biosupplytrends
QUARTERLY
WINTER 2023 CRITICAL CARE

Long COVID

Another Post-Acute Infection Syndrome?

Children's Mental Health: NO LONGER AN IGNORED CRISIS

RMPs: THE KEY TO PREVENTING AND LESSENING DRUG SHORTAGES

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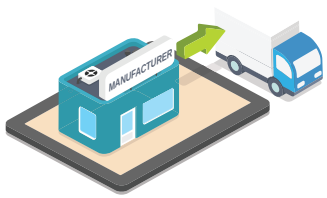
Guaranteed Channel Integrity®
8 Critical Steps

STEP 1

Purchasing

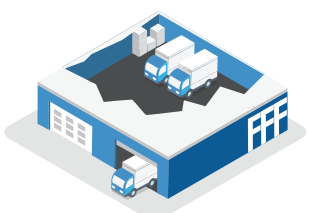
At FFF, we only purchase product from the manufacturer–never from another distributor or source–so the integrity of our products is never in question.



STEP 2

Storage

The healthcare products we store and transport are sensitive to temperature variations. Our state-of-the-art warehouse is temperature-controlled, monitored 24/7, and supported with backup generators in the event of power loss. In addition, we only stack products double-high to minimize pressure on fragile bottles and containers.



STEP 3

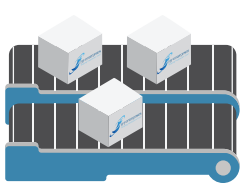
Specialty Packaging

At FFF, we use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

STEP 4

Interactive Allocation

FFF's unique capability of interactive allocation allows us to do that through our field sales team's close relationship with our customers. Our team understands customers' ongoing requirements, responds to their immediate crises, and allocates product in real-time to meet patients' needs.



Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record. The 8 Critical Steps to Guaranteed Channel Integrity have resulted in more than 11,600 counterfeit-free days of safe product distribution.

800.843.7477 | Emergency Ordering 24/7

STEP 5

Delivery

Our delivery guidelines are in compliance with the State Board of Pharmacy requirements. Products we deliver must only be transported to facilities with a state-issued license, and only to the address on the license. We make no exceptions. And we will not ship to customers known to have a distributor's license.

STEP 6

Methods of Delivery

We monitor for extreme weather conditions, and when the need arises, we ship overnight to maintain product efficacy. We also track patient need during life-threatening storms to make sure products are delivered when and where patients need them most.

STEP 7

Verification

In compliance with U.S. Drug Supply Chain Security Act (DSCSA) requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History, and Transaction Statement.

STEP 8

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

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Many National Healthcare Crises Accentuated by the Pandemic

THE COVID-19 pandemic created a host of economic and personal hardships in the healthcare arena. Medical staff experienced burnout, exhaustion and trauma that led to staff shortages nationwide, and health systems experienced sharp declines in revenue. For patients, health inequities that have existed for years have been revealed; delayed treatments worsened chronic conditions and resulted in missed diagnoses; and many lost employer-sponsored health insurance. But, there are upsides to this pandemic: By accentuating many national healthcare crises that have been in the making for decades, solutions could be on the horizon.

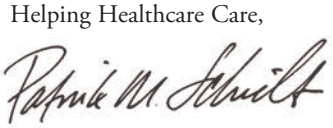
For instance, one challenging issue for healthcare providers is long-COVID, which causes lingering symptoms of the SARS-CoV-2 virus for some individuals with oftentimes devastating effects. But these types of lingering symptoms are not new; they share a strong similarity to other post-acute infection syndromes (PAISs) that have long been a mystery. As we explore in our article "Long COVID: Shedding Light on Other Viral Infections" (p.20), the emergence of long COVID was an "aha" moment, especially relating to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that was often dismissed as a problem that was "all in one's head." In fact, it has historically been believed that once an infection is cleared, symptoms can't persist. However, now that it is known that the SARS-CoV-2 virus can cause long-term symptoms, researchers are reexamining other viral infections such as ME/CFS to determine the validity of PAISs. It is hoped that this will result in treatments for patients who have been ignored for too long.

Another crisis brought to the forefront during the pandemic is the troubling mental health crisis faced by children. Our article "Addressing the Mental Health Crisis in Children" (p.24) points out that while data show one in five children experienced an episode of major depression between 2013 and 2019, the issue is only now being acknowledged after signs of mental distress emerged when children returned to the classroom — a problem that continues to escalate. Incidents include fights among students, violence against school staff and students harming themselves. In response, public health officials are finally calling for a national agenda to address mental health issues in children both in and out of the classroom.

Finally, while drug shortages are nothing new, they became a national issue during the pandemic due to unprecedented demand by large numbers of critically ill patients with COVID-19. As we highlight in our article "How FDA's Risk Management Program Can Help Prevent or Lessen Future Drug Shortages" (p.28), the high price of drugs during shortages affect patients (especially those with rare diseases), providers and payers. Fortunately, the attention paid to this issue during the pandemic resulted in a U.S. Food and Drug Administration risk management program (RMP) guidance document to combat future drug shortages. In addition, Congress enacted the Coronavirus Aid, Relief and Economic Security Act requiring redundancy RMPs for certain lifesaving or life-sustaining drugs.

As always, we hope you enjoy the additional articles in this issue of *BioSupply Trends Quarterly*, and find them both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

biosupplytrends QUARTERLY

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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$11 Million Approved for Vaccine to Prevent Smallpox and Monkeypox

The U.S. Department of Health and Human Services (HHS) will provide approximately $11 million to support the first U.S.-based fill and finish manufacturing of JYNNEOS, a vaccine approved to prevent smallpox and monkeypox. The agreement will aid the company in accelerating the fill and finish manufacturing qualification and production in its recently expanded Grand River Aseptic Manufacturing (GRAM) facility in Grand Rapids, Mich. The funding will allow GRAM to purchase additional equipment necessary for JYNNEOS production and recruit and train additional staff to operate the line. Vaccine production at the facility is expected to be underway later this year, months ahead of the nine-month schedule typical for this type of work.

"Rapidly increasing the supply and safe delivery of monkeypox vaccine to at-risk Americans is a top priority," said Assistant Secretary for Preparedness and Response Dawn O'Connell. "BARDA's [Biomedical Advanced Research and Development Authority] support helps ensure success in doubling the capacity available to fill and finish this vaccine, improves preparedness for smallpox bioterrorism, and strengthens the security of the U.S. supply chain. Production of JYNNEOS in the U.S. creates jobs and speeds the availability of the vaccine." ❖

HHS Funds U.S.-Based Production of Smallpox and Monkeypox Vaccine. U.S. Department of Health and Human Services press release, Aug. 29, 2022. Accessed at www.hhs.gov/about/news/2022/08/29/hhs-funds-us-based-production-of-smallpox-and-monkeypox-vaccine.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=september-4-2022.

$2 Million Awarded to Study Risks and Benefits of Social Media on Youth

Two million dollars in funding has been awarded to the American Academy of Pediatrics to establish a National Center of Excellence on Social Media and Mental Wellness. According to the U.S. Department of Health and Human Services (HHS), the center's purpose is to develop and disseminate information, guidance and training on the impact, including risks and benefits, that social media use has on children and young people, especially risks to their mental health. It will also examine clinical and social interventions that can be used to prevent and mitigate the risks. "There are benefits to social media use, but there are clearly risks, too — especially when it comes to mental health," said HHS Secretary Xavier Becerra. "This new center will help our families better protect our children from lurking dangers. And it's one more example of HHS' commitment to strengthen mental health."

The Center will focus on three priorities: 1) education and resources around the risks and benefits of social media use for children and youth; 2) culturally and linguistically appropriate technical assistance focusing on active learning, consultation and support on how to best assist children and youth when interfacing with the digital world in a way that enhances their mental health while reducing harm; and 3) best practices and research updates.

The HHS funding provides $2 million per year, up to five years. ❖

HHS Announces Award of $2 Million Grant to the American Academy of Pediatrics to Establish National Center of Excellence on Social Media and Mental Wellness. U.S. Department of Health and Human Services press release, Sept. 2, 2022. Accessed at www.hhs.gov/about/news/2022/09/02/hhs-announces-award-2-million-grant-american-academy-of-pediatrics-establish-national-center-of-excellence-on-social-media-mental-wellness.html?utm_source=news-releases-email&utm_medium=email&utm_campaign=september-11-2022.

HHS Launches a National Biotechnology and Biomanufacturing Initiative

The U.S. Department of Health and Human Services (HHS) has launched a National Biotechnology and Biomanufacturing Initiative to help drive research and development, improve access to quality federal data, grow domestic manufacturing capacity, expand market opportunities for biobased products, train a diverse and skilled workforce, streamline regulatory processes for products of biotechnology, advance biosafety and biosecurity to reduce risk, protect the U.S. biotechnology ecosystem and build a thriving and secure global bioeconomy with partners and allies.

HHS intends to leverage biotechnology and biomanufacturing to achieve medical breakthroughs, reduce the overall burden of disease and improve health outcomes. The organization will lead the U.S. government in strategically advancing biosafety and biosecurity innovation as part of a growing bioeconomy to ensure biotechnology research and development and biomanufacturing infrastructure break new ground while reducing risk. ❖

HHS Takes Action on Executive Order Launching a National Biotechnology and Biomanufacturing Initiative. U.S. Department of Health and Human Services fact sheet, Sept. 14, 2022. Accessed at www.hhs.gov/about/news/2022/09/14/fact-sheet-hhs-takes-action-executive-order-launching-national-biotechnology-biomanufacturing-initiative.html.

Report Released on Chronic Diseases and Related Risk Factors

In September, the U.S. Centers for Disease Control and Prevention (CDC) released the 2021 data from the Behavioral Risk Factor Surveillance System (BRFSS), which are now available through CDC's easy-to-use web-based tool. Data topics include health-related risk behaviors, chronic health conditions, healthcare access and use of preventive services. Topics include alcohol use, tobacco use, cardiovascular disease, cancer, mental and physical health, healthy days, depression, diabetes, arthritis, HIV testing, immunizations, obesity and overweight, asthma and physical activity or exercise.

According to CDC, the tool allows users to understand important health issues in their states and make state and national comparisons quickly and easily. It also offers various ways to display survey results from more than 438,000 residents of the United States and U.S. territories.

Per the CDC's website, "BRFSS provides a sound basis for understanding health issues in states, assessing and maintaining public health programs, and making progress on improving health and reducing health disparities. The prevalence and trends tool offers fast access to a large portion of the 2021 data set and can be a helpful resource to reporters, students, public health officials and decision-makers." The tool is updated every year and can be accessed at www.cdc.gov/brfss/brfssprevalence. ❖

CDC Releases Data on Chronic Diseases and Related Risk Factors. U.S. Centers for Disease Control and Prevention press release, Sept. 27, 2022. Accessed at www.cdc.gov/media/releases/2022/a0927-BRFSS-2021.html.

HHS Releases New Reports on Positive Impact of Inflation Reduction Act on Prescription Drug Prices

The U.S. Department of Health and Human Services (HHS) released two new reports that illustrate the urgency of addressing skyrocketing prescription drug costs in the U.S. HHS's analyses of prescription drug prices from 2016 to 2022 show that if the Inflation Reduction Act had been in place from July 2021 to July 2022, more than 1,200 prescription drugs potentially would have been subject to the new provision requiring drug manufacturers to pay rebates to Medicare if they enact price increases greater than inflation for drugs. Price increases on those drugs in the month the price change took effect averaged more than 30 percent.

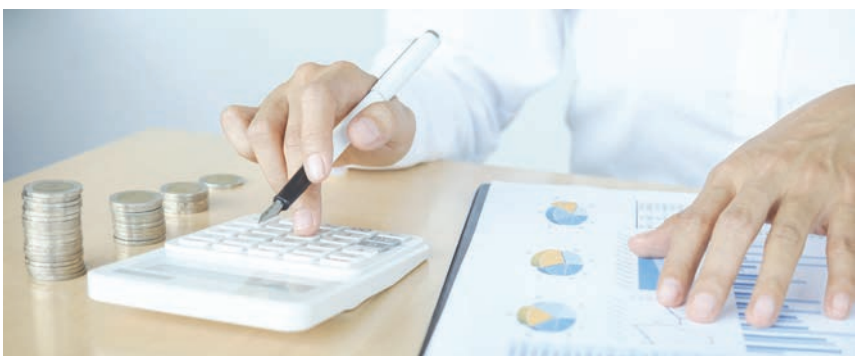
Publication of these reports coincides with a key date related to a provision of the Inflation Reduction Act, which requires drug manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation for the 12-month period beginning Oct. 1, 2022. A similar provision for Part B drugs takes effect in January 2023. In addition, the Inflation Reduction Act requires the federal government to negotiate drug prices on certain high spending prescription drugs for Medicare beneficiaries.

"In recent years, prescription drug prices have skyrocketed, but thanks to the Inflation Reduction Act, America's families will soon start seeing relief," said HHS Secretary Xavier Becerra. "The Biden-Harris Administration is focused on providing high-quality, affordable healthcare to people across the country. No one should have to choose between buying groceries or a prescription, making a home repair or going to the doctor, or splurging on a grandkid or seeking treatment." ❖

New HHS Reports Illustrate Potential Positive Impact of Inflation Reduction Act on Prescription Drug Prices. U.S. Department of Health and Human Services press release, Sept. 30, 2022. Accessed at www.hhs.gov/about/news/2022/09/30/new-hhs-reports-illustrate-potential-positive-impact-inflation-reduction-act-prescription-drug-prices.html.

The Inflation Reduction Act: A Radically Different Market Environment

By Bonnie Kirschenbaum, MS, FASHP, FCSHP



THE 2022 Inflation Reduction Act (IRA) significantly changes the U.S. prescription drug pricing regulations, creating a radically different market environment. The federal government will regulate the price of prescription drugs in Medicare, limit drug manufacturers' ability to increase wholesale prices and make changes to the Medicare Part D prescription drug benefit. In addition, Medicare Parts B and D gain negotiation powers for the price of some drugs without generic or biosimilar competition. The Act ends a 19-year-old ban on Medicare from negotiating the price of prescription medicines with manufacturers.

The provisions of the IRA cover inpatient, outpatient and ambulatory components of medication use and span several years. Here's what you need to know:

The Affordable Care Act

• As of Oct. 1, 2022, people with Affordable Care Act insurance plans continue to save during 2023 open enrollment.

Medicare Part B

• *Qualifying biosimilars*. As of Oct. 1, 2022, Medicare will temporarily pay average sales price (ASP) +8% of the reference add-on (Table).

• *Drug rebates.* As of Jan. 1, 2023, drug rebates from manufacturers are required if prices for certain Part B drugs increase faster than the rate of inflation. Payment for inflation rebates for quarters in 2023 and 2024 must be invoiced by Sept. 30, 2025.

• *Coinsurance.* Beginning April 1, 2023, coinsurance may be lowered for some drugs if its price increased faster than the rate of inflation in a benchmark quarter.

• *Payment caps.* Beginning July 1, 2024, payments for new biosimilars will be capped when ASP data is not available.

Medicare Part D

• *Drug rebates.* Starting Oct. 1, 2022, drug manufacturers must pay rebates to Medicare if their prices for certain Part D drugs increase faster than the rate of inflation over the 12-month period and must be invoiced by Dec. 31, 2025.

• *Drug price negotiation program*. The first cohort of Medicare Part D drugs selected for negotiation will be announced by Sept. 1, 2023, and cohorts of 10-20 Part B or Part D drugs for negotiation will be announced by Feb. 1 in each subsequent year through 2029. The Centers for Medicare and Medicaid Services will publish maximum fair prices by Nov. 30 each subsequent year until 2029. Prices will go into effect on a rolling basis between 2026 and 2031.

• *Premium stabilization*. Beginning Jan. 1, 2024, limits to the average premium increase across most Part D plans will be set at six percent; protection continues through 2029. Stabilization plans for premiums will be implemented in 2030 onward.

• *Catastrophic phase*. In 2024, elimination of the five percent cost-sharing in the catastrophic phase will begin after enrollees reach $7,050 in out-of-pocket costs for covered drugs.

• *Out-of-pocket limit*. In 2025, out-of-pocket costs will be capped at $2,000; costs can be paid in monthly increments.

• *Manufacturer discount program*. In 2025, a manufacturer discount program will replace the coverage gap discount program that will apply to both the initial coverage and catastrophic phases.

• *Government reinsurance*. In 2025, government reinsurance in the catastrophic phase will decrease from 80 percent to 20 percent for brand name drugs, biologicals and biosimilars and from 80 percent to 40 percent for generics. In 2026, it will be 40 percent for Medicare Part D drugs selected for negotiation in their applicability period.

Cost-sharing

• *Insulin.* As of Jan. 1, 2023, out-of-pocket payments for people enrolled in a Medicare prescription drug plan will be capped at $35 for a month's supply

Proposed Payment Systems and Fee Schedules in 2023

HCPCS Code	Short Description	HCPCS Code Dosage	Payment Limit
Q5101	Injection, Zarxio	1 mcg	0.273
Q5103	Injection, Inflectra	10 mg	30.945
Q5105	Injection, Retacrit esrd on dialysis	100 units	0.813
Q5106	Injection, Retacrit non-esrd use	1,000 units	8.134
Q5107	Injection, Mvasi	10 mg	0.310
Q5110	Nivestym	1 mcg	0.400
Q5112	Injection, Ontruzant	10 mg	63.120
Q5113	Injection, Herzuma	10 mg	52.971
Q5114	Injection, Ogivri	10 mg	45.318
Q5115	Injection, Truxima	10 mg	53.020
Q5116	Injection, Trazimera	10 mg	40.006
Q5117	Injection, Kanjinti	10 mg	32.699
Q5118	Injection, Zirabev	10 mg	38.664
Q5119	Injection, Ruxience	10 mg	39.741
Q5123	Injection, Riabni	10 mg	48.600

of each insulin they are prescribed that is covered by their drug plan and dispensed at a pharmacy or through a mail-order pharmacy. Part D deductibles won't apply. As of July 1, 2023, traditional Medicare beneficiaries using insulin through a traditional pump (covered through the Part B durable medical equipment benefit) won't pay more than $35 for a month's supply of insulin; the deductible doesn't apply to the insulin.

• *Vaccines.* As of Jan. 1, 2023, adult vaccines recommended by the Advisory Committee on Immunization Practices will be available at no cost to people covered by Medicare Part D.

• *Low-income subsidy program (LIS or "Extra Help").* In 2024, some low-income individuals covered by Medicare Part D will receive financial help with prescription drug cost-sharing and premiums.

Action Steps

1) Ensure your pharmacy drug and change description master files are up to date and in sync using the appropriate brand-specific healthcare common procedural code set (HCPCS). Biosimilar HCPCS codes are brand-specific and not interchangeable. The differentiation between end-stage renal disease (ESRD) and non-ESRD for some codes remains.

2) 2023 annual ICD-10 code update: Remember that any of these code changes (effective Oct. 1, 2022) have an impact on prior authorizations (PAs), as well as national and local coverage determinations. Evaluate active local coverage determination articles published by your Medicare administrative contractor (MAC), and examine the national coverage determinations and PAs for commercial and Medicare Advantage payers. Failure to do so will automatically result in denials for lack of medical necessity.

3) Use appropriate current procedural terminology (CPT) codes 96401-96549 for chemotherapy and other highly complex drug or highly complex biologic agent administration. An appropriate modifier applies to billing for noncovered services. See CPT codebook for specifics. ❖

Resources

1. Centers for Medicare and Medicaid Services. October 2022 Update of the Hospital Outpatient Prospective Payment System (OPPS). Accessed at www.cms.gov/files/document/mm12885-october-2022-update-hospital-outpatient-prospective-payment-system-opps.pdf.
2. Centers for Medicare and Medicaid Services. 2022 ASP Drug Pricing Files. Accessed at www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2022-asp-drug-pricing-files.
3. Centers for Medicare and Medicaid Services. Part B Biosimilar Biological Product Payment. Accessed at www.cms.gov/medicare/medicare-fee-for-service-part-b-drugs/mcrpartbdrugavgsalesprice/part-b-biosimilar-biological-product-payment.
4. Centers for Medicare and Medicaid Services. Inflation Reduction Act: CMS Implementation Timeline. Accessed at www.cms.gov/files/document/10522-inflation-reduction-act-timeline.pdf.

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How to Rectify the Growing Nursing Shortage

Hospitals across the country are implementing creative strategies to address the ongoing gap between nurses and the patients who need care.

By Diane L.M. Cook

NURSING SHORTAGES in the United States are not new, but the COVID-19 pandemic exaccerbated the problem when it put an unprecedented strain on the healthcare system at large — and nurses in particular.

