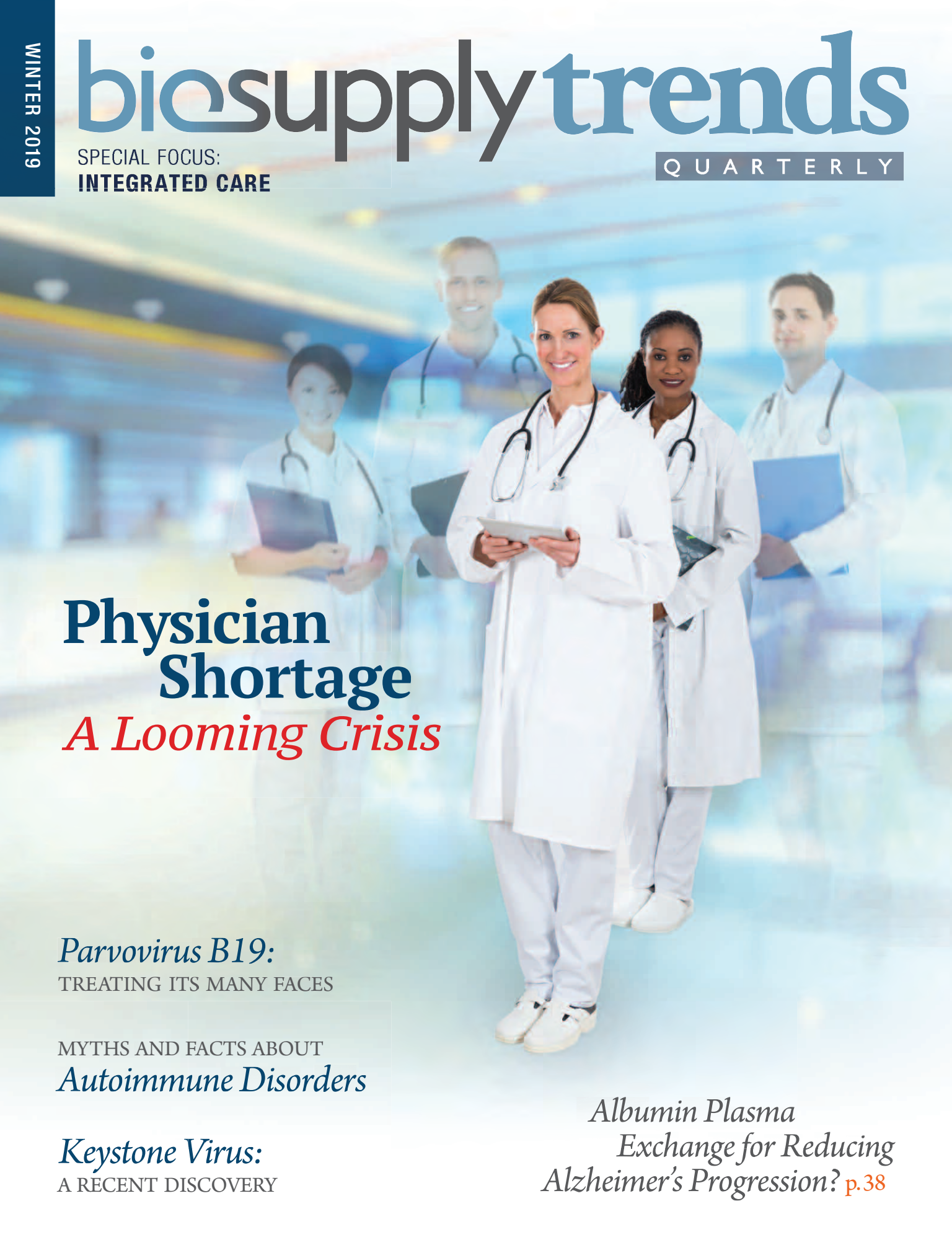
WINTER 2019

biosupply trends

QUARTERLY

SPECIAL FOCUS:
INTEGRATED CARE



Physician Shortage
A Looming Crisis

Parvovirus B19:
TREATING ITS MANY FACES

MYTHS AND FACTS ABOUT
Autoimmune Disorders

Keystone Virus:
A RECENT DISCOVERY

Albumin Plasma Exchange for Reducing Alzheimer's Progression? p. 38

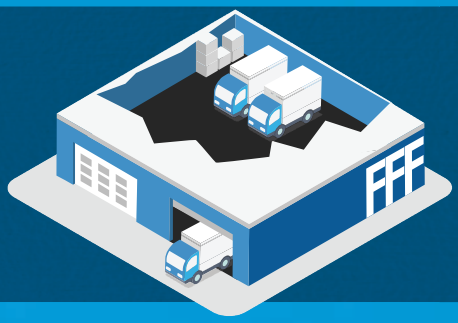
8 Critical Steps

Purchasing

At FFF, we only purchase products from the manufacturer–never from another distributor or source. This means the integrity of our products is never in question from tampering or mishandling.

Storage

We store and transport viable protein compounds that are sensitive to temperature variations. Temperature controlled, monitored 24/7, and supported with backup generators in the event of power loss.

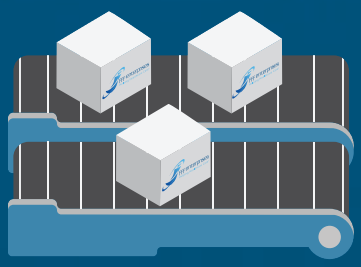


Specialty Packaging

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

Interactive Allocation

Assures responsible, demand-based distribution of critical-care products in challenging market conditions. Reduces potential for gray-market purchasing to accommodate critical demand issues.



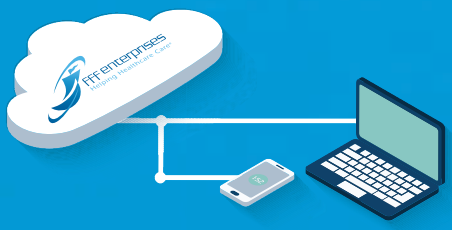
To Guaranteed Channel Integrity™

Delivery

We deliver only to facilities with a state-issued license, and only to the address on the license. We make no exceptions. It is our commitment to do everything in our power to prevent products from entering a secondary distribution channel.

Methods of Delivery

Monitoring and adjusting for extreme weather conditions allows time-sensitive delivery to ensure product integrity.



Verification

In compliance with 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.

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.

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

FFF enterprises
Helping Healthcare Care®

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BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

BioSupply Trends Quarterly (ISSN 1948-2620) is a national publication, with quarterly themed issues.

Publisher: FFF Enterprises, Inc., 44000 Winchester Road, Temecula, CA 92590

Subscriptions to *BioSupply Trends Quarterly* are complimentary. Readers may subscribe by calling (800) 843-7477 x1351.

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Keeping Pace with the Changing Healthcare Landscape

THE HEALTHCARE landscape is constantly changing with new challenges faced by the medical profession, as well as emerging and evolving diseases that threaten the public's health. In this issue, we highlight several of these concerns that are making headlines.

As the rising demand continues for physicians to care for an aging population, the threat of an imminent physician shortage is causing alarm. It's predicted that by 2030, the U.S. healthcare system will be understaffed by some 15,000 to 50,000 primary and specialty care physicians. While it would seem the problem stems from a declining number of medical school students, the truth is medical school admissions and graduation are at an all-time high. Unfortunately for graduates, there is a lack of federal funding for residency programs for these students to complete their medical training. Add to this the changing demographics that require increased medical care and the ensuing doctor burnout, and the shortfall grows larger. As we discuss in our article "Combating the Shortage of Primary and Specialty Care Physicians" (p.16), steps to remedy this issue have commenced, and new measures are being put in place such as team-based care, better utilization of technology to lessen workloads, and investment in new medical schools in underserved areas to address the doctor shortage in rural and nonurban areas.

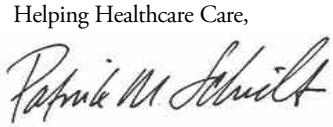
Another looming challenge for healthcare professionals arises primarily from the use of electronic health records. In 2017, 83 percent of physicians surveyed reported experiencing some form of a cyber attack through phishing, computer viruses and, mostly, ransomware. In fact, healthcare practices are extremely vulnerable to cyber attacks since patient data is so lucrative on the black market — much more so than even credit card numbers. But, while not all forms of cyber attacks can be prevented, thwarting most can be achieved by implementing some best practices that involve both employee training and technology safeguards. These methods for reducing the likelihood of cyber attacks, as well as how to respond when they occur, are presented in our first new Health Management column "Preventing and Responding to Cyber Attacks" (p.10).

On the patient front, antibiotic-resistant illnesses are not only increasing, but have become a serious threat. Once considered miracles for their exceptional effectiveness in treating infections, antibiotics have for years been overprescribed, misused and abused, rendering them ineffective in treating microorganisms that have morphed into superbugs. As we highlight in our article "The Growing Threat of Antibiotic-Resistant Illnesses" (p.20), healthcare organizations are vigilant about this threat, and are responding by implementing a wide range of programs across the globe.

Also affecting patients are newly discovered diseases, the most recent of which is known as Keystone virus. While it was first identified more than half a decade ago, the first case in humans was confirmed just this year. As our article "Heads-Up on Keystone Virus Disease" (p.30) explains, the vector-borne disease is largely confined to the Gulf Coast region, but much is still unknown about the risks it poses, and answers to many questions remain at large.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it both relevant and helpful to your practice.

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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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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CMS Launches Medicare Advantage Qualifying Payment Arrangement Incentive Demonstration

The Centers for Medicare and Medicaid Services (CMS) is launching the Medicare Advantage Qualifying Payment Arrangement Incentive (MAQI) demonstration. MAQI is designed to test whether exempting merit-based incentive payment system (MIPS)-eligible clinicians who participate to a sufficient degree in certain payment arrangements with Medicare Advantage Organizations (MAOs) from the MIPS reporting requirements and payment adjustment will increase or maintain participation in payment arrangements similar to advanced alternative payment models (APMs) with MAOs. In addition, it is designed to test whether it will change the manner in which clinicians deliver care. Specifically, the demonstration will test whether:

- There is an increase in clinician participation arrangements with MAOs that meet the criteria of qualifying payment arrangements;
- Participating in qualifying payment arrangements and advanced alternative payment models to the degree required to be eligible for the demonstration waiver incentivizes providers to transform their care delivery (assessed by interviews with participating clinicians);
- There is a change in utilization patterns among participants in the demonstration; and
- If there are changes in utilization, how those changes affect Medicare Advantage plans.

The MAQI demonstration, which will be tested under the authority of Section 402 of the Social Security Amendments Act of 1967, began in 2018 and will last for five years. ❖

The Medicare Advantage Qualifying Payment Arrangement Incentive Demonstration. Centers for Medicare and Medicaid Services press release, July 12, 2018. Accessed at www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2018-Fact-sheets-items/2018-07-12.html.

CMS Final Rule Updates 2019 Medicare Payment Rates and Wage Index for Hospices

The Centers for Medicare and Medicaid Services (CMS) has issued a final rule that updates the 2019 Medicare payment rates and wage index for hospices servicing Medicare beneficiaries. Under the rule, hospices will receive a 1.8 percent ($340 million) increase in payments for 2019. The new payment system includes a statutory aggregate cap of $29,205.44 that limits the overall payments made to a hospice annually.

Also included in the final rule are updates to the hospice quality reporting program requirements that reduce payments by 2 percent if hospices fail to meet those requirements; finalized procedural policies, including a review and correction timeframes for data submitted using the hospice item set; and specific updates and improvements to hospice, including the public display of hospice item set-based hospice comprehensive assessment measure and hospice visits when death is imminent.

Lastly, the final rule recognizes that as of 2019, the Bipartisan Budget Act of 2018 allows physician assistants to be recognized along with physicians and nurse practitioners as attending physicians for Medicare hospice beneficiaries. ❖

Morse S. Hospices Get 1.8 Percent Payment Increase for 2019. Healthcare Finance News, Aug. 1, 2018. Accessed at www.healthcarefinancenews.com/news/hospices-get-18-percent-payment-increase-2019.

Court Upholds Reimbursement Cut for 340B Drug Discount Program

On July 17, the U.S. Court of Appeals for the District of Columbia upheld the reimbursement cut that took effect on Jan. 1 for drugs purchased under the 340B Drug Discount Program reimbursed under the Medicare hospital Outpatient Prospective Payment System (OPPS). As such, 340B-covered entity hospitals must continue to absorb a 28.5 percent cut under OPPS. However, the court did say it would consider the merits of the case in the future, so many hospitals are assessing the ruling's financial impact and taking steps to preserve potential remedies if the cuts are ultimately overturned or reversed.

A final rule issued last year by the Centers for Medicare and Medicaid Services reduced reimbursement under OPPS for 340B drugs from the drug's average sales price (ASP) plus 6 percent to the current rate of ASP minus 22.5 percent. ❖

Church RP, Severson RJ, and Matava EM. 340B Update: D.C. Court of Appeals Upholds Medicare B Reimbursement Cut. K&L Gates, July 20, 2018. Accessed at www.klgates.com/340b-update-dc-court-of-appeals-upholds-medicare-part-b-reimbursement-cut-07-20-2018.

Revised Medical Program Integrity Manual Is a 'Roadmap' to LCD Process

The Centers for Medicare and Medicaid Services has revised Chapter 13 of the Medicare Program Integrity Manual to include instructions, policies and procedures that Medicare Administrative Contractors (MACs) use to administer the Medicare fee-for-service program. The revisions, the first since August 2015, revamp the format of the manual so it can be used as a "roadmap" for the local coverage determination (LCD) process. Important changes include:

- Requiring a consistent, standardized summary of the clinical evidence supporting LCD decisions;
- Including a beneficiary representative

and other healthcare professionals in addition to physicians such as nurses and social workers on Contractor Advisory Committees that inform LCDs; and

- Ensuring Contractor Advisory Committee meetings are open to the public.

In addition, the revisions include a new process that takes further steps to be responsive to patient needs by allowing patients to request a new LCD and by holding open meetings virtually (e.g., by webinar) instead of in-person to allow for broader participation.

A full list of changes to the manual can be found at www.cms.gov/newsroom/fact-sheets/summary-significant-changes-medicare-program-integrity-manual-chapter-13-local-coverage. ❖

CMS Accelerates Innovation and Promotes Patient Access to Medical Technology. Centers for Medicare and Medicaid Services press release, Oct. 3, 2018. Accessed at www.cms.gov/newsroom/press-releases/cms-accelerates-innovation-and-promotes-patient-access-medical-technology.

Grants Awarded to Fund New Clinical Trials for Products to Treat Rare Diseases

The U.S. Food and Drug Administration (FDA) has awarded 12 new clinical trial research grants to principal investigators from academia and industry totaling more than $18 million over the next four years to enhance the development of medical products for patients with rare diseases. The grants were awarded through the Orphan Products Clinical Trials Grants Program, which are intended for clinical studies evaluating the safety and effectiveness of products that could either result in or substantially contribute to FDA approval of products targeted to the treatment of rare diseases. Grant applicants were reviewed and evaluated for scientific and technical merit by more than 100 rare disease experts.

One-third of the new awards aim to accelerate cancer research by enrolling patients with rare forms of cancer, including advanced pancreatic cancer and neck squamous cell carcinoma, myelodysplastic syndrome and acute myeloid leukemia. Another 25 percent of the new awards fund studies evaluating drug products for rare endocrine disorders, including Cushing disease, dopamine agonist intolerant hyperprolactinemia and congenital adrenal hyperplasia. Another study addressed an unmet need in primary sclerosing cholangitis, a rare, chronic and potentially serious bile duct disease. Approximately 42 percent of the grants fund studies that enroll children and adolescents, targeting a variety of rare diseases in children such as Stargardt disease, dystrophic epidermolysis bullosa and bronchopulmonary dysplasia.

To date, the program's grants have supported research that led to the marketing approval of more than 60 orphan products. "Since its creation in 1983, the Orphan Products Grants Program has provided more than $400 million to fund more than 600 new clinical studies," said Debra Lewis, OD, acting director of FDA's Office of Orphan Products

Development. "We are encouraged to see so much interest in our grants program and are pleased to support research for a variety of rare diseases that have little or no treatment options for patients." ❖

FDA Awards 12 Grants to Fund New Clinical Trials to Advance the Development of Medical Products for the Treatment of Rare Diseases. U.S. Food and Drug Administration press release, Sept. 24, 2018. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm621490.htm?elqTrackId=14E2501EBAA03912B88DE9588EB09938&elq=afa442eef32942a389ebf9363077cf25&elqaid=5200&elqat=1&elqCampaignId=4157.

Impacts of the Opioid Crisis Response Act

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE FINAL VERSION of the Opioid Crisis Response Act (H.R. 6) has been signed into law to address the nationwide opioid crisis by expanding and creating programs for prevention, treatment and recovery. Its far-reaching provisions affect health insurance, law enforcement, the pharmaceutical industry and IT capabilities and offerings. By temporarily eliminating the cap on Medicaid payments for large treatment facilities, the bill allows states to receive federal Medicaid matching funds for up to 30 days per year for services provided in institutions for mental diseases to adults aged 21 years to 64 years for substance-use disorders. It addresses health insurance for former foster youth, maternal and infant health, and parity in Children's Health Insurance Program (CHIP) mental health and substance-use disorder benefits. It also seeks to stymie illicit opioids shipped to the United States from other countries by helping the U.S. Postal Service better screen packages for illegal drug shipments, especially synthetic fentanyl and its analogs that are fueling the rise in overdose deaths.

Impacts on Pharma

The bill encourages the pharmaceutical industry to pursue the development of nonaddictive painkillers and other medication-assisted treatment. It provides manufacturers and wholesale distributors access to information about pharmacies' controlled substance orders. And, it clarifies the term "suspicious order" and adds requirements for wholesale distributors, manufacturers and the drug enforcement agency related to detection and reporting of suspicious orders. In addition, the use of medication therapy management (MTM) to address cost-effective means for disposal of controlled substances is required by January 2021. Lastly, certain states will be provided with grant funding for disposal of controlled substances.

