratios (SIRs) for CDI for any quarter in 2020 compared to 2019. The CDI SIR steadily declined from 0.63 to 0.55 in 2019 and remained stable at 0.52 for each quarter in 2020.

Petrosillo said precautions and increased training on personal protective equipment to prevent COVID-19 might have led to a reduction in *C difficile*. This may have been important in reducing transmission of *C difficile* spores, which are often resistant to alcohol-based hand sanitizer.

Another theory is that clinicians were so focused on COVID-19 that fewer patients underwent CDI testing. Although it remains to be seen what the exact factors were in reducing CDI, infection prevention control measures certainly played a role and could continue to work, the presenter said.

In the session titled, "Results from ECOSPOR III, a Phase 3 Placebo-Controlled Trial of SER-109, an Investigational Microbiome Therapeutic to Reduce Recurrence of *Clostridioides difficile* Infection," Barbara McGovern, MD, vice president for medical affairs, Seres Therapeutics, discussed studies around this oral therapeutic. Seres Therapeutics is a late clinical stage biotechnology company that advances microbiome therapeutics.

SER-109 is an investigational microbiome therapeutic, administered orally following antibiotics, to reduce recurrence of *C difficile*. The pharmacokinetics of it show that SER-109 spores germinate into metabolically active bacteria that colonize the gastrointestinal tract, a process called engraftment that induces broad compositional and functional changes associated with a clinical response.

SER-109 met its phase 3 primary end point, showing a highly statistically significant 30.2% absolute reduction in the rate of *C difficile* infection recurrence compared with placebo, according to studies. "SER-109 was more favorable to outcomes to placebo," McGovern said. SER-109 also had a safety profile comparable with placebo. ▲

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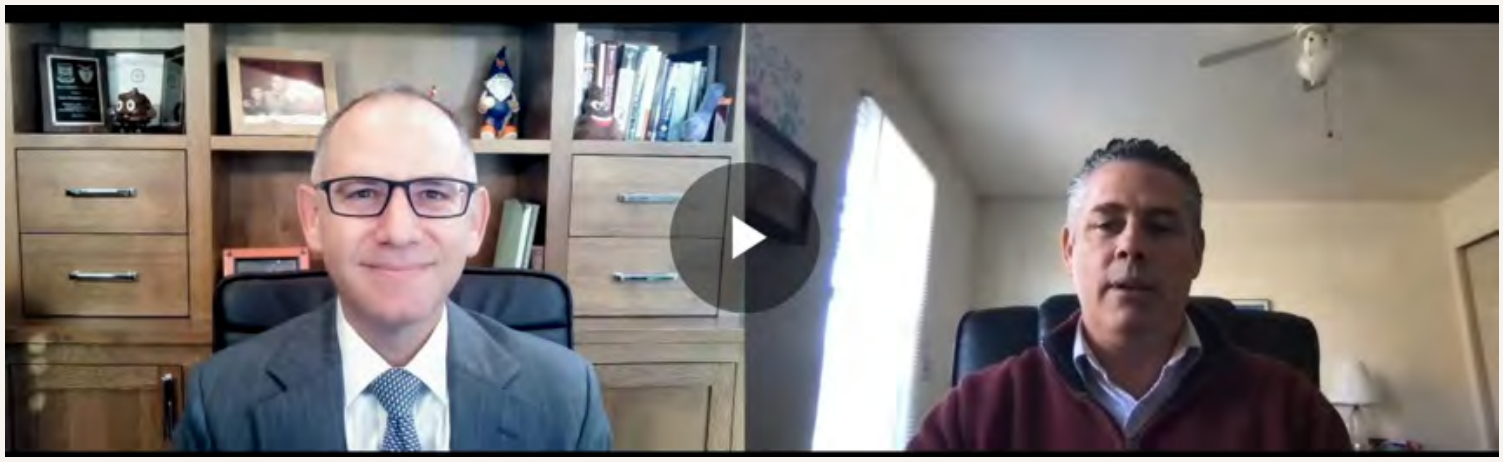

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An End in Sight for *C Difficile*?

by JOHN PARKINSON

The 9th Annual International *C. diff.* Live-Online Conference & Health EXPO Conference Cochair and Keynote Speaker Paul Feuerstadt, MD, FACG, AGAF, attending gastroenterologist, PACT Gastroenterology Center, Connecticut, says there are reasons to be optimistic about *C difficile* treatment and preventing recurrent *C difficile* infection. "We are at the precipice of greatness with *C difficile* right now; it is such an exciting time." ▲

Recurrent Infections and Other Challenges of *C difficile* Prevention

by NINA COSDON

The 9th Annual International *C. diff.* Live-Online Conference & Health EXPO took place from November 4-5, 2021. *Contagion*® covered both days of the conference; following are highlights of presentations from the first day.