Traveling nurses help ease the burden by working with independent staffing agencies to fill gaps across the country by contracting with healthcare facilities in dire need of employees for a short-term assignment in exchange for higher-than-average pay (30 percent more than staff nurses, on average).[1] But traveling nurses come at a premium: High pay and low commitment don't address the long-term problem, and things are expected to worsen over the next decade.[2]

The U.S. Bureau of Labor Statistics reports that employment of registered nurses (RNs) is projected to grow six percent between 2021 and 2031, with about 203,200 expected each year.[3] According to the American Association of Colleges of Nursing (AACN), the problem is fueled by increased demand for nursing services from the aging population; a high number of retiring nurses that will continue over the next decade; and new employment opportunities for nurses at all levels. Further, the American Nurses Association (ANA) says that while attrition significantly contributes to the limited supply and availability of nurses, three other major factors exacerbate the shortage, including unhealthy work environments, heavy workloads and burnout and compensation dissatisfaction. ANA Director of Nursing Programs Katie Boston-Leary, PhD, MBA, MHA, RN, NEA-BC, urges, "Without swift and sufficient action, the nation's nurses, patients and communities will continue to suffer."[4] Thankfully, hospitals, healthcare associations and nursing colleges are working diligently to address the myriad of issues causing the shortages.

Partnering to Solve Problems

ANA collaborated with AACN and other healthcare organizations to form a task force charged with identifying priority issues and developing short-term, actionable strategies that could help offset the ongoing crisis. The task force identified action items in six key areas:[5]

1) *Healthy work environment.* Elevate clinician psychological and physical safety to equal importance with patient safety, and investigate evidence related to scope of practice and minimum safe staffing levels for patients.

2) *Diversity, equity and inclusion (DEI).* Integrate DEI ideals.

3) *Work schedule flexibility.* Build a workforce with flexible schedules, shifts and roles.

4) *Stress injury continuum.* Address burnout, moral distress and compassion, and incorporate nurse well-being as an organizational value.

5) *Innovative care delivery models*. Implement a holistic delivery model.

6) *Total compensation*. Develop and formalize an innovative, customizable, transparent pay philosophy and program, and include benefits such as paid time off for self-care, wellness and wealth planning.

Strategies in Practice

According to the Society of Hospital Medicine, hospitals across the nation are implementing novel strategies to address the shortage and retention of nurses in local hospitals, including offering attractive compensation packages; providing desirable perks; implementing robust training and mentoring programs; and even utilizing nonclinical staff to perform peripheral patient-care tasks. Chatham Hospital in Siler City, N.C., Providence Medical Hospital in Mission Viejo, Calif., Anne Arundel Medical Center in Annapolis, Md., and Akron Children's Hospital in Akron, Ohio, all exemplify what's happening across the country.

- *Attractive compensation*. Hospitals are increasing salaries and offering bonuses to keep their existing nursing staff. For example, Chatham Hospital increased

nurse salaries by $2 per hour, then gave a 2.5 percent raise in January 2022. Nurses also received an incentive bonus of 2.5 percent at the end of October 2022. Akron Children's Hospital offers bonus incentive pay programs to staff willing to work extra hours.[6]

Hospitals are also recruiting new nurses by offering attractive compensation packages and bonuses for working in high-need areas. Chatham Hospital began to offer sign-on bonuses for two-year commitments, plus relocation assistance for out-of-area candidates. Providence Mission Hospital offers referral bonuses to recruit experienced nurses. Chatham Hospital and Anne Arundel Medical Center offer tuition assistance programs.[6]

• *Desirable perks.* Hospitals are improving benefits packages by reducing short-term disability waiting periods and giving staff members who work 24-hour workweeks full-time health benefits. Also, many reward nurses who work weekends. Some also offer the flexibility of part-time work and schedule accommodations to cater to the needs of their many nursing students.[6]

• *Training and mentorship.* Chatham Hospital forged a strong relationship with a local community college with an RN program and is bringing back licensed practical nurses (LPNs) to inpatient and emergency department positions. Providence Hospital utilizes a program called Transition into Practice, which allows for on-boarding of more new graduate nurses with better retention and clinical skills after orientation. They also created a patient care technician role for nursing students. Akron Children's Hospital created the Helping Hands Program in which nurses who work in nonclinical settings are offered refresher training so they can support care delivery at bedside, and they utilize nursing students as patient care assistants. Akron Children's Hospital also has a 10-week nurse technology program for students from underrepresented groups, and it offers an accredited nurse residency program that supports new graduate nurses' transitions to practice throughout the entire first year after graduation.[6]

• *Utilizing other staff.* Nonclinical staff are increasingly used for essential nonclinical tasks to ease the burden on nurses. Educators and medical, nursing and pharmaceutical students are also helping fill gaps: They do everything from helping transport patients and lab specimens to delivering meal trays and emptying trash cans.[7]

Nursing Schools Are Strained, Too

Training new nurses to meet the need is easier said than done. Qualified nurse educators are also in short supply, which significantly limits class offerings and sizes. According to Robert Rosseter, chief communications officer at AACN, "Nursing schools must increase enrollment in programs that prepare nursing faculty, since the shortage of nurse educators is limiting the ability of nursing schools to expand new student enrollment."[8] As it stands, nursing schools cannot train enough new nurses to meet the significant need.

To help expand the pipeline into nursing, AACN convened the Nursing Community Coalition to advocate for increases in federal Title VIII funding, which provides scholarships to entry-level and advanced nursing students, as well as funding to schools to expand capacity.

AACN also works with practice leaders and corporate stakeholders to offer scholarships to students and funding to faculty. Rosseter says these entities are "needed to fund scholarships, support outreach programs to middle and high school students, provide space for student training, raise money for faculty recruitment and encourage ongoing nursing education." He also encourages "working with partner organizations to highlight careers in nursing, including those requiring graduate level preparation." Rosseter says AACN believes that all stakeholders, including federal and state governments, the business community, foundations and advocacy groups, must take a larger role in addressing this nationwide crisis.

All Hands on Deck

Unless the current and growing nursing shortage is rectified soon, over the next decade there will be decreased access to healthcare, the quality of healthcare will be diminished and certain services such as emergency departments will be temporarily or permanently closed. The call for action to rectify these shortages is now. ❖

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Guidelines

WHO Publishes First Guideline for Treating Ebola

The World Health Organization (WHO) has published its first guideline for Ebola virus disease therapeutics, with new strong recommendations for the use of two monoclonal antibodies. The drugs, Regeneron's Inmazeb (REGN-EB3) and Ridgeback Bio's Ebanga (mAb114), use laboratory-made monoclonal antibodies that mimic natural antibodies in fighting off infections.

The two recommended therapeutics have demonstrated clear benefits and can be used for all patients confirmed positive for Ebola virus disease, including older people, pregnant and breastfeeding women, children and newborns born to mothers with confirmed Ebola within the first seven days after birth. According to WHO, patients should receive recommended neutralizing monoclonal antibodies as soon as possible after laboratory confirmation of diagnosis.

"Advances in supportive care and therapeutics over the past decade have revolutionized the treatment of Ebola. Ebola virus disease used to be perceived as a near certain killer. However, that is no longer the case," said Robert Fowler, MD, of the University of Toronto, Canada, and co-chair of the guideline development group. "Provision of best supportive medical care to patients, combined with monoclonal antibody treatment — mAb114 or REGN-EB3 — now leads to recovery for the vast majority of people."

WHO is making strong recommendations for the use of the two therapeutics; however, the organization stresses there is a need for further research and evaluation of clinical interventions since many uncertainties remain. Further, WHO says improvements could be made in supportive care, as well as in the understanding and characterization of Ebola virus disease and its longer-term consequences to ensure continued inclusion of vulnerable populations (pregnant women, newborns, children and older people) in future research. ❖

WHO Makes New Recommendations for Ebola Treatments, Calls for Improved Access. World Health Organization press release, Aug. 19, 2022. Accessed at www.who.int/news/item/19-08-2022-who-makes-new-recommendations-for-ebola-treatments-----calls-for-improved-access.

Research

Experimental RSV Vaccine Shows Promise in Mice

An experimental vaccine shows promise for protecting mice from the respiratory syncytial virus (RSV), the pathogen that most commonly causes the chest infection bronchiolitis in young children. The vaccine, developed at Boston Children's Hospital, contains key immune-stimulating molecules, called adjuvants, along with a fragment of a protein that RSV uses to enter cells, called F protein.

In a study of the vaccine, 12 newborn mice, aged 4 to 7 days old, were injected with the vaccine or a saline solution, and were then exposed to RSV seven weeks later. Approximately two weeks after RSV exposure, the virus was found in the lungs of the mice that were given saline, but not in the vaccinated mice. The concentration of RSV in the noses of the vaccinated mice was also 100 times lower than in the control mice, suggesting the virus had more effectively infected the upper airways of the unvaccinated mice. The researchers also looked at the vaccinated mice's immune response to RSV. "The adjuvant combination robustly enhanced antibody and useful T-cell responses and indicated protection against RSV infection in infant mice," said Ofer Levy, MD, PhD, director of the precision vaccines program and senior physician in pediatrics in the division of infectious diseases at Boston Children's Hospital.

When tested in human blood cells taken from newborns, the vaccine also generated a favorable immune response. However, one limitation of the study is that the mice were adults by the time the experiment ended. In people, RSV causes bronchiolitis in young children. The immune response of the mice at several weeks old, when they were adults, may therefore not apply to young children.

The researchers hope to next test the vaccine in nonhuman primates and then people. ❖

Wong, C. RSV Vaccine That May Protect Against Bronchiolitis Has Promise in Mice. New Scientist Live, Aug. 2, 2022. Accessed at www.newscientist.com/article/2331669-rsv-vaccine-that-may-protect-against-bronchiolitis-has-promise-in-mice.

Research

Study Finds Pfizer's RSV Vaccine Effective in Preventing Illness in Older Adults

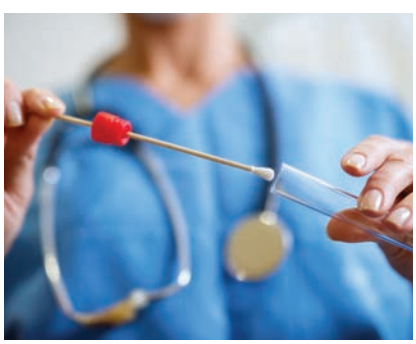
Results of a recent study show Pfizer's experimental vaccine for respiratory syncytial virus (RSV) is nearly 86 percent effective in preventing severe illness in older adults. The vaccine was also found to be approximately 67 percent effective in preventing milder illness from the virus and caused no serious safety concerns. The bivalent vaccine candidate, called RSVpreF, is composed of two preF proteins selected to optimize protection against RSV A and B strains. Results of the study were based on an early analysis of a Phase III trial of 37,000 adults ages 60 and older. The protein-based vaccine was administered in a single dose.

Experts say the findings are significant as there are currently no approved vaccines to prevent RSV infections, which are responsible for 177,000 hospitalizations and 14,000 deaths in older adults each year, according to the Centers for Disease Control and Prevention. ❖

Lovelace, B Jr. Pfizer Says Its RSV Vaccine Protects Against Severe Illness in Older Adults. NBC News, Aug. 25, 2022. Accessed at www.nbcnews.com/health/health-news/pfizers-rsv-vaccine-protects-severe-illness-older-adults-rcna44683?utm_campaign=KHN%3A%20Daily%20Health%20Policy%20Report&utm_medium=email&_hsmi=224070048&_hsenc=p2ANqtz-_VZXZOVB6KPBqgl7T7JxY7FgquXswFjNLjqLpGuyrMg6aEs00-q5gGqbfoXWmAoB1nsKWLkZDAGY4oJBSE3RMwsgN-RA&utm_content=224070048&utm_source=hs_email.

Diagnostics

New Test Identifies Patients at Risk of Severe COVID-19



U.S. scientists have developed a new genomic test that can predict a patient's risk of developing severe COVID-19, an advance that could help doctors quickly begin tailored treatment. The test proved more than 90 percent accurate at predicting patient outcomes for COVID-19 among more than two dozen patients in intensive care and 100 patients from publicly available data.

AMPEL Biosolutions' CovGENE analyzes genes expressed in a person's blood to determine whether they may experience a severe disease course with increased risk of death. "We have come far in the prevention and treatment of COVID-19 in the past two years," said Alexandra Kadl, MD, at the University of Virginia. "Regardless, we still struggle to identify patients at highest risk for severe disease. Our study uses a gene-analysis approach to identify an immune cell signature, distinct from other respiratory illnesses, that correlates with worse outcomes."

The test has the potential to help evaluate patients' immune profile with commonly, readily available tests to identify patients at risk for bad outcomes who would benefit from closer monitoring and advanced therapies to aid their recovery. Immune profiling helps to understand why one person may differ from another in their immune response to a virus, looking specifically at the immune markers (proteins) and cells present over time. ❖

Novel Test Can Identify Patients at Risk of Severe COVID-19. The Hindu, Sept. 19, 2022. Accessed at www.thehindu.com/sci-tech/health/novel-test-can-identify-patients-at-risk-of-severe-covid-19/article65909544.ece.

Research

Researchers Develop a New mRNA Vaccine to Treat Cancer

U.S. researchers have developed a new mRNA vaccine against cancer that delivers the drug directly to the lymphatic system and stimulates a strong immune response. Animal tests have shown the new vaccine effectively blocks the development of the tumor, in most cases until it completely disappears. This new vaccine works the same way as the mRNA-based coronavirus vaccines in which the body's cells "read" the genetic information received in the vaccine and begin producing viral antigens that activate the immune system. For cancer, the mRNA vaccine is therapeutic rather than preventive. It is administered to people to treat existing tumors and/or prevent against relapse.

In the study, the researchers studied ways to increase the immune response by changing the point that the antigens entered the body. mRNA molecules were delivered directly to the lymphatic systems, and not to the liver as was done previously. Testing on mice showed the new mRNA vaccine causes a more powerful immune reaction and, in combination with other therapy, effectively suppresses the tumor. In 40 percent of cases, a complete remission was seen.

Currently, mRNA technology is being used to develop preventive tools for HIV, influenza, malaria and other infections. ❖

Researchers Have Developed an mRNA Vaccine to Fight Cancer. Life4me+, Aug. 20, 2022. Accessed at life4me.plus/en/news/9170.

Medicines

FDA Approves Humira Biosimilar to Treat Autoimmune Disorders

The U.S. Food and Drug Administration (FDA) has approved Samsung Bioepis' Hadlima (adalimumab-bwwd) for the treatment of several autoimmune disorders, including rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and Crohn's disease. FDA's approval was specifically for a citrate-free, high-concentration version of Hadlima (adalimumab-bwwd). While FDA had already approved a low-concentration version of the medication, this new version will help provide an alternative for people who are prescribed Humira. According to rheumatologist Joseph R. Martinez, MD, "The FDA approval of Hadlima adds to the growing list of treatment options accessible to patients with certain autoimmune conditions. Patients can discuss this treatment option with their rheumatologist and decide if this is a good choice for them."

The citrate-free component of this medication is one of the critical factors, ideally making this feature more available to consumers. "The citrate-free version of Humira has been effective in treating inflammatory symptoms of arthritis types without the side effects of the initial drug," explained Nancy Mitchell, a registered nurse and contributing writer at *Assisted Living*. "Originally, senior patients taking Humira complained of experiencing discomfort, possibly due to the citrate buffer in the serum. The citrate worked to maintain optimum pH levels and, in turn, preserve the shelf life and viability of the drug. Some studies have shown a slight correlation between citrates in synovial fluid and inflammation in the joints."

Samsung Bioepsis will begin preparing to launch Hadlima, which will take place in the United States on or after July 1, 2023, in accordance with a licensing agreement with AbbVie Inc., the maker of Humira (adalimumab). ❖

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Research

Study Finds Universal Influenza B Vaccine Induces Broad and Lasting Protection

A study by researchers at Georgia State University's Institute of Biomedical Sciences has found a new universal flu vaccine has been found to protect against influenza B viruses that offer broad defenses against different strains and improve immune protection. The double-layered protein nanoparticle vaccine, constructed with a stabilized portion of the influenza virus (the hemagglutinin [HA] stalk), induces broadly reactive immune responses and conferred robust and sustained cross-immune protection against influenza B virus strains of both lineages.

Influenza B has two lineages that are genetically distinct and trigger different immune responses. And, since seasonal flu vaccines are developed with one or both lineages of influenza B viruses, they're limited by the ability to circulate strains to escape the immune system or vaccination, often making these vaccines ineffective because the variable portion of the influenza virus (the HA head) evolves. As a result, seasonal influenza vaccines need to be reformulated and updated frequently. To overcome these limitations, a universal influenza vaccine containing conserved parts of the virus and providing substantial broad cross-protection against diverse virus strains is needed.

"In this study, we generated structure-stabilized HA stalk antigens from influenza B and fabricated double-layered protein nanoparticles as universal influenza B vaccine candidates," said Baozhong Wang, PhD, senior author of the study and distinguished university professor in the Institute for Biomedical Sciences at Georgia State University. "We found that layered protein nanoparticles incorporated with structure-stabilized constant antigens have potential as a universal influenza vaccine with improved immune protective potency and breadth."

The nanoparticle vaccine was tested in cell culture and in mice. Studies in cell culture found the protein nanoparticles were effectively taken up to activate dendritic cells that are critical for inducing protective immune responses against pathogens. The vaccine was found to be safe, biocompatible, biodegradable and highly immunogenic in animals.

"Our next aim is to combine the influenza A nanoparticles from our previous study with the influenza B nanoparticles we have fabricated and tested here to create a multivalent universal influenza nanoparticle vaccine against both influenza A and B," Dr. Wang said. ❖

Study Finds Universal Influenza B Vaccine That Induces Broad and Lasting Protection. The Print, July 9, 2022. Accessed at theprint.in/science/study-finds-universal-influenza-b-vaccine-that-induces-broad-and-lasting-protection/1032606.

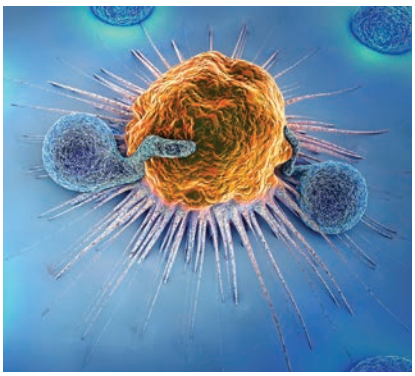
Research

TIL Therapy Found More Effective for Metastatic Melanoma Than Current Treatments

A Phase III clinical trial has found tumor-infiltrating lymphocyte (TIL) therapy, a new treatment for advanced melanoma, was more effective than ipilimumab, the leading existing therapy. The randomized, controlled study shows for the first time that cell therapy can be efficacious and beneficial for patients with solid cancers. "For patients with melanoma, we see a 50 percent reduction in the chance of progression of the disease or dying from the disease, which is absolutely practice-changing," said John Haanen, MD, PhD, who is associated with the Netherlands Cancer Institute in Amsterdam and lead author of the clinical trial.

In the trial, 168 people with metastatic melanoma were randomly assigned to receive either TIL treatment or ipilimumab. Ipilimumab is typically used in people who don't respond to a first-line treatment called anti-PD-1 therapy. Nearly all of the participants in the trial had not responded to that treatment. After following the patients for a median of almost three years, the researchers found that patients on TIL therapy had a 49 percent reduction in disease progression and death compared to 21 percent for people taking ipilimumab. The study participants are reportedly still being tracked, but the median overall time of survival for people who received TIL therapy was more than two years compared to slightly more than 1.5 years for those receiving ipilimumab.

TIL therapy is not widely known by the public and has not yet been approved by the U.S. Food and Drug Administration. However, it has been researched for several years in clinical trials and there has been much anticipation about its potential. TIL therapy is somewhat similar to CAR-T cell therapy, a recently developed immunotherapy treatment, but TIL therapy involves encouraging immune cells to multiply, as opposed to strengthening them. ❖



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Vaccines

First Malaria Vaccine Prequalified by WHO

The World Health Organization (WHO) has prequalified the first malaria vaccine, RTS,S/AS01 (also known as Mosquirix), manufactured by GSK, bringing it closer to reaching millions more children at risk of malaria. The vaccine, which is recommended for use among children living in areas of moderate to high P. falciparum malaria transmission, has already been given to more than one million children through pilot implementation that began in 2019 in areas of Ghana, Kenya and Malawi.

"Prequalification of the first malaria vaccine is a major advancement for child health," said Ashley Birkett, PhD, global head for Malaria Vaccines and Biologics at PATH. "Prequalification further demonstrates WHO's confidence in the safety, effectiveness and quality of the vaccine for African countries who are considering adding it to their immunization programs. A vaccine has been a missing piece of the malaria toolkit for a long time and could save tens of thousands of young lives every year, on top of existing malaria interventions."

WHO prequalification is a critical step toward expanding access to the vaccine. This designation allows UNICEF to purchase the vaccine, and Gavi, the Vaccine Alliance is ready to provide financial assistance to eligible countries to introduce the vaccine. Gavi recently opened a $155.7 million funding window to support the introduction of malaria vaccines between 2022 and 2025. Gavi-eligible countries can apply for support when a funding window opens toward the end of 2022 and closes in January 2023. ❖

PATH Welcomes WHO Prequalification of the First Malaria Vaccine. Malaria Vaccine Initiative, Sept. 6, 2022. Accessed at www.malariavaccine.org/news-events/news/path-welcomes-who-prequalification-first-malaria-vaccine.