Impacts on Providers

At the facility level, the bill creates a demonstration program to promote alternatives to opioids in emergency departments and care coordination for drug overdose patients. Most important are revisions to the Hospital Consumer Assessment of Healthcare Providers and Systems questions about pain management and improvements in coordination of prescription drug monitoring programs. In July, facilities will be provided access to telehealth to expand treatment of substance use disorders. The Centers for Medicare and Medicaid Services is charged with issuing guidance to states about options for federal reimbursement for substance-use disorder services and treatment using telehealth, including assessment, medication-assisted treatment, counseling, medication management and medication adherence with prescribed medication regimens under Medicaid.

At the clinician and healthcare practitioner level, the bill permits more providers to prescribe therapies with medication-assisted treatments by permanently allowing nurse practitioners and physician assistants to prescribe buprenorphine, as well as allowing nurse anesthetists, nurse midwives and clinical nurse specialists to prescribe it for the next five years. An increase in innovative research on pain treatment is supported as well.

Implementation of the Act

Many of the federal requirements have phase-in dates, especially those that fall under Medicare. As of January 2021: 1) Electronic prescribing is required for Schedule II-V controlled-substance prescriptions (under Medicare Advantage [MA] and Part D plans), but that does not affect pharmacists' ability to dispense prescriptions that are not electronically prescribed or the plans' ability to cover otherwise valid written, oral or faxed prescriptions; 2) Prescription drug plan sponsors and MA organizations must provide standardized electronic prior authorization requests from prescribers and subsequent responses; and 3) At-risk beneficiaries are eligible for MTM under Part D; however, mandatory drug management programs (lock-ins) for at-risk beneficiaries are delayed until January 2022.

Since some responsibilities fall to the states, implementation may vary. The Centers for Disease Control and Prevention is tasked with providing

support for prescription drug monitoring program (PDMP) enhancements, and providers must check the PDMP before prescribing Schedule II controlled substances. States are also being encouraged by Medicaid to administer a "qualified" PDMP that satisfies minimum criteria related to the timeliness of information, content and workflow. In addition, states are permitted to create plans to impose certain drug review and utilization requirements intended to prevent "doctor shopping." These include safety edits (prescriber overrides) for opioid refills and the maximum morphine equivalent that can be prescribed for chronic pain, as well as an automated claims review process that monitors concurrent opioid and benzodiazepine or antipsychotic prescriptions.

Education and Evidence-Based Resources

On a federal level, the U.S. Department of Health and Human Services (HHS) is charged with developing educational materials for pharmacists, healthcare providers and patients related to the pharmacists' ability to decline to fill controlled substance prescriptions. HHS will consult with pharmacists pertaining to a report to House and Senate committees that will contain options for revising payment to providers and suppliers of services and coverage related to the use of multidisciplinary, evidence-based, nonopioid treatments for acute and chronic pain management for Medicare beneficiaries. And, the U.S. Food and Drug Administration (FDA) will consult with pharmacists and other stakeholders to develop evidence-based opioid analgesic prescribing guidelines for indication-specific treatment of acute pain.

Approved Risk Evaluation and Mitigation Strategies (REMS)

The FDA Amendments Act of 2007 gave FDA the authority to require REMS from manufacturers to ensure the benefits of a drug or biological product outweigh its risks. This bill expands FDA's REMS authority to potentially require safety-enhancing packaging and disposal features.

In addition, FDA has determined a REMS is necessary for all opioid analgesics intended for outpatient use to ensure the benefits of these drugs continue to outweigh the risks. The Opioid Analgesic REMS, approved on Sept. 18, 2018, is one strategy among multiple national and state efforts to reduce the risk of abuse, misuse, addiction, overdose and deaths due to prescription opioid analgesics. The extension of the REMS program for opioids includes "all immediate-release (IR) medications for outpatient use and requires new labeling for IR products detailing healthcare provider educational information related to safe use of these drugs."

> "At the facility level, the bill creates a demonstration program to promote alternatives to opioids in emergency departments and care coordination for drug overdose patients."

The REMS program also requires training be made available to all healthcare providers involved in managing patients with pain, including nurses and pharmacists. The goal is to reduce unnecessary and/or inappropriate exposure to opioids by making certain healthcare providers are properly informed about appropriate prescribing recommendations, understand how to identify abuse by individual patients and know how to get patients with opioid use disorder into treatment.

To meet this requirement, drug companies with approved opioid analgesics must provide unrestricted grants to accredited continuing education providers to develop education courses for healthcare providers based on FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. These new training programs and modules will be created by March 2019 for all clinicians who treat patients for pain, including nonprescribers such as pharmacists. However, there is no mandatory federal requirement that prescribers or other healthcare providers take the training, and there is no precondition to prescribing or dispensing opioid analgesics to patients. But, FDA's Opioid Policy Steering Committee is considering whether there are circumstances when FDA should require some form of mandatory education for healthcare providers, and how the agency would pursue that goal. ❖

BONNIE KIRSCHENBAUM, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

Resource

A Prescriber's Guide to the New Medicare Part D Opioid Overutilization Policies for 2019. *MLN Matters*, Nov. 1, 2018: www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/SE18016.pdf

Preventing and Responding to Cyber Attacks

By Ronale Tucker Rhodes, MS

A SURVEY CONDUCTED by the American Medical Association and Accenture in 2017 revealed more than four in five U.S. physicians (83 percent) experienced some form of a cyber attack. And 55 percent of the 1,300 physicians responding to the survey were either very or extremely concerned about future attacks in their practice. Their main concerns were that future attacks could interrupt their clinical practices (74 percent), compromise the security of patient records (74 percent) or affect patient safety (53 percent). And, while these attacks were twice as likely to happen to physicians from medium and large practices than those in small practices, even small physician practices are easy targets.[1]

The most common type of cyber attack reported by survey respondents was phishing (55 percent), followed by computer viruses (48 percent). But cyber attacks are also increasingly coming in the form of ransomware, which occurs when an organization's data is scrambled by an attacker who promises to unscramble it for a price. Indeed, in 2016, the healthcare industry was the victim of 88 percent of all ransomware attacks in the U.S. The reason: Cyber criminals know healthcare organizations tend to pay the ransom amount that is demanded in return for patient data.[2] And, patient data is lucrative. Medical information is worth 10 times more than a credit card number on the black market.[3] What's more, hospitals are the most vulnerable, with a prediction ransomware attacks will quadruple by 2020.[4]

Steps to Preventing a Cyber Attack

The most effective way to prevent cyber attacks is to implement cybersecurity best practices, which involve a combination of employee training and technology safeguards.

Unfortunately, employee training often takes second seat to technology safeguards. And, this is an oversight, because employees are the biggest potential vulnerability, who should be trained to recognize potential scams related to both digital and paper breaches, says Paige Schaffer, president and CEO of Generali Global Assistance's Identify and Digital Protection Services Global Unit.[3] According to the U.S. Department of Health and Human Services, which manages breaches of unsecured protected health information (PHI) affecting 500 or more individuals, in the last six months of 2017, almost three million individuals were affected by breaches caused by paper and films being leaked to email security breaches (often the result of poor network security), lost portable electronic devices or a break that occurred through a desktop computer.[5] Schaffer recommends employees be trained to:[3]

- Keep digital files instead of physical ones whenever possible;
- Safeguard paper files with as much vigilance as digital ones;
- Collect only the information needed; and
- Shred any physical documents they no longer need.

In addition, written cyber policies on how to protect devices and data should be provided to employees. And, mandatory HIPAA (Health Insurance Portability and Accountability Act) training should be required. In fact, HIPAA requires healthcare organizations provide training for all employees and to provide periodic refresher training. And, while the definition of "periodic" is not defined, best practice is considered to be annual training.[6]

Organizations should also conduct annual HIPAA risk assessments. Indeed, government regulations require health-

care providers submit their systems to an annual security evaluation.[7]

From a technology standpoint, the following are best practice steps:

Devices. Inventory hardware by listing all devices that belong to the practice, providers and employees, and determine which access PHI and which portable devices can be removed from the practice. Those left in the practice should be locked up after business hours. All devices should have passwords and go into sleep mode when left idle. And, settings should be enabled to allow someone in the practice to wipe all devices remotely if they go missing.[8] Organizations that let employees bring their own devices to work should establish a well-defined bring-your-own-device policy to help prevent infected devices from introducing malware into the organization's network and infecting other devices.[9]

Data. Stored and transmitted PHI can be protected by encrypting sensitive information such as medical records, addresses, Social Security numbers, etc. Even data that is stored and not actively used should be encrypted.[9]

Data access should be carefully controlled. One way to do this is to designate different access levels. For instance, a receptionist may not need to see a patient's full record. In addition, passwords should be changed regularly, and passwords should be disabled for employees who leave the organization's employment.[8]

Networks. While guests often expect Internet access at healthcare facilities, they should not be allowed to access the same network healthcare workers use. Instead, subnets (separate networks) should be created for workers and guests, access keys should be regularly changed and all data should be encrypted.[9] However, while subnets will prevent local cyber attacks, they can't always protect attacks coming from the outside. To accomplish this, patient data should be covered by a company grade advanced network security system that can quickly detect indicators of compromise.[7]

Insurance. Lastly, although it is new, most major insurers now offer cyber insurance to help mitigate losses from data breaches. Providers can ask about specific cybersecurity policies or tools that can help reduce premiums.[8]

Responding to a Cyber Attack

For most healthcare facilities, it's not a matter of if but when a data breach will occur. Therefore, a response plan must be established. Tom Saine, chief information officer for Spok, a company that specializes in healthcare communications, outlines eight steps organizations should take to respond to a cyber attack:[10]

1) Create a response team that includes representatives from the organization's executive, IT, legal, risk management, privacy, public relations/marketing and customer service teams, as well as any required third parties to develop, document and maintain an incident response plan. The plan should define how to determine whether a breach is occurring, what information to collect about the breach and how, and who to notify under what circumstances.

2) When a breach has occurred, determine how to put the response plan in motion.

3) Identify the source of the breach and how it was caused, and then quarantine the affected system and remove the attacker.

4) Once contained, hire an external team of experts to perform testing to ensure it is fixed and to identify other unknown issues that a future attacker could exploit.

5) Have investigators perform a root-cause analysis to prevent the problem from reoccurring.

6) Perform a risk assessment to determine whether the 2013 HIPAA Omnibus Final Rule applies to the breach. According to the rule, hospitals must perform notifications for any breach involving unsecured PHI unless the covered entity can demonstrate there is a low probability the PHI has been compromised.

7) If notification is required, the organization must contact the affected individuals no later than 60 days from the discovery of the breach. And, if the breach involves more than 500 individuals, details must be provided to the U.S. Department of Health and Human Services, and prominent media outlets in the region must be notified.

8) Continually evaluate the plan and implement policies, procedures and technology updates.

Preparing for the Future

History dictates there is no question healthcare data breaches are going to increase. Employees are going to fall victim to scams, and providers are continuing to transition to electronic data storage and transmission. Yet, while no security system can ever be 100 percent certain, applying best practices can certainly reduce the most common, controllable types of breaches. ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly* magazine.

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Medicines

Single-Dose Flu Drug Given Priority Review by FDA

Genentech's baloxavir marboxil, an experimental, single-dose flu drug, has been given priority review by the U.S. Food and Drug Administration (FDA). Baloxavir marboxil is taken by mouth and behaves in a different way than other antivirals by targeting a protein that is critical for the replication of the influenza virus. It can also tackle various flu varieties such as H7N9 and H5N1. "The severity of the recent flu season underscores the need for new options beyond currently available treatments, and if approved, baloxavir marboxil would be the first flu medicine with a novel proposed mechanism of action in nearly 20 years," said Genentech chief medical officer Sandra Horning, MD. ❖

Mukherjee S. This New Single Dose Flu Drug Could Be Coming to the U.S. Before the Next Flu Season. *Fortune*, June 28, 2018. Accessed at fortune.com/2018/06/28/fda-single-dose-flu-drug-genentech.

Research

Cervical Cancer Vaccines Safe and Effective in Girls and Women

A study that examined data from more than 73,000 girls and women shows vaccines designed to prevent infection with human papillomavirus (HPV) are effective in protecting against precancerous cervical lesions in women, particularly in those vaccinated between age 15 and 26 years.

The study, conducted by the scientific network the Cochrane Review, examined 26 studies across the world over the past eight years to analyze the effect of the vaccines on all women, whether or not they had HPV when they were vaccinated. Specifically, they looked at evidence for two types of HPV vaccine: the bivalent vaccine targeting HPV16 and 18, and the quadrivalent vaccine targeting HPV16 and 18, as well as two other low-risk types of HPV that cause genital warts. In young women who did not carry the virus, they found the vaccine significantly reduced the risk of developing cervical precancer.

About 164 per 10,000 women who received a placebo went on to develop precancerous cells, compared with just two in 10,000 women who received the vaccine. Results for all women showed the vaccines reduced the risk of cervical precancer (linked to HPV16 and 18) from 341 to 157 per 10,000 women. And, the vaccines reduced the risk of any type of precancer lesions from 559 to 391 per 10,000. However, the analysis could not judge whether the vaccines had helped to prevent cervical cancer since the disease can take years to develop following HPV infection, and none of the trials has been long enough. The researchers also found a side effect rate of about 7 percent among both those who had been vaccinated and the control group. ❖

Blanchard S. HPV Vaccine Is Safe: Study Finds Just 0.001% of Those Given the Life-Saving Jab Proven to Protect Against Several Forms of Cancer Will Experience 'Serious' Side Effects. DailyMail.com, Sept. 19, 2018. Accessed at www.dailymail.co.uk/health/article-6184793/HPV-vaccine-safe-Analysis-finds-no-unexpected-effects-jab-proven-prevent-cancer.html.

Medicines

New Hemophilia A Treatment Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved Bayer's Jivi (BAY94-9027) as a preventive treatment for bleeding in hemophilia A. Treatment was based on two years of Phase II/III clinical trials that showed the regular intravenous treatment protected patients from bleeding for a median of nearly two years. In the trial, 141 patients were split into preventive and on-demand groups between April 2012 and June 2014. Results showed Jivi seemed effective as an on-demand response to bleeding, resolving 91 percent of severe bleedings with one or two treatments. ❖

FDA Approves New Hemophilia A Treatment. *FDAnews Drug Daily Bulletin*, Sept. 5, 2018. Accessed at www.fdanews.com/articles/188254-fda-approves-new-hemophilia-a-treatment?utm_campaign=Drug%20Daily%20Bulletin&utm_source=hs_email&utm_medium=email&utm_content=65677406&_hsenc=p2ANqtz-9UcP3uxMPYAnLQjR6JXo8Qj4ZizbKJ-DGWSsQjQJf2THXd0x26nDv4CPUwm_ykxFHDhHz2YfHKKZPlMweSpZSf46_Y8Q&_hsmi=65677406.

Medicines

FDA Approves HPV Vaccine for 27- to 45-Year-Old Men and Women

Merck's Gardasil 9 human papillomavirus (HPV) vaccine has been approved by the U.S. Food and Drug Administration (FDA) for an expanded indication for men and women between the ages of 27 years and 45 years. Previously, the vaccine was approved for people only ages 9 years through 26 years. Approval is based on the expansion on results of a study of 3,200 women followed over three and a half years that found Gardasil 9 was 88 percent effective in the prevention of vulvar, vaginal and cervical precancerous lesions, cervical cancer and genital warts caused by the nine HPV strains. The vaccine's effectiveness in men was "inferred" from the study's data, as well as a clinical trial of 150 men ages 27 years to 45 years who received a three-dose vaccination regimen over a six-month period. FDA also looked at data from studies of younger men ages 16 years to 26 years.

Prior to this expanded indication, recommendations by the Centers for Disease Control and Prevention (CDC) were for HPV vaccination for boys and girls to begin between the ages of 11 years and 12 years, although the regimen could begin as early as age 9 years. If it is begun before age 15 years, boys and girls receive two doses of the vaccine, with the second vaccine given six months to 12 months after the first dose. If it's not given by age 15 years, CDC recommends girls ages 15 years to 26 years and boys ages 15 years to 21 years receive three doses, with the second dose given one month or two months after the first and the third dose given six months after the first. ❖

LaMotte S. FDA Approves Use of HPV Vaccine for Adults 27 to 45. CNN, Oct. 5, 2018. Accessed at www.cnn.com/2018/10/05/health/gardasil-hpv-vaccine-approved-older-ages-bn/index.html.

Research

Study Shows Newborns' Immune Systems Ramp Up After Birth

A new study shows newborns' immune systems ramp up immediately after birth, which has been difficult to assess previously because doing so has relied on samples taken from the umbilical cord immediately after birth. In this study, researchers used a new immune cell analysis technique to follow 100 premature and full-term babies for their first few weeks of life, and they found "drastic changes in the babies' immune systems between each sampling," showing their immune systems are highly dynamic early in life," said Petter Brodin at the Science for Life Laboratory and the department of women's and children's health at Karolinska Institute in Sweden. "What surprised us was how similar the changes were amongst babies," he said. "It seems as if all babies follow one and the same pattern, with their immune systems responding with exactly the same sequence of dramatic changes. It's almost like a well-choreographed dance, a practiced routine."

According to Brodin, by monitoring the development of the immune system, it may be possible to prevent autoimmune diseases and allergies that are partly related to the development of the immune system. In addition, this understanding may help to develop better vaccines tailored to the neonatal immune system. The researchers plan to enroll more babies in their study and follow them into childhood to see which of them develop diabetes, allergies, asthma and inflammatory bowel disease. ❖

Preidt R. Newborns' Immune Systems Ramp Up After Birth. WebMD, Aug. 24, 2018. Accessed at www.webmd.com/parenting/baby/news/20180824/newborns-immune-systems-ramp-up-after-birth.

Medicines

First EpiPen Generics Get FDA Approval

The U.S. Food and Drug Administration (FDA) has approved Teva Pharmaceuticals' generic epinephrine auto-injector in 0.3 mg and 0.15 mg strengths, the first generic versions of Mylan's EpiPen and EpiPen Jr. According to FDA Commissioner Scott Gottlieb, the approval is part of FDA's "longstanding commitment to advance access to lower-cost, safe and effective generic alternatives once patents and other exclusivities no longer prevent approval."