BRINGING A *CLOSTRIDIOIDES DIFFICILE* SOLUTION TO LIGHT

High school juniors Emma Brashear and Layla Ouldnouri have been researching *Clostridioides difficile* infection (CDI) for more than 2 years and identified its invisible spores as among the greatest challenges in preventing CDI. Their solution was a wipe that makes *C difficile* spores visible under UV light and thus easier to clean. Germinating *C difficile* spores release the chemical compound dipicolinic acid, which illuminates under UV light when combined with terbium chloride. The presenters highlighted the importance of their research, citing *C difficile* infections as costing the US $8.2 billion a year and causing more deaths annually than drunk driving and HIV combined.

"MICROBIOME THERAPEUTICS IN 2021: ALMOST THERE FOR *C DIFFICILE*"

Sahil Khanna, MS, MBBS, professor of medicine in the Mayo Clinic Division of Gastroenterology and Hepatology, Rochester, Minnesota, gave this presentation. He described recurrent CDI as among the greatest problems in modern medicine.

Khanna called microbiota restoration the "holy grail" for managing recurrent CDI and cited it as being more than 85% effective in treating recurrent CDI. Additionally, he said microbiota restoration is superior to oral vancomycin and has fewer recipient contraindications.

Fecal microbiota transplant (FMT) is also safe and effective for recurrent CDI. FMT practices are heterogeneous, although donor FMT is superior to autologous FMT. When treating CDI, Khanna also advocated for eliminating modifiable risk factors such as proton pump inhibitors, hospitalization, sick contacts, and antibiotics. Khanna called standardized microbiota restoration "the future," citing positive data from the RBX2660 phase 3 (NCT03244644), SER-109 phase 3 (NCT03183128), CP101 phase 2 (NCT03110133), RBX7455 phase 2 (NCT02981316), and VE303 phase 2 (NCT03788434) trials.

"INTRODUCTION TO MICROBIOTA AND MICROBIOTA RESTORATION FOR RECURRENT *C DIFF* INFECTIONS"

Presented by Ken Blount, chief scientific officer of Rebiotix, this research also focused on recurrent CDI. Rebiotix is a Ferring Therapeutics company that specializes in microbiota restoration therapy. Blount detailed the various ways everyone's complex and diverse community of microbes influences health.

Antibiotics disrupt an individual's normal bacterial microbiome, leading to CDI and recurrent CDI. The goal of investigational live biotherapeutics is to restore healthy microbiota and reduce recurrent CDI. Blount cited the RBX2660 and RBX7455 clinical trials as evidence of restoring microbiota and metabolite compositions to fight CDI.

"CP101, AN INVESTIGATIONAL ORALLY ADMINISTERED MICROBIOME THERAPEUTIC DESIGNED TO PREVENT RECURRENT CDI"

The final presentation on the first day of the conference was given by Shrish Bedree, MD, PhD, medical director and head of clinical microbiome science at Finch Therapeutics. Finch works to develop novel therapeutics to treat serious conditions linked to a disruption of the microbiome. Bedree highlighted that recurrent CDI is a significant burden on the health care system, noting that Finch is the only company with complete and targeted approaches for developing microbiome therapeutics.

CP101 is an orally administered investigational microbiome therapeutic that offers a complete microbial community. One administration of CP101 resulted in a rapid and sustained increase of microbiome diversity in Finch's PRISM3 trial (NCT03110133).

CP101 met its primary efficacy end point in PRISM3 and demonstrated statistically significant prevention of recurrent CDI. By week 8, CP101 achieved 33.8% relative risk reduction for CDI recurrence. There were no treatment-related serious adverse events reported for the CP101 arm. ▲

Final Diagnosis: Pott Puffy Tumor With Subdural Empyema

A rare case of Pott puffy tumor occurs in an atypical patient with no risk factors, likely due to untreated sinus infection.

by REBECCA FALLIS, MD; *and* KEITH LEE

REBECCA FALLIS, MD

Rebecca Fallis, MD, is an attending physician specializing in infectious disease at Jefferson Abington Hospital, Pennsylvania. She completed her residency and fellowship at Temple University Hospital in Philadelphia, Pennsylvania.