Vaccines

Regen BioPharma Files Patent for mRNA Cancer Vaccine

Regen BioPharma has filed a provisional patent application covering utilization of dendritic cell technologies to augment efficacy of its patented survivin mRNA cancer immunotherapeutic vaccine. In 2021, the company was granted a patent on composition of matter of survivin modified-mRNA useful for teaching the immune system to kill cancer. That patent covered specific types of dendritic cells, means of generating specialized dendritic cells and the planned formulation that will enter clinical trials.

"We are proud of our collaborators and colleagues who have worked on our first issued survivin patent, which was filed in 2015, before the world realized the potency of modified-mRNA technology that was first successfully commercialized with the COVID-19 vaccines by Moderna and Pfizer," said David Koos, PhD, DBA, CEO, and chairman of Regen BioPharma. "The currently filed application discloses means of significantly increasing efficacy by combining modified-mRNA with unique cellular immunotherapy, as well as adjuvant approaches. We chose this strategy to maximally protect our intellectual property around this potentially very valuable mRNA cancer immunotherapy vaccine."

Immunotherapy of cancer represents a large market that is currently being led by the class of drugs called "checkpoint inhibitors" and "CAR-T" cells. To date, there is no mRNA immunotherapy available for treating cancer. ❖

Regen BioPharma, Inc. Files Provisional Patent Application on Second Generation Survivin mRNA Cancer Immunotherapy Vaccine. Regen BioPharma press release, July 26, 2022. Accessed at www.prnewswire.com/news-releases/regen-biopharma-inc--files-provisional-patent--application-on-second-generation-survivin-mrna-cancer-immunotherapy-vaccine-301593795.html.

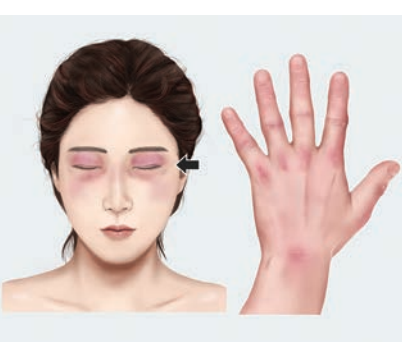
Research

Study Finds IVIG Effective for Treating Dermatomyositis

A study evaluating intravenous immune globulin (IVIG) for the treatment of dermatomyositis has found it significantly improved patient outcomes.

In the 16-week study involving adults with dermatomyositis, 95 patients were assigned in a 1:1 ratio to receive IVIG at a dose of 2.0 grams per kilogram of body weight or placebo every four weeks for 16 weeks. The patients who received placebo and those without confirmed clinical deterioration while receiving IVIG could enter an open-label extension phase for another 24 weeks. The primary end point was a response defined as a Total Improvement Score (TIS) of at least 20 (indicating at least minimal improvement) at week 16 and no confirmed deterioration up to week 16. The TIS is a weighted composite score reflecting the change in a core set of six measures of myositis activity over time; scores range from 0 to 100, with higher scores indicating greater improvement. Key secondary end points included at least moderate improvement (TIS ≥40) and major improvement (TIS ≥60), and change in score on the Cutaneous Dermatomyositis Disease Area and Severity Index.

Forty-seven patients were assigned to the IVIG group and 48 to the placebo group. At 16 weeks, 79 percent of the patients in the IVIG group (37 of 47) and 44 percent of those in the placebo group (21 of 48) had a TIS of at least 20. The results with respect to the secondary end points, including at least moderate improvement and major improvement, were generally in the same direction as the results of the primary end-point analysis, except for the change in creatine kinase level (an individual core measure of the TIS), which did not differ meaningfully between the two groups. Over 40 weeks, 282 treatment-related adverse events occurred in the IVIG group, including headache (42 percent of patients), pyrexia (19 percent) and nausea (16 percent). A total of nine serious adverse events that were considered to be related to IVIG occurred, including six thromboembolic events. ❖



Aggarwal, R, Charles-Schoeman, C, Schessl, J, et al. Trial of Intravenous Immune Globulin in Dermatomyositis. *The New England Journal of Medicine*, Oct. 6, 2022. Accessed at www.nejm.org/doi/full/10.1056/NEJMoa2117912?query=featured_home.

Medicines

First Once-Daily Oral Plaque Psoriasis Drug Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved Sotyktu (deucravacitinib), a once-daily oral pill by Bristol Myers Squibb, for adults who have plaque psoriasis (a chronic, systemic, immune-mediated disease) severe enough to make them candidates for systemic therapy and phototherapy. Sotyktu is the first oral treatment for plaque psoriasis that can be taken just once daily and the first oral medication approved for the disease in a decade.

FDA approved the drug based on two clinical trials comparing Sotyktu to Otezla in nearly 1,700 adults with a mean age of 46 years. Participants all had moderate to severe plaque psoriasis and, on average, they experienced psoriasis for 17 years on a quarter of their bodies. More than one-fifth had clinically severe psoriasis, and nearly 40 percent had used biological therapies to control their condition.

In the trials, one group of participants took a six milligram tablet of Sotyktu once per day, while other participants took 30 milligrams of Otezla twice daily or received a placebo. By month four, nearly 60 percent of patients achieved a meaningful benchmark: Psoriasis Area and Severity Index (PASI) 75, a measurement indicating 75 percent improvement in the amount of skin surface area covered by plaques. In comparison, fewer than 13 percent in the placebo group and 35 percent in the Otezla group reached PASI 75. Additionally, plaques cleared or nearly cleared in more than half of the people treated with Sotyktu, in contrast to only about seven percent of those in the control group. And, patients who took Sotyktu continued to improve over time. After six months of treatment, 69 percent reached PASI 75 compared with 38 percent of those who took Otezla.

Unlike existing treatment for this population, Sotyktu doesn't require laboratory follow-up and seems to be well-tolerated, said April Armstrong, MD, MPH, professor of dermatology and associate dean of clinical research at the University of Southern California, who led the clinical trials. "This is a breakthrough medication and, in my opinion, this drug will be the leading oral agent for our patients with psoriasis because of its robust efficacy and good safety profile. I'm very excited to talk to my patients about this drug."

Sotyktu is the first to target tyrosine kinase 2 (TYK2), an enzyme that is linked to susceptibility for psoriasis. TYK2 is a member of the Janus kinase (JAK) family. Many treatments for autoimmune disorders target JAKs, but most JAK inhibitors don't do much to affect TYK2. By blocking this specific enzyme, the drug interrupts some of the cellular processes that are key for forming psoriatic lesions. Plus, a TYK2 inhibitor drug could be safer because it has a narrow target compared to other JAK inhibitors, which can have a broad effect on the immune system. "By having more specific targeting of the pathways that are involved in psoriasis, we avoid essentially hitting the other pathways that are important for our normal human functions," Dr. Armstrong said. These include the effects on blood cell counts, lipid and other types of metabolism, and other types of immunity.

Sotyktu works similarly to the widely-used psoriasis biologic agent Stelara (ustekinumab), but that drug is a monoclonal antibody that needs to be injected in a hospital setting. Sotyktu, on the other hand, comes as an oral pill that patients can easily take at home or while traveling. ❖

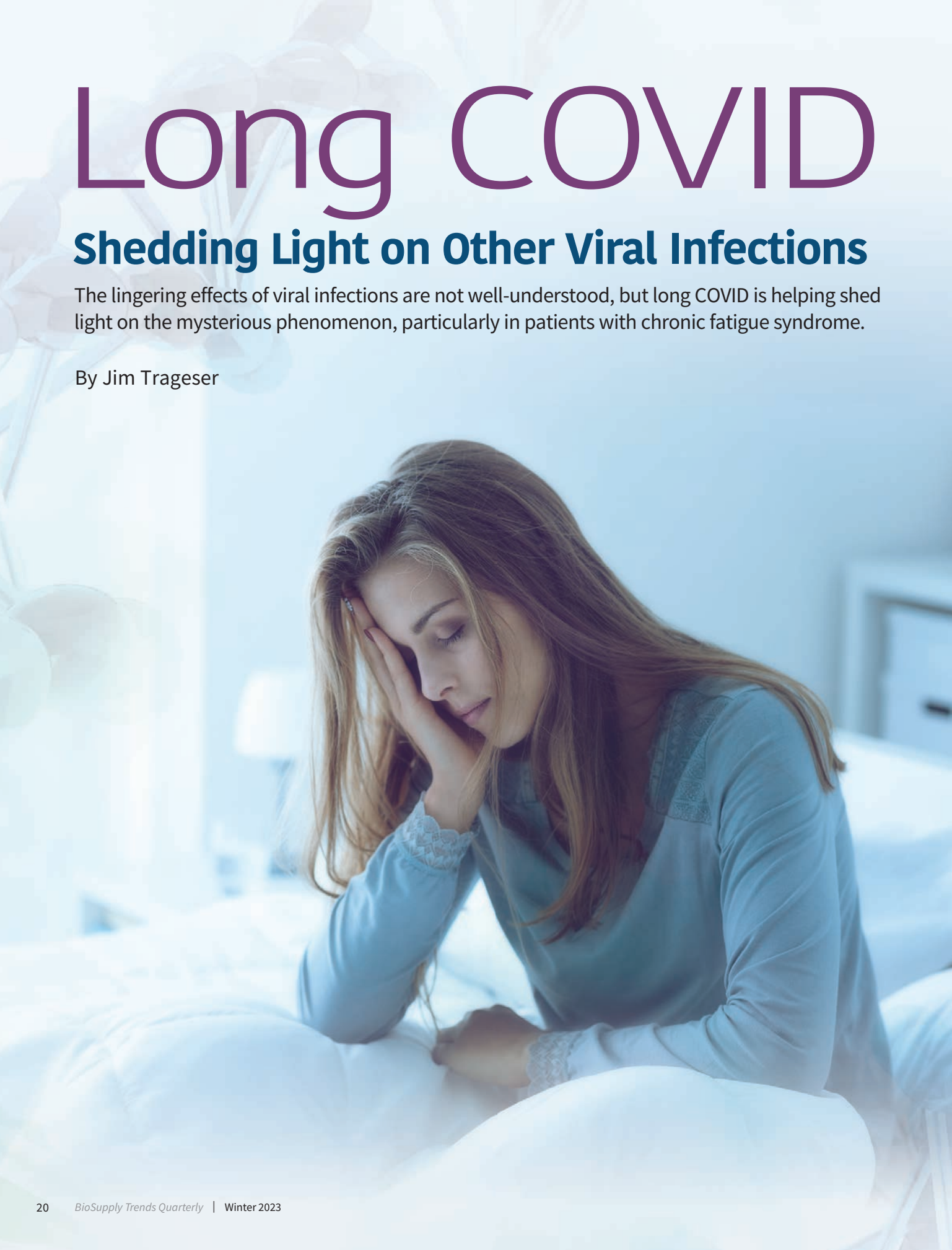
Mercer, H. FDA Approves First Once-Daily Oral Plaque Psoriasis Drug. VeryWell Health, Sept. 18, 2022. Accessed at www.verywellhealth.com/fda-approves-first-once-daily-oral-plaque-psoriasis-drug-6735912.

Long COVID

Shedding Light on Other Viral Infections

The lingering effects of viral infections are not well-understood, but long COVID is helping shed light on the mysterious phenomenon, particularly in patients with chronic fatigue syndrome.

By Jim Trageser



FOR MANY lay people, "long COVID" is the first introduction to a condition caused by a previous infection that has run its course, a condition that lingers indefinitely without an easily identifiable cause and no single test to make a diagnosis. However, among doctors with experience treating myalgic encephalomyelitis (ME), commonly known as chronic fatigue syndrome (CFS), the emergence of long COVID was an "aha" moment.

For decades, a small but committed number of physicians treating patients suffering from ME/CFS have struggled to get their patients' conditions taken seriously by the larger medical establishment and insurers. Originally dismissed as "yuppie flu"[1] and written off by many as a psychological disorder, the few doctors who did treat ME/CFS suspected the condition was likely the aftereffect of a previous viral infection.

The symptoms of long COVID are remarkably similar to those of ME/CFS, with many overlapping. They include post-exertion fatigue, lingering low-grade fever, decreased mental acuity, joint and/or muscle pain, depression and anxiety, digestive issues and dry cough.[2] While symptoms of ME/CFS mimic common infectious diseases like influenza or a cold, they tend to be more severe, even debilitating, so much so that patients whose symptoms interfere with daily life are motivated to continue to seek medical help after repeatedly being told nothing is wrong with them. Under existing protocols, a patient had to have these symptoms for six months to be diagnosed with ME/CFS.[3]

While our studies of long COVID are understandably still in their infancy, one difference between long COVID and ME/CFS is already being noted: Since physicians are more likely to know if a patient has previously contracted COVID-19, even mild symptoms of long COVID are taken seriously, but while the cause of ME/CFS was not — and still is not — known, patients suffering from it are often told nothing is wrong with them.

Historically, there has been little interest in conducting research into ME/CFS, and not much more interest in treating it. (A recent article in *The Atlantic* noted that only about a dozen physicians attended a 2018 conference intended to found a coalition supporting ME/CFS treatment and research.[4])

Contributing to the widespread indifference to ME/CFS is the fact that too many physicians had been taught in medical school that "there has to be an antigen [such as a viral protein] in the system to drive the immune system to make it create sickness, and the immune system should shut off when it's done," as Nancy G. Klimas, MD, director of the Institute for Neuro-Immune Medicine at Nova Southeastern University in Miami put it in a recent interview.[5] Yet in a mere two years, the notion that a viral infection can continue to cause significant, even severe, side effects long after the infection has ended has become broadly accepted, thanks to the avalanche of evidence regarding long COVID. The rise of long COVID is triggering a reexamination of other cases in which patients have presented with seemingly inexplicable symptoms to see if there are more post-acute infection syndromes (PAISs) than had previously been suspected.

While it is too early in the research process to know what will be discovered, it may very well turn out that rather than being an outlier, long COVID is instead a typical post-infection side effect that has mostly gone undetected (and untreated) until now.

A Brief History of PAISs

The history of PAISs is both historic and heavily tilted toward the recent.

In 1750, Sir Richard Manningham described a condition similar to what we know as ME/CFS that he termed "febriclua," meaning "little fever." Modern researchers now believe that it is likely that both Florence Nightingale and Charles Darwin suffered from it.[6]

Since physicians are more likely to know if a patient has previously contracted COVID-19, even mild symptoms of long COVID are taken seriously, but while the cause of ME/CFS was not — and still is not — known, patients suffering from it are often told nothing is wrong with them.

By the late 1800s, the condition was observed that patients who contracted polio could relapse years — even decades — later, with no sign of a renewed infection and without being contagious. In 1934, staff members at Los Angeles County Hospital exhibited symptoms consistent with ME/CFS. At the time, it was attributed to a variant of polio. Just 21 years later, a similar outbreak

occurred among staff at the Royal Free Hospital in London. Post-poliomyelitis syndrome (PPS) was only recognized as an accepted medical condition in 1980, but even today elderly patients who had polio before widespread vaccination was adopted in the 1950s can develop PPS.[7]

But the symptoms of PPS were fairly similar to the symptoms of polio itself, so making the connection between the poliovirus and PPS was a fairly straightforward process. Trying to determine the cause of, or even argue for the existence of other PAISs, has been more of a struggle.

The rise of long COVID is triggering a reexamination of other cases in which patients have presented with seemingly inexplicable symptoms to see if there are more post-acute infection syndromes than had previously been suspected.

The medical establishment's current relationship with PAISs likely began on the shores of Lake Tahoe in 1984 when two physicians noticed an outbreak of what they originally diagnosed as influenza, yet the patients didn't seem to recover even as weeks and months passed. The patients exhibited a spectrum of symptoms, but common ones were debilitating fatigue that worsened with physical or mental exertion and difficulty sleeping and concentrating. They showed no signs of a current infection, and their physiological test results were normal.

While many of the patients tested positive for antibodies for the Epstein-Barr virus (the virus that causes mononucleosis), most of the patients were adults, and outbreaks of adult-onset mononucleosis are extremely rare. So, the two physicians asked for assistance from the Centers for Disease Control and Prevention (CDC).[1] CDC dispatched a team that determined the Epstein-Barr antibody levels weren't out of the anticipated range for adults who had previously been exposed. High antibody counts for other viruses in the herpes family were also found in some patients, but not in others.

Two years later, a strikingly similar outbreak occurred on the shores of Lake Ontario in New York state, this time affecting mostly children. Again, tests were unable to uncover consistent results across all patients, so the mystery only deepened.

As more and more cases were reported by physicians across the United States, as well as in Canada and Great Britain, CDC finally added CFS to its list of official diseases in 1988 — but no one was any closer to understanding what exactly it is, much less what causes it.

Since then, other PAISs have been identified, including post-dengue fatigue syndrome (PDFS),[8] post-Ebola syndrome (PES)[9] and post-chikungunya chronic inflammatory rheumatism.[10]

The Arrival of Long COVID

Within the first year of the COVID-19 pandemic, physicians and researchers noted that some patients who had contracted COVID-19 — even some who were asymptomatic — were exhibiting lingering symptoms months after they were testing negative for an active infection with the SARS CoV-2 virus.[11] Symptoms primarily included lingering fever, fatigue and cough.

But nearly three years later, even though long COVID is now accepted as a real condition, it nevertheless remains somewhat fuzzy and undefined. As Avindra Nath, MD, clinical director of the National Institute of Neurological Disorders and Stroke, part of the U.S. National Institutes of Health, put it recently, "There is no good definition of long COVID, and people define it differently."

Dr. Nath pointed out that the volume of COVID-19 patients, and the similarities to ME/CFS, have made this a unique opportunity to try to learn more about how the immune system reacts to viral infections and how those reactions can continue to impact patient health even after the infection has abated. He is now heading up a clinical study for the U.S. government to try to answer some basic questions regarding both long COVID and ME/CFS. "People with ME/CFS have been saying for decades that they develop a constellation of persistent new symptoms following some kind of infection. They go to doctors, and they often cannot find anything abnormal. Every test comes back normal. The patients are very frustrated and often say, 'You think that this is all in my head? This is real. I was perfectly fine before this happened. And now my life is devastated.'"[12]

Both sides remain frustrated. "The doctors are frustrated because they don't know what is wrong with the patient, and the patients are frustrated because they think the doctor doesn't believe their symptoms," explains Dr. Nath. "So ME/CFS kind of lingers out there in no-man's land."[12]

With regard to COVID-19 and the myriad of people it's affecting, Dr. Nath

observes, "If other infections trigger ME/CFS, then you would think that COVID-19 would surely do it too. And it is true that many of the symptoms that we see in long COVID patients are similar to what we see in ME/CFS patients as well. There is substantial overlap between the two conditions. All clinical studies of long COVID patients would be relevant to ME/CFS."[12]

Getting Answers

Now that long COVID is being studied with the kind of resources of which advocates for ME/CFS could have only dreamed, some researchers are also looking at other viral infections to see if they could be responsible for other PAISs — or to perhaps identify the virus or viruses responsible for ME/CFS.[13]

With nearly one-fifth of all COVID-19 patients developing some level of long COVID, the number of people suffering from a PAIS is obviously increasing dramatically.[14] And since doctors can test for a previous SARS-CoV-2 infection, there is a control here that was previously not available, since doctors didn't even know which virus to test for when studying ME/CFS.

Researchers are looking into two areas right now for long COVID: What are the specific triggers that cause some patients to develop long COVID, and what treatment regimens are most effective? A parallel line of research as outlined by Dr. Nath is trying to determine the cause of ME/CFS. In fact, even before the COVID-19 pandemic, research was slowly proceeding into ME/CFS.

One pre-pandemic study out of Norway looked at the influenza virus as a possible cause of ME/CFS, specifically looking into whether the flu vaccine could be causing it. The study found that although there was no evidence to suggest the vaccine increased the odds of developing ME/CFS, it did find that H1N1, the dominant influenza strain in 2009, was associated with an increase in ME/CFS.[15] While not providing a definitive causative link, the study did provide hard evidence for the notion that ME/CFS is a post-viral condition and identified one likely culprit. CDC also notes that there is a correlation between Epstein-Barr virus and ME/CFS, as well as Q fever, a disease caused by the agricultural bacteria Coxiella burnetii.[16]

One concern for those who treat, study and support patients with ME/CFS is that the first federal bill to provide funding for long COVID research did not include language directing ME/CFS to be part of the studies. Advocates are now working with members of Congress in both houses to try to insert new language into a second bill now making its way through the legislative process, so that at least a portion of the allocation would go toward ME/CFS research.[5]

Looking Ahead

The existence of PAISs is no longer questioned — neither their existence, nor the importance of learning more about them.

Whether or not Congress specifically funds new research into ME/CFS, the rapid expansion of research into long COVID will definitely have a spillover effect. There are currently 306 studies examining long COVID, another 37 examining post-COVID-19 syndrome and 149 studies evaluating ME/CFS listed on clinicaltrials.gov. That number would have been unthinkable just three years ago.