Though other injectors are available, these are the first FDA has said are the equivalent of the EpiPen, which means they can automatically be substituted for EpiPen in pharmacies across the United States. The price of the drugs and their launch date were not available as of this writing. ❖

FDA Approves First EpiPen Generics. U.S. Food and Drug Administration News, Aug. 21, 2018. Accessed at www.fdanews.com/articles/188081-fda-approves-first-epipen-generics?utm_campaign=Drug%20Daily%20Bulletin&utm_source=hs_email&utm_medium=email&utm_content=65327858&_hsenc=p2ANqtz-9y44i6Ivqz32HfSSSRLbegEzA8WpJNsUbyvwF_0pzkXVD72yWZFQObTNHodNMvrqq40X0D2xOGWwbgPhIN10Q-bspLoA&_hsmi=65327858.

Medicines

FDA Approves Fast-Acting, Single-Dose Flu Medication

After the deadly 2017-18 influenza (flu) season in the U.S., the U.S. Food and Drug Administration (FDA) has approved a new, single-dose medication to treat people 12 years and older who have had the flu for no more than 48 hours. Baloxavir (Xofluza) is the only single-dose oral medication approved to treat the flu. According to Genentech, if patients see their doctors within 48 hours of symptom onset, one dose of Xofluza can significantly reduce the duration of flu symptoms. "Although there is no substitute for the flu vaccine, we appreciate the development of any medication that assists in the treatment of influenza," said Rebekah Gee, MD, secretary of the Louisiana Department of Health. "These medications can be life-saving for those seriously ill, and the single dose makes it a much easier treatment to complete."

Approval was based on two randomized controlled clinical trials of 1,832 patients who were assigned either the drug, a placebo or another antiviral flu treatment within 48 hours of experiencing flu symptoms. In both trials, Xofluza patients' symptoms were alleviated more quickly compared with the placebo. In the second trial, there was no difference in time to relieve symptoms between those who took Xofluza and another flu treatment. The most common adverse reactions to Xofluza included diarrhea and bronchitis.

More than 900,000 people were hospitalized and more than 80,000 people died from the flu in the U.S. in the 2017-18 season. ❖

O'Donnell J. The Flu: FDA Approves Fast-Acting, Single-Dose Oral Medication After Deadliest Season in 40 Years. *USA Today*, Oct. 24, 2018. Accessed at www.usatoday.com/story/news/health/2018/10/24/fda-approves-single-dose-oral-flu-medicine-baloxavir-genentech-xofluza/1752905002.

Medicines

Rituxan Approved to Treat Severe Pemphigus Vulgaris

The U.S. Food and Drug Administration (FDA) has approved Genentech's Rituxan (rituximab) to treat moderate-to-severe phemphigus vulgaris (PV), the first biologic therapy approved and the first major advancement in the treatment of the condition in more than 60 years. PV is a rare and serious potentially life-threatening autoimmune condition characterized by progressive painful blistering of the skin and mucous membranes.

FDA approval was based on the Ritux 3 trial conducted in France that compared Roche's European Union (EU)-approved rituximab product plus short-term corticosteroids (CS) to CS alone as a first-line treatment in patients with newly diagnosed, moderate-to-severe PV. Results showed 90 percent of PV patients treated with the Ritux 3 regimen met the primary endpoint of complete remission at month 24 without the use of CS for two or more months, compared to 28 percent of PV patients treated with CS alone.

With this FDA approval, Rituxan is now approved to treat four autoimmune diseases: PV, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis. ❖

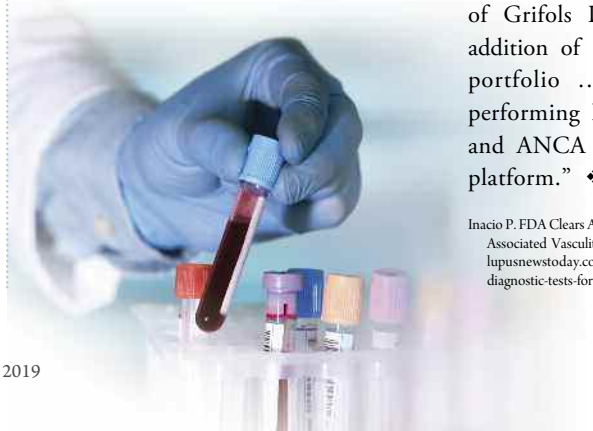
Banks L. Genentech's Rituxan Approved for Rare Skin Disease. PharmaPhorum, June 8, 2018. Accessed at pharmaphorum.com/news/genentechs-rituxan-rare-skin-disease.

Disease Testing

FDA Approves Diagnostic Tests for Lupus and ANCA-Associated Vasculitis

New automated diagnostic tests for lupus and ANCA-associated vasculitis, a form of blood vessel inflammation, have been approved by the U.S. Food and Drug Administration (FDA). Both tests use fluorescent antibodies to detect markers of disease in a patient's blood sample utilizing the HELIOS system (developed by AESKU), which is the first and only automated system capable of processing and analyzing a patient's blood sample in a single run.

The new automated test for lupus, called nDNA, is an indirect immunofluorescence assay (IFA) that detects anti-dsDNA antibodies in the serum of lupus patients. The second test, known as the AESKUSLIDES ANCA, will help diagnose ANCA-associated vasculitis, including granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis.



Grifols is the exclusive distributor of both diagnostic tests. "The recent approvals by the U.S. Food and Drug Administration of the ANCA and nDNA assays provide clinical laboratories with an efficient and reliable way to test for autoimmune diseases such as vasculitis and lupus," said Carsten Schroeder, president of Grifols Diagnostic Division. "The addition of these assays to our current portfolio … enables our customers performing IFA to detect anti-dsDNA and ANCA using one automated IFA platform." ❖

Inacio P. FDA Clears Automated Diagnosis Tests for Lupus and ANCA-Associated Vasculitis. *Lupus Today News*, June 1, 2018. Accessed at lupusnewstoday.com/2018/06/01/fda-approves-fully-automated-diagnostic-tests-for-anca-vasculitis-and-lupus.

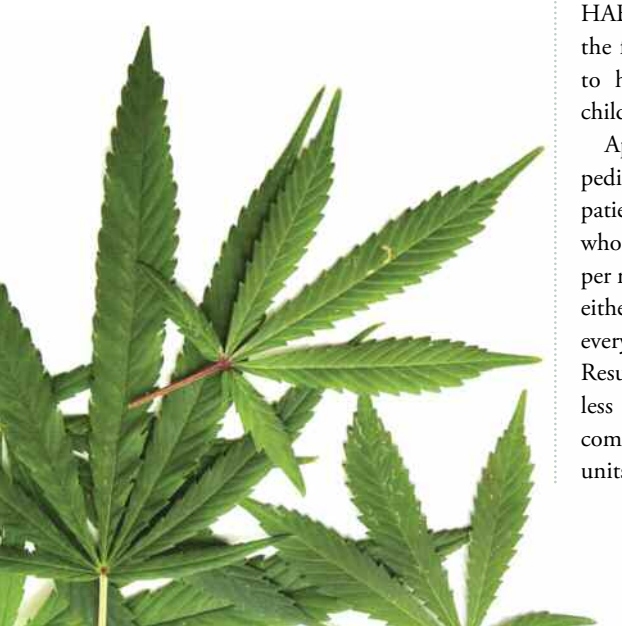
Medicines

FDA Approves Marijuana-Based Drug for Seizures

The first prescription drug made from marijuana has been approved by the U.S. Food and Drug Administration (FDA). Epidiolex is a strawberry-flavored syrup indicated for the treatment of two rare forms of epilepsy in patients 2 years and older. The syrup is a purified form of cannabidiol (CBD), a chemical ingredient in the cannabis plant that does not get users high. Treatment was approved based on studies of more than 500 children and adults with hard-to-treat seizures. According to FDA, the drug reduced seizures when combined with older epilepsy drugs. "This approval serves as a reminder that sound development programs that properly evaluate active ingredients contained in marijuana can lead to important medical therapies," said FDA Chief Scott Gottlieb.

Manufactured by GW Pharmaceuticals, Epidiolex is expected to launch in the fall. FDA has previously approved synthetic versions of another cannabis ingredient for medicine use, including severe weight loss in patients with HIV. ❖

Perrone M. Medical Milestone: U.S. OKs Marijuana-Based Drug for Seizures. Associated Press, June 25, 2018. Accessed at apnews.com/16829deb1ce0489aa7e0bd1afa02eb73.



Medicines

Second JAK Inhibitor Drug for RA Approved by FDA

The U.S. Food and Drug Administration (FDA) has approved Incyte Corp.'s Olumiant (baricitinib) 2 mg once-daily oral medication to treat adults with moderately to severe active rheumatoid arthritis (RA). Olumiant is the second oral janus kinase (JAK) inhibitor approved for RA in the U.S., following approval of Pfizer's Xeljanz (tofacitinib) in November 2012. It is indicated for patients who have had an inadequate response to one or more tumor necrosis factor inhibitor therapies. However, approval of Olumiant comes with a boxed warning for the risk of serious infections, malignancies and thrombosis.

In April, FDA declined to approve the 4 mg dose of Olumiant after an independent advisory panel voted against it over concerns related to its safety profile. ❖

FDA Approval of Low Dose RA Drug Olumiant Gives Eli Lilly and Incyte Edge in Immediate Future. Global Data press release, June 18, 2018. Accessed at www.drugs.com/newdrugs/fda-approves-olumiant-baricitinib-2-mg-adults-moderately-severely-active-rheumatoid-arthritis-4760.html.

Medicines

Cinryze Approved for Preventing Pediatric Angioedema Attacks

The U.S. Food and Drug Administration (FDA) has approved Shire's Cinryze (C1 esterase inhibitor [human]) to prevent angioedema attacks in children 6 years and older with hereditary angioedema (HAE). First approved in 2008 for routine preventive treatment against attacks in adults and teens with HAE, this label extension makes Cinryze the first approved treatment in the U.S. to help prevent angioedema attacks in children as young as 6 years old.

Approval was based on data from a pediatric Phase III study that included 12 patients ages six years through 11 years who had at least one angioedema attack per month. The children received Cinryze either in a 500-unit or 1,000-unit dose every three to four days for 12 weeks. Results showed patients had fewer and less severe attacks when taking Cinryze compared to a placebo. Five hundred units of Cinryze reduced the number of angioedema attacks per month by 71.1 percent, and 1,000 units reduced attacks by 84.5 percent. Patients also reduced the use of acute treatment after taking Cinryze. The most common adverse reactions were headache, nausea, fever and redness of the skin at the infusion site. ❖

Henriques C. FDA Approves Shire's Cinryze for Preventing Pediatric Angioedema Attacks. *Angioedema News*, June 28, 2018. Accessed at angioedemanews.com/2018/06/28/fda-approves-cinryze-prevention-pediatric-hereditary-angioedema-attacks.

Combating the Shortage of Primary and Specialty Care Physicians

Realizing that a shortage of physicians is on the horizon, academic medicine is making diligent efforts to identify its causes and make changes to reverse course.

By Meredith Whitmore

FOR YEARS, A growing shortage of physicians has been forecast by medical schools and others in the healthcare community, and the threat and resulting concern have quietly crept closer. Gradually, even predictably, patients in rural underserved areas of the United States have begun to see the forecast's frustrating effects as they've been unable to find the healthcare resources and physicians they need.[1] And, by 2030, the country as a whole will face a potentially crippling and widespread shortage of doctors, including primary and specialty care physicians.

The numbers are sobering. In its report "The Complexities of Physician Supply and Demand: Projections from 2016-2030," the Association of American Medical Colleges (AAMC) foresees the country will experience a shortage of at least 120,000 physicians. To be more specific, the association projects a shortage of between 14,800 and 49,300 primary care physicians by 2030 and a shortage of between 40,300 and 76,900 specialty physicians. What's worse: This comes at a time when demand for treatment is rising with an aging population.[2]

In 2018, AAMC President and CEO Darrell G. Kirch, MD, explained that "this year's analysis reinforces the serious threat posed by a real and significant doctor shortage. With the additional demand from a population that will not only continue to grow but also age considerably over the next 12 years, we must start training more doctors now to meet the needs of our patients in the future." Echoing Dr. Kirch's prediction, AAMC Chief Healthcare Officer Janis M. Orlowski, MD, stated: "There is going to be a significant workforce shortage under all of the likely projections. We see that, quite frankly, only getting worse as the population ages."[3]

The Roots of the Problem

What has caused this looming threat? First, let's dispel a common myth. The projected shortage has not been caused by a decreasing number of medical school students. In fact, students' interest in medical school is at an all-time high, and admissions and graduates have increased. But, hindering this is the disproportionate growth in federally supported residency training positions that new doctors need to complete their training and go into practice. Unless the government raises the federal cap on financial support for graduate medical education, even increased medical school enrollment and graduation rates will not ease the coming shortage.[4]

"Medical schools and teaching hospitals are working to ensure that the supply of physicians is sufficient to meet demand and that those physicians are ready to practice in the healthcare system of the future," said Dr. Kirch. "To address the doctor shortage, medical schools have increased class sizes by nearly 30 percent since 2002. Now, it's time for Congress to do its part. Funding for residency training has been frozen since 1997, and without an increase in federal support, there simply won't be enough doctors to provide the care Americans need."[3]

Also contributing to the shortage, as Drs. Kirch and Orlowski alluded, are changing demographics as seniors enter Medicare. Baby boomers will double the number of older Americans by 2040. And, because senior citizens typically have the greatest healthcare needs of any group, the number of doctors in practice must increase simply to remain proportionate to the senior population's needs. Since boomers outnumber other generations, however, and because of the lengthy time required for doctor training (an average of seven years for primary care physicians who typically require the shortest residency), the physician supply cannot stay apace with the country's growing needs.[4]

In addition, the Affordable Care Act has enabled many more people of all ages to seek treatment they would not have otherwise had. Consider, too, the more personal reasons for the shortage among physicians. Under the increasing demands a growing and aging population represents, doctors are burning out. One 2011 study found 41 percent of the more than 7,000 doctors surveyed had experienced or were experiencing burnout. And, a 2014 follow-up study showed burnout rates were up among all physicians from all specialties.[5] Add to this the fact that physicians are growing older themselves and are either working decreased hours or retiring in increasing numbers.[6]

Finding a Hopeful Future

Despite the grim forecast, academic medicine is facing the coming shortage directly and innovatively. The AAMC is taking what it calls a multipronged approach, which includes more focused utilization of team-based care in which health professionals of various disciplines and types work together to ensure patients' holistic care. Utilizing technology more efficiently in order to lessen doctor's workloads will help as well. But, Dr. Orlowski believes the most important solution will be training more physicians.[7]

Despite the grim forecast, academic medicine is facing the coming shortage directly and innovatively.

Merely having more doctors, however, does not guarantee a physician shortage will be resolved in rural and inner-city areas. Any approach must also address the maldistribution of primary and specialty care doctors in these areas. "Sixty-seven percent of the health professional shortage areas are in nonurban areas," explained Erika Schillinger, MD, a Stanford University clinical professor. "Fewer than 1 percent of final-year medical residents would prefer to practice in communities of 10,000 people or less. Basically, people who train in cities set down roots in those cities. They tend to want the connections and amenities of a city. They tend not to come from rural areas to begin with, and then they become acculturated to more urban areas because of their long training there. To change this, perhaps medical schools need to diversify their thinking and reach out to people who have a passion for science and interacting with people from rural and underserved areas. Perhaps medical schools must also change their thinking regarding what makes the best kind of doctor in terms of admissions. Then, we could focus on bringing more medical schools to rural areas in the first place. Students would invest in those communities and be more likely to stay there — especially if they came from them in the first place." And, responding to some in the medical community who believe the projected physician shortage is inflated and not a common problem, Dr. Schillinger tells them to "get outside of their bubble and go to a rural area or urban underserved community to see the problem firsthand."[8]

Thankfully, colleges and universities have already begun to recognize the importance of investing in new medical schools that will be located in and specifically serve rural and inner-city areas. These schools will focus on retaining students who have trained there, encouraging them to invest in the communities they are likely from and, hopefully, have come to love. In fact, during the last 15 years, there has been a large increase of new medical schools that focus on underserved areas.

The future Keck Graduate Institute School of Medicine, in Claremont, Calif., is a good example. It will focus on primary care, with the hope that graduates will stay on to practice medicine in eastern Los Angeles County, an area that historically suffers a dearth of healthcare professionals. "Our goal is to recruit them from here, train them here and keep them here," said Sheldon Schuster, PhD, president of Keck, which is located in a community of mostly Spanish-speaking people. "There is such an incredible demand for people who … understand the community and who speak the language."[9]

Already, physicians are beginning to practice in underserved areas. Douglas Grover, MD, a psychiatrist who trained at the University of California, Riverside, returned to his hometown of Moreno Valley, Calif., so he could practice his specialty in his underserved community. "If we open more opportunities here [in Moreno Valley] for college students to enter medical school," he said, "it will provide more physicians over the long run and, hopefully, help with the disparities in these areas." Dr. Grover hopes, along with many others, that more specialists will see the

need to return to their rural hometowns, or to even move to set up practice in high-need communities.[9]

Existing teaching hospitals and medical schools are also adapting methods of instruction and adopting new training programs to better equip incoming physicians who will tackle the rising needs among an aging population. Dr. Schillinger, for example, is an optimistic voice leading future doctors into a demanding profession. As a family doctor and vice chief for education in the division of primary care and population health at Stanford University, she has the privilege of introducing many medical students to primary care. "One of my division's goals," she explained, "is to make primary care irresistible to medical students." As for her own goals, she said, "I feel a responsibility, in a very personal way, to help shape a future of medical education that is so compelling, interesting and relational that it's really a rewarding career, which it is. It should stay that way."[8]

But even Dr. Schillinger's upbeat outlook recognizes primary care, and family medicine in particular, a field she has joyfully devoted her career to at Stanford, is challenging. As a result, primary care is potentially less appealing to medical students than some other types of medicine. "We could pay primary doctors more to encourage medical students to go into primary care," she suggested. "This is not to say that we are not paid well, but medical students looking at their debt load see that their salary is disproportionate to the relative challenges of the work. Primary care practice is so intensely rewarding. It is also complex, in equal measure, both intellectually and interpersonally."[8]

Loan repayment, too, is another issue Dr. Schillinger believes could be improved. "More loan repayment for residents who are going to serve in underserved areas would help as well," she said. "There are also areas of the country that have a surfeit of subspecialists, where access drives demand. [For instance], the more cardiologists they have in Florida, the more interventional bypass surgeries are offered. More procedures are done because there are more specialists. Which is an example of too much of a good thing."[8] But, ensuring primary care physicians in rural and inner-city areas are compensated on par with specialists in cities could distribute primary care doctors in ways that are helpful to the entire country.