KEITH LEE

Keith Lee is a third-year medical student, class of 2023, at Philadelphia College of Osteopathic Medicine in Pennsylvania. He is interested in internal medicine.

FINAL DIAGNOSIS

Pott puffy tumor with subdural empyema

HISTORY OF PRESENT ILLNESS

An African American female, age 64 years, presented to the emergency department with a chief complaint of headache that had been increasing in intensity for 4 days. The headache was mainly located across the frontal region of the head and worsened with movement. Pain was also present in the neck whenever she sat up. In the emergency department, the patient was febrile with a temperature of 100.9 °F, hypertensive to 191/111 mm Hg, and found to have elevated liver enzymes. Initial work-up with a CT angiogram of the head and neck was negative for acute findings but showed chronic maxillary, ethmoid, and frontal sinus disease. Ultrasound of the abdomen showed mild dilation of the common bile duct. The patient was admitted and treated for hypertensive urgency thought to be the cause of her headaches, and gastroenterology was consulted for hepatobiliary workup. Antibiotics were held.

MEDICAL HISTORY

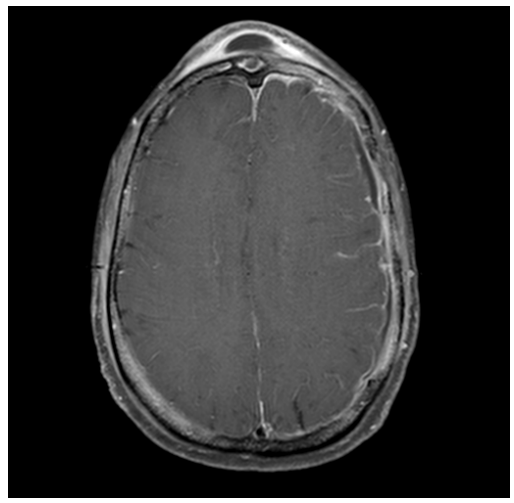
The patient's medical history included hypertension, non-Hodgkin lymphoma with last chemotherapy treatment 4 years prior to presentation, and a remote history of pulmonary emboli treated with 6 months of anticoagulation. Surgical history included cholecystectomy and tubal ligation.

KEY MEDICATIONS

The patient was taking aspirin, garlic capsules, potassium chloride, magnesium citrate, and coenzyme Q10.

EPIDEMIOLOGICAL HISTORY

The patient had no recent sick contacts, had not traveled recently, and had not noticed any tick bites or rashes. She was widowed and retired. She had no pets at home and never smoked or drank alcohol. Her mother died from cerebral hemorrhage.



T1-weighted postcontrast axial view MRI demonstrating a frontal subperiosteal abscess, subdural empyema with leptomeningeal enhancement, and mild enhancement within the marrow of the calvarium.

PHYSICAL EXAMINATION

Upon admission to the hospital, the patient was found to have a temperature of 100.9 °F (38.3 °C), pulse of 108 beats/min, blood pressure of 192/111 mm Hg, respiratory rate of 20 breaths/min, and oxygen saturation of 97% on room air. She was in no acute distress and an examination of the chest and abdomen were unremarkable. Neurological examination showed normal results.

On day 3 of hospitalization, the patient was found to have a maximum temperature of 102.7 °F, pulse of 76 beats/min, and blood pressure of 172/85 mm Hg. She had chattering teeth and was warm to the touch. There was a fluctuant, soft, fluid-filled mass in the center of her forehead, and she exhibited very mild nuchal rigidity. The remainder of the examination was unremarkable.

STUDIES

Initial laboratory studies demonstrated a white blood cell count of 10,900 cells/μL (4,000-11,000 cells/μL), creatinine of 0.79 mg/dL (0.70-1.40 mg/dL), aspartate aminotransferase of 246 U/L (7-35 U/L), alanine aminotransferase of 280 U/L (< 30 U/L), and alkaline phosphatase of 177 U/L (25-120 U/L). Blood cultures showed no growth.