With an estimated 146 million Americans having had COVID-19, and one-fifth of those likely to develop long COVID symptoms, there will not be a general practitioner in this country who won't see a patient for the condition.[17]

While those suffering from ME/CFS wouldn't wish their symptoms on anyone and have more sympathy for people with long COVID than anyone else possibly can, they are undoubtedly relieved that moving forward they will never again have to try to convince their physician or insurance carrier that their disease is real, or that any other patient suffering from a PAIS will face the kind of doubtful response from clinicians as they did. ❖

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Addressing the Mental Health Crisis in Children

The pandemic made a troubling mental health trend in children much worse. What's being done to help them?

By Trudie Mitschang

WHEN MILLIS PUBLIC SCHOOLS in Boston reopened its doors for the 2021-22 school year, teachers and staff were excited to see students back in real classrooms. Within weeks, that excitement quickly shifted to concern as students presented with noticeable and troubling signs of mental and emotional stress.[1] "From the beginning, we've seen elevated levels of stress, anxiety and different behavioral issues in students," said Bob Mullaney, the superintendent of the suburban Boston school district. Of course, Mullaney's district is far from alone when it comes to dealing with unprecedented mental health challenges in student populations. According to staff, pediatricians and mental healthcare workers, K-12 schools across the country have been overwhelmed by students struggling with a range of mental health symptoms. Not only has this surge made the return to classrooms more challenging for educators, it's also taxing an already strained healthcare system in the United States.

A Pre-Pandemic Concern Escalates to a National Emergency

The rise in children's mental health symptoms didn't start in 2020: It's a problem years in the making. Studies indicate that the pandemic exacerbated an already growing crisis in youth mental health. The Centers for Disease Control and Prevention (CDC) states that one in five teenagers in the United States has experienced an episode of major depression at some point, according to data collected between 2013 and 2019. The findings were pulled from nine federal surveillance systems of children's mental health, including the National Health and Nutrition Examination Survey, the National Survey on Drug Use and Health and the Youth Risk Behavior Survey. "The fact that this report precedes the pandemic is stunning," said Richard

Besser, MD, pediatrician and the president of the Robert Wood Johnson Foundation. "What it says to me is that this is a dramatic underestimation in terms of how significant this crisis truly is."[2]

CDC data also show that the proportion of mental health emergency visits for kids began going up very early in the pandemic, and by the fall of 2020, the American Academy of Pediatrics (AAP), the Children's Hospital Association (CHA) and the American Academy of Child and Adolescent Psychiatry (AACAP) declared an emergency in child and adolescent mental health.[3] The incidents have continued to escalate. According to CHA, there were more than 47,000 mental health visits to emergency departments at 38 children's hospitals around the country in the first three quarters of 2021 — nearly 40 percent higher than the same period in 2020.[4]

Increased Violence and Self-Harm

In the Millis school district, Mullaney notes that fights among students have risen at an alarming rate, while there have also been reports of violence against those in authority. A school principal in Massachusetts, for example, was assaulted by a student, and other schools in his district have had staff members assaulted by students.[1]

Sadly, many students are also resorting to hurting themselves. Based on data from nearly 40 children's hospitals around the country, there were 14,630 emergency room visits for children aged 5 years to 18 years between January and September of 2021. "Unfortunately, younger children are experiencing higher rates of this than they have in the past," said Amy Knight, president of CHA, who moderated a congressional briefing on the youth mental health crisis.[5]

Again, while the pandemic certainly put a magnifying glass on childhood mental health crises, it's a concern that has been simmering for over a decade. Alexandre T. Rotta, MD, division chief of pediatric critical care medicine at University Hospitals Rainbow Babies and Children's Hospital and senior author of a recent study, analyzed data from the Nationwide Emergency Department Sample database for years 2008 through 2013. Dr. Rotta and his team hoped to characterize the magnitude of the problem and spot any trends in the number of children and adolescents being treated for deliberate self-harm. "We found a slight decrease in the number of emergency department visits in the usual self-harm group — the 16- to 19-year-old age group over the six-year study period," Dr. Rotta says. "But the 13- to 15-year-old group had a 45 percent increase in visits for self-harm. For children 11 to 12 years old, the increase was 94 percent."[6]

The *Journal of Clinical Pediatrics* adds, "Historically, it was thought that children in this age group could not develop the concept of the finality of death. It was believed that due to their concrete operational thinking patterns, this age group could not estimate the lethality or outcomes of their self-destructive acts. With more research focus and attention being paid to the pediatric population as a whole with regard to suicide and self-harm, it has been suggested that even children this young can exhibit suicidal behavior and thinking."[6]

The Cry for a National Agenda

Stakeholders at all levels of public health are recognizing the need for a national agenda to address mental health issues in children and adolescents. In his March 2022 State of the Union address, President Joe Biden laid out a national strategy to tackle our nation's mental health crisis. As the administration implements a whole-of-government strategy to transform mental health services for all Americans, one of the key goals is to ensure all children and families have easy, affordable and equitable access to the care, support and services they need, including $35 million in funding opportunities to strengthen and expand community mental health services and suicide prevention programs for America's children and young adults.[7] "As the President made clear in the State of the Union, children's mental health needs are a national priority," said Health Resources and Services Administration (HRSA) Administrator Carole Johnson. "At [HRSA], we are answering [President

Biden's] call by focusing on expanding pediatric mental health services, training more mental healthcare providers and making mental health a key part of primary care to ensure that children get the quality care they need and deserve."

There are also some notable ways psychologists are working to address students' mental health challenges. By bringing mental health into the classroom, the American Rescue Plan Act, passed in March 2021, included $170 billion for school funding, and many schools used the funding to hire mental health workers, including psychologists.[8]

Other federal and state funding is being allocated toward training more psychologists. For example, Nevada State College received funding to create a new program to train school mental health clinicians, including psychologists.

While the field of psychology recognizes a shortage of mental health services for kids, addressing those needs may not be a realistic solution until the workforce grows. "Relying on temporary funding to hire permanent staff isn't financially sustainable for lower-income districts," said Kenneth Polishchuk, senior director for congressional and federal relations at the American Psychological Association (APA). As a result, Polishchuk said, many schools are hiring mental health providers on a short-term basis, as well as taking a preventive approach that trains teachers in psychology principles.[8]

"Psychologists in some districts are training teachers in basic social and emotional skills to help students cope with stress and anxiety in real time," said Kathryn H. Howell, PhD, associate professor of child and family psychology at the University of Memphis and chair-elect of APA's Committee on Children, Youth and Families. Dr. Howell said equipping kids with coping skills in the classroom can prevent strain on school psychologists while also improving students' ability to learn. "As psychologists, we don't just want to bring in interventions that only we as experts can deliver," Dr. Howell said. "We need to make it sustainable by teaching those on the frontlines how to equip kids with the skills they need to thrive."[8]

Trauma Training in the Classroom Setting

To address mental health symptoms in the student populations, some teachers are incorporating formal mental health lessons into their curriculum with help from psychologists. New York state requires basic mental health education in health classes, and Peter Faustino, PsyD, a school psychologist in Scarsdale, N.Y., said he's been receiving requests from teachers for help incorporating pandemic-relevant topics like anxiety, trauma and warning signs of suicide into their classes. Other schools, he said, are investing in social and emotional health training programs for staff such as Yale University's Ruler Program, which teaches school leaders and teachers how to equip students with emotional intelligence skills.[9]

Along with more minor mental and behavioral health concerns, teachers are also facing an unprecedented number of students with trauma, said Laurie McGarry Klose, PhD, president of the National Association of School Psychologists and director of the School Psychology Program at Trinity University in San Antonio, Texas. Studies show that roughly half of American school children have experienced at least some form of trauma, from neglect to abuse and violence. In response, educators often find themselves having to take on the role of counselors, supporting the emotional healing of their students, not just their academic growth.[10]

It's not surprising that many teachers don't feel equipped to handle their students' struggles. A 2020 survey by the

New York Life Foundation and American Federation of Teachers found that only 15 percent of educators said they felt comfortable addressing grief or trauma tied to the pandemic.[11]

As a result, psychologists are finding new ways to share their expertise with school personnel. For example, Samuel Song, PhD, a professor of school psychology at the University of Nevada, Las Vegas, is working on a grant with colleagues to deliver a four-part web-based curriculum on trauma-informed practices. Programs like this can help teachers identify signs of trauma in students and also cope with their own trauma, which Dr. Klose says are equally important. Teachers are more likely to dismiss trauma-driven behaviors as belligerence when they're under strain, so with proper resources and training, they can better identify kids who are struggling and route them to appropriate support services within the school system.[10]

Another resource titled Mental Health Primers was developed by the Coalition for Psychology in Schools and Education. This topical-based resource identifies mental health symptoms in children based on specific scenarios and potential triggers. It also provides information for teachers to identify behaviors in the classroom that are symptomatic of mental health and other psychological issues, with the goal of directing teachers to access appropriate resources for their students.[12]

A Multipronged Approach for Lasting Change

Whether kids are facing trauma because of child abuse, loss of a family member or everyday anxiety about the pandemic, they need even more support now — all amid a significant shortage of children's mental health resources.

AAP, AACAP and CHA universally acknowledge that the challenges facing children and adolescents are so widespread that policymakers at all levels of government and advocates for children and adolescents are tasked with working together to create sustainable support systems and lasting change.[3] Proposals for change include:

- Increasing federal funding dedicated to ensuring all families and children, from infancy through adolescence, can access evidence-based mental health screening, diagnosis and treatment, with particular emphasis on under-resourced populations.
- Addressing regulatory challenges and improving access to technology to assure continued availability of telemedicine mental health services to all populations.
- Increasing sustainable funding for and implementation of effective models of school-based mental healthcare, including clinical strategies and models for payment.
- Accelerating adoption of effective and financially sustainable models of integrated mental healthcare in primary care pediatrics.
- Strengthening efforts to reduce the risk of suicide in children and adolescents through prevention programs in schools, primary care and community settings.
- Fully funding comprehensive, community-based systems of care that connect families in need of behavioral health services and supports for their child with evidence-based interventions.
- Advancing policies that ensure compliance with and enforcement of mental health parity laws.

"We know one-on-one therapy won't be possible for every kid who's struggling, so we need a multipronged approach to help build the capacity of teachers and staff to support kids in the classroom setting," said Melissa Pearrow, PhD, a professor of counseling and school psychology at the University of Massachusetts, Boston.[8]

At a national level, awareness of the issues has been acknowledged, and as new laws continue to go into effect, stakeholders at all levels are committed to finding new ways to address children's mental health, not only for their own well-being but for the future success of society as a whole. "It's not only the right thing to do to make sure people can have as full a life as they possibly can," said Alan Leshner, PhD, the former director of the National Institute on Drug Abuse and former deputy and acting director of the National Institute of Mental Health. "Young people are critical to the future of society, so it's in society's interest to make sure we don't lose the talent youth could contribute to a set of problems that can be alleviated."[8] ❖

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How FDA's Risk Management Program Can Help Prevent or Lessen Future Drug Shortages

By Amy Scanlin, MS

Preparation and communication are key for mitigating the problems of a pinched drug supply and maintaining access to essential medications.

THE SEVERE CONSEQUENCES of drug shortages played out on an international and public stage during the COVID-19 public health emergency (PHE). Yet, combating drug shortages has been a focus of both regulators and the medical industry for decades.

Drug shortages impact every level of healthcare: They cause delays in patient care, lead to the use of alternative and potentially less safe and effective medicines, and divert clinicians' attention when searching for drug alternatives. Patients have unknowingly and increasingly become vulnerable to a global drug supply chain.

This global supply chain has grown longer and more complex, with many raw materials, in-process goods and even finished goods produced overseas before being imported to the United States. Regulatory constraints intended to ensure a minimum quality standard also contribute to the drug supply challenge through bureaucratic roadblocks that slow the ability to pivot as alternatives are assessed when drug production is in crisis. Add to that a pricing structure that incentivizes low-cost drugs over innovation, and an industry that needs to flex in a time of crisis instead tends to sputter before it regroups and responds.

A recent U.S. Food and Drug Administration (FDA) guidance document outlines risk management programs (RMPs) intended to help combat future drug shortages by providing a framework with which stakeholders can assess risk and make plans to mitigate them. Though nonbinding, guidance documents share FDA's current thinking and recommendations for best practices.

Drug Shortages Are Everyone's Problem

The cost of drug shortages is enormous — for everyone, at every level — because they typically result in higher price points, making drug products more expensive for patients, providers and taxpayers. Drug substitutes also become more expensive thanks to increased demand. A 2019 report from the American Hospital Association, the Federation of American Hospitals and the American Society of Health-System Pharmacists found that almost 80 percent of hospitals see moderate to large increases in spending when drugs are in short supply,[1] amounting to $359 million each year in labor and $200 million attributed to substituting alternative drugs for those in short supply. Though staggering, these numbers may actually be underreported. Quantifying additional staff, rescheduled procedures, updating technology and patient burdens cannot be reasonably assessed. For instance, substituting a formulary drug with a nonformulary alternative requires multiple additional steps, including the creation of a new physician order, preparation and administration of the drug by pharmacists and nurses, as well as development of designed algorithms of its pharmacologic and pharmacokinetic properties to successfully implement mitigation strategies.[2]

It should be noted that patients with only one drug option such as those with rare diseases are particularly vulnerable to drug shortages.[3] During the pandemic, two examples of drug shortages that have since been resolved were hydroxychloroquine and chloroquine, which are both used in the management of many autoimmune diseases. However, other shortages lingered, including drugs that treat heart disease and blood clots. In fact, a number of drugs that were in short supply are used in the treatment for many of the top-five causes of death (heart disease, cancer, unintentional injuries, chronic lower respiratory diseases and stroke). Drug shortages and adverse events from drug substitutions can negatively impact mortality rates.[4]

Drug Shortages to Date

In 2012, with the enactment of the Food and Drug Administration Safety and Innovation Act, Congress empowered FDA with tools that enabled the agency to work in collaboration with industry to prevent or mitigate drug supply disruptions and drug shortages. It also clarified current good manufacturing practice requirements relevant to oversight and controls of drug manufacturing quality. That focus honed in on quality issues as a common reason for supply chain shortages. FDA encouraged the industry to develop a long-term solution after a peak in drug shortages in 2011.[5] Drug shortages then began a downward decline with low points reached in both 2015 and 2016 before beginning to again increase. Since 2018, the number of new drug shortages has remained steady, according to FDA; however they have grown more persistent due to lengthier active drug shortages. However, by mid-2020, during the COVID-19 PHE, the number of drug shortages amounted to 87 percent of the entire preceding year.[4]

Though quality issues certainly contribute significantly to drug shortages, natural disasters, discontinuation of components by suppliers, poor forecasting for future drug needs, cyber attacks against drug manufacturers and market withdrawals all can have an impact, too. The drug industry needs an improved plan of action.

Implementation of the CARES Act and RMPs

With the passage of the Coronavirus Aid, Relief and Economic Security Act (commonly known as the CARES Act), Congress added section 506C(j) to the Federal Food, Drug and Cosmetic Act (FD&C Act) requiring manufacturers of certain lifesaving or life-sustaining drug products to develop, maintain and implement a redundancy RMP. This RMP requires identifying and evaluating risks to the drug supply for each manufacturing establishment that supports their production. In particular, certain drug products with less redundancy in their supply chains are at higher risk of shortage.

The first step of an RMP is to recognize everything that might go wrong, consider the subsequent effect on the supply chain and drug production and identify the resulting risk to patients.

Manufacturers must proactively notify the agency in the event of their permanent discontinuance or of significant manufacturing disruptions (and their justifications) that would negatively impact supplies of drugs and their active pharmaceutical ingredients (APIs). FDA also has the authority to include a review of RMPs as part of an inspection.

While RMPs are required by manufacturers of certain drugs, the principles of assessment and mitigation strategies are valuable for manufacturers of all drug products, with FDA recommending RMPs be considered across the drug industry. The ability to accurately anticipate supply challenges enables pivots that could potentially ward off manufacturing complications.

Which Products Require an RMP?

There are three categories of drug products for which development of an RMP per section 506C(j) is mandatory. This affects all stakeholders as described in section 506C(a) of the FD&C Act and contract facilities producing lifesaving or life-sustaining drugs, including those used to treat or prevent debilitating diseases or conditions and those used to treat rare conditions for which there is no appropriate alternative such as biologics, including recombinant therapeutic proteins, monoclonal antibody products, vaccines, allergenic products, plasma-derived products and their recombinant analogs, as well as cellular and gene therapy products. Stakeholders producing APIs used in those drugs and medical devices used for their preparation or administration, including any constituent part of a drug-device and biologic-device combination product and constituent parts of drug-led and biologic-led products, are also included in section 506C(j).

Voluntary RMPs are recommended for additional drug categories, including products that treat rare diseases, products with only one API manufacturer source in the supply chain, products with only one finished dosage form in the supply chain and products produced in facilities (including packaging and laboratories) that received an official action indicated following an FDA inspection within the last five years and for which there are no other qualified manufacturing facilities that can produce the product. Finally, countermeasures produced in response to PHEs caused by a terrorist attack are recommended to have a voluntary RMP.

The level of the RMP will likely vary, FDA acknowledges, based on the stakeholder's position in the drug supply chain. A primary stakeholder's RMP will be broader in scope, developing strategies to not only identify materials and services at risk, but assess those risks and create mitigation strategies, including repairing the supply chain post-disruption. Primary stakeholders are recommended to share their RMP with secondary stakeholders such as establishments involved in blending and tableting or otherwise physically processing since they may not have visibility over the supply chain in its entirety. Finally, other stakeholders such as those producing inactive ingredients, packagers and distributors are included in RMP discussions as appropriate. This creates a holistic approach to risk mitigation up and down the supply chain and prevents duplication of efforts. Through sharing of information, secondary stakeholders have a broader opportunity to address any risks they face that might lead to shortages in the drug product's lifecycle.

The requirement for RMP development does not apply to establishments that only perform testing, relabeling or repackaging operations. However, regardless of whether an RMP is required by FDA, manufacturers would be wise to consider how shortages or changes to the supply chain would affect their products and plan accordingly.

Quality Is Integral to an RMP

Using the International Council for Harmonisation Q9 framework as a base for RMP structure, FDA recommends quality risk assessments at all stages of the supply chain. This includes analytics to forecast demand throughout the year and development of strategies to repair unavoidable supply chain interruptions.

The first step of an RMP is to recognize everything that might go wrong, identify the subsequent effect on the supply chain and drug production and consider the resulting risk to patients. Next, RMPs should analyze the likelihood and severity of each possible disruption. These considerations should include a review of past incidences, how they were handled and their outcomes.

Steps to accomplish this include looking at inventory management and facilities such as utilities, water systems, ventilation, air conditioning and heating. Also, critical questions should be asked, including what is the lifespan of the manufacturing equipment from this point forward? What are the maintenance requirements, including replacing outdated software or replacing parts that are difficult to source? Are any of the stakeholders located in an area with geopolitical instability or regulatory uncertainty? Are supporting laboratory services nearby? How complex is the distribution chain? Is the facility in an area prone to natural disasters, particularly at key times of the year when demand is expected to be high? Is there a back-up manufacturing capability? Also, employee retention in key areas and with critical specialties should be considered, taking into account the plant's ability to surge production rates beyond normal capacity if the need arises.

Some risks are worth accepting with no mitigation plans necessary, but others require RMPs to decrease the likelihood of risk occurring. RMPs should be reviewed annually throughout the drug's lifecycle and as part of a post-action report if the RMP was used to assess its effectiveness. RMPs must also be reviewed when any changes to processes, facilities or suppliers are made.

Shortages may also be warded off by reviewing the drug's stability data to determine whether it supports efficacy and safety beyond the stated use-by date.

Communication is key. FDA recommends proactively talking not only with regulators but also with appropriate stakeholders about the risk of impending shortages and established plans to adapt to them. While the comment period for FDA draft guidance closed in July 2022, the industry is already building and strengthening RMPs pending final guidance. Though imperfect, abiding by FDA's recommendation for the creation and implementation of effective RMPs can only improve outcomes during times of future drug shortages. ❖

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Increased Demand for Specialty Pharmacies Due to Chronic Illness

As chronic diseases continue to rise, high-touch, personalized care improves patient access and adherence to life-changing medications.

By Rachel Maier, MS

AS PREVALENCE OF chronic disease continues to increase, demand for targeted medications to treat these diverse conditions also goes up, but the gap between need and access separates many patients from the medicine they need. Specialty pharmacies have emerged as a strategic solution to improve patient access and adherence to complex treatments by dispensing highly specialized medications and providing high-touch, coordinated care to help them manage their treatment plan and complicated reimbursement issues.