What Will Happen?

Even with the best, most effective and diligent efforts to curb the coming primary and specialty physician shortage, there will still be an increasingly problematic healthcare scarcity for some as 2030 and beyond draw closer. But Dr. Schillinger maintains her realistic optimism: "The best-case scenario for the shortage is right now we recognize that this is a real crisis and we engage all hands on deck. We employ team-based care to the maximum, we use technology to the maximum, we redistribute payment models and salaries. We change the culture of training and build programs in rural and urban underserved areas. It will take many years to stem the shortage. We have to start now because our nation's health depends on it."[8]

Even with the best, most effective and diligent efforts to curb the coming primary and specialty physician shortage, there will still be an increasingly problematic healthcare scarcity for some as 2030 and beyond draw closer.

Only time will tell how healthcare systems, medical students and new measures in training and compensation will help patients and doctors in the future. But, it is heartening to know that many passionate physicians, educators and administrators are making decisive, strategic efforts to help as many people as possible now, and many more in the future. ❖

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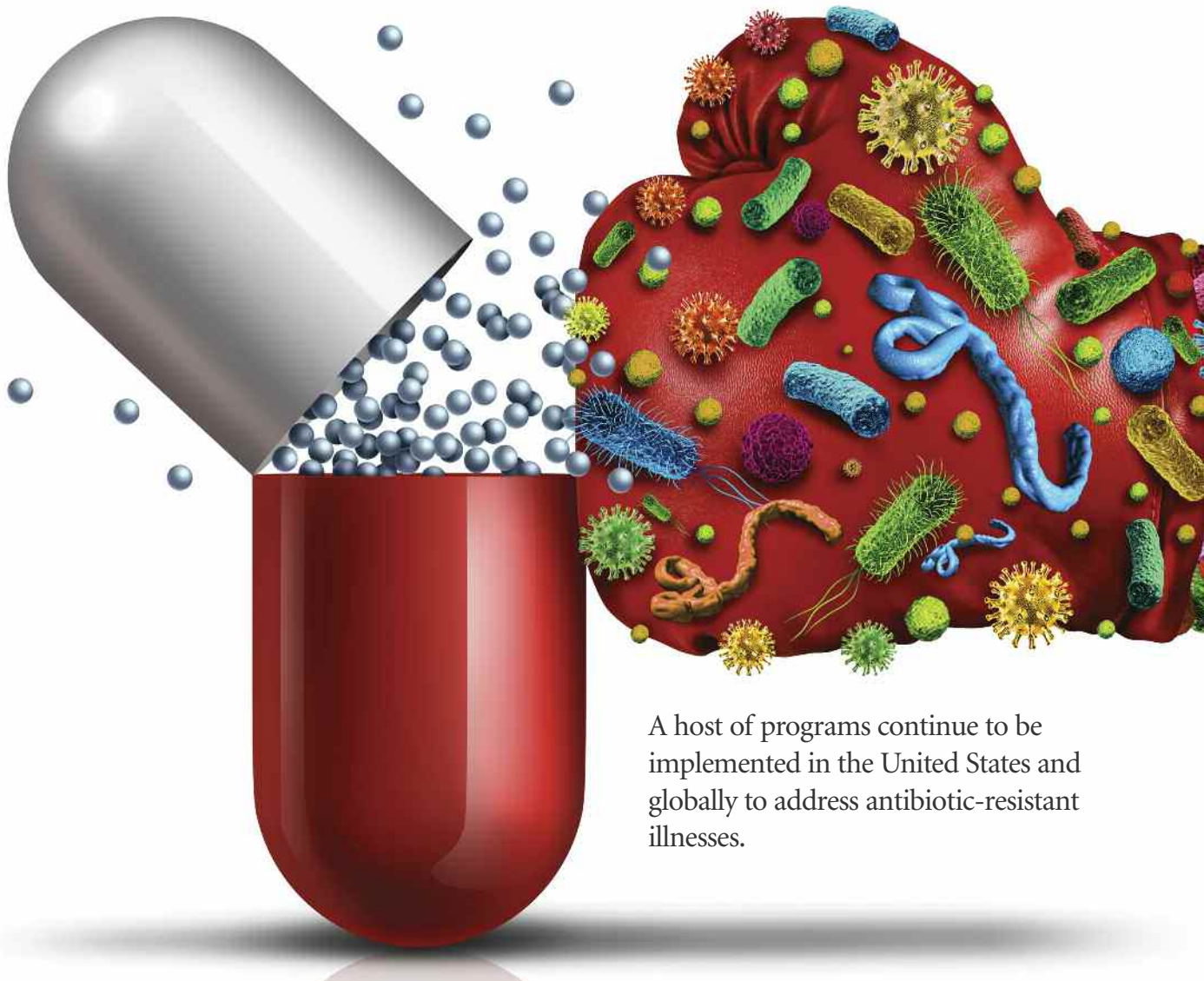
The Growing Threat of **Antibiotic-Resistant Illnesses**

By Diane L.M. Cook

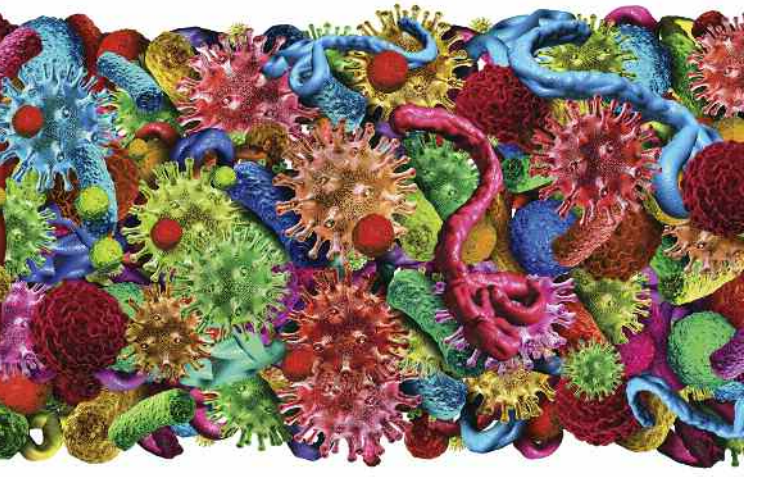


A host of programs continue to be implemented in the United States and globally to address antibiotic-resistant illnesses.

SINCE PENICILLIN WAS first used in humans in 1942, doctors have been treating patients who suffer from bacterial infections with antibiotic drugs, the most commonly prescribed drugs used in human medicine, with exceptional success. Antibiotics have greatly reduced illness, disability, morbidity and mortality from infectious diseases in millions of people in the United States and globally. But, after almost 80 years of long-term widespread use and overuse, overprescription by physicians of antibiotics for nonbacterial infections, and either misuse or abuse of antibiotic prescriptions by patients, the resulting phenomenon is antimicrobial resistance (AMR). Indeed, the global threat of antibiotic-resistant illnesses is so prevalent that the World Health Organization (WHO) classified it as a "serious threat [that] is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country."[1]

AMR versus Antibiotic Resistance

According to WHO, AMR occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective. When microorganisms become resistant to most antimicrobials, they are often referred to as "superbugs." AMR is the broader term for resistance in different types of microorganisms and encompasses resistance to antibacterial, antiviral, antiparasitic and antifungal drugs. Antibiotic resistance, specifically, occurs when bacteria change in response to the use of antibiotics used to treat bacterial infections (such as urinary tract infections, pneumonia and bloodstream infections), making them ineffective.[2]



How Does Antibiotic Resistance Occur?

Alexander Kallen, MD, MPH, a medical epidemiologist and outbreak response coordinator in the Division of Healthcare Quality Promotion at the Centers for Disease Control and Prevention (CDC), says antibiotic resistance can manifest in two ways: "First, in some situations, bacteria that is initially sensitive to antibiotics becomes resistant when the bacteria are exposed time and time again to the antibiotic. This is called inducible resistance and can happen through a mutation in the bacteria or when the bacteria 'turns on' a resistance mechanism that it already has. Second, bacteria that is already resistant to antibiotics can be transmitted from one person to another and can cause an infection. Antibiotics can also play a role here as these drugs can destroy a person's normal sensitive bacteria, providing a niche for these resistant bacteria to exploit."

CDC outlines two pathways in which antibiotic resistance can spread. In the first pathway, animals receive antibiotics and develop resistant bacteria in their guts. Because drug-resistant bacteria can remain on meat from animals, when it is not handled or cooked properly, the bacteria can spread to humans. Also, fertilizer or water containing animal feces and drug-resistant bacteria is used and can remain on food crops, which can then be transferred to the human gut.

In the second pathway, individuals who receive antibiotics can develop resistant bacteria in their gut, which they can then spread to the general community. Or, patients who receive care at a hospital, nursing home or other inpatient care facility can develop resistant bacteria in their gut and either a) the resistant bacteria can spread to other patients from surfaces within the healthcare facility or b) the resistant germs can spread directly to other patients or indirectly on unclean hands of healthcare providers. After the patients go home, they can spread resistant bacteria in the general community.[3]

WHO further explains how AMR occurs when microorganisms such as bacteria, fungi, viruses and parasites are exposed to antimicrobial drugs such as antibiotics, antifungals, antivirals, antimalarials and anthelmintics. While AMR occurs naturally over time, usually through genetic changes, exposure to drugs kills the sensitive strains and encourages proliferation of resistant ones. As previously stated, microorganisms that develop antimicrobial resistance to multiple drugs are referred to as "superbugs." With superbugs, medicines become ineffective, and infections persist in the body, increasing the risk of spread to others.

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In addition, says WHO, AMR microbes are found in people, animals, food and the environment (in water, soil and air), and they can spread between people and animals, including from food of animal origin and from person to person. Poor infection control, inadequate sanitary conditions and inappropriate food handling encourage the spread of AMR. However, says WHO, misuse and overuse of antimicrobials are accelerating the AMR process. In many places, antibiotics are overused and misused in people and animals, and they are often given without professional oversight.[4]

What Are the Most Common AMR Illnesses?

According to CDC, 18 bacteria cause severe infections in humans. These bacteria are categorized into three levels of antibiotic-resistant threats: urgent, serious and concerning.[3]

Urgent threat bacteria include:

- Clostridium difficile
- Carbapenem-resistant Enterobacteriaceae
- Drug-resistant Neisseria gonorrhoeae

Serious threat bacteria include:

- Multidrug-resistant Acinetobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae
- Vancomycin-resistant Enterococcus
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant non-typhoidal Salmonella
- Drug-resistant Salmonella Typhi
- Drug-resistant Shigella
- Methicillin-resistant Staphylococcus aureus
- Drug-resistant Streptococcus pneumoniae
- Drug-resistant tuberculosis

Concerning threat bacteria include:

- Vancomycin-resistant Staphylococcus aureus
- Erythromycin-resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

In November 2017, CDC kicked off U.S. Antibiotic Awareness Week and World Antibiotic Awareness Week.

AMR bacterial infection consequences include prolonged and/or more complicated illnesses; compromised success of organ transplants, major surgery and cancer chemotherapy; more expensive tests and/or treatments; use of stronger and/or more expensive drugs; additional doctor visits and more healthcare use (extended hospital stays); higher healthcare costs; and dramatically higher rates of infections, disabilities, morbidity and mortality.[3]

How Is Antibiotic Resistance Being Addressed?

Many government organizations have made tremendous headway to address the spread of resistant bacteria in the last several years.

- In November 2017, CDC kicked off U.S. Antibiotic Awareness Week and World Antibiotic Awareness Week. CDC recognizes U.S. Antibiotic Awareness Week with an updated education effort titled Be Antibiotics Aware: Smart Use, Best Care (formerly Get Smart About Antibiotics), which is an annual one-week observance to raise awareness of the threat of antibiotic resistance and the importance of appropriate antibiotic prescribing and use.[5,6] "Prescribing the right antibiotic at the right time, in the right dose and for the right duration helps fight antibiotic resistance, protects patients from unnecessary side effects and helps ensure these lifesaving medicines will be available for future generations," says CDC.[7]

- In 2016, CDC implemented the Antibiotic Resistance (AR) Solutions Initiative that supports national infrastructure to detect, respond, contain and prevent resistant infections across healthcare settings, food and communities. The AR Solutions Initiative's goals are to improve antibiotic use through antibiotic stewardship, sepsis recognition and prevention through: 1) setting national goals to improve antibiotic use (cut inappropriate prescribing practices by 50 percent in doctor offices and 20 percent in hospitals); 2) implementing effective stewardship programs using CDC's Core Elements in doctor offices, hospitals and nursing homes, and integrated with sepsis early recognition programs; 3) supporting collaboration to develop and evaluate stewardship activities; 4) providing data about antibiotic use and trends to better understand prescribing practices; 5) expanding state healthcare-associated infections and AR prevention programs to help implement best practices; and 6) supporting early recognition of sepsis.[8]

Under the AR Solutions Initiative, CDC built the AR Laboratory Network that can identify resistant bacteria quicker and stop its spread with interventions supported by public health. The initiative also puts state and local AR laboratory and epidemiological expertise in every state and makes investments in public health innovation to fight AR across healthcare settings, food and communities.[9] According to Dr. Kallen, "Many states now have the capacity to react when just a single instance of a bacteria with high levels of resistance is identified from a clinical culture. Reductions in the proportion of infections caused by some resistant bacteria have already been noted. In a recent publication, the CDC showed that the proportion of a type of healthcare infection caused by a highly resistant bacteria called carbapenem-resistant Enterobacteriaceae, or CRE, fell from 10.6 percent to 3.1 percent between 2006 and 2015."

Also under the AR Solutions Initiative is the AR Investment Map that shows the activities to meet national goals to prevent drug-resistant infections. The 2017 map features more than 170 state-reported successes such as rapidly identifying and containing rare and concerning resistant germs to protect communities, with each state reporting multiple successes.[10]

- In June 2015, CDC and the U.S. Food and Drug Administration (FDA) created the Antibiotic Resistance Isolate Bank that provides information on resistance to support innovation

in diagnostics and drug development. Under this program, CDC provides isolates (bacteria isolated from a specimen such as blood or food) to approved institutions. The AR Isolate Bank helps to 1) strengthen diagnostics by validating lab tests; 2) inform research and development to develop drugs such as antibiotics and antifungals; diagnostic devices, tests or assays; and satisfy a request or support an application to FDA; 3) perform testing to ensure drug effectiveness; 4) study biology and pathogenic mechanisms; and 5) detect new and unusual public health resistance threats.

The AR Isolate Bank is unique because CDC has one of the largest collections of isolates gathered from national reference labs and tracking activities taken from specimens in healthcare, food and the community. In the bank, samples are assembled based on public health threats, isolates are delivered in panels rather than piecemealed, researchers can quickly and easily obtain the specific samples they need, obstacles that might keep companies or researchers from engaging in finding resistance solutions are reduced, samples are accompanied by publicly available data to improve efficiencies, and a convenient ordering system increases efficiency.[11]

• Under the National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB), a five-year plan created in March 2015, the United States is working domestically and internationally to prevent, detect and control illness and death related to infections caused by resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections. The goals of CARB include 1) slowing the emergence of resistant bacteria and preventing the spread of resistant infections; 2) strengthening national One-Health Surveillance efforts to combat resistance; 3) advancing development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria; 4) accelerating basic and applied research and development for new antibiotics, other therapeutics and vaccines; and 5) improving international collaboration and capacities for antibiotic-resistance prevention, surveillance and control and antibiotic research and development.

CARB will also result in improved antibiotic stewardship in healthcare settings, prevention of the spread of drug-resistant threats, elimination of the use of medically important antibiotics for growth promotion in food animals, and expanded surveillance for drug-resistant bacteria in humans and animals. Other significant outcomes include creation of a regional public health laboratory network, establishment of a specimen repository and sequence database that can be accessed by industrial and academic researchers, development of new diagnostic tests through a national challenge, and development of two or more antibiotic drug candidates or nontraditional therapeutics for treatment of human disease.[12]

• Established in 1996, the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) is a collaboration among CDC, FDA and the U.S. Department of Agriculture (USDA), as well as state and local public health departments. This national public health surveillance system tracks changes in the antimicrobial susceptibility of certain enteric (intestinal) bacteria found in ill people (CDC), retail meats (FDA) and food animals (USDA) in the United States. NARMS helps protect public health by providing information about emerging bacterial resistance, the ways in which resistance is spread and how resistant infections differ from susceptible infections.[13]

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• In cooperation with other government agencies, FDA has launched several initiatives to address antibiotic resistance. Initiatives include drug-labeling regulations that emphasize the prudent use of antibiotics and encourage healthcare professionals to prescribe antibiotics only when clinically necessary and to counsel patients about the proper use of such drugs and the importance of taking them as directed. FDA is also encouraging the development of new drugs, vaccines and improved tests for infectious diseases.[14]

• FDA participates on the Interagency Task Force on Antimicrobial Resistance created in 1999. Co-chaired by CDC and the National Institutes of Health, it includes nine participating agencies and includes 11 goals divided into four focus areas. Focus Area I: Surveillance aims to improve the detection, monitoring and characterization of drug-resistant infections in humans and animals. Focus Area II: Prevention and Control aims to develop, implement and evaluate strategies to prevent the emergence, transmission and persistence of drug-resistant microorganisms. Focus Area III: Research aims to encourage, conduct and support basic and translational research to enhance the understanding of factors leading to the development of AMR microorganisms, their transmission in various settings and optimal modes of prevention,

diagnosis and therapy. Focus Area IV: Product Development aims to encourage the development of new antimicrobial products to improve the capacity to diagnose, prevent and treat infections, including infections caused by resistant microorganisms.[15]

• FDA's Limited Population Pathway for Antibacterial and Antifungal Drugs: Guidance for Industry (LPAD Pathway) issued draft guidance "describing criteria, processes and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial and antifungal drugs." This guidance is intended to assist sponsors in developing certain new antibacterial and antifungal drugs for approval under the LPAD Pathway. It is also intended to assist sponsors in developing labeling, including prescribing information, patient labeling and carton/container labeling.[16]

• FDA issued the final guidance Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases: Guidance for Industry in August 2017. This guidance is intended to assist sponsors in the clinical development of new antibacterial drugs. Specifically, the guidance explains FDA's current thinking about possible streamlined development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need, including patients who have a serious bacterial disease for which effective antibacterial drugs are limited or lacking.[17]

In its report dated July 18, 2018, WHO says "Countries are making significant steps in tackling antimicrobial resistance, but serious gaps remain and require urgent action."