CT angiogram of the head and neck with contrast showed chronic right maxillary, ethmoid, and frontal sinus disease. Abdominal ultrasonography showed a mildly dilated common bile duct and normal appearance of the liver. MRI of the abdomen was within normal limits without choledocholithiasis. CT of the chest with intravenous contrast showed no pulmonary embolism and no change in the previously noted mediastinal and hilar lymphadenopathy.

CLINICAL COURSE

On day 3 of hospitalization, the patient began to develop higher fever with a maximum temperature of 102.7 °F. Infectious diseases was consulted at this time for fevers of unclear etiology. During the initial consultation, physical examination revealed a soft, nontender, fluid-filled protrusion on the patient's forehead. Vancomycin, ceftriaxone, and ampicillin were started for empiric meningitis coverage. An MRI of the head was ordered stat, and the neurosurgery and otolaryngology departments were consulted at the request of infectious disease staff. MRI of the brain with and without contrast revealed right maxillary frontal sinusitis with an associated frontal subperiosteal abscess, left subdural empyema with leptomeningeal enhancement and associated mass effect, as well as calvarium osteitis. This confirmed the diagnosis of Pott puffy tumor with subdural empyema. Metronidazole was added for anaerobic coverage. Soon after the MRI results were obtained, the patient began to clinically decline, becoming increasingly lethargic and confused overnight. The patient was transferred to the neurosurgery intensive care unit.

DIAGNOSTIC PROCEDURES AND RESULTS

Otolaryngology staff performed a nasal endoscopy, which showed bilateral edema of the nasal mucosa with no pus. On day 4 of admission, patient was taken to the operating room (OR) by neurosurgery and

Section Editor:
BRIONNA MATT, DO

otolaryngology staff. Patient underwent a left craniectomy and evacuation of subdural empyema with a Jackson-Pratt drain left in place, along with concomitant septoplasty and right maxillary antrostomy with frontal sinus drain. OR cultures taken from the collection grew viridans group *Streptococcus intermedius* and methicillin-susceptible *Staphylococcus epidermidis*. Acid-fast bacilli cultures, fungus cultures, and cytology gave negative results.

TREATMENT AND FOLLOW-UP

Following surgery, the patient's clinical and neurological status improved within 48 hours. Drains were removed after 2 days. She was discharged on postoperative day 7 with high-dose ceftriaxone and metronidazole for 8 weeks. During follow-up in clinic, patient had complete resolution of all symptoms and returned to neurologic baseline. A brain MRI 4 weeks post surgery showed resolution of Pott puffy tumor and a diminished subdural empyema. A follow-up MRI 3 months post surgery showed complete resolution of the empyema.