Chronic Disease: A Complicated, Costly Problem

An estimated six in 10 Americans live with chronic diseases such as heart disease, diabetes and cancer, and four in 10 manage more than one chronic disease.[1] This number is rising: By 2030, an estimated 171 million Americans will have one or more chronic disease.[2] Chronic disease is the leading cause of death and disability in the United States.[1]

The term "chronic disease" is broadly defined as conditions lasting one year or more that require ongoing medical attention, interfere with daily living or

both and include familiar conditions such as heart disease, cancer, hypertension, diabetes, arthritis and Alzheimer's disease. But beneath the umbrella of chronic disease are autoimmune diseases (those in which immune cells mistakenly attack the cells they are meant to protect) and rare diseases. In the United States, rare diseases are classified as any disease that affects fewer than 200,000 Americans. Collectively, rare diseases affect 25 million Americans and include conditions such as primary immunodeficiency, cystic fibrosis and Lou Gehrig's disease, among many others.[3]

Chronic disease is responsible for $4.1 trillion in U.S. healthcare costs annually.[1] An estimated 84 percent of healthcare costs are attributed to the treatment of chronic disease.[4] Pharmaceutical expenditures in the U.S. grew 7.7 percent in 2021 compared to 2020 for a total of $577 billion. Nearly half of this spending is attributed to specialty medications used by only one to two percent of these patients.[5] Further, prescription drug spending is expected to rise four to six percent in 2022, with specialty and cancer drugs expected to be two of the driving forces.[6]

The Promise of Specialty Drugs

Because chronic disease states are complicated, the drugs needed to treat the rarest of them are scarce. Of the 7,000 recognized rare diseases in the U.S., an estimated 90 percent of them do not have an approved treatment.[7] Encouragingly, 58 percent of all new drug approvals in 2020 were designated for rare diseases, and more than 1,000 therapies are in the pipeline.[8] For those living with chronic illnesses — especially rare ones — specialty drugs offer real hope.

But the promise of highly targeted specialty drugs comes at an exorbitant cost. On average, major pharmaceutical companies spend approximately 17 percent of their revenues on research and development for new drugs. And this number is expected to keep increasing, with costs expected to grow by three percent each year, reaching over $203 billion by 2024.[9] Not surprisingly, these costs are passed on to patients. According to the American Association of Retired Persons' latest Rx Price Watch Report, which looked at 180 widely used specialty prescription drugs, the average annual cost for one specialty medication used on a chronic basis was $84,440 in 2020.[10]

Further, specialty drugs come with other complexities, too, including the way they are administered, the management of side effects, the diseases or conditions they treat, special access conditions required by the manufacturer, payer authorization or benefit requirements, patient financial hardship or any combination of these.[2]

While specialty drugs are life-improving — and in some cases lifesaving — their extremely high price tag makes them cost-prohibitive for patients to initiate, let alone maintain. Patients with more than one chronic disease must manage multiple medications at once, choosing which to take and when, stretching what they do have and skipping some altogether because they simply cannot afford them. Prior authorizations make an already complicated problem worse. Deciding whether a prescribed medication will be covered by the insurance payer is a lengthy process, one that often involves complex transactions that impact patient access and delays or interrupts treatment.[11] Clinical outcomes are negatively impacted by limited access and nonadherence to the medication(s) they need.

Improved access to specialty drugs is only part of the solution. Since treatment plans for chronic disease are often complicated, patients can easily feel overwhelmed by them and may need extra support to implement and maintain them. They need help understanding how and when to take their medications, and why.

Specialty Pharmacies: A Strategic Solution

Specialty pharmacies emerged as a strategic solution that addresses patient access, affordability and adherence. They are a unique subset of pharmacies that dispense high-cost, high-touch, specialized medication to treat a wide variety of rare, complex diseases while also partnering with the entire care team to help patients remain adherent to their medication regimens.[4]

The average annual cost for one specialty medication used on a chronic basis was $84,440 in 2020.

According to the National Association of Specialty Pharmacy, specialty pharmacies "provide services that include training on how to use these medications, comprehensive treatment assessment, patient monitoring and frequent communication with caregivers and the patient's physician or other healthcare providers. The expert services that specialty pharmacies provide drive adherence and persistency, proper management of medication dosing and side effects and ensure appropriate medication use."[2]

They accomplish this by partnering with patients, helping them adhere to their highly specific treatment plans through advocacy, education and reimbursement assistance.[2,8] Also, specialty pharmacies often have distribution infrastructure already in place.

Exponential Growth

Before 1970, specialty pharmacies were little-known to the average American since they served the small population of chronically ill patients with rare diseases (such as hemophilia, cancer and the like) that needed highly specialized medications.[12] But by the 1990s, drug manufacturers had made ground-breaking headway into identifying new drug classes, differentiated molecular entities and unique delivery mechanisms for a wide range of disease states.[12] The Orphan Drug Act (ODA) of 1983 helped make this possible by incentivizing drug manufacturers to research and develop drugs for rare diseases through tax credits, market exclusivity agreements and research grants.[13] The ODA helped make specialty drugs profitable for manufacturers, so they are increasingly investing in research and development efforts to bring new medications to market quickly.[15] Over time, the increase in highly specialized drugs necessitated a new dispensing model.

Today, specialty pharmacies are better-known and increasingly used. In fact, over the past six years, specialty pharmacies have grown an astounding 315 percent from 378 in 2015 to 1,570 in 2021.[14] Approximately 50 percent of therapies approved by the U.S. Food and Drug Administration in 2018 and 2019 were considered specialty medications.[1]

What Makes Specialty Pharmacies Different

Since retail pharmacies lack the training and expertise to dispense complex medications, unique, highly focused pharmacies are well-positioned to offer collaborative care that supports patients in a way retail pharmacies simply cannot. Specialty pharmacies improve access to highly complex medications not only by dispensing them, but also helping patients find programs to help offset co-pays, which makes medication more affordable. They also improve patient adherence through a comprehensive approach to the management and implementation of treatment plans. Specialty pharmacies prioritize:[8,16]

Specialty pharmacies have grown an astounding 315 percent from 378 in 2015 to 1,570 in 2021.

- Offering high-touch care emphasizing patient support through specialty pharmacists, clinical nurses and nonclinical patient support specialists, including insurance and reimbursement specialists.
- Coordinating special handling needs, including refrigeration, overnight delivery and shipment tracking.
- Communicating with care providers to coordinate continuity of care.
- Educating patients about their condition, medication, expected clinical outcome and potential adverse events.
- Addressing potential side effects with urgency, compassion and personalized care.
- Tracking patient medication cycle and identifying issues between refills that could negatively impact adherence.

Solving Complex Problems

A specialty pharmacy's model is designed to provide comprehensive, coordinated care, achieve superior clinical and economic outcomes and expedite patient access to care.[17] Specialty pharmacies are typically subsets of large health insurance providers, retail providers or pharmacy benefit managers that coordinate these services. Independent specialty pharmacies also exist.[17]

One such example is Nufactor, a specialty infusion company that provides infusion medications for patients with a variety of conditions, including bleeding disorders, movement disorders, immune deficiencies and many autoimmune conditions such as immune mediated neuropathies, autoimmune mucocutaneous blistering diseases and more. Nufactor helps patients navigate complicated insurance requirements, obtain prior authorizations, find co-pay assistance programs and appeal denials.

Like so many specialty pharmacies, Nufactor has experienced significant growth over the past decade. Chief Operations Officer Leslie Vaughan, RPh, IgCP, CSP, attributes this growth largely to high-touch service offering: "Patients like the level of service they receive. Each patient is assigned a single point of contact throughout their time on service with us. They like being able to directly reach someone who can help them navigate any issues from reimbursement to clinical concerns."

Further, not only does Nufactor employ specialized pharmacists and nurses that consistently monitor patients, but it also assigns each patient a unique client service specialist (CSS) who contacts them monthly to discuss adherence and any problems with the medication

(including side effects, clinical concerns and reimbursement issues). The CSS then coordinates care with the appropriate team member should concerns arise. Vaughan says the high-touch, patient-centered model makes patients happy. In fact, she reports a 99 percent patient satisfaction rate year after year. "If patients are forced to leave us (for instance, to find new insurance when we are out of network), they may select a different insurance the subsequent benefit year just to be able to come back to our service," explains Vaughan. "Our people are what makes us special and successful. [We] value patient care."

Targeted Help Offers Patients Hope

As chronic illnesses continue to rise, specialty pharmacies will continue to serve this diverse patient population by improving access and adherence to life-changing medications. Targeted, expensive treatments are a complicated source of both frustration and hope for patients. They can be life-changing, but barriers to access limit patient adherence. Specialty pharmacies offer tangible hope by prioritizing high-touch, personal care, supporting patients through each step of their treatment journey. ❖

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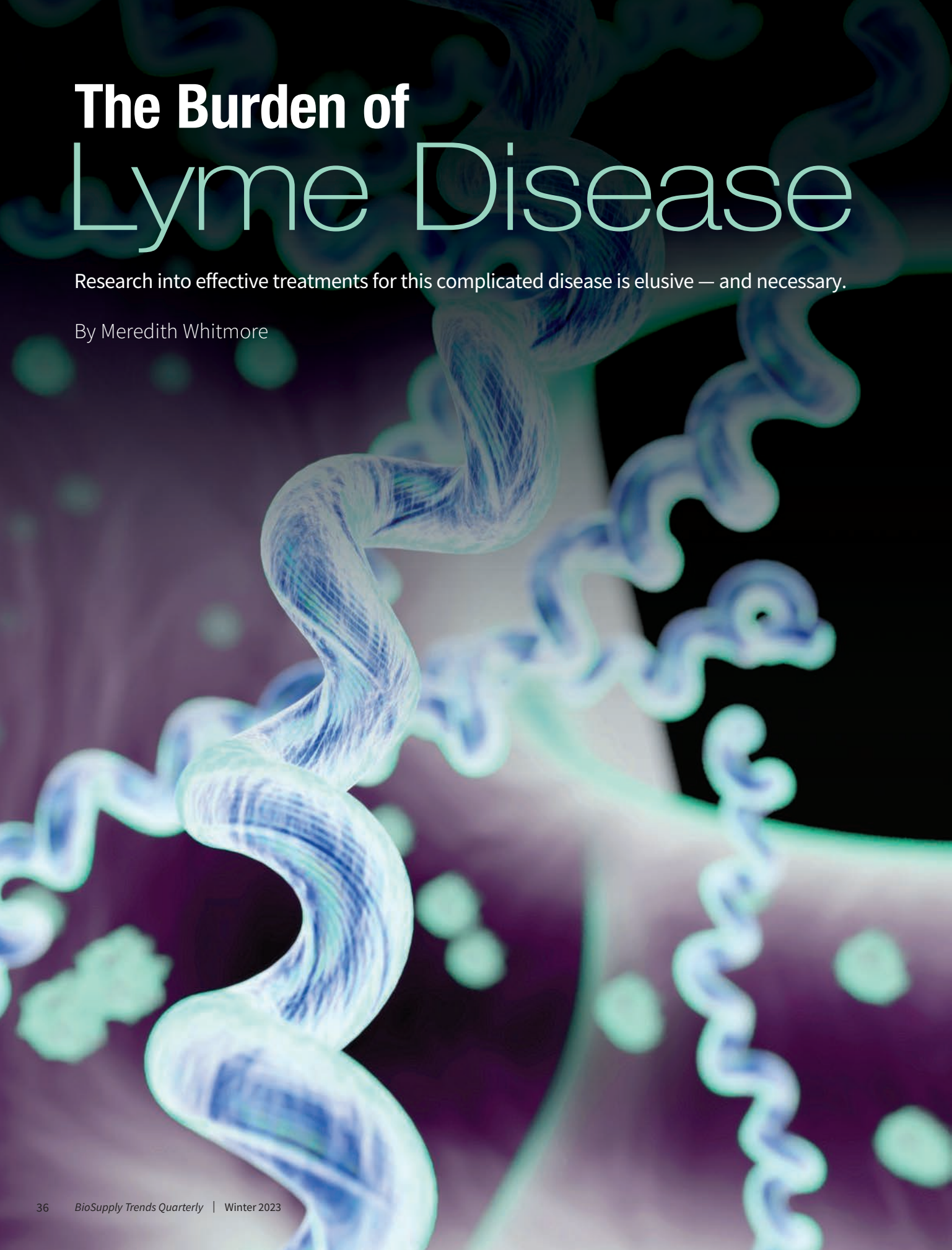
The Burden of Lyme Disease

Research into effective treatments for this complicated disease is elusive — and necessary.

By Meredith Whitmore



IMAGINE YOUR BODY inexplicably failing. Your health declines for weeks, first slowly and then seemingly all at once. Your body fails in crippling ways that make everyday actions such as standing, dressing, walking, breathing and even eating so difficult that it feels easier to give in to the pain and frustration than continue to rage.

When you feel your very worst but look perfectly healthy, you're told your labs test negative for everything. In other words, you're deemed well. Your doctors mention psychosomatic symptoms, emotional problems and psychotropic medication, not to mention individual and family counseling. If healthcare professionals notice a physical problem, it's likely to be misdiagnosed. Lupus, Crohn's disease, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), rheumatoid arthritis, syphilis, chronic fatigue syndrome, fibromyalgia and other names are hurled at you as inconclusive possibilities, but you know none of them quite fit.

Lyme disease is the most common vector-borne disease in North America, with an estimated 300,000 infections occurring each year. Those numbers have grown exponentially in the past 20 years, and they continue to rise.[1] That means healthcare workers must learn more about this surprisingly controversial and politicized illness caused by the bacterium Borrelia burgdorferi. There is no one-size-fits-all approach to Lyme disease's multiple manifestations; it can present many ways beyond the classic "bulls-eye rash," which appears in only 30 percent of patients. As a result, even in highly endemic areas, Lyme goes undiagnosed, though its consequences are painfully visible.

"It just doesn't seem possible," field entomologist David Simser, PhD, says of the black-legged tick nymph, "that this poppy-seed-sized thing is going to make you bedridden, possibly for the rest of your life."[2]

What Lyme Sufferers Wish Professionals Knew

From a patient's point of view, Lyme disease is personal. Unlike clinicians who view Lyme disease as a diagnosis, patients often view it as the enemy that took their lives away. Dorothy Leland, board president of Lymedisease.org, says, "Early symptoms of Lyme — such as fever, fatigue and achiness — are common to many other conditions. Plus, the bull's-eye rash most associated with Lyme disease doesn't show up in everyone who is infected." She adds that "diagnostic testing for Lyme disease is problematic. The standard test for Lyme is undependable — it often says you don't have Lyme when you actually do." According to Leland, patients still have difficulty being appropriately diagnosed and treated, even in highly endemic areas.

Unlike clinicians who view Lyme disease as a diagnosis, patients often view it as the enemy that took their lives away.

"A negative Lyme test does not mean you don't have Lyme," Leland adds. "Lyme can cause wildly divergent symptoms — affecting your heart, digestive tract, joints, muscles and/or brain — to name a few. Lyme-related pain can migrate around the body, and symptoms can wax and wane. Hence, patients can have good days and bad days in terms of fatigue, pain and other symptoms. Lyme disease symptoms can persist for months or years, even after treatment."

Writer and author Suzanne Hadley Gosselin experienced firsthand the frustration of long-Lyme conventional treatments that availed no healing. She contracted the disease in 1999 but was misdiagnosed in 2000. Her experience falls outside of traditional medicine and even more progressive International Lyme and Associated Disease (ILADS) guidelines. "A rheumatologist diagnosed me with a connective tissue disorder that fell somewhere in the crack between rheumatoid arthritis and lupus and put me on prednisone for the pain," she said. "I was also prescribed Celebrex to address my symptoms."

Unsatisfied with the connective tissue diagnosis, her mother dug deeper and discovered that Lyme disease often mimics other conditions. "The rheumatologist was unwilling to entertain the possibility of Lyme," Gosselin adds. "We sought out a [doctor of osteopathic medicine] who administered the Western blot test. I tested positive but the battery of tests were inconclusive. Still, the doctor diagnosed Lyme disease and administered a six-week course of amoxicillin."

After finding no relief from standard protocols, Gosselin worked with an outpatient naturopathic clinic that specialized in treating long-Lyme disease. "My six weeks at the clinic, where I received homeopathic therapies and sessions in a hyperbaric chamber, decreased my symptoms and allowed me to wean off prednisone nearly a year after I had first taken it. Still, my main symptoms continued to be debilitating joint pain and fatigue. I could not climb stairs and struggled to lift a hairdryer to dry my own hair.

In 2001, I worked with a chiropractor and naturopath who treated me with various therapies that were focused on eliminating the Lyme spirochetes from my body. My symptoms slowly began to fade, and by early 2002, they were all but gone. After 2002, my symptoms never reoccurred."

Unlike Gosselin, who was unable to take a long courses of antibiotics because of a severe Herxheimer reaction, many others experience dramatically positive results with them. Gosselin herself demonstrates that effective treatments do not lie exclusively within the Centers for Disease Control and Prevention's (CDC) narrow protocol. Unfortunately, proper treatment of any sort often occurs only after years-long battles with debilitating symptoms that are often written off. For example, Nikki Kent is a chronically ill young Canadian woman who underwent more than 17 inconclusive tests in the two years prior to being diagnosed with Lyme disease in the United States. According to her mother, "You've got to just believe the patient, and believe they are sick. There's something wrong with them, and they need to get help."[4]

Similar results have been found in other studies.[5]

Conflicting Definitions and Treatments

"Typical" Lyme disease is considered to respond to treatment within a four- to six-week course of doxycycline or amoxicillin, the standard antibiotics prescribed by mainline physicians. However, chronic Lyme disease, the "disease du jour" as skeptics call it, is very often dismissed as a myth or misdiagnosed. According to standard protocol, any symptoms lasting longer than four to six weeks after treatment have been said to be caused by the "aches and pains of daily living."[2] Chronic Lyme disease, or long-Lyme, as many sufferers will attest, is too often scoffed at by skeptical professionals who say it does not exist. More progressive groups consider long-term antibiotics, and often multiple antibiotics simultaneously, to be the most effective way to eradicate the illness in patients who continue to manifest a variety of symptoms.

The argument against long-Lyme is perhaps based on the fact that this is a complex disease, and ticks can transmit multiple diseases with one bite. Board certified internist Richard Horowitz, MD, a Lyme expert in Hyde Park, N.Y., says, "It's possible that years ago patients were only getting pure Lyme disease, and this might explain why there's such a disparity [of protocol] in the literature. But we're now seeing that ticks contain multiple organisms." These organisms, he further explains, contribute to overwhelming the immune system with pathogens, which he says cause patients to be much, much sicker because they do not have simply Lyme. He purports that multiple other illnesses cause symptoms to linger instead, causing mainstream medicine to consider chronic Lyme a myth.[2]

Of course, countless Lyme patients and growing numbers of doctors disagree.

Maureen McShane, MD, another Lyme expert who practices in upstate New York, has treated Lyme patients for well over 20 years and opposes mainline treatments for longer-term symptoms. "I almost fainted the first time I gave our prescriptions for two antibiotics at the same time because I was so apprehensive about losing my license," she says. "But [patients] responded, and it was almost like a miracle. I had never, ever practiced medicine where I would see responses within a month, two months, three months. Their lives were changed. This was a huge impact, and some of these people had been ill for years and years.

"I believe that evidenced-based medicine is the problem," which is why, she says, there is such a division regarding Lyme treatment. "The medical journals that we doctors are raised on — [that] we go through medical school believing — [cause physicians to believe] that if it's not evidence-based medicine, forget about it," Dr. McShane explains. "They will not publish an article on adequate treatment of chronic Lyme disease. So your regular doctors in Canada [and the United States] have no idea what to do."[4]

Groups such as Lymedisease.org support Dr. McShane's argument. With regard to CDC and the Infectious Diseases Association of America's (IDSA) guidelines for a brief course of antibiotics, ILADS has published a rigorous assessment of the evidence. It found mainline treatment failure rates ranging from 16 percent to

Unfortunately, the voice of Lyme disease patients has been ignored for too long.

A Lymedisease.org survey of more than 3,000 patients with chronic Lyme disease found that patients suffer a worse quality of life than those with most other chronic illnesses, including congestive heart failure, diabetes, MS and arthritis. More than 70 percent of patients with chronic Lyme disease reported fair or poor health versus 62 percent for congestive heart failure.