• Like the CDC and FDA, WHO has been leading multiple initiatives to address AMR. In October 2015, WHO, the Food and Agriculture Organisation of the United Nations and World Organization for Animal Health implemented the Global Action Plan on Antimicrobial Resistance (GAP). GAP comprises surveillance, education, monitoring and regulating consumption and use of antimicrobials in human health, animal health and production, as well as plants and the environment. The goals of GAP are to ensure prevention and treatment of infectious diseases with safe and effective medicines. It includes five strategic objectives: 1) Improve awareness and understanding of AMR; 2) Strengthen surveillance and research; 3) Reduce the incidence of infection; 4) Optimize the use of antimicrobial medicines; and 5) Ensure sustainable investment in countering AMR.[18]

• In its report dated July 18, 2018, WHO says, "Countries are making significant steps in tackling antimicrobial resistance, but serious gaps remain and require urgent action." The report charts progress in 154 out of 194 countries responding and reveals wide discrepancies. Specifically, it looks at surveillance, education, monitoring and regulating consumption and use of antimicrobials in human health, animal health and production, as well as plants and the environment, as recommended in GAP.[19]

• Every November since 2015, WHO supports global and national action for World Antibiotic Awareness Week with the theme "Antibiotics: Handle with Care." The global, multi-year campaign includes an increasing volume of activities during the week of the campaign.[20]

• In October 2015, WHO launched the Global Antimicrobial Surveillance System (GLASS) to support GAP on AMR. Early implementation of GLASS is from 2015 through 2019. Its aim is to support global surveillance and research to strengthen the evidence base on AMR and to help inform decision-making and drive national, regional and global actions. GLASS promotes and supports a standardized approach to the collection, analysis and sharing of AMR data at a global level by encouraging and facilitating the establishment of national AMR surveillance systems capable of monitoring AMR trends and producing reliable and comparable data.

The six GLASS objectives are: 1) Foster national surveillance systems and harmonized global standards; 2) Estimate the extent and burden of AMR globally by selected indicators; 3) Analyze and report global data on AMR on a regular basis; 4) Detect emerging resistance and its international spread; 5) Inform implementation of targeted prevention and control programs; and 6) Assess the impact of interventions.[21] WHO's first release of surveillance data on AMR on Jan. 29, 2018, revealed high levels of resistance to a number of serious bacterial infections in both high- and low-income countries. Specifically, GLASS revealed widespread occurrence of antibiotic resistance among 500,000 people with suspected bacterial infections across 22 countries.[22]

• In a joint initiative of WHO and the Drugs for Neglected Diseases initiative (DNDi), the Global Antibiotic Research and Development Partnership (GARDP) was created in May 2016 as an important element of WHO's GAP on AMR, which calls for new public-private partnerships to encourage research and development of new antimicrobial agents and diagnostics. GARDP addresses global public health needs by developing and delivering new or improved antibiotic treatments, while endeavoring to ensure their sustainable access. It aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. By 2023,

the partnership aims to develop and deliver up to four new treatments through improving existing antibiotics and accelerating the entry of new antibiotics.[23]

• The United Nations (UN) secretary-general established the Interagency Coordination Group on Antimicrobial Resistance (IACG) to improve coordination between international organizations and ensure effective global action. The IACG is co-chaired by the UN deputy secretary-general and the director general of WHO and comprises high-level representatives of relevant UN agencies, other international organizations and individual experts across different sectors.[24]

• Originally launched in 1977, WHO's Essential Medicines List (ELM) for 2017 provides new advice on which antibiotics to use for common infections and which to preserve for the most serious circumstances. ELM groups antibiotics into three categories — ACCESS, WATCH and RESERVE — with recommendations on when each category should be applied. ELM recommends antibiotics in the ACCESS group be available at all times as treatments for a wide range of common infections. The WATCH group includes antibiotics recommended as first- or second-choice treatments for a small number of infections. And, antibiotics in the RESERVE group are considered last-resort options and used only in the most severe circumstances when all other alternatives have failed such as for life-threatening infections due to multidrug-resistant bacteria.[25]

• In 2017, WHO developed the Global Priority Pathogens List (Global PPL) whose major objective is to guide the prioritization of incentives and funding, help align research and development priorities with public health needs, and support global coordination in the fight against antibiotic-resistant bacteria. Global PPL of bacteria is divided into three areas (12 families of bacterial "supervillains" considered the most serious threats to human health): Priority 1: Critical includes the three most feared resistant bacteria in the world. These bacteria thrive in hospitals and facilities and infect patients on ventilators and catheters, causing potentially deadly blood and respiratory infections. They are resistant to even the most powerful antibiotics. Priority 2: High and Priority 3: Medium include a list of the other nine high- and medium-risk resistant bacteria.[26]

Looking Ahead

According to Dr. Kallen, CDC believes bacteria will continue to develop new ways to evade the effects of the best antibiotic drugs: "As long as we rely on these drugs to combat infections, we will need to be vigilant to the threat of antimicrobial resistance. The new investments that the CDC has made in infrastructure to detect and respond to antibiotics has made our ability to respond to new and emerging threats more nimble and more effective. With these new tools, we can slow the spread of resistant bacteria."

Elizabeth Tayler, team lead of the National Action Plans and Monitoring Team with WHO, adds: "Addressing antimicrobial resistance properly involves strengthening systems that detect, prevent and manage infection in human health, decreasing the overuse of antibiotics in food production and reducing environmental contamination. These actions need to happen in a sustainable way, at scale. To achieve this will be quite a challenge for high-income countries, but it is particularly challenging for low-income countries. Therefore, it is unlikely that all countries will ever be able to reach the highest levels in all elements of the Global Action Plan, but we encourage all countries to focus on those areas that will have the highest impact and are most readily achievable. It is vital that this happens over the next five years as resistance levels are rising across the world." ❖

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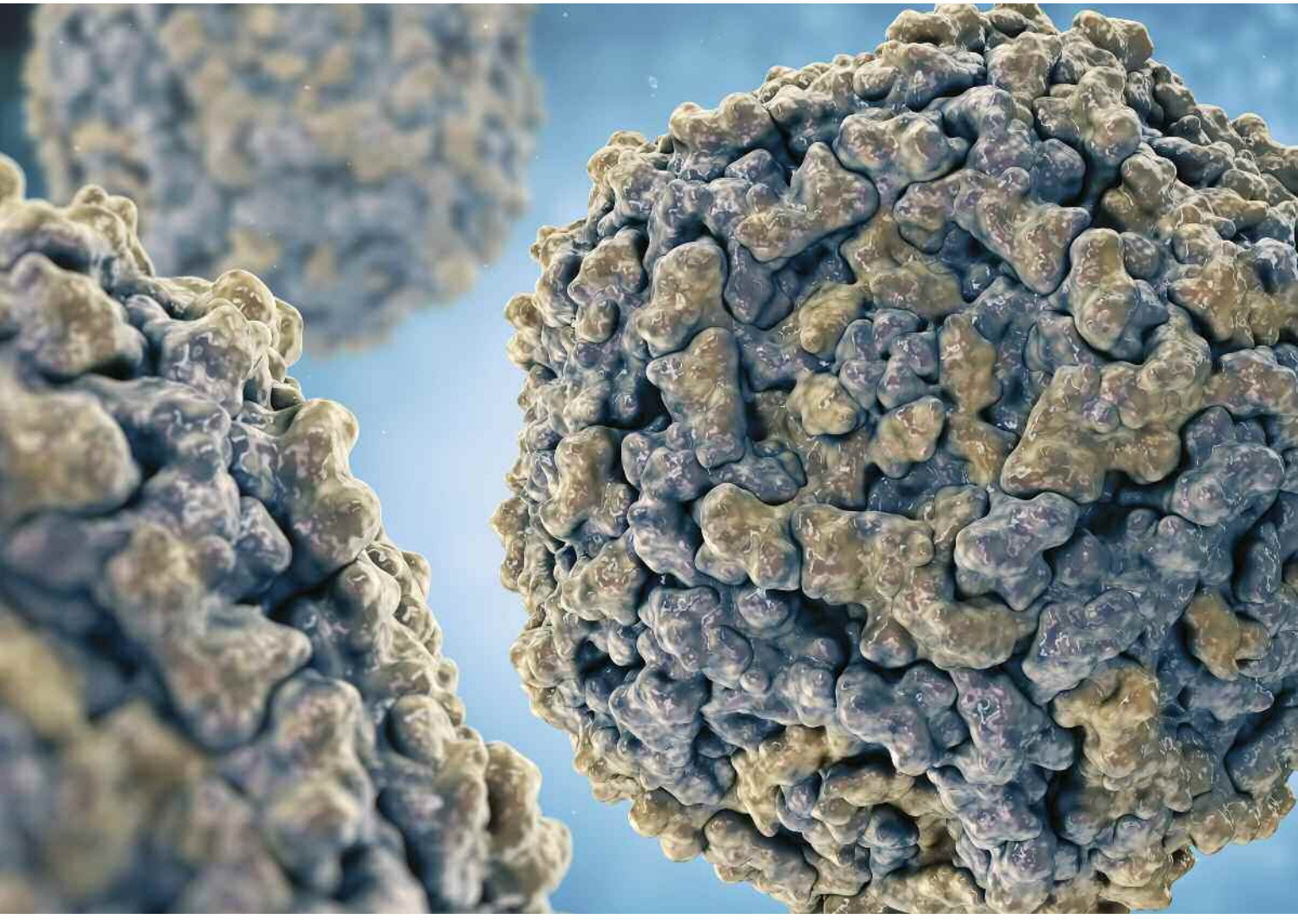
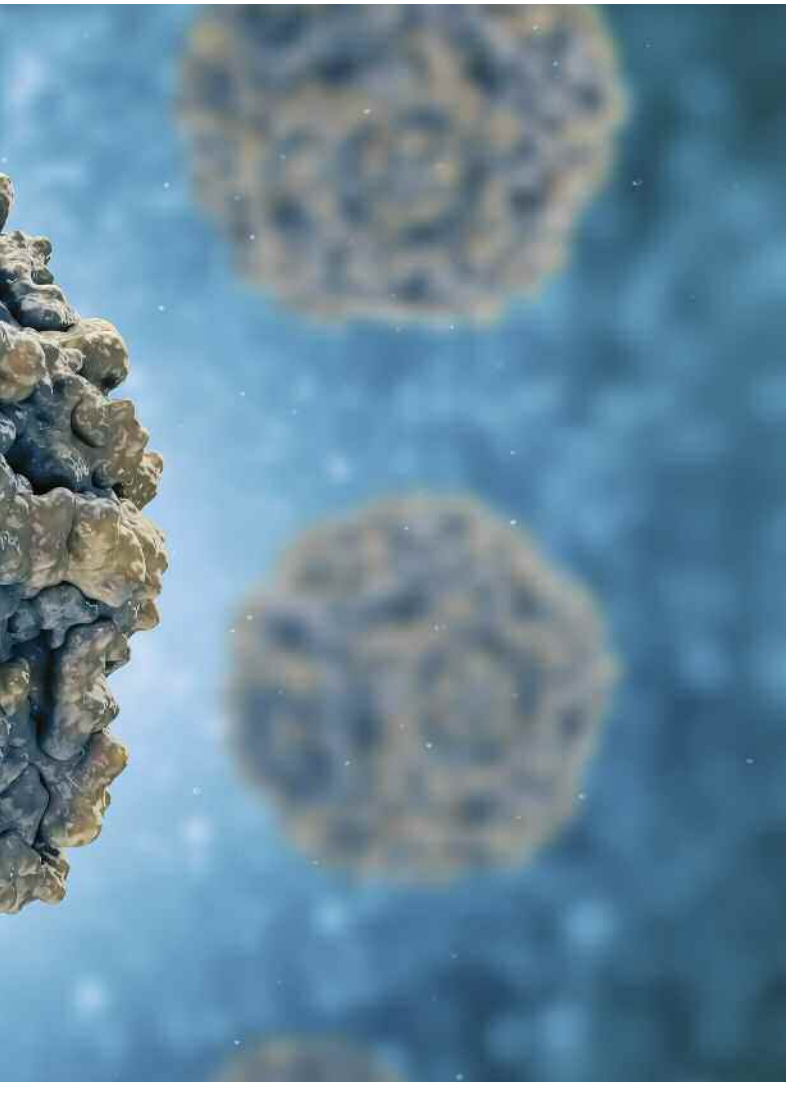
The Many Faces of Parvovirus B19: IVIG to the Rescue?



This common virus manifests in a host of systemic illnesses that are mostly curable with human intravenous immune globulin therapy.

By E. Richard Stiehm, MD



PARVOVIRUS B19 INFECTION is a common viral infection that most individuals will contract in their lifetime. Usually, it is acute, but sometimes it is chronic. The infection can cause a wide spectrum of clinical disorders, both acute and chronic, the latter of which are mostly curable with human intravenous immune globulin (IVIG) therapy.

The presence of IgG antibodies to the virus indicates past infection. These antibodies, which are present in 70 percent to 80 percent of older adults and 25 percent to 35 percent of young adults, provide lifetime immunity to parvovirus and explain their presence in the plasma pools used for IG manufacture.

A Parvovirus Vignette

A 15-year-old boy presented with an 18-month history of recurrent low-grade fever, malaise, body aches and poor sleep. These symptoms occurred following a bout of diarrhea and dehydration on a camping trip. Multiple doctor visits and blood tests were unrevealing, including viral titers. The working diagnosis was chronic fatigue syndrome (CFS), which was interfering with his school work and preventing his participation in athletics.

My examination was unremarkable except for flushed cheeks. And, unlike most teens with CFS, he did not exhibit la belle indifférence, a lack of concern or interest in his illness: Both he and his parents wanted a diagnosis.

All of his multiple blood tests were normal except for one not previously performed. He had a positive IgG antibody test to parvovirus indicating past infection. But, he also had a positive IgM antibody test, suggesting current or recent infection. Next, a polymerase chain reaction test was used to look for circulating parvovirus in his blood. This was positive. Could he have chronic parvovirus causing CFS? A few adults with CFS due to parvovirus had been reported, but this would be the first case in a youngster.

The only treatment for chronic parvovirus is large doses of human intravenous immune globulin (IVIG) containing antibody to parvovirus, as well as other viruses. Following an initial dose of IVIG without side effects, eight hours later, he woke with a stiff neck and severe headache. He had aseptic (i.e., noninfectious) meningitis, a rare side effect of IVIG.

Next, small weekly doses of IG subcutaneously (SCIG) were administered for several months, but the fatigue continued and the virus remained in the blood. Finally, a large dose of IVIG preceded by a hefty dose of corticosteroids was given. He tolerated this well, and after six more monthly infusions, the virus disappeared from his blood and his symptoms disappeared. He was cured!

After his recovery, the boy heard me tell the referring doctor attending my clinic his was a unique case, and we should write a paper about his illness. At that point the boy said: "Write a paper about me? I would like to write the paper!" I gave him my file on parvovirus, and he wrote a credible draft for his science class. We polished it for publication in the *Journal of Pediatric Infectious Disease*.* Then a high school senior, he added this peer-reviewed paper to his college application. That helped him gain admission to the University of California. He is now an emergency medical technician.

*Source: McGhee SA, Kaska B, Liebhaber M, and Stiehm ER. Persistent Parvovirus-Associated Chronic Fatigue Treated with High Dose Intravenous Immunoglobulin. *Pediatric Infectious Disease Journal*, 2005; 24:272-4.

Parvovirus was first identified in 1975 in plate B of serum 19 during a search of blood specimens for the hepatitis B virus,[1] thus the term parvovirus B19. It is a DNA virus that like other DNA viruses does not mutate.[2,3] Other strains of parvovirus occur in animals, but only B19 afflicts humans. Its receptor is the red blood cell P antigen present in most people, except for those with the rare blood type pp who cannot be infected.[4] The P receptor is strongly expressed on erythroid precursors, but also on megakaryocytes, hepatocytes, endothelial cells and fetal myocardium, which explains the rarer forms of parvovirus infection.[5]

Diagnosis of parvovirus B19 is suspected by identifying serum parvovirus IgM antibodies with or without IgG antibodies and confirmed by PCR for circulating virus.[2,3]

Individuals can be infected with parvovirus B19 year-round, but childhood epidemics may occur in late winter and early spring.[2] Infection is usually spread by close contact with an infected subject. Less commonly, it is acquired by blood products or from stem cell or organ transplant from an infected donor.[2,6-8]

Manifestations of Parvovirus B19

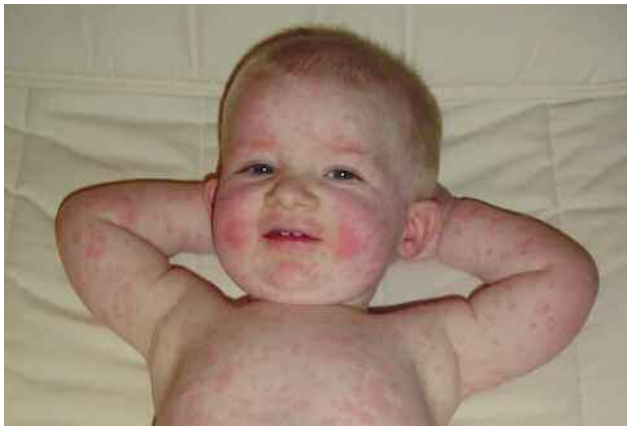
Slapped cheek syndrome. Acute slapped cheek syndrome (i.e., erythema infectiosum, fifth disease) is the most common manifestation of parvovirus infection (Figure). After an incubation period of seven days to 14 days, the child develops a three- to 10-day episode of fever, chills and malaise followed by a fiery red rash of the cheeks.[2] This may be followed by a generalized macular rash and mild arthritic symptoms. When the rash appears, the child is no longer contagious.