DISCUSSION

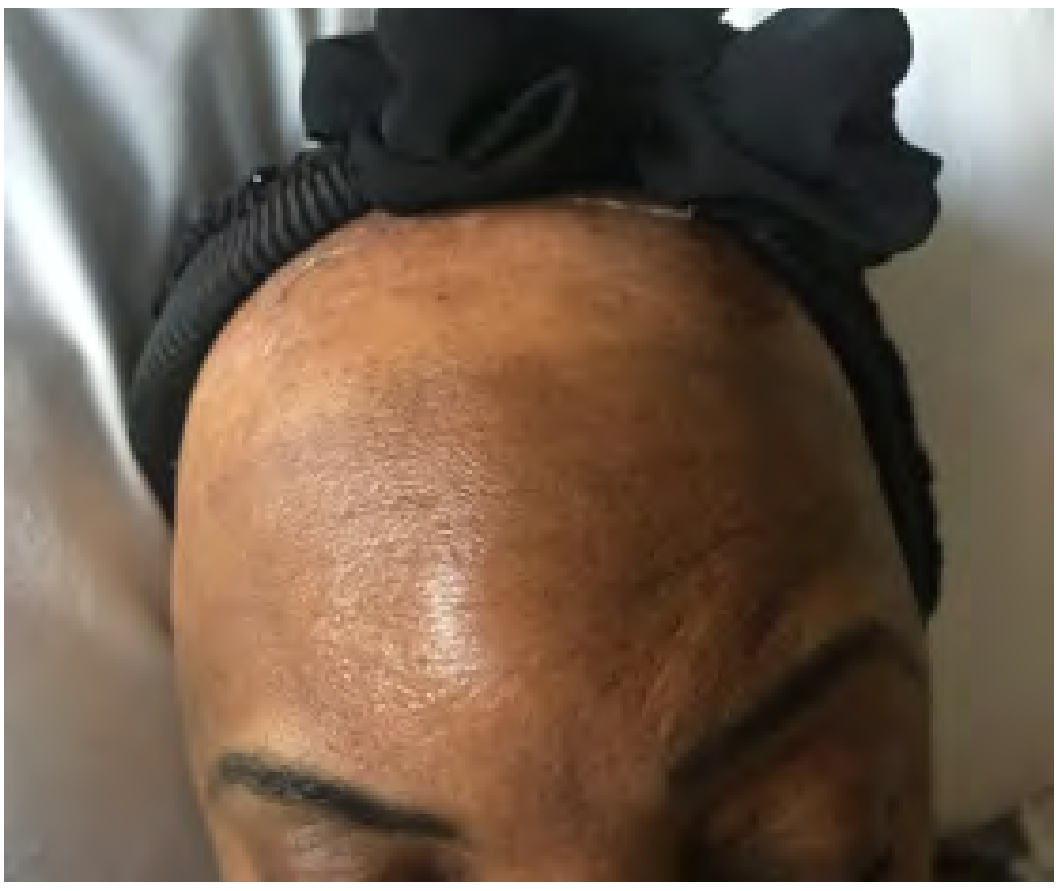
Pott puffy tumor is a rare clinical entity first described in the 18th century by Sir Percivall Pott, an English surgeon, as a subperiosteal abscess of the frontal bone with underlying osteomyelitis. Infection from the frontal sinus may spread either by direct extension into the underlying bone, causing osteomyelitis, or through hematogenous spread with infectious thrombophlebitis.[1] The diploic veins between the inner and outer layers of the cortical bone are valveless and thin walled, which facilitates the hematogenous spread of the sinus infection. When the infection extends posteriorly, this can cause meningitis, epidural abscess, subdural empyema, and septic dural or cavernous sinus thrombosis.[1,2] Pott puffy tumor can also result from head trauma and, less commonly, craniotomy, dental infection, cocaine abuse, and insect bites. Risk factors for developing Pott puffy tumor include diabetes and immunosuppression; male adolescents tend to be most affected.[1,2]

On physical examination, Pott puffy tumor is classically described as a fluctuant, tender, erythematous, soft swelling of the forehead. It usually presents with associated symptoms of headaches, fevers, rhinorrhea, and nasal congestion.[1-3] Often the first study to confirm the diagnosis is a CT of the head with contrast, which will show frontal sinusitis along with a subperiosteal effusion and possible intracranial extension.[2] An MRI of the head is the preferred imaging tool for diagnosis because it shows greater detail of intracranial involvement. MRI is also the preferred imaging technique following recovery.[2,3]

Treatment of Pott puffy tumor includes a combination of systemic antibiotics and surgical debridement. It is usually considered a surgical emergency. Surgery can either be open with a craniotomy to remove the infected bone and drain abscesses, or minimally invasive with endoscopic sinusotomy.[4] The most common organisms involved include nonenterococcal streptococci, staphylococci species, and oral anaerobes.[5] Empiric antibiotics should include broad-spectrum coverage for gram-positive cocci and anaerobes and have good penetration of the blood–brain barrier. A typical regimen would include vancomycin, a third-generation cephalosporin, and metronidazole. Antibiotic therapy can then be targeted to the culture results. Patients will typically need 4 to 8 weeks of intravenous antibiotics.[2,5] Successful recovery from Pott puffy tumor is dependent on rapid diagnosis and initiation of treatment. The prognosis is worse if there is greater intracranial involvement or if the infection is left untreated for an extended period.[6]

Pott puffy tumor is a rare clinical entity…a subperiosteal abscess of the frontal bone with underlying osteomyelitis.

Our rare case of Pott puffy tumor occurred in an adult female, not a male adolescent, with no known risk factors. Etiology was most likely from an untreated sinus infection. The case is moreover unique in that her presentation seemingly developed and progressed during her admission. There was no abscess noted on the admission CT angiogram of the head or the initial physical examination by the hospitalist. This case emphasizes the significance of the daily physical examination in contributing to a time-sensitive critical diagnosis. It is important for physicians to be aware of this rare clinical examination finding and to know what the next steps are to employ once it is discovered. ▲



Preoperative photograph of swelling in the midfrontal area

References are available at ContagionLive.com.

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