39 percent for early treatment. Estimates for patients with chronic Lyme disease are much higher, ranging from 26 percent to 50 percent.[5]

"We feel that CDC guidance regarding Lyme disease is seriously flawed," Leland said. "We believe that, unfortunately, the voice of Lyme disease patients has been ignored for too long. LymeDisease.org seeks to rectify this in a variety of ways. For instance, we amplify the lived experience of patients through our MyLymeData research project. This is a patient-driven registry and research platform that permits patients to quickly and privately pool their personal experiences. Participants answer questions about the progress of their symptoms, response to treatment and what works and doesn't work for them. Having data from thousands of patients permits researchers to evaluate care as it is provided in real-world practice. It can also generate research hypotheses and help recruit patients for clinical trials. There are currently more than 16,000 patients enrolled in MyLymeData, and our team works with researchers at many prominent institutions." (For more information on MyLymeData, see mylymedata.org.)[5]

CDC treatment guidelines, in conjunction with IDSA, state that Lyme can be treated with roughly four to six weeks of doxycycline or amoxicillin, and that any residual symptoms after treatment are unrelated to Lyme.[3] Despite showing impressive results in many long-Lyme patients, long-term antibiotics and use of multiple antibiotics simultaneously are considered unconventional, and therefore unacceptable, by many healthcare providers.[4] Still, CDC estimates that at least between 10 to 20 percent of patients treated conventionally remain ill. A recent study of early Lyme disease patients reported 36 percent remain ill.[5]

The Bacteria and Its Impact

"The spirochete that causes Lyme is b. Burgdorferi and related borrelia," pathologist and renowned Lyme researcher Alan MacDonald, MD, states. "The model I have used to try to understand all of the possible things Lyme disease can do is the syphilis model." He explains that if a syphilis spirochete, t. pallidum, which shares many traits with b. Burgdorferi, can cause multiple manifestations in multiple systems, then the borrelia spirochete, over time, might cause illnesses such as Alzheimer's disease, ALS, MS and Parkinson's disease — all named neurological conditions for which no cause is yet known. Dietrich Klinghardt, MD, PhD, founder of the American Academy of Neural Therapy, medical director of the Institute of Neurobiology and lead clinician at the Sophia Health Institute in Woodinville, Wash., supports Dr. MacDonald's theory, saying, "[At my clinic], we never had a single MS patient, a single ALS patient, a single Parkinson's patient who did not test positive borrelia Burgdorferi. Not a single one."[2] In other words, b. Burgdorferi is likely at the root of many illnesses, including long-Lyme.

Christine Green, MD, a Lyme-treating physician who serves on the LymeDisease.org board of directors, points out how b. Burgdorferi can form a biofilm, which often prevents brief, traditional courses of antibiotics from being effective because the film protects the bacteria. Dr. Green explains that in addition to forming biofilm, Borrelia include efflux pumps, allowing the microorganisms to regulate their internal environment by removing toxic substances, including antimicrobial agents, metabolites and quorum sensing signal molecules. These efflux pumps push out heavy metals and other chemicals, but they also expel brief courses of antibiotics before they've had a chance to work.[6,7]

Final Thoughts

Perhaps CDC itself unintentionally supports the argument against standard protocol when it states: "Additional research is needed to better understand how to treat, manage and support people with persistent symptoms associated with Lyme disease. In light of these research gaps, recommendations for treatment of persistent symptoms in people previously treated for Lyme disease are not provided here."[3]

This begs the question that if additional Lyme protocol research is needed, why aren't unconventional treatments with outstanding results not researched or even considered? Many professionals have many political, sometimes finance-related viewpoints about the answer to this question. Suffice it to say, however, that Lyme disease will not soon be eradicated, and healthcare providers need to educate themselves regarding both standard and more progressive treatment protocols. There needs to be no stone left unturned when it comes to the treatment of acute and chronic Lyme disease. Providers' diligence could very well spare patients years of suffering. ❖

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Myths & Facts: COVID-19

While the COVID-19 pandemic is "officially over," hospitalizations and deaths continue, many of which are due to the myths continuing to circulate about this deadly virus.

By Ronale Tucker Rhodes, MS

IT'S BEEN THREE years since the start of the COVID-19 pandemic. And while President Biden officially declared on Sept. 20, 2022, in a "60 Minutes" broadcast that the pandemic is over[1] due to the falling rates of COVID-19 infections and deaths, the SARS-CoV-2 virus still poses a serious threat. So serious, in fact, that as of this writing, each day an average of more than 37,000 new cases are diagnosed, more than 300 people die and more than 3,200 people are hospitalized due to the virus.[2] The good news is that over two-thirds of the U.S. population is considered fully vaccinated,[3] so there is a much lower chance of individuals developing severe disease or needing hospitalization. The bad news is that many people who are unvaccinated are ending up hospitalized — or worse — and these COVID-19 cases allow the virus to mutate, resulting in more variants.

Unfortunately, misinformation about COVID-19 continues to spread online and in communities, which poses a real challenge for healthcare professionals as they try to combat it and increase vaccine confidence. According to a Kaiser Family Foundation COVID-19 vaccine report, based on a survey of more than 1,500 vaccinated and unvaccinated U.S. adults, "a substantial number of people either believe or are unsure about several common misconceptions about COVID-19 and the vaccines used to prevent it. This includes statements about the vaccine's effects on pregnancy and infertility, and statements that the federal government is lying about the number of deaths caused by COVID-19 vaccines and by the disease itself."[4]

"Misinformation is widespread and is a recognized public health crisis," said Sarah Coles, MD, chair of the Academy's Commission on Health of the Public and Science, and an assistant professor in the Department of Family, Community and Preventive Medicine at the University of Arizona College of Medicine — Phoenix Family Medicine Residency. "Family physicians are key to combating misinformation for our patients and communities." Indeed, it is paramount for providers on the frontline of healthcare to provide the facts about COVID-19 so that, as Dr. Coles explains, patients know what to believe and what not to believe.[4]

Separating Myth from Fact

Myth: COVID-19 is no worse than the seasonal flu.

Fact: While the SARS-CoV-2 virus is similar to the influenza virus since they are both contagious respiratory diseases and some symptoms are the same, the viruses are different and they affect people differently. Symptoms of COVID-19 generally appear two to 24 days after exposure, while symptoms of flu generally appear one to four days after exposure. COVID-19 is always more contagious and spreads more quickly than the flu. In addition, people infected with the SARS-CoV-2 virus may lose their sense of taste and/or smell, and severe illness such as lung injury is more frequent than with the flu. COVID-19 also causes different complications than the flu such as blood clots and multisystem inflammatory syndrome in children, as well as higher death rates.[5]

Myth: The data surrounding COVID-19 infections and deaths cannot be trusted.

Fact: This myth stems from flawed reasoning about data collected by the Centers for Disease Control and Prevention (CDC) that show most people who died of COVID-19 had multiple causes, mostly other pre-existing conditions such as heart or lung disease, weakened immune systems, severe obesity or diabetes. But, these people would have lived far longer had they not contracted COVID-19. "For deaths with conditions or causes in addition to COVID-19, on average, there were 2.6 additional conditions or causes per death," said a statement by CDC.[5]

Also, since the SARS-CoV-2 virus was novel, information concerning it changed as scientists learned more. Unfortunately, this led many people to mistrust the reliability of the data and information. On top of that, partisan differences led to a great deal of mistrust.[5] A study published in *The Lancet* showed that this lack of trust, as well as government corruption, "are strongly correlated to higher COVID-19 infection rates around the world." What's more, "high levels of government and social trust, as well as lower government corruption, were all associated with higher vaccine coverage."

The study evaluated data from 177 countries, with findings suggesting "that if all societies had trust in government at least as high as Denmark, which is in the 75th percentile, the world would have experienced 13 percent fewer infections. If social trust (trust in other people) reached the same level, the effect would be even larger: 40 percent fewer infections globally."[6]

Myth: COVID-19 tests can't distinguish between the SARS-CoV-2 virus and the flu or a cold.

Fact: The mostly widely used COVID-19 tests originally could detect only the SARS-CoV-2 virus; they could not detect cold viruses or the flu.[7] However, in July 2021, CDC began using a new test that can check for both influenza and COVID-19 simultaneously, known as the "multiplexed method," which caused many to believe that the original tests couldn't distinguish between the SARS-CoV-2 virus and the influenza virus. But, according to pathologist and microbiologist Jana Broadhurst, MD, PhD, "The original test could detect the presence of SARS-CoV-2 with very high specificity." Specificity means the test is designed to detect only one type of virus. "The PCR test is validated against many different coronaviruses and common respiratory viruses, including influenza so that it would not give false-positive results," explained Dr. Broadhurst. In fact, when subjecting the PCR test to many different samples to see if it would give the wrong result, it correctly identified SARS-CoV-2 out of all of these samples. CDC switched to the multiplexed PCR test since it can diagnose both viruses at the same time.[8]

Myth: Only a COVID-19 PCR test can diagnose whether someone has the SARS-CoV-2 virus.

Fact: PCR tests are considered the "gold" standard for diagnosing COVID-19. However, rapid tests provide a diagnosis in minutes rather than days, which can be helpful to determine whether someone is contagious and can spread the virus to others. The main difference between PCR tests and rapid tests is that PCR tests are based on detecting the genetic material inside the coronavirus, which means it can detect an infection in the earliest stages, often days before symptoms start. Rapid tests look for a protein found on the surface of the virus (an antigen). The more virus found in someone's nose, the more likely they are

While the SARS-CoV-2 virus is similar to the influenza virus since they are both contagious respiratory diseases and some symptoms are the same, the viruses are different and they affect people differently.

to have a positive rapid test and be capable of spreading the virus.

"Having a positive rapid test indicates that you are infected with high enough levels of the virus to be contagious to others," said Emily Somers, PhD, an epidemiologist at Michigan Medicine who has advised school districts and public health agencies on the use of rapid testing to steer quarantine and isolation guidance. "If you're negative on a rapid test, you may not be infected, or you might be in the early or late stages of an infection, before or after the contagious period."[7]

There is currently no evidence that COVID-19 vaccines cause fertility problems in women or men.

Myth: Natural immunity to the SARS-CoV-2 virus is better than immunity from the COVID-19 vaccines.

Fact: There was some truth to this myth in the beginning when individuals infected with COVID-19 had greater protection against the Delta variant with natural immunity. But when the Omicron variant emerged, which has been responsible for the largest surge in COVID-19 cases, that was no longer the case. Now, the COVID-19 vaccines provide greater protection. "Omicron has a large number of mutations that all appeared at once. It's very different from previous versions, including Delta," explains Lisa Maragakis, MD, MPH, senior director of infection prevention at Johns Hopkins Medicine. "It has over 50 mutations, many in the spike protein, which is how it gets into our cells in the first place. The spike protein is also one of the most prominent exterior features of the virus that our immune system recognizes, responds to and uses to develop antibodies. Unfortunately, Omicron is a perfect storm: Mutations gave it the ability to escape weak immune responses *and* become more transmissible from person to person."[9]

One main difference between natural immunity and vaccinations is that natural immunity from a past COVID-19 infection varies greatly, whereas vaccine-related immunity has been studied in-depth and is relatively consistent. The COVID-19 vaccines provide safer, better and longer-lasting protection against serious illness than an infection. It's much safer to get vaccinated than it is to risk a potentially severe bout with COVID-19 that can leave lasting effects.[7]

Myth: Since herd immunity will end the pandemic, vaccines aren't necessary.

Fact: Also referred to as "community immunity," herd immunity is a public health term used to describe a case in which the potential for person-to-person spread is significantly reduced due to the broader community's resistance against a particular pathogen. High levels of herd immunity have enabled the United States to largely control polio and measles, which are caused by viruses that have not undergone significant evolution. However, achieving herd immunity with respiratory viruses such as influenza, which continually mutate, has been less successful.

According to Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), David M. Morens, MD, senior scientific advisor to the NIAID director, and Gregory K. Folkers, chief of staff to the NIAID director, "achieving classical herd immunity against SARS-CoV-2 is unlikely due to the virus' ability to continually mutate to new variants; asymptomatic virus transmission, which complicates public health control strategies; the inability of prior infection or vaccination to provide durable protection against reinfection; suboptimal vaccination coverage; and adherence to nonpharmacologic interventions."[10]

According to virologist Sabra Klein, PhD, MS, MA, co-director of a the National Cancer Institute Center of Excellence, immunity from natural infection starts to decline after six to eight months, whereas immunity after being fully vaccinated lasts for a year or longer. But that's the puzzle: While it's not known why vaccines lead to better immunity than natural infection, it is known that infected individuals' immune systems have been trained to target all parts of the virus, whereas vaccines target just the spike protein — the part of the virus essential for invading cells. So, the assumption is that natural immunity would provide better protection, but it doesn't. "It's like a big red button sitting on the surface of the virus. It's really sticking out there, and it's what our immune system sees most easily," says Dr. Klein. "By focusing on this one big antigen, it's like you're making our immune system put blinders on and only be able to see that one piece of the virus."

On the flip side, current vaccines recognize the COVID-19 variants and induce excellent immunity against them. Yet while previously infected individuals' immune systems will recognize the variants, it is unknown what level of immunity against a specific variant or how degraded the immune response will be. It's possible these individuals might actually be susceptible to reinfection with one of the variants.[11]

Myth: mRNA vaccines are not really vaccines.

Fact: mRNA vaccines may be different from other types of vaccines since they are manufactured using a new methodology,

but they still obtain the same results by triggering an immune response inside the body. The difference is that mRNA vaccines work by teaching cells in the body to make a harmless piece of a spike protein found on the surface of the virus that causes COVID-19. Once made, the cells then display this spike protein on their surface, and since the immune system doesn't recognize it, it responds by producing antibodies against the virus to get rid of it. This differs from many other vaccines that use a piece of, or weakened version of, the germ that the vaccine protects against, which is how the measles and influenza vaccines work. When that germ is introduced into the body, the immune system produces antibodies to fight the germ since it doesn't recognize it.[12]

Also, it's important to understand that the mRNA technology is not new; research and development of this type of vaccine has been underway for years.

Myth: The COVID-19 vaccine ingredients are dangerous.

Fact: According to CDC, there is nothing dangerous about the COVID-19 vaccine ingredients: They don't contain eggs, gelatin, preservatives, pesticides, tissues (such as aborted fetal cells), antibiotics, medicines, latex or metals, so they cannot make people magnetic. They also don't contain microchips or any live virus, so they can't make people sick with the SARS-CoV-2 or monkeypox viruses.[12,13]

The ingredients in the Pfizer-BioNTech and Moderna vaccines are very similar. They both contain mRNA (messenger ribonucleic acid), which is the only active ingredient in the vaccines, lipids to protect the mRNA and to help deliver it to the cells, salts and sugar. The Moderna vaccine also contains acetic acid and acid stabilizers. The Johnson & Johnson vaccine contains a modified and harmless version of a different virus (Adenovirus 26) that delivers a DNA gene sequence to produce the coronavirus spike protein, as well as acids, salts, sugars and ethanol. The Novavax vaccine contains a SARS-CoV-2 recombinant spike protein made from moth cells; an adjuvant that contains saponins, a soap-like substance derived from the soapbark tree; salts; food additives (disodium hydrogen phosphate dihydrate and sodium dihydrogen phosphate monohydrate); cholesterol; phosphatidylcholine (a chemical found in many foods such as eggs and soybeans); and water for injection.[14]

Myth: COVID-19 mRNA vaccines can alter DNA.

Fact: The rumor that mRNA vaccines can alter a person's DNA is simply not true. The mRNA vaccines never enter the nucleus of the cell, where a person's DNA is stored. Instead, after injection, the mRNA from the vaccine is released into the cytoplasm of the cells, and once the viral protein is made and on the surface of the cell, mRNA is broken down and the body permanently rids itself of it, therefore making it impossible to change a person's DNA.[14] In short, all of the vaccine ingredients are discarded after the body produces an immune response because they are no longer needed by the cells.

Myth: COVID-19 vaccines can affect people's fertility.

Fact: There is currently no evidence that COVID-19 vaccines cause fertility problems in women or men. In fact, several studies evaluating the safety and efficacy of vaccines on fertility and pregnancy have all shown that the COVID-19 vaccines are safe for people who are pregnant, or who want to have a child in the future. For instance, data from v-safe and from eight U.S. healthcare systems show COVID-19 vaccines do not prevent people from becoming pregnant, which is confirmed by an in vitro fertilization study that showed people who had been vaccinated against COVID-19 were just as likely to get pregnant as people who had not been vaccinated or recently had COVID-19. Another study that compared sperm before and after vaccination with an mRNA COVID-19 vaccine (Pfizer or Moderna) found vaccination did not affect how much sperm men had or how it moved.

It's unwise for women who are pregnant not to get a COVID-19 vaccine since getting infected with the SARS-CoV-2 virus when pregnant can cause preterm birth, stillbirth and other pregnancy complications. And, it is known that vaccination either before conception or early during pregnancy is the best way to reduce maternal and fetal complications. In the largest study of its kind, researchers found mRNA COVID-19 vaccines are highly effective at protecting pregnant and breastfeeding people against COVID-19. And, two other studies (published in the *Morbidity and Mortality Weekly Report* and *American Journal of Obstetrics & Gynecology*) showed that babies received protection through the vaccinated parent's placenta and milk.[15]

Myth: COVID-19 vaccines don't protect against the variants.

Fact: There is no evidence that shows the COVID-19 vaccines don't protect against variants, and boosters are now being designed to target the latest variants. In a study that evaluated a third and fourth COVID-19 vaccine dose, researchers found they offered substantial protection among adults with healthy immune systems who were eligible to receive them during Omicron variant evolution in early 2022. The study, conducted from mid-December 2021 through mid-June 2022, examined VISION Network data on more than 214,000 emergency department/urgent care visits and more than 58,000 hospitalizations with a COVID-19-like illness diagnosis in 10 U.S. states. Findings showed:

• When BA.1 was the predominant variant, vaccine effectiveness (VE) was 61 percent for two doses against COVID-19-associated hospitalizations, and VE increased to between 85 and 92 percent after receipt of a third/booster dose.

• When BA.2/BA.2.12.1 became predominant, vaccine effectiveness with two doses was 24 percent against COVID-19-associated hospitalizations and increased to 52 to 69 percent after a third/booster dose.

• Patterns were similar for emergency department and urgent care encounters, with lower VE during BA.2/BA.2.12.1 predominance and higher VE with three or four doses compared to VE with two doses.

• Among adults ages 50 years and older during BA.2/BA.2.12.1, vaccine effectiveness against COVID-19-associated hospitalization was 55 percent more than four months after a booster/third dose and increased to 80 percent more than a week after the fourth dose.

Importantly, stopping the spread of the SARS-CoV-2 virus decreases the ability for the virus to mutate, which helps prevent the emergence of any other variants. Vaccines remain the single most important tool to protect people against serious illness, hospitalization and death — even as variants continue to emerge.[16]

Myth: COVID-19 is not really dangerous anymore because treatments are widely available.

Fact: There are treatments available for COVID-19, but again, the best way to avoid severe illness, hospitalization and death is by getting vaccinated against the SARS-CoV-2 virus. Currently, there are two FDA-approved treatments: the intravenous antiviral drug Veklury (remdesivir) for adults and certain pediatric patients and the immune modulator Olumiant (baricitinib) for certain hospitalized adults. There are also other treatments authorized by FDA's emergency use authorization, including several monoclonal antibodies for the treatment, and in some cases prevention (prophylaxis), of COVID-19 in adults and pediatric patients, as well as two oral antiviral pills, Paxlovid and Lagevrio (molnupiravir), authorized for patients with mild-to-moderate COVID-19, with strong scientific evidence they can reduce the risk of progressing to severe disease, including hospitalization and death. However, most monoclonal antibodies must be taken within a few days of infection, and antivirals need to be taken within the first five to seven days of infection.[17]

Myth: There are other treatments that can prevent or cure a COVID-19 infection.

Fact: There is one treatment, Evusheld, that can help protect some people from COVID-19 before they are exposed to the SARS-CoV-2 virus, but CDC emphasizes that it is not a substitute for a COVID-19 vaccine. Individuals who may be eligible for this long-acting antibody treatment are those who:[18]

• Are at high risk for serious COVID-19

• Have not tested positive for COVID-19

• Have not been recently exposed to someone who has tested positive for COVID-19

However, a great number of myths are being spread about the use of other treatments to prevent or treat COVID-19, including the use of antibiotics, exposure to cold weather, taking vitamin D supplements, drinking water, ingesting highly toxic products and even taking medicines approved for animals.

Antibiotics can only treat a bacterial infection, not a virus, so antibiotics should not be used to prevent or treat the SARS-CoV-2 virus. There is no evidence whatsoever that cold weather can kill the SARS-CoV-2 virus or that vitamin D supplementation can prevent or treat COVID-19. While it's important to hydrate, drinking water will not wash the virus down a person's throat and into the stomach where it will be killed by stomach acid, and water won't prevent the virus from entering the lungs or making a person sick.

The final two treatment myths are the most dangerous. Disinfectants, bleach and rubbing alcohol should not be ingested or rubbed on the body because they are toxic substances. And, while many people believe taking Ivermectin, a medicine that controls parasites in animals and humans, will prevent or cure COVID-19, this is false. In fact, the formulas reported to FDA that humans are taking are different than for people and can be very toxic to humans.[18]

Myth: There are no long-term effects of COVID-19.

Fact: While most people who contract the SARS-CoV-2 virus recuperate within a few weeks, there are individuals whose symptoms last for a long time afterward.

While most people who contract the SARS-CoV-2 virus recuperate within a few weeks, there are individuals whose symptoms last for a long time afterward.

There are a variety of names for this, including post-COVID-19 syndrome, post-COVID conditions, long COVID, long-haul COVID-19 and post acute sequelae of SARS COV-2 infection.