Acute and chronic aregenerative anemias. When parvovirus B19 attaches to erythroid precursors via the P antigen, the result is cellular death and interruption of erythropoiesis. This then results in a progressive normocytic, normochromic anemia with absence of reticulocytes. The anemia can be acute or chronic, often occurring in patients with another chronic health problem.

About 10 percent of pregnant women with a parvovirus infection transmit the virus to their fetus.

Pure red cell aplasia is the most severe form of parvovirus anemia leading to sudden cessation of erythropoiesis with pallor fatigue and weakness that often requires red blood cell transfusions.[9] In many cases, the disorder is self-limiting if the patient makes a neutralizing antibody. However, this may not occur if the patient has an underlying immune deficiency.

Figure. A Child with Slapped Cheek Syndrome



Chronic aregenerative anemias are common in patients with increased erythropoietic activity due to a hemolytic anemia (e.g., hydrops fetalis) or a hemoglobinopathy (e.g., sickle cell anemia).[10-12]

Parvovirus-induced anemia may also occur in primary or secondary immunodeficiency (e.g., HIV infection), during immunosuppressive treatment for hematologic malignancies or following organ transplantation.[13-15]

Parvovirus during pregnancy/hydrops fetalis. About 4 percent of seronegative women develop parvovirus during pregnancy.[12,13] Of special risk are school teachers, day care workers or mothers of school-age children. Fetal loss occurs in 5 percent of these infections, nearly always from infection in the first half of pregnancy.

About 10 percent of pregnant women with a parvovirus infection transmit the virus to their fetus. The fetus may develop hydrops fetalis with severe anemia, ascites, heart failure and possible death (10 percent).[10,16] Affected fetuses can be treated with an intrauterine blood transfusion.[17] One hydropic fetus was successfully treated with intraperitoneal IG.[18] Some surviving infants are born with anemia, myocarditis, hepatitis or central nervous system problems. Yet, despite these illnesses, parvovirus is not considered a teratogen.

Other illnesses. Parvovirus may cause an acute transient arthritis resembling Lyme disease or rheumatoid arthritis. It is particularly common in young females, usually affecting the wrists and fingers.[19]

More than 50 other systemic illnesses have been caused by parvovirus (Table). These include systemic, hematologic, rheumatic/autoimmune, dermatologic and neuro/psychiatric disorders. Therefore, parvovirus should be suspected in any undiagnosed chronic illness, particularly if the patient had a sudden onset of disease or a possible exposure to an infected subject.

Prevention and Treatment

No vaccine or antiviral drugs for parvovirus are available. Hospitalized patients with parvovirus anemias should be kept in isolation. Pregnant women exposed to a child with erythema infectiosum can be tested for immunity to the virus. A pregnant woman with parvovirus should be monitored by ultrasonography for carrying a hydropic infant.[20] Organ and stem cell donors can be tested for parvovirus prior to transplant. Blood donors are not routinely tested for parvovirus.[8]

Since IVIG has high titers of parvovirus antibody, chronic parvovirus infections can be treated with 400 mg/kg to 600 mg/kg per week of IVIG for one month.

Since IVIG has high titers of parvovirus antibody, chronic parvovirus infections can be treated with 400 mg/kg to 600 mg/kg per week of IVIG for one month.[9,14,15,21] This is my recommendation, although there is no standardized dose or duration of IVIG therapy. Other patients may require long-term IVIG therapy such as in the vignette or those with compromised immune systems. The effectiveness is determined by clearance of the virus from the blood three months after completing IVIG therapy. ❖

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Table. Partial List of Manifestations of Parvovirus Infection[5]

Systemic
- Pneumonia
- Hepatitis
- Myocarditis
- Nephritis

Hematologic
- Chronic anemia/pure red cell aplasia
- Transient aplastic crisis
- Hydrops fetalis/congenital anemia
- Thrombocytopenic purpura

Rheumatic/Autoimmune
- Polyarthritis
- Vasculitis
- Systemic sclerosis
- Lupus erythematosus

Dermatologic
- Erythema infectiosum
- Papular-purpuric gloves and socks syndrome
- Erythema multiforme
- Henoch-Schönlein purpura

Neurologic
- Meningitis/encephalitis
- Guillain-Barré syndrome
- Facial palsy
- Peripheral neuropathy
- Chronic fatigue syndrome/fibromyalgia

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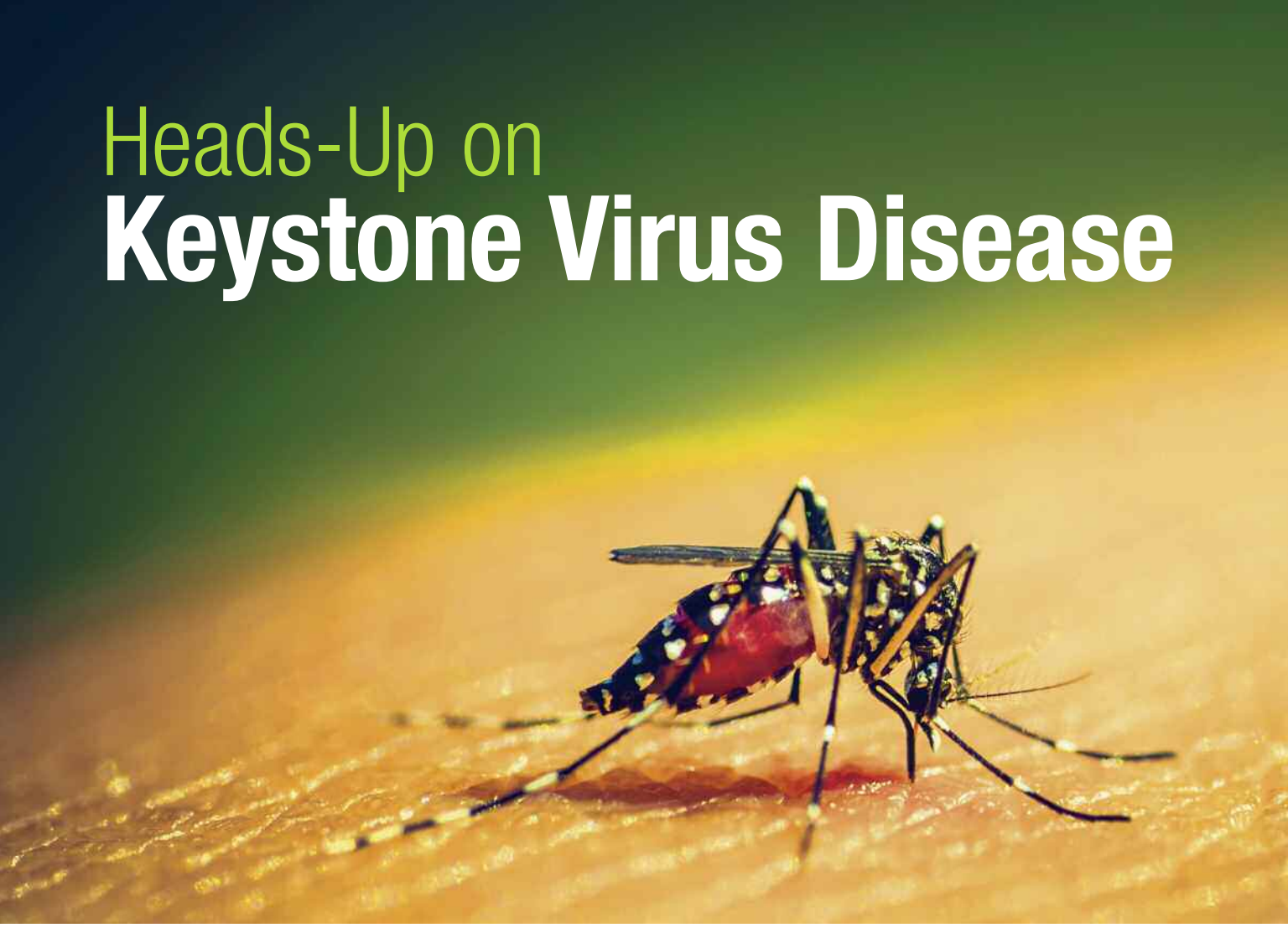
Heads-Up on Keystone Virus Disease



Little is yet known about this vector-borne disease that has been diagnosed in only one human to date and appears confined to Gulf Coast states, but researchers are investigating to learn more.

By Jim Trageser

ONE OF THE most recent disease discoveries, Keystone virus, was identified in wildlife in 1964, but the first human case wasn't confirmed until the summer of 2018, when scientists identified it as the cause of a Florida teenager's 2016 illness.[1] Still, because it is such a recently discovered disease, physicians, researchers and public health agencies do not yet know the full extent of the risks Keystone virus poses, including the normal progression of an infection, all possible vectors or the answers to a host of other questions.

With the first case now identified in humans, one question is: How many others have been infected? Researchers suspect the number is probably fairly large in the Florida area, where the virus has been found in the local mosquito population and wildlife for decades.[1] And, an official with the Florida Department of Health told *USA Today* there was a reported case of a young child diagnosed with Keystone virus infection in 1964 near Sarasota, although no further details were provided to the newspaper.[2]

However, the fact that it is not really known how many human infections have occurred at least suggests the risks of Keystone probably aren't severe at this point. Otherwise, more cases would have been diagnosed and reported.

What Is Keystone Virus?

The Keystone virus belongs to a family of about a dozen or so arboviruses known as the California serogroup (CSG), one of 18 serogroups belonging to the genus Orthobunyavirus in the Peribunyaviridae family. Other members of this group include the California encephalitis virus, the La Crosse virus, the snowshoe hare virus and the Jamestown Canyon virus. All are transmitted by mosquito, and most can infect other mammals such as white-tailed deer and raccoons. The Keystone virus seems

to be carried by several species of mosquito, including Aedes atlanticus and Aedes infirmatus, among others.[2]

Many of the viruses in this serogroup are associated with encephalitis in both animals and humans. But, the Florida teenager diagnosed with Keystone virus did not develop any symptoms of encephalitis, and instead exhibited only a rash and fever.[3]

In studies looking at other CSG viruses with known human infections, researchers have determined that due to generally mild symptoms, human infection rates are almost certainly underreported. However, in rare cases of CSG infection, the disease can progress to encephalitis or meningoencephalitis. One case in particular led to permanent brain damage (postencephalitic dementia) in a 73-year-old New Brunswick man who had to be relocated to an assisted living facility.[4] It is believed he was infected with Jamestown Canyon or snowshoe hare virus.

In the typical life cycle of a CSG virus, it is transmitted by a vector (mosquito or tick) to a warm-blooded host, where new viruses are replicated. When an uninfected vector feeds on the now-infected host, the virus enters the mosquito or tick, and the cycle repeats. However, in some cases, the mammal or bird is infected by the virus, but the virus is unable to replicate itself in its environment. In this case, the host can still become ill, but it will not pass on the virus. This is known as a "dead-end host."

The 2016 Florida patient is unlikely the first to contract an infection from Keystone virus since earlier studies have shown up to one-fifth of people in the Tampa area had Keystone antibodies in their system.[5] However, researchers point out that this was the first case of a person becoming ill with noticeable symptoms directly attributed to Keystone virus. And, because the boy's symptoms were fairly mild and similar to those of other viruses, it is likely prior Keystone infections were simply undiagnosed or attributed to influenza or other common viruses.[6]

Transmission of Keystone Virus

Keystone disease is caused when the Keystone virus is introduced into the body — almost assuredly via a mosquito bite. Studies to date have indicated the Keystone virus, which was first described in samples taken from Keystone, Fla., near Tampa 54 years ago, is largely confined to the Gulf Coast of the United States, but can extend from Texas to Maryland.[7]

Symptoms and Progression of Keystone Virus Infection

With only a single diagnosed case so far, it's far too early to speak of general symptoms or disease progression of Keystone virus infection. However, the diagnosed boy was brought by his family to urgent care during the Zika virus outbreak of 2016 after he developed a fever and rash. His symptoms did not worsen, and he never developed encephalitis, which is known to occur with some other California serogroup infections.[1]

Looking again at other CSG infections in humans, the symptoms and progression are roughly the same as with other viruses: low-grade fever and possible rash. In rare cases, as noted above, CSG infections have progressed to encephalitis. With other CSG infections, symptoms typically manifest in three to 15 days after infection, and the illness will usually run its course in approximately one week. Researchers believe most CSG infections are asymptomatic, and patients never even know they had the virus.

However, until more cases are diagnosed and studied, it will not be known with any specificity what the "normal" progression of Keystone virus disease is. Researchers are making only educated guesses based on the one diagnosed patient and their knowledge of how Keystone virus' closest relatives have affected humans.

Diagnosis of Keystone Virus

Currently, there is no common test to diagnose Keystone virus infection. It took 18 months of intense laboratory work to diagnose the only confirmed case.[8]

If a patient has an undiagnosed viral infection and has spent time in the Southeastern United States, a possible Keystone

diagnosis could be made through a process of elimination. If symptoms worsen, particularly if encephalitis develops, and no other cause can be determined, a physician may consider contacting researchers at the University of Florida for additional follow-up.

Treatment of Keystone Virus

There are no antiviral drugs that target Keystone virus. Treatment is palliative, which is the same for other viral infections. In mild cases, the patient will be advised to drink plenty of fluids and rest. Over-the-counter anti-inflammatory drugs such as aspirin, acetaminophen and ibuprofen can help reduce fever.

With the first case now identified in humans, one question now is: How many others have been infected?

In the rare case that encephalitis develops, that condition would become the immediate focus of treatment. The Centers for Disease Control and Prevention's (CDC) guidelines for the closely related La Crosse virus disease (LACV) emphasizes the need for immediate hospitalization and supportive care. Encephalitis caused by LACV can result in seizures, but CDC notes that nearly all patients who contract LACV-caused encephalitis recover completely, with no recurring or ongoing symptoms.[9]

Prevention of Keystone Virus

Keystone virus infection is prevented in the same manner as other diseases spread by mosquito such as malaria or Zika: Cover as much of the body as possible with light-colored clothing, including full-length sleeves and pants; sleep under mosquito netting; keep doors and windows closed (or use screens); and use insect repellents containing DEET, IR3535 or icaridin (all of which are safe for use by pregnant women).[10] Keystone can also be prevented by draining standing water around one's home after a rain, including empty flower pots, wading pools and other containers where mosquitoes can breed. Public health agencies should work with local authorities on vector control: draining nonprotected bodies of water (including abandoned or unused swimming pools), spraying for mosquito larvae and restoring habitat for birds, fish and other animals that prey on mosquitoes.

Ongoing Research

Most research into Keystone virus is currently in the very basic stage. Questions being investigated include: How common is it in humans? What is its range? What threat, if any, does it pose to both public health and individual patients? Until these fundamental questions are answered, further questions into a cure, improved treatment options or even a vaccine are unlikely to gain funding or much in the way of interest from the larger research community.

In several interviews, the authors of the University of Florida study who diagnosed the teenage boy with Keystone virus infection indicated they are continuing to study the virus, and are trying to answer the basic questions posed above.

But, as of early October, the National Institutes of Health's ClinicalTrials.gov portal listed no studies into Keystone virus or any of the other California serogroup viruses discussed. There are, however, some 330 studies listed investigating arbovirus infections, including some looking at new methods of mosquito control and eradication that hold promise for preventing Keystone virus as well.

Looking Ahead

This is truly a "breaking story" in medical research right now. Since Keystone virus has been identified for more than a half-century and there is only a single confirmed human case, the current threat to public health seems low. However, physicians who practice in the Gulf Coast region should be vigilant and consider looking at Keystone virus as a possible cause of otherwise unexplained, undiagnosed infections — particularly with patients likely to have been exposed to mosquito bites. More evidence about how common Keystone virus is, its geographic range and the typical course of infection should become more established in the years to come. ❖

JIM TRAGESER is a freelance journalist in the San Diego area.