With long COVID, individuals experience new, returning or ongoing symptoms that last more than four weeks after contracting the virus, and for some, these symptoms last for months or years, causing disability. According to the latest research, one in five people ages 18 to 64 years has at least one medical condition that can be attributed to COVID-19, and among those age 65 and older, one in four individuals has at least one medical condition attributed to the virus. Most common symptoms include fatigue, symptoms that get worse after physical or mental effort and fever and lung (respiratory) symptoms, including difficulty breathing or shortness of breath and cough. But other more serious symptoms include:[19]

- Neurological symptoms or mental health conditions, including difficulty thinking or concentrating, headache, sleep problems, dizziness when standing, loss of smell or taste, pins-and-needles feeling and depression or anxiety
- Joint or muscle pain
- Heart symptoms or conditions, including chest pain and fast or pounding heartbeat
- Digestive symptoms, including diarrhea and stomach pain
- Blood clots and blood vessel (vascular) issues, including a blood clot that travels to the lungs from deep veins in the legs and blocks blood flow to the lungs (pulmonary embolism)
- Other symptoms such as a rash and changes in the menstrual cycle

Myth: The COVID-19 pandemic is over.

Fact: Yes, President Biden did declare that the pandemic is over[1] due to the falling rates of COVID-19 infections and deaths. However, it's too early for individuals to let their guard down due to ongoing hospitalization and death rates. According to Harvard T.H. Chan School of Public Health experts, as of Oct. 7, 2022, "Some parts of the U.S. are seeing an uptick in COVID cases and hospitalizations, although experts are unsure whether the increases foretell a winter surge in the U.S. If more people get the new bivalent vaccine, it could keep numbers down, but so far only eight million out of 200 million eligible people have gotten them. And uptake of previous boosters has already been sluggish."[20]

Dispelling the Myths Now

The COVID-19 pandemic has caused many hardships — both economic and personal. After almost three years, it's safe to say that the public is in a state of pandemic fatigue, causing many to let their guard down. But while we would all like to return to life as normal, it is important to understand the facts about this deadly virus that has killed more than six and a half million people worldwide.

According to Robert M. Califf, MD, commissioner of the U.S. Food and Drug Administration (FDA), "The distortions and half-truths of misinformation and disinformation pose enormous dangers to the effectiveness of science and to public health itself through the negative impact it has on individual behavior. That's why I've made combating misinformation one of my priorities. Providing factual info is the key to helping people make the best informed decisions about their health."

FDA recommends individuals, especially providers, take three easy steps to prevent rumors from spreading: 1) Don't believe the rumors, 2) Don't pass them along and 3) Get health information from trusted sources such as FDA and its government partners: usa.gov/health, coronavirus.gov and vaccines.gov.[13] ❖

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During her 18-year battle with chronic symptoms, single mom Charlotte Cobb has lost friends and been labeled a hypochondriac.

Lyme Disease: *A Patient's Perspective*

By Trudie Mitschang

PERSISTENT HEALTH symptoms eventually led Utah-resident Charlotte Cobb to a diagnosis of Lyme disease. Despite her severe health challenges, Charlotte graduated college with honors and will soon earn her master's degree, and she continues to take it one day at a time and live life to the fullest.

BSTQ: When did you first notice symptoms of Lyme disease?

Charlotte: I was 22 years old when I first got sick. Almost overnight I went from a healthy, extremely active college student and single mom to what I can only describe as living in hell. I lost everything within weeks. I was a professionally trained ballet dancer, an eight-mile-a-day runner and gym enthusiast. I was in college full time and raising my son who had been diagnosed with autism the year before. It was an unusually cool night when I woke up feeling like someone was holding a lighter on my feet and up and down both legs. It lasted about an hour and I was alarmed, but eventually fell back asleep, and when I woke up the next day it was gone. I went about my usual life for about two more weeks. Then, when I was getting ready for class one morning, I suddenly realized my face was numb. The numbness then spread to my neck and down my spine. I felt vaguely achy and a bit feverish, and I knew something was very wrong. Ten days in the hospital yielded no answers. I had an MRI, a lumbar puncture and too many vials of blood to count — and they found nothing. I was sent home with an antidepressant and told I was just a stressed-out single mom.

BSTQ: Did your symptoms progress?

Charlotte: My early symptoms were almost exclusively neurological. I lost feeling in my hands, legs and face. I felt crawling sensations in my scalp and an unexplainable pressure in my head; it felt like my brain was trying to escape my skull. Sometimes when I was driving, I would forget where I was in the city I'd been living in practically my whole life. I couldn't recall simple words. I knew I was sick but multiple doctors told me there was nothing wrong. I had to drop out of college and my days were spent in emotional and physical darkness.

BSTQ: How were you diagnosed?

Charlotte: I took my son to see his pediatrician for a routine check-up. The doctor asked me how I was and, for some reason, I told him. He listened intently and then told me he thought he knew what was wrong. I was skeptical but willing to do anything, so when he gave me a lab slip, I went to have blood drawn. The next Sunday morning, the doctor himself called me. He had just gotten the results back and said I had Lyme disease and mycoplasma pneumonia. I had no idea how long the road was ahead of me; I was just ecstatic to have answers and know I wasn't crazy. I felt vindicated!

BSTQ: How did your treatment plan progress?

Charlotte: I found out very quickly that mainstream medicine was not willing to accept Lyme disease as my answer. My doctor was called a quack and even as my symptoms began to improve on the prescribed antibiotics, they told me I absolutely did *not* have Lyme disease and that it was definitely all just stress. That is when my 18-year journey with this monster called Lyme disease began. I lost friends and family who believed I had become a hypochondriac and that I couldn't possibly look healthy but really be so desperately ill. Lyme disease is an incredibly isolating experience. My son was eventually diagnosed with Lyme disease, Bartonella and mycoplasma. My mom and my brother were also diagnosed with Lyme disease. We still have no idea how we all got it.

BSTQ: What treatments seemed to help?

Charlotte: For years, we tried antibiotics, both oral and IV, and saw countless doctors, naturopaths and nutritionists. After five years, I finally went into remission only to relapse again a few years later. I have not yet been able to get back to remission. We are all doing the best we can, but I always say Lyme disease (and co-infections) is a disease for the rich. It's impossible for a struggling single mom to pay for years of treatment, not just for myself but my son, too. We have good days and bad days.

BSTQ: What do you wish the medical community understood about Lyme disease?

Charlotte: I wish the mainstream medical community understood how unreliable the testing for it is. I wish they understood chronic and persistent Lyme disease and that they would stop labeling people as stressed, tired or mentally ill.

BSTQ: What has this experience taught you?

Charlotte: Lyme disease has taught me who my real friends and family are. It has taught me to be tenacious and resilient. It has taught me to never stop asking questions and fighting for answers. It has taught me most of all that when you know something isn't right, no matter what anyone else says, you keep looking until you find the answers. ❖

In addition to his clinical background, Dr. Cameron has been actively involved in research and is the lead author of the International Lyme and Associated Diseases Society's (ILADS) treatment guidelines for tick-borne diseases.

Lyme Disease: *A Physician's Perspective*

AS A BOARD-CERTIFIED internist and epidemiologist, Daniel Cameron, MD, MPH, is also a nationally recognized expert in the treatment of tick-borne diseases. He has lectured at numerous medical and scientific conferences in the United States, Europe and Canada, and he is often interviewed by the news media, including nationally syndicated radio and television programs. For more than 25 years, he has been treating patients with Lyme and other tick-borne diseases through his private practice in Westchester County, N.Y.

BSTQ: You've been called a Lyme disease pioneer. What has driven your passion for treating Lyme disease?

Dr. Cameron: I have patients who have turned their lives around with a more individualized approach to Lyme disease. Having treated thousands of patients, we understand the emotionally devastating toll the illness can have on both the patient and family members, and we offer the highest quality of care in a compassionate, nonjudgmental environment.

BSTQ: Tell us about the International Lyme and Associated Diseases Society (ILADS) and its treatment guidelines.

Dr. Cameron: ILADS is a nonprofit, international, multidisciplinary medical society that promotes understanding of Lyme through research and education and strongly supports physicians and other healthcare professionals dedicated to advancing the standard of care for Lyme and its associated diseases. The ILADS guidelines document the evidence for an individualized approach to treating acute and chronic manifestations of Lyme disease.

BSTQ: What are the most prevalent misconceptions about chronic Lyme disease (CLD)?

Dr. Cameron: CLD has emerged as an umbrella term for the broad range of chronic manifestations of Lyme disease. The National Institutes of Health (NIH) trials enrolled three categories of individuals with chronic manifestations of Lyme disease: Lyme encephalopathy; persistent symptoms after Lyme disease with negative serologies; and post-Lyme disease syndrome (PLDS). PLDS was coined based on the NIH assumption that Lyme disease has been adequately treated after a two- to three-week course of antibiotics. Yet, there are no validated tests to rule out persistent infection. CLD typically does not assume that a short-term course of antibiotics is adequate to cure a patient. Some doctors believe chronic Lyme disease does not exist. Others believe patients suffer from posttreatment Lyme disease syndrome and not a persistent infection. Yet, there is no reliable test to be sure a persistent infection has resolved.

BSTQ: Are there a core set of symptoms with Lyme disease?

Dr. Cameron: The most common symptoms can mimic chronic fatigue and fibromyalgia. In one study, a series of individuals was ill for up to 14 years before being correctly diagnosed. These patients suffered with fatigue, sleep disturbance, poor memory and concentration, headaches, light-headedness, irritability, chest pain, joint pain, fibromyalgia and paresthesias. Physicians may also mistakenly rule out Lyme disease in patients who have had prior treatment for the disease. But those patients can still exhibit symptoms and benefit from antibiotic therapy.

BSTQ: What should practitioners know about coinfections?

Dr. Cameron: Coinfections can be challenging to diagnose since clinical features often overlap with many other tick-borne diseases. However, the importance of identifying and treating polymicrobial infections is critical in getting a patient well. Practitioners should consider coinfections in the diagnosis when a patient's symptoms are severe, persistent and resistant to antibiotic therapy. Coinfections typically exacerbate Lyme disease symptoms.

BSTQ: What are the core tests you use to diagnose Lyme infections?

Dr. Cameron: I routinely order a Lyme titer, IgG and IgM Western blot test for Lyme disease, and IgG and IgM for babesia, ehrlichia, anaplasmosis and bartonella.

BSTQ: Tell us how you address the emotional symptoms of Lyme disease.

Dr. Cameron: I actually devote much of my office visit to emotional symptoms. There simply is no one-size-fits-all treatment protocol. So, it's critical to invest time with patients to thoroughly understand their medical history and to closely monitor symptoms and treatment response to determine the best therapy to restore their health. ❖

TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

Message for At-Risk Adults: Flu Vaccination Will Reduce Your Risk of Cardiovascular Disease and Death

An ounce of prevention is worth a pound of cure. — Benjamin Franklin[1]

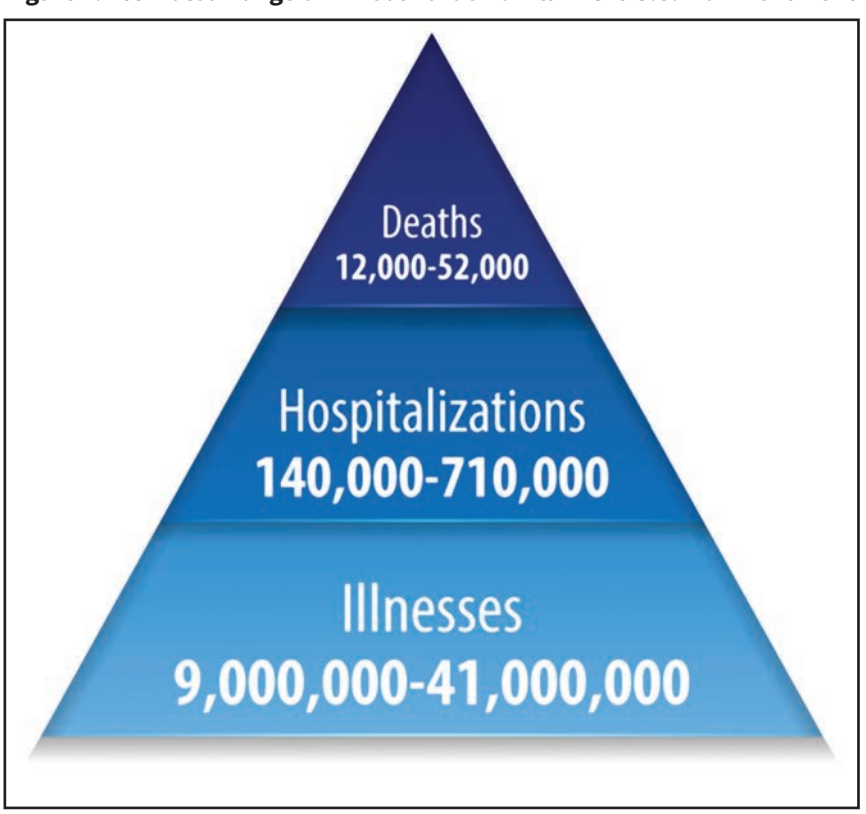
By Keith Berman, MPH, MBA

WITH INFLUENZA apparently returning with a vengeance this season, the Centers for Disease Control and Prevention is once again alerting the public that vaccination is the most effective way to prevent infection from and to minimize risk of severe symptoms and hospitalization for serious flu-related complications.[2] Yet only about half of all U.S. adults plan to get a flu vaccine during the 2022-2023 flu season, according to a survey conducted this fall by the National Foundation for Infectious Diseases.[3]

As one would expect, flu vaccination rates differ widely by age category. Over the 2021-2022 flu season, 74 percent of adults age 65 and older received a flu jab, far higher than the 52 percent and 37 percent vaccination rate for adults age 50 to 64 years and 18 to 49 years, respectively.

Nevertheless, at least one-quarter of all seniors will not receive a flu vaccine, leaving them unnecessarily exposed to increased risk of severe complications that can result in hospitalization and death. In older as well as nonelderly adults, preexisting cardiovascular disease, diabetes, renal disease, asthma, cancer history and HIV/AIDS are known major risk factors for flu-related hospitalization and death. An estimated 94 percent of U.S. adults hospitalized with flu-related complications last season had at least one underlying medical condition or other risk factor. Yet just 43 percent of adults age 18 to 49 years with one or more existing chronic health conditions (mainly heart disease, diabetes and/or lung disease) were vaccinated against flu during the 2021-2022 season.[2]

Figure 1. Estimated Range of Annual Burden of Flu in the U.S. from 2010-2020

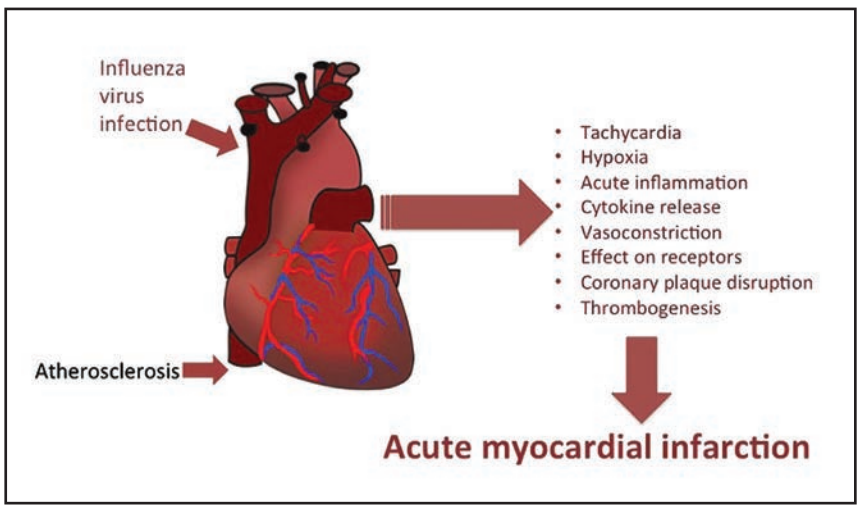


Source: Centers for Disease Control and Prevention. Burden of Flu. Accessed at www.cdc.gov/flu/about/burden/index.html.

Depending on multiple factors, including the pathogenicity of the circulating viruses, the protective effect of the flu vaccine and the vaccination rate, U.S. hospitalizations can range from roughly 150,000 to 700,000 and influenza-related deaths from around 10,000 to more than 50,000 over a single flu season (Figure 1).[4]

This grim toll could be reduced by simply increasing the vaccination rate, particularly for individuals in high-risk categories. But this hasn't happened to date; plainly, the messaging from providers and public health agencies isn't overcoming apathy or entrenched resistance. But some remarkably powerful findings of several newly published studies now present an opportunity to shift the argument for flu vaccination from "you can cut your risk of getting the flu and end up in the hospital" to "you can cut your risk of a heart attack or other acute cardiovascular event, and possibly death."

Figure 2. Mechanisms by Which Influenza Virus Infection May Precipitate Acute Myocardial Infarction



Reproduced from MacIntyre CR, Mahimbo A, Moa AM, et al. Influenza vaccine as a coronary intervention for prevention of myocardial infarction. *Heart* 2016;102:1953-6.

Flu and Cardiovascular History Begets Risk of New Cardiovascular Events

Existing cardiovascular disease is well-known to predispose individuals who contract seasonal influenza to a much-increased risk of hospitalization for pneumonia and other serious flu-related illness. In turn, the risk of a major adverse cardiovascular event (MACE) skyrockets in cases of influenza severe enough to land the patient in the hospital. In a cross-sectional study evaluating a sample of more than 80,000 U.S. adults hospitalized with laboratory-confirmed influenza over a recent eight-year period, nearly 12 percent — about one in every eight — experienced an acute cardiovascular event, most commonly acute heart failure and acute ischemic heart disease.[5] Nearly one-third of these stricken patients were admitted to the intensive care unit, and seven percent died in the hospital.

The temporal association between influenza infection and acute myocardial infarction (MI) is well-documented.[6] The virus is believed to predispose individuals with atherosclerotic coronary artery disease to heart attacks through a multiplicity of mechanisms (Figure 2), including inflammatory release of cytokines that result in a pro-thrombotic state; physiological effects, including hypoxia and tachycardia; increased metabolic demand resulting in inadequate coronary artery flow; and possibly even direct effects of the virus on the heart muscle itself.[7]

Can administering a standard flu vaccine therefore reduce the risk of a major cardiovascular event in patients hospitalized with influenza, in particular in those at increased risk of such an event? A Canadian-led investigative team set out to answer this question in a landmark meta-analysis of five high-quality randomized, placebo-controlled trials.[8] Across all enrolled subjects with and without a cardiovascular disease history, vaccination was associated with a 36 percent lower risk of composite cardiovascular events (2.9 percent vs. 4.7 percent; relative risk [RR], 0.64; 95 percent confidence interval [CI], 0.48-0.86). But a highly significant interaction was detected in the 36 percent of subjects with a history of acute coronary syndrome (ACS) over the previous year: Their relative risk of composite cardiovascular events dropped to 0.45, while subjects without recent ACS had a nonsignificant relative risk of 0.94. "The use of standard influenza vaccine was associated with a lower risk of major adverse cardiovascular events," the study authors concluded, and "the greatest treatment effect was seen among the highest-risk patients with more active coronary disease."

Over just the last two years, several new studies have both validated these findings and helped to more clearly quantify the extent to which a single 0.5 mL dose of seasonal influenza vaccine can reduce the risks of hospitalization, acute cardiovascular events and death in at-risk older individuals and those with preexisting cardiovascular disease.

Existing cardiovascular disease is well-known to predispose individuals who contract seasonal influenza to a much-increased risk of hospitalization for pneumonia and other serious flu-related illness.

Table. Key Primary and Secondary Outcomes from a Randomized, Placebo-Controlled Trial of Inactivated Influenza Vaccine After Myocardial Infarction[5]

Clinical Endpoint	Influenza Vaccine (n=1,272)	Placebo (n=1,260)	P Value
All-cause death, MI, stent thrombosis	67 (5.3%)	91 (7.2%)	0.040
All-cause death	37 (2.9%)	61 (4.9%)	0.010
Cardiovascular death	34 (2.7%)	56 (7.2%)	0.014
Myocardial infarction	25 (2.0%)	29 (2.4%)	0.86 (NS)
Stent thrombosis	6 (0.5%)	3 (0.2%)	0.34 (NS)

MI: Myocardial Infarction
NS: Nonsignificant

Post-Myocardial Infarction Flu Vaccination Cuts Risk of Death

Influenza Vaccination After Myocardial Infarction (IAMI) study. With support from the Swedish Heart-Lung Foundation and an unrestricted grant from Sanofi Pasteur, the multinational IAMI study randomized participants to receive inactivated influenza vaccine or a saline placebo injection within 72 hours after an invasive coronary procedure or hospitalization precipitated by a myocardial infarction (MI) event.[9] Because flu vaccination is already considered standard medical practice, placebo group patients were permitted to independently pursue vaccination outside the trial; 13 percent actually did so, which the investigators acknowledged would actually understate the vaccine's reported protective effect.

The primary endpoint — a composite of all-cause death, MI or stent thrombosis at 12 months — occurred in 67 of 1,272 participants assigned to receive flu vaccine (5.3 percent) and 91 of 1,260 participants assigned to placebo (7.2 percent), yielding a 28 percent reduction in MACE (95 percent CI, 0.52-0.99; p=0.040). The 2.9 percent mortality rate for subjects who were vaccinated was 41 percent lower than the 4.9 percent death rate in those who received placebo injections (HR, 0.59; 95 percent CI, 0.39-0.89; p=0.010). (Table)

While rates of MI in the two treatment groups were not significantly different (2.0 and 2.4 percent, respectively), the rate of cardiovascular death in the flu vaccine group was significantly lower by a remarkable 41 percent — 2.7 percent compared to 4.5 percent in the placebo group (HR, 0.59; 95 percent CI, 039-0.89; p=0.014). There was no increase in serious adverse events associated with post-MI flu vaccine administration, confirming its safety in the immediate post-MI period.

> Can administering a standard flu vaccine therefore reduce the risk of a major cardiovascular event in patients hospitalized with influenza, in particular in those at increased risk of such an event?

The IAMI investigators concluded that their findings "support and even strengthen" an existing American Heart Association/American College of Cardiology Guideline in place since 2006, which recommends flu vaccination for all patients with established coronary artery disease.

The nonsignificant reduction seen in postvaccination MI events over the 12-month follow-up period is consistent with a recent meta-analysis of 16 mainly observational studies, comprising almost 240,000 patients, that found just a 13 percent relative risk reduction in MACE over a median follow-up of 20 months.[10] But this modest benefit of flu vaccination in reduced heart attack risk is dwarfed by its very large benefit in reduced risk of all-cause and cardiovascular death.

In an accompanying editorial, the commenters pointed out that the IAMI study's impressive reduction in the cardiovascular death rate occurred in post-MI patients who were also well-managed with the full spectrum of supportive cardiac, anti-thrombotic, lipid-lowering and other drug treatments following hospital discharge. "The benefit of influenza vaccine was incremental to [these treatments]," they noted.[11]

Updated meta-analysis of IAMI plus five other randomized controlled trials (RCTs). Published in April 2022, this new meta-analysis pooled a total of 9,001 patients from the IAMI trial and five high-quality RCTs evaluating trivalent or quadrivalent flu vaccine against placebo or no treatment.[12] Four of the six trials enrolled hospital inpatients or outpatients with recent ACS or stable coronary artery disease with planned percutaneous

coronary intervention, while the other two trials enrolled unselected outpatients.

Once again, subjects with a recent ACS history who received a standard flu vaccine experienced a 45 percent lower risk of MACE than nonvaccinated control subjects. No treatment interaction was detected for those without a recent ACS (RR, 1.00, 95 percent CI, 0.68-1.47). Administration of flu vaccine was associated with an even more impressive 56 percent reduction in risk of cardiovascular mortality relative to nonvaccinated subjects.

How does flu vaccination so substantially reduce the cardiovascular and all-cause death rate in even the highest-risk post-MI population? In simplest terms, it likely boils down to the extent of the vaccine's ability to prevent infection, mitigate symptomatic influenza infections and lessen the severity of a constellation of cardiovascular disease complications in individuals who do become infected (Figure 3).

DANFLU-1: High Dose, Lower Death Rate

The natural decline in immunity with age largely accounts for the fact that people age 65 and older account for the majority of hospitalizations and 80 to 90 percent of U.S. flu-related deaths. To address this problem, Sanofi Pasteur developed the Fluzone High-Dose vaccine, which delivers four-fold higher quantities of haemagglutinin antigens than the standard 15 ug per strain and elicits substantially higher hemagglutinin inhibition titers.

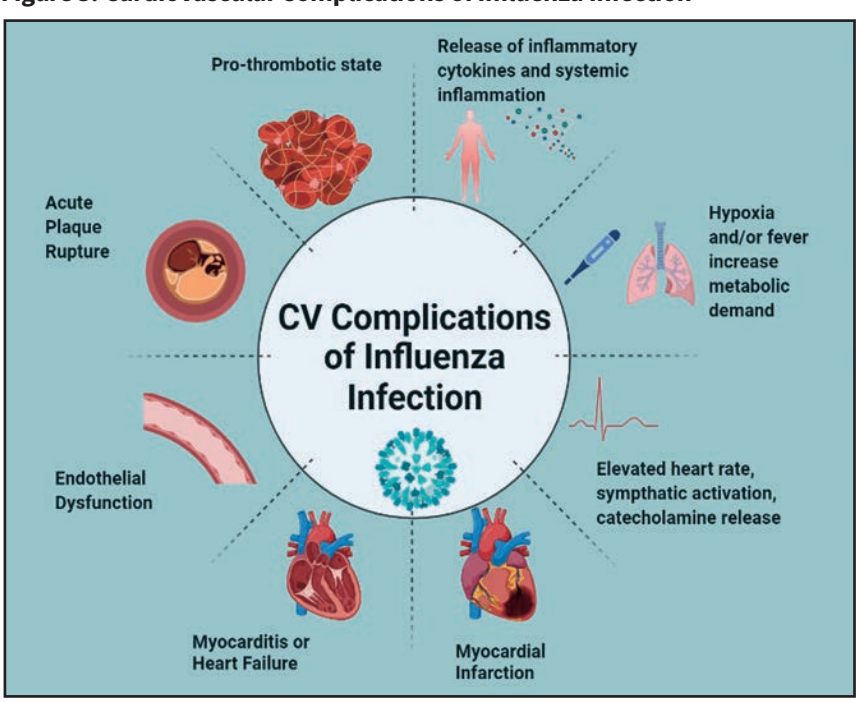
The postulate that this higher antigen dose could translate into a lower rate of laboratory-confirmed influenza-like illness (ILI) was validated by a landmark U.S.-Canadian trial of Sanofi Pasteur's Fluzone High-Dose vaccine nearly a decade ago.[13] A subsequent retrospective cohort analysis of insurance claims for more than 2.5 million Medicare beneficiaries found that the high-dose flu vaccine was associated with 22 percent lower rates of both ILI and influenza-related hospital admissions than standard-dose flu vaccine.[14]

Then in August of this year, results from DANFLU-1, a Danish open-label pragmatic feasibility trial conducted in collaboration with Sanofi Pasteur, were presented at the European Society of Cardiology Congress in Barcelona. In 1,000 vaccination sessions across Denmark organized by a private vaccination provider, a total of 12,477 participants aged 65 to 79 years were randomized to receive quadrivalent high-dose or standard-dose vaccine. Their baseline characteristics were comparable to the overall Danish population of the same age; in particular, 20.4 percent of trial participants had chronic cardiovascular disease compared to 22.9 percent of the national population.

High-dose flu vaccine recipients had a nearly 65 percent lower risk of being hospitalized for influenza or pneumonia, with 10 cases (0.016 percent) compared to 28 cases (0.045 percent) among standard-dose recipients. And despite the fact that just one of every five participants in both groups had known preexisting cardiovascular disease, high-dose flu vaccine recipients experienced half the risk of all-cause mortality relative to standard-dose vaccine, with 21 versus 41 deaths, respectively. There were no significant differences in serious adverse events between the two dosage groups.

Now that the feasibility of integrating administrative health registries with an influenza vaccine trial has been demonstrated, "the next step is to conduct a fully powered trial of high-dose versus standard-dose quadrivalent flu vaccine in older adults," according to lead investigator

Figure 3. Cardiovascular Complications of Influenza Infection



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Professor Tor Biering-Sørensen at the University of Copenhagen. This new trial, dubbed DANFLU-2, is expected to enroll roughly 200,000 participants.

To date, no head-to-head studies have reported cardiovascular event outcomes with CSL Seqirus' standard-dose MF59-adjuvanted influenza vaccine (Fluad) compared with nonadjuvanted flu vaccine. But numerous studies have established that, in adults age 65 years and older, Fluad elicits a greater immune response, has superior vaccine effectiveness and is more effective in preventing hospitalization caused by influenza complications.[15] There is every reason, then, to postulate that Fluad Quadrivalent can also confer better protection against major cardiovascular complications in older individuals with preexisting cardiovascular disease than standard nonadjuvanted flu vaccines.

post-MI patients in particular, he offers several suggestions:

- Add influenza vaccination to their drug checklist, along with their cardiac and lipid-lowering drugs and lifestyle recommendations;
- Offer vaccination in the hospital before discharge; and
- Double-check and confirm receipt of vaccination on enrollment in cardiac rehabilitation.

In the future, large-scale studies like DANFLU-2 will provide more definitive estimates of the benefits of flu vaccination in reduced cardiovascular morbidity and mortality in older adults and in those with preexisting cardiovascular disease, as well as those with other risk factors such as diabetes and chronic lung disease. But in truth, we now have more than ample evidence that the lives of many thousands of these individuals can be saved each year by convincing them to receive a single dose of low-cost flu vaccine.

> The natural decline in immunity with age largely accounts for the fact that people age 65 and older account for the majority of hospitalizations and 80 to 90 percent of U.S. flu-related deaths.

To Patients: Get the Shot to Prevent MI, Death

"It is time to change the thinking around vaccination as just being a prevention strategy for the avoidance of viral illness, but as a prevention strategy for avoidance of cardiovascular morbidity and mortality," says University of Toronto cardiologist and flu vaccine clinical trialist Jacob Udell, MD, MPH.[11] Going a step further, Dr. Udell calls for new implementation strategies to boost vaccination rates in demographic groups at highest risk of a heart attack or other MACE. For

Flu vaccination is important for everyone, but it is especially so for those at higher risk from potentially serious complications of flu. But now, thanks to IAMI, DANFLU-1 and the newest published meta-analyses, you as physicians, pharmacists and ancillary medical staff have all the justification you need to encourage your resistant patients to get the flu vaccine recommended for them, and to deliver your message with perhaps a bit more clout: We're in the flu season, and complications if you get the flu can be as severe as a fatal heart attack. The flu vaccine we're recommending is safe and it's the only effective treatment we have to help prevent that from happening to you. Now it's your choice. ❖

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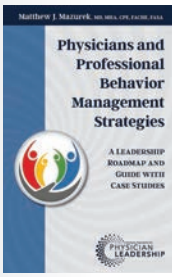

Physicians and Professional Behavior Management Strategies: A Leadership Roadmap and Guide with Case Studies

Author: Matthew J. Mazurek, MD, MHA, CPE, FACHE, FASA

Physicians and Professional Behavior Management Strategies aims to assuage one of the most difficult tasks physician leaders regularly face: managing and mitigating unprofessional physician conduct complaints from patients, colleagues, nurses and staff. It also aims to instill confidence by providing practical advice and guidance on managing disruptive behavior with real-world case examples and in-depth discussion on the process. Case examples include sexual harassment, physical aggression, substance abuse, and how to have difficult conversations and conduct meetings with proactive follow up. Complementing the case discussions are strategies to reduce and mitigate disruptive behavior.

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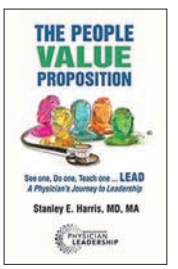
The People Value Proposition: See One, Do One, Teach One ... LEAD, A Physician's Journey to Leadership

Author: Stanley E. Harris, MD, MA



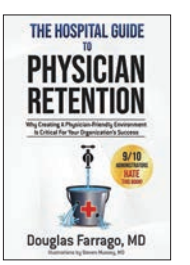
From topics like "The Journey to Leadership," "Defining the Leader You Want to Become" and "Inspiration and Innovation," *The People Value Proposition* acknowledges that leadership begins with the individual, but emphasizes that by recognizing and nurturing the value of others, everyone succeeds. Author Stanley Harris, MD, MA, discusses the importance of empathy, engagement and motivation to sustain connectivity, inspire innovation and enable new leaders to emerge. Written as a semi-autobiographical account of leadership development that covers key principles of leadership, the book is conveyed from the unique perspective of the author's life and experience. It challenges both leaders and potential leaders to acknowledge and promote the value of every individual, enabling optimal utilization of resources and continued team success.

www.amazon.com/People-Value-Proposition-Physicians-Leadership/dp/0996663274

The Hospital Guide to Physician Retention: Why Creating a Physician-Friendly Environment Is Critical For Your Organization's Success

Author: Douglas Farrago, MD

This book explains why doctors are leaving their jobs and answers the question "What is the Great Resignation?" while giving readers actionable ideas about how to fix it. Creating the right work environment is critical to keeping good doctors who will help recruit other doctors — all of which leads to happier and more satisfied patients. Douglas Farrago, MD, uses the insights he has learned from 25 years as a family physician, his vast experience being an employed physician and physician leader, and his vast connections to other doctors to give readers the inside scoop on how to keep physicians happy so they stay longer.



www.amazon.com/Hospital-Guide-Physician-Retention-Physician-Friendly-ebook/dp/B09TDJV855

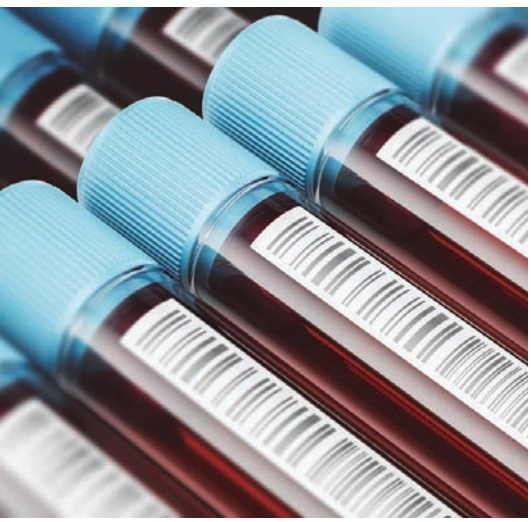
Ig Therapy Products and Risk Factors Chart

Author: Immunoglobulin National Society

The Ig Therapy Products and Risk Factors Chart contains information about U.S. Food and Drug Association-approved immune globulin (IG) brands, patient and product risk factors and risk mitigation strategies. Included are dosing and administration guidelines, formulation differences, available sizes and storage, and a risk factors and interventions tear sheet. The poster can be downloaded free of charge for reference.

ig-ns.org/product/ig-therapy-products-and-risk-factor-chart

Antibody Targeting Tissue Factor Pathway Inhibitor (TFPI) Sharply Reduces Bleeding Rate in Hemophilia A and B Patients



Subcutaneous administration of marstacimab, an investigational human monoclonal antibody targeting tissue factor pathway inhibitor (TFPI), resulted in a roughly 10-fold lower annualized bleeding rate (ABR) in 26 hemophilia patients than comparable control individuals in previous clinical trials who were treated on-demand with recombinant factor replacement therapy. This Phase Ib/II clinical study was sponsored by Pfizer, which is developing marstacimab for treatment of hemophilia A and B with and without inhibitors.

Sixteen (61.5 percent) and seven (26.9 percent) of treated study subjects had hemophilia A without and with inhibitors, respectively, and three (11.5 percent) had hemophilia B. Twenty-four of the 26 subjects had joints with a history of multiple bleeds (target joints). Once-weekly dosages ranged from 150 mg to 450 mg.

The mean ABR was 2.67 across all marstacimab-treated subjects, compared to an ABR of 27.62 in historical control subjects who received on-demand ReFacto (moroctocog alfa) or BeneFIX (nonacog alfa). Both TFPI and peak thrombin levels increased with marstacimab treatment, indicative of effective targeting of TFPI. Marstacimab was "generally safe and well-tolerated at all dose levels," according to the investigators, with no thrombotic events or serious treatment-related adverse events. Decreases in circulating fibrinogen relative to baseline were observed at all dosage levels, but were not below the lower limit of the normal range and were reversible with treatment discontinuation.

An ongoing Phase III study (NCT03938792) evaluating marstacimab is enrolling a planned 145 adult and adolescent subjects with severe hemophilia A or moderately severe to severe hemophilia B. All participants are initially receiving a 300 mg loading dose followed by 150 mg weekly; a 300 mg weekly dosage is prescribed for those who meet dose escalation criteria. ❖

Mahlangu JN, Lamas JL, Morales JC, et al. A Phase 1b/2 clinical study of marstacimab, targeting human tissue factor pathway inhibitor, in haemophilia. *Br J Haematol* 2022 Aug 23. Online ahead of print.

RNA Interference Therapeutic Reduces Hepatotoxic Mutant Z-AAT Levels in Patients With Alpha1-Antitrypsin Deficiency

In a Phase II trial of participants with hepatic disease associated with congenital alpha1-antitrypsin deficiency (AATD), subcutaneous administration of fazirsiran, an investigational RNA interference therapeutic, reduced both serum and hepatic levels of the mutant hepatotoxic AAT protein Z-AAT, with concurrent improvements in enzymatic and histological markers of liver function. Individuals with the homozygous PiZZ genotype produce mutant Z-AAT protein that accumulates in hepatocytes, leading to progressive liver disease and fibrosis.

Twelve patients with the PiZZ genotype and liver fibrosis received fazirsiran at a dose of 200 mg, and four others received 100 mg, on day 1, week 4 and then every 12 weeks. Reduced liver accumulation of Z-AAT was documented in all patients, with a median reduction of 83 percent at week 24 or 48. Concentrations of alanine aminotransferase decreased in all 12 patients whose levels were above the upper limit of the normal range at baseline.

Fibrosis regression was observed in seven of 12 patients receiving the 200 mg dose of fazirsiran after 24 or 48 weeks, including two patients with cirrhosis, but in none of the three patients who received the lower 100 mg dose. Fazirsiran treatment was also associated with a 69 percent reduction in histologic globule burden, from a mean score of 7.4 at baseline to mean score of 2.3 after 24 or 48 weeks. Four serious adverse events resolved spontaneously, and there were no adverse events leading to trial or drug discontinuation. Fazirsiran is being co-developed by Arrowhead Pharmaceuticals and Takeda Pharmaceuticals. ❖

Strnad P, Mandorfer M, Choudhury G, et al. Fazirsiran for liver disease associated with al-pha1-antitrypsin deficiency. *New Engl J Med* 2022 Aug 11;387(6):514-24.

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2023, through March 31, 2023

	Product	Manufacturer	J Codes	ASP + 6% (before sequestration)	ASP + 4.3% (after sequestration)
IVIG	ASCENIV	ADMA Biologics	J1554	$963.54	$948.09
	BIVIGAM	ADMA Biologics	J1556	$140.98	$138.72
	FLEBOGAMMA DIF	Grifols	J1572	$83.07	$81.74
	GAMMAGARD SD	Takeda	J1566	$147.18	$144.82
	GAMMAPLEX	BPL	J1557	$104.75	$103.07
	OCTAGAM	Octapharma	J1568	$82.13	$80.81
	PANZYGA	Octapharma/Pfizer	90283/J1599	$143.17	$140.87
	PRIVIGEN	CSL Behring	J1459	$95.14	$93.61
IVIG/SCIG	GAMMAGARD LIQUID	Takeda	J1569	$91.10	$89.64
	GAMMAKED	Kedrion	J1561	$95.59	$94.06
	GAMUNEX-C	Grifols	J1561	$95.59	$94.06
SCIG	CUTAQUIG	Octapharma	J1551	$126.27	$124.24
	CUVITRU	Takeda	J1555	$150.58	$148.17
	HIZENTRA	CSL Behring	J1559	$126.24	$124.22
	HYQVIA	Takeda	J1575	$160.42	$157.85
	XEMBIFY	Grifols	J1558	$129.75	$127.67

Calculate your reimbursement online at www.FFEnterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	ASCENIV LIQUID, 10%	ADMA Biologics	PI	5 g
	BIVIGAM LIQUID, 10%	ADMA Biologics	PI	5 g, 10 g
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	0.5 g, 2.5 g, 5 g, 10 g, 20 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Takeda	PI, ITP, B-cell CLL, KD	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g, 25 g
	OCTAGAM Liquid, 10%	Octapharma	ITP, DM	2 g, 5 g, 10 g, 20 g, 30 g
	PANZYGA Liquid, 10%	Octapharma/Pfizer	PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Takeda	IVIG: PI, MMN	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI	
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	1 g, 5 g, 10 g, 20 g
			SCIG: PI	
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
SCIG	CUTAQUIG Liquid, 16.5%	Octapharma	PI	1 g, 1.65 g, 2 g, 3.3 g, 4 g, 8 g
	CUVITRU Liquid, 20%	Takeda	PI	1 g, 2 g, 4 g, 8 g, 10 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g 1 g PFS, 2 g PFS, 4 g PFS
	HYQVIA Liquid, 10%	Takeda	PI	2.5 g, 5 g, 10 g, 20 g, 30 g
	XEMBIFY Liquid, 20%	Grifols	PI	1 g, 2 g, 4 g, 10 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
DM Dermatomyositis
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease
PFS Prefilled syringes

2022-2023 Influenza Vaccine

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Product	Manufacturer	Presentation	Age Group	Code
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	3 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	6 months and older	90687/90688
FLUAD (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90694
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	6 months and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	6 months and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUMIST (LAIV4)	ASTRAZENECA	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	6 months and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE HIGH-DOSE (IIV4)	SANOFI PASTEUR	0.7 mL PFS 10-BX	65 years and older	90662

ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray

* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

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