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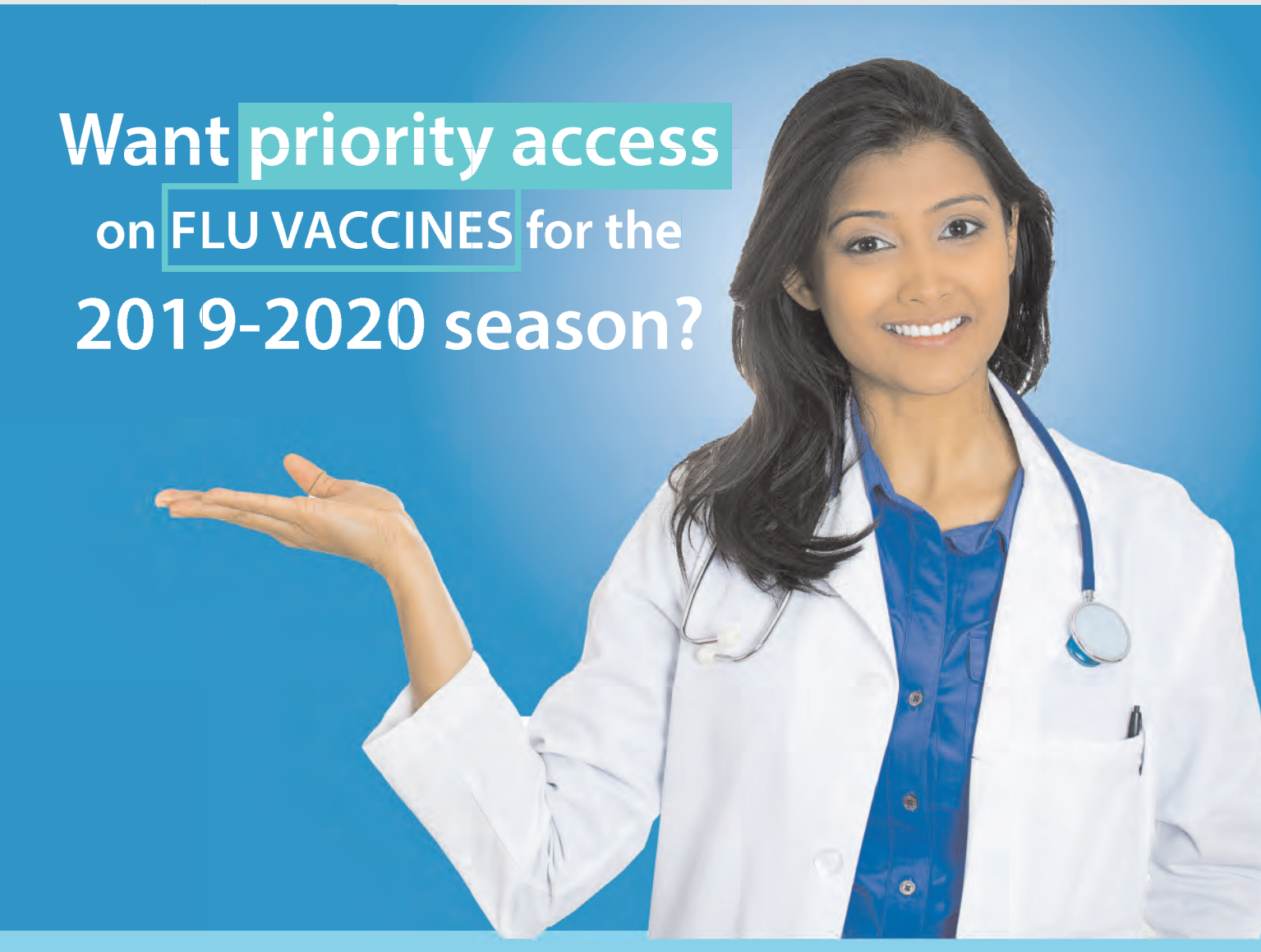

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Myths and Facts: Autoimmune Disorders

Until more is discovered about the causes of autoimmune disorders, these chronic but sometimes fatal disorders will continue to increase in numbers of diseases and individuals affected.

By Ronale Tucker Rhodes, MS

JUST A DECADE or two ago, most people had likely never heard of an autoimmune disorder (AD). But, today, the growing number of individuals diagnosed with an AD is alarming. The National Institutes of Health (NIH) estimates more than 23 million Americans live with an AD, whereas the American Autoimmune Related Diseases Association (AARDA) says that number is 50 million.[1,2] To put this in perspective, the AD prevalence equals heart disease and cancer combined.[3]

ADs affect women at a rate of about two to one compared with men, and the disease often starts during their childbearing years.

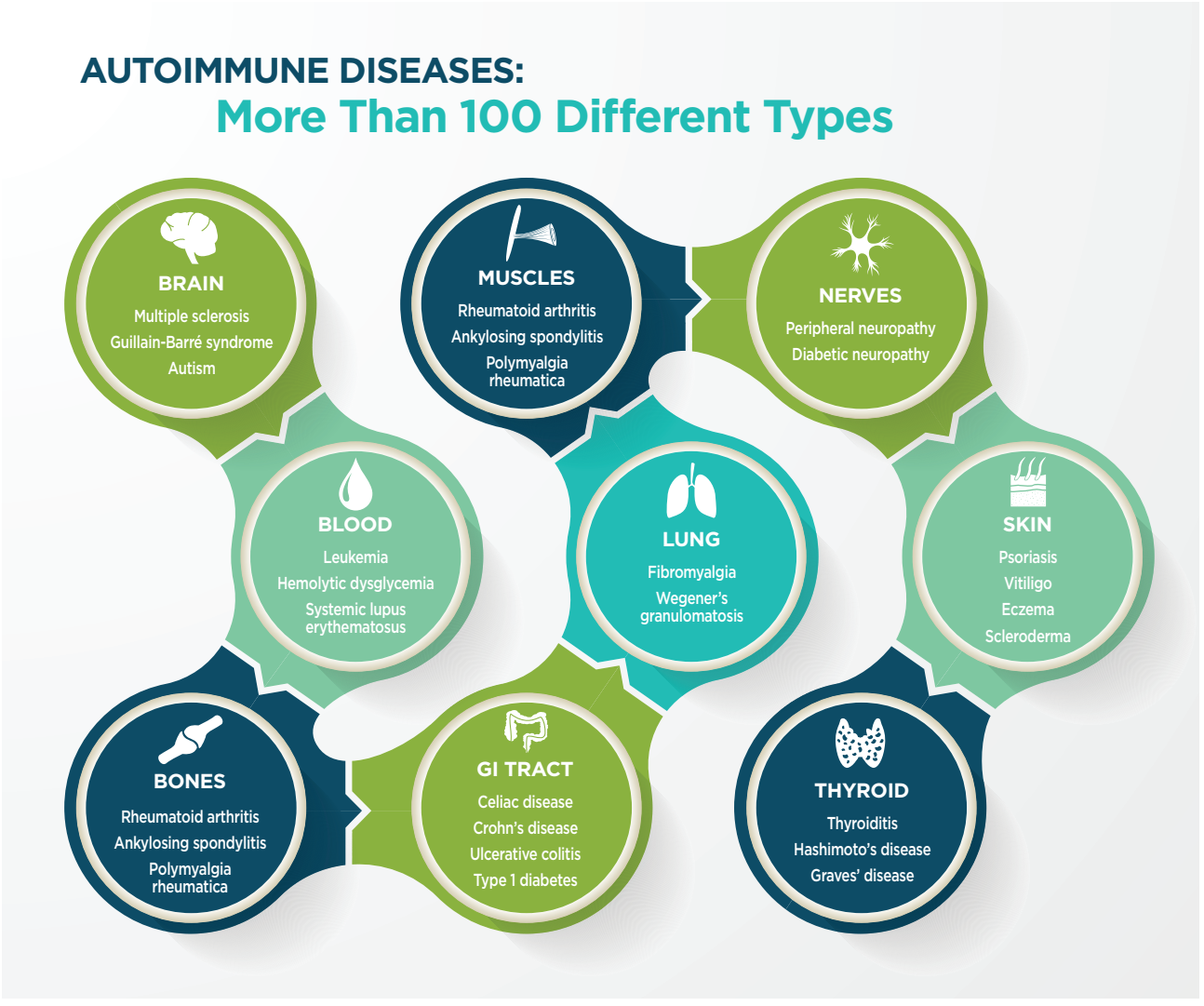
What's more, each year, it appears the incidence rate of ADs is increasing. According to Geoff Rutledge, MD, PhD, a California-based physician and chief medical officer at HealthTap (a technology company delivering a suite of connected health apps), "A recent review of literature concluded that worldwide rates of rheumatic, endocrinological, gastrointestinal and neurological autoimmune disorders are increasing by 4 to 7 percent per year, with the greatest increases seen in celiac disease, type 1 diabetes and myasthenia gravis, and the greatest increases occurring in countries in the Northern and Western Hemispheres."[1] In addition, the American Diabetes Association found type 1 diabetes alone increased by 23 percent between 2001 and 2009.[4]

In the 1940s, autoimmunity was a fairly new concept, with little evidence to support it as a cause of pathology.[5] Then, in the 1950s, Henry G. Kunkel, MD, known as the father of immunopathology, began studying patients with rheumatoid arthritis and lupus in The Rockefeller Hospital. Using newly developed tools of protein chemistry, Dr. Kunkel and colleagues demonstrated that certain antibodies in the blood of these patients reacted with other antibodies as if they were antigens. This was later coined the "rheumatoid factor," which is now used as a test to measure the amount of proteins produced by the immune system that can attack healthy tissue in the body, which can help to pinpoint an AD diagnosis.[6,7]

ADs affect women at a rate of about two to one compared with men (6.4 percent of women vs. 2.7 percent of men), and the disease often starts during their childbearing years (ages 14 through 44). Some ADs are more common in certain ethnic groups. For instance, lupus affects more African-American and Hispanic people than Caucasians. And, certain ADs such as multiple sclerosis and lupus run in families with a susceptibility.[8]

Yet, while it is not definitively understood what causes AD, researchers suspect environmental factors like infections and exposures to chemicals and solvents are interfering with the immune system's ability to distinguish self from nonself. Indeed, it is universally agreed by scientists that most of the risk of autoimmunity comes from environmental exposures rather than from genetic susceptibilities.[8,9] In addition, the Western diet is suspected as a trigger because it is high in fat, sugar and processed foods that cause inflammation. Another theory is the hygiene hypothesis, which suggests that because kids aren't exposed to as many germs today, their immune system may overreact to harmless substances.[8] And, for women specifically, some clinical scientists suspect estrogen may be the culprit, causing a woman's immune system to produce more antibodies and increasing the likelihood that her body will turn on itself.[10]

What is certain about ADs is their effects on an increasing number of people and how much remains unknown about them, which is likely the reason many myths and misconceptions surround ADs.



Separating Myth from Fact

Myth: There are not that many types of ADs.

Fact: While the jury is out on how many ADs there are in the U.S, there are *a lot* of ADs that have been identified, and it is predicted many more diseases could have an autoimmune basis. The NIH report that stated 23.5 million Americans are living with AD mentions 80 different diseases, but it bases that number on another report that refers to only 24 diseases, as well as potential misdiagnosis and underdiagnosis and the possibility more ADs might be discovered. The AARDA website states the number of Americans living with AD is 50 million based on its determination that more diseases could be autoimmune. Indeed, AARDA states researchers have identified 80 to 100 different ADs and suspect at least 40 more of having an autoimmune basis.[11]

The Autoimmune Registry (ARI), a 501(c)3 nonprofit corporation founded in 2016 to create a hub for research, statistics and patient data on all autoimmune illnesses, is working with four academic medical centers to examine their electronic medical records to determine how many people suffer from the diseases believed to be caused by autoimmunity. While ARI acknowledges it will not be able to account for misdiagnosis and underdiagnosis since not all diseases have medical codes and medical codes are often wrong, its goal is to develop statistics reasonably consistent for the U.S. population.[11]

Myth: If someone looks well, he or she can't be suffering from an AD.

Fact: Many ADs are invisible, so individuals' appearance doesn't necessarily reflect their health or how they feel. Unlike most diagnosed cancer patients who look sick (especially under treatment), most AD patients look superficially well, even while suffering significant morbidity, lost productivity and debilitating financial stress.[3]

Myth: Younger people can't get ADs, and symptoms of AD in older adults are just a result of age.

Fact: The age at which people can be affected by an AD depends on the disorder/disease. While women are more likely to be diagnosed with an AD during childbearing years, ADs can affect people of any age. There's no such thing as being too young, and the effects of the disease as one ages are different from the natural aging process.[12] Indeed, ADs tend to arise early in life. For instance, type 1 diabetes starts in childhood or adolescence, and rheumatoid arthritis and systemic lupus erythematosus (SLE) start during the 20s and 30s. However, these conditions often worsen and lead to complications later in life when they become more noticeable, which is why ADs are often thought to more likely affect the elderly.[13]

A 12-year study of irritable bowel disease (IBD), one of the most common ADs that affects about 1.2 million Americans, found the incidence rate in children doubled between 1991 and 2002.[3] Other very common ADs in children include liver disease, celiac disease, Addison's disease, autoimmune thyroiditis, juvenile arthritis, juvenile scleroderma, type 1 diabetes, Kawasaki's disease, multiple autoimmune syndrome and pediatric lupus.[14] In adults, the most common ADs include type 1 diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, lupus, IBD, Crohn's disease, ulcerative colitis, Addison's disease, Graves' disease, Sjogren's syndrome, Hashimoto's thyroiditis, myasthenia gravis, vasculitis, pernicious anemia and celiac disease.[15]

General symptoms of AD have the maximum probability of emerging in the very beginning, whereas other unique abnormalities might appear later.

Myth: People with ADs experience the same symptoms.

Fact: Symptoms of AD depend on the disease pathology. There are two types of ADs: systemic and localized. Systemic ADs tend to spread to various organs, from the skin to the kidneys, as well as the heart. Localized ADs have an effect on a particular body organ like the thyroid, liver or adrenal glands. ADs can have an effect on any body part since they can affect joints, blood vessels, red blood cells, connective tissues, muscles or even endocrine glands (such as the pancreas or thyroid).[14]

General symptoms of AD have the maximum probability of emerging in the very beginning, whereas other unique abnormalities might appear later. In adults, each AD has its own peculiar set of symptoms, yet many share similar features such as muscle aches, joint pain, signs of inflammation (redness, heat or pain) and flu-like symptoms. Fatigue is a defining symptom of many ADs.[16] In children, the first very common symptoms are dizziness, slight fever, fatigue, dry mouth or eyes, weight loss, diffuse joint pain and skin rashes.[14]

Myth: ADs are contagious.

Fact: At this time, experts do not believe ADs are spread to others like bacterial or viral infections. For instance, ADs caused by white blood cells contracted through shared needles, blood transfusion or organ transplant aren't contagious possibly because the number of white blood cells transferred by these methods is relatively small. While researchers have been able to transfer some ADs in mice by transferring certain white blood cells, this only occurs when the mice are already immune-deficient specially bred mice that are already prone to AD. Organ transplants are also unlikely to transfer AD, again presumably because the amount of white blood cells is still relatively small, and the person's normal immune system handles it (even though transplant patients are immunocompromised).[17]

The only known transfer of autoimmunity occurs between mother and fetus during pregnancy, and that is still rare even in affected mothers. For example, mothers with lupus can give birth to babies with neonatal lupus; similarly, myasthenia gravis can cause neonatal myasthenia gravis.[17]

Interestingly, though, one study points to a higher risk of developing a nonceliac AD by spouses of people who have celiac disease in which a person's immune system attacks the lining of their small intestines when gluten-containing foods are eaten. This connection indicates potentially some sort of shared environment, or even gut bacteria, is the culprit. The study's authors also suggest the connection could be the result of something called ascertainment bias, where a spouse of someone with celiac disease is more likely to seek medical advice about similar symptoms.[18]

Myth: ADs are easy to diagnose.

Fact: ADs consist of a host of diseases, many of which are very rare, widely scattered over a number of medical specialties, and usually grouped by body system (digestive, joints, metabolic) rather than as a category with common causal mechanisms (immune system attacks own tissues). That's why diagnosis and treatment are a notoriously exhausting journey, with patients seeing on average five doctors over three and a half years before receiving a diagnosis.[4]

Furthermore, diagnosis can be tricky. This is because symptoms often come and go, which makes it difficult to pinpoint the problem unless the physician happens to know the individual has a family history of AD. In many cases, it's necessary to follow a patient for a while so the disease will manifest itself.[16]

As mentioned earlier, a rheumatoid factor test is one blood test primarily used to help pinpoint a diagnosis. A positive rheumatoid factor test result indicates a high level of rheumatoid factor was detected in the blood, which is associated with AD.[19] But, it's important to know that blood tests that look for autoantibodies can yield positive results even when someone doesn't have an AD.[16] For instance, a num-

ber of other diseases and conditions can raise rheumatoid factor levels, including cancer, chronic infections, inflammatory lung diseases, mixed connective tissue disease, Sjögren's syndrome and SLE. In addition, some healthy people (particularly older adults) have positive rheumatoid factor tests, although it's not understood why. Even some people who have rheumatoid arthritis (one of the most common forms of AD in adults) have low levels of rheumatoid factor.[19]

Other blood tests used to pinpoint a diagnosis include the anti-nuclear antibody, anti-cyclic citrullinated peptide antibodies, C-reactive protein and erythrocyte sedimentation rate tests.[19]

Myth: ADs can be cured.

Fact: Despite the growing number of ADs, scientists are still in the dark regarding interventions that can help cure them. While some may resolve, usually spontaneously and for unknown reasons, most do not. But, ADs can go into remission with therapy. The main goal of therapy is to suppress disease flares and extend periods of remission, if remission is attainable.[20]

Treatment for ADs include medication, physical therapy, exercise, nutrition and, for some, complementary and alternative medicine (CAM). Medications prescribed depend on the disease, its severity and symptoms. These include nonsteroidal anti-inflammatory drugs such as ibuprofen and aspirin to relieve mild symptoms; prescription drugs to relieve more severe symptoms such as pain, swelling, depression, anxiety, sleep problems, fatigue or rashes; medicines that replace vital substances the body no longer makes such as insulin, hormones and enzymes; corticosteroids to decrease inflammation and reduce the activity of the immune system; biologics (immune-suppressing drugs) to control inflammation and help control disease process and preserve organ function; plasmapheresis to remove antibodies from the bloodstream, thereby preventing them from attacking their targets; and immune globulin (protein replacement therapy).[21,22]

When an AD affects joints, muscles and bones, physical therapy can help to reinforce muscles and help individuals move body parts more easily. Eating a well-balanced diet and getting regular exercise can also help individuals feel better. In addition, physicians may suggest supplements to replace insulin, hormones or vitamins.[14]

While it's hard to know if CAM therapies will work for ADs, some people do opt to try them. Some examples of CAM therapies include herbal products, chiropractic, acupuncture and hypnosis. However, there are limited studies on these therapies, and it's important for patients to discuss them with physicians since some products can cause health problems or interfere with medicines.[22]

Myth: ADs are not life-threatening.

Fact: With an estimated 100-plus ADs today, most are usually chronic and not fatal; however, some can lead to death. In fact, ADs are one of the 10 leading causes of death for girls and women in all age groups (up to 64 years old).[2] The most common ADs that can cause death include Graves' disease, giant cell myocarditis, Addison's disease, granulomatosis with polyangiitis and SLE.[13,23]

Dispelling the Myths Now

While ADs were barely even heard of until the last couple of decades, they are growing in both numbers of diseases and individuals affected. Thankfully, the novel approach to the study of immunology by Dr. Kunkel, who discovered autoimmunity, has vastly expanded our knowledge of how immune cells work and how they can go awry.[5] Now, more is understood about these mostly chronic but sometimes fatal disorders, but much remains to be learned.

In 2003, NIH released its Autoimmune Diseases Research Plan encouraging research into the causes, treatments and prevention of AD, with the goal of obtaining additional funding. Since then, the National Institute of Allergy and Infectious Diseases has made it a priority to study ADs because "the chronic and debilitating nature of these diseases, which can lead to high medical costs and reduced quality of life, is a burden on patients and also affects their families and communities."[24] Indeed, based on data from the last decade, estimates of the total AD financial burden are around $100 billion.[3] It can only be hoped, then, that continued study will improve outcomes for the millions of people affected by ADs. ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

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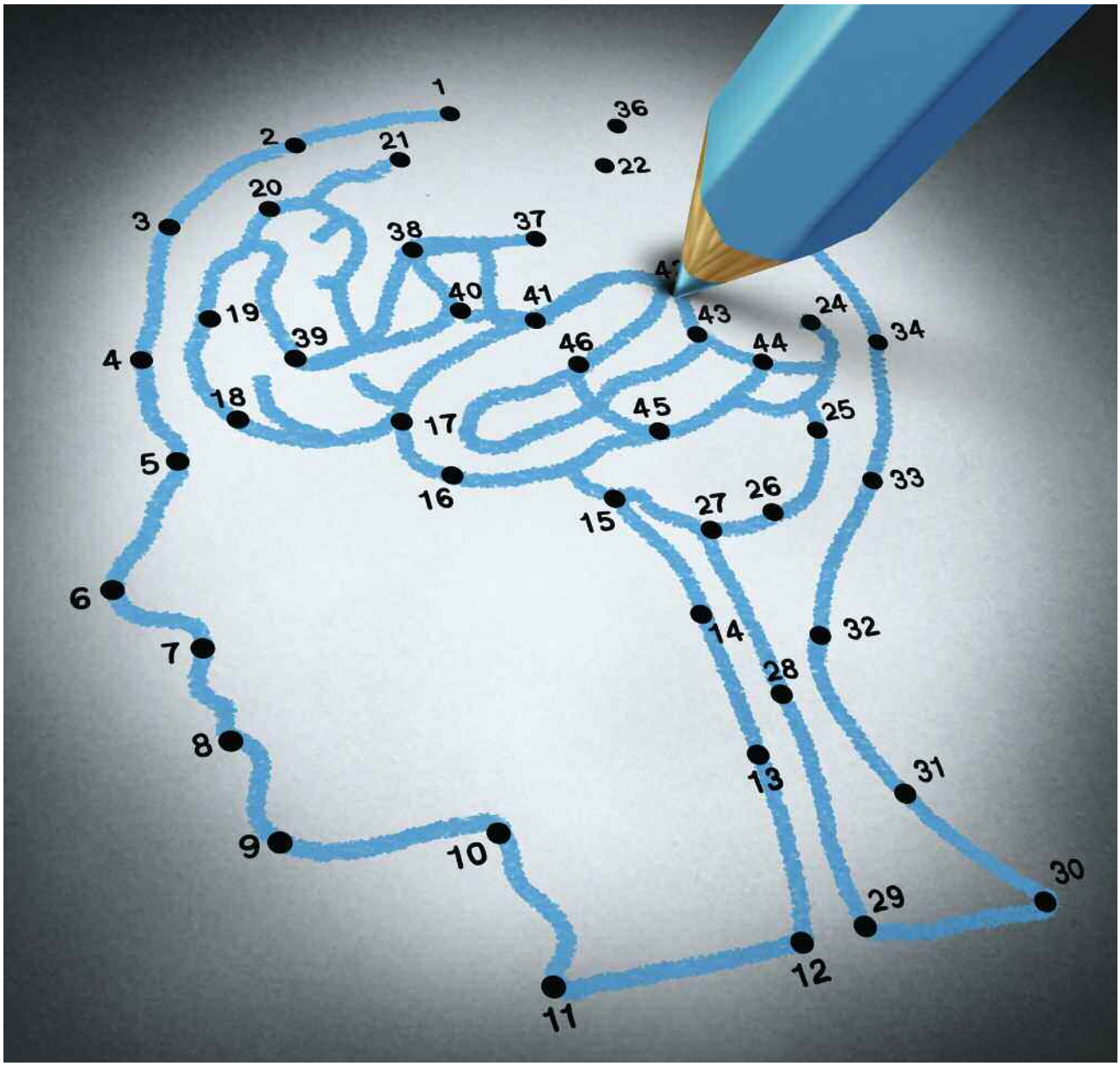
Grifols' AMBAR Study Findings: *Albumin Plasma Exchange May Reduce Progression of Moderate Alzheimer's Disease*

By Keith Berman, MPH, MBA



IN WHAT COULD prove to be the first-ever demonstration of an effective disease-modifying treatment for Alzheimer's disease (AD), top-line findings from Grifols' Phase IIb Alzheimer Management by Albumin Replacement (AMBAR) clinical trial found long-term plasmapheresis with albumin replacement — plasma exchange — importantly reduced disease progression in a prespecified subset of patients with AD of moderate severity.

Forty-one participating treatment sites — 20 in Spain and 21 in the United States — recruited 496 patients age 55 years to 85 years with mild or moderate AD. Of these, 347 patients were randomized to a placebo arm receiving sham treatments, or to one of three arms treated with a series of six weekly conventional plasma exchange procedures with 5% albumin replacement, followed by 12 monthly low-volume plasma exchange procedures with 20% albumin replacement (Figure 1). Two of the three plasma exchange/plasmapheresis treatment arms additionally received three infusions of 10 or 20 grams of intravenous immune globulin (IVIG) over the 14-month study period, while the third arm did not receive replacement IVIG.

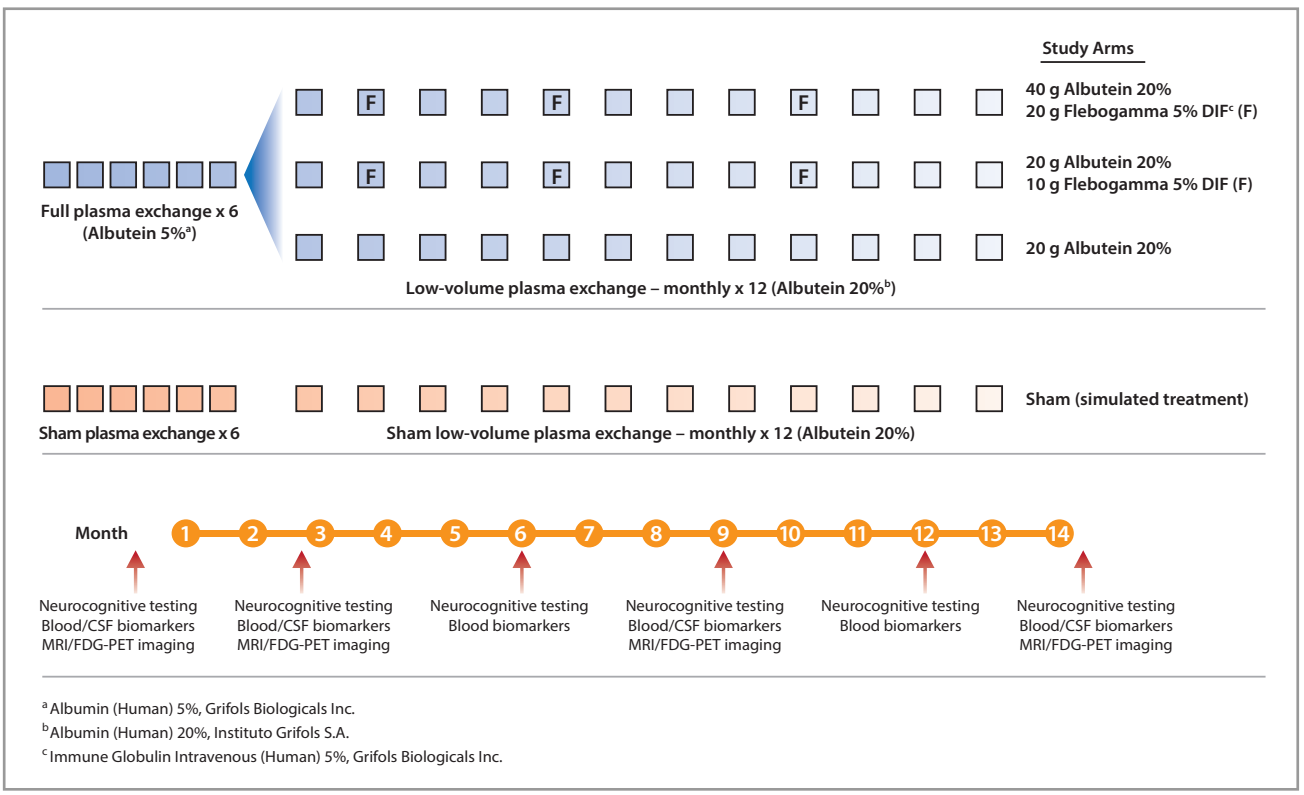
The primary study outcomes were changes from baseline to end-of-study treatment month 14 in well-validated scales of cognition (ADAS-Cog) and activities of daily living (ADCS-ADL). The study employed both a randomized and double-blind design to ensure neither patients nor evaluators knew whether subjects were receiving active treatment or placebo treatment.

Plasma Exchange Reduces Progression in Moderate Disease

In an evaluation of all subjects regardless of disease severity, the combined arm including all patients treated with albumin plasma exchange experienced 66 percent less decline in the ADAS-Cog scale over the period from baseline to 14 months than the placebo arm, nearly reaching statistical significance ($p = 0.06$); for the ADCS-ADL scale, the combined albumin plasma exchange arm had a statistically significant 52 percent less decline than the placebo arm ($p = 0.03$).

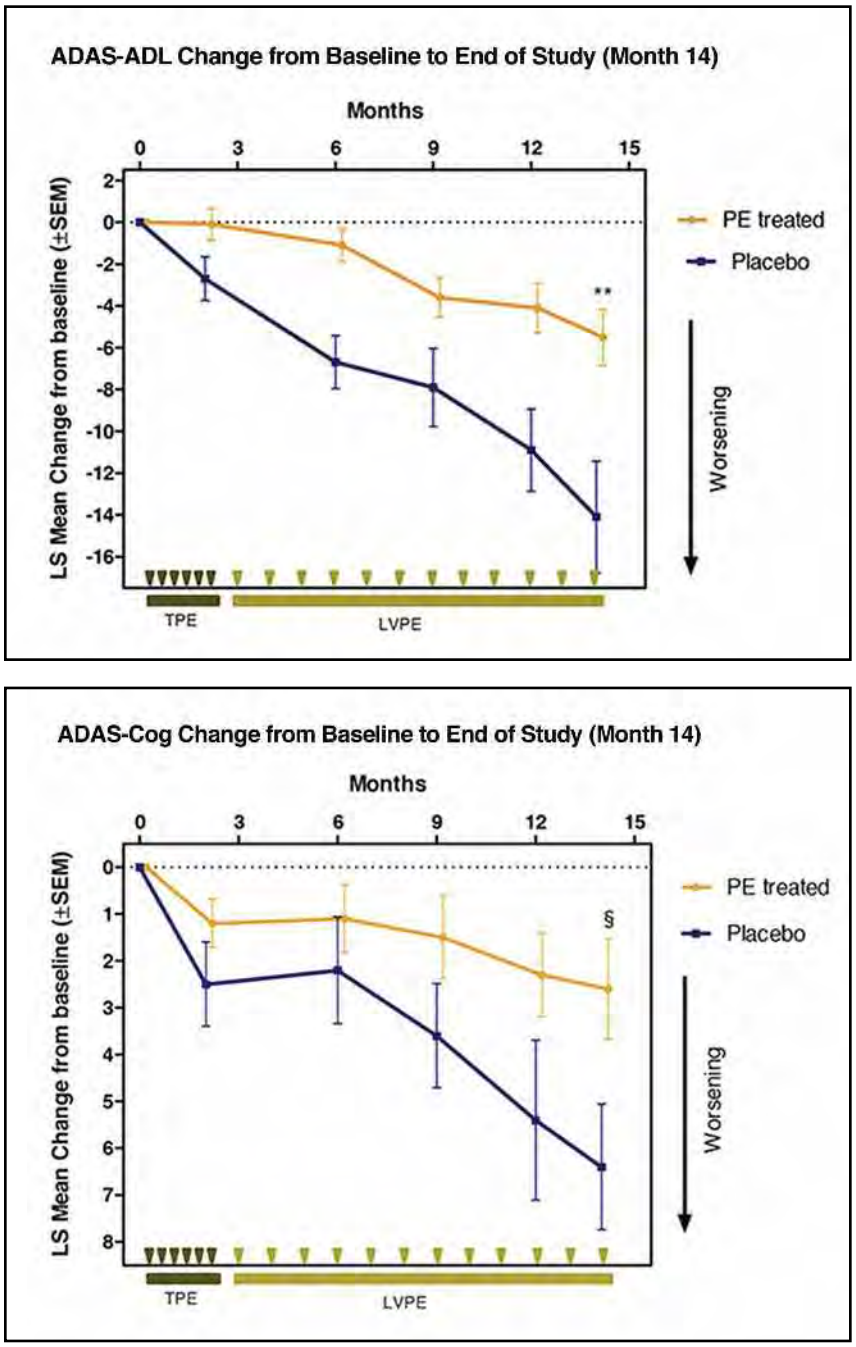
The investigators then conducted the same analyses after stratifying on baseline disease severity. In prespecified patients with mild AD at baseline, a consistent delay in progression of disease was observed in the treatment arms, and a similar pattern was observed in the

Figure 1. Grifols' Alzheimer Management by Albumin Replacement (AMBAR) Study Design



[a] Albumin (Human) 5%, Grifols Biologicals Inc.
[b] Albumin (Human) 20%, Instituto Grifols S.A.
[c] Immune Globulin Intravenous (Human) 5%, Grifols Biologicals Inc.

Figure 2. Changes from Baseline in Cognitive (ADAS-Cog) and Activities of Daily Living (ADCS-ADL) Scales in Patients with Moderate Alzheimer's Disease



LS, least squares; LVPE, low volume plasma exchange; SEM, standard error of mean; PE, plasma exchange; TPE, therapeutic plasma exchange

Source: www.grifols.com/en/view-news/-/new/grifols-ambar-results-demonstrate-a-significant-reduction-in-the-progression-of-moderate-alzheimers-disease

placebo arm. Differences in cognitive and functional decline tended to favor the combined active treatment arms relative to the placebo arm, but did not reach statistical significance. Therefore, the investigators suggested that "more follow-up time is needed to observe disease progression in milder disease."

Conversely, over the 14-month study period, patients with moderate AD who were treated with albumin plasma exchange experienced 61 percent less decline in both the ADAS-Cog and ADCS-ADL scales than patients randomized to placebo (Table 1 and Figure 2). The difference between combined albumin plasma exchange arms and the placebo arm was statistically significant for the ADAS-Cog scale, and highly significant for the ADCS-ADL scale. When analyzed by plasma exchange combination type, all three treatment combinations for moderate AD patients reached statistical significance for ADCS-ADL relative to the placebo arm.

"The treatment effect observed in the group with moderate severity is remarkable and those findings open new avenues…that have the potential to offer Alzheimer's disease patients a new modality of treatment," said Oscar Lopez, MD, director of the Alzheimer's Disease Research Center at the University of Pittsburgh.

Detailed safety and efficacy data are anticipated shortly in a full published report, but Spanish co-investigator Mercé Boada, MD, PhD, characterized the albumin plasma exchange procedures as "safe and feasible," citing more than 1,000 plasma exchange procedures performed at her center in Barcelona and close to 5,000 in the entire study.

The Therapeutic Principle Behind Plasma Exchange

Given the long and diverse list of investigational drugs intended to slow AD progression that failed in large-scale clinical trials, no one can be faulted for not getting too excited over these promising findings. Yet the principle that underpins a chronic regimen of plasmapheresis with albumin replacement to battle AD is compelling:

- Extensive evidence points to an etiologic role of certain neurotoxic amyloid-β

Table 1. Progression of Declines in Cognition (ADAS-Cog) and Activities of Daily Living (ADCS-ADL) in Three Combined Albumin Plasma Exchange Treatment Arms Compared to Placebo Arm

	% Lesser Decline for Combined PE Arms vs. Placebo Arm			
	ADAS-Cog	*p*	*ADCS-ADL*	*p*
Mild and moderate Alzheimer's disease	66%	0.06	52%	0.03
Moderate Alzheimer's disease only	**61% less for PE arms** (2.6/PE vs. 6.4/placebo)	**0.05**	**61% less for PE arms** (-5.5/PE vs. -14.1/placebo)	**0.002**

(Aβ) peptides, which are able to cross between the circulation and brain tissue through the blood-brain barrier (BBB). Aβ aggregates that accumulate as neuritic plaques are a histopathological hallmark of AD.

• As much as 90 percent of circulating Aβ in healthy individuals is not free in plasma but instead is bound to albumin, a 67-kilodalton nonglycosylated protein that accounts for more than one-half of total protein in plasma and cerebrospinal fluid (CSF).

• Albumin undergoes glycation with normal aging, attenuating its physiologic Aβ binding capacity; eventually, this results in increased levels of unbound neurotoxic Aβ in the plasma and CSF.

• Glycation attenuates antioxidant and anti-inflammatory properties mediated by human albumin; a chronic pro-inflammatory state is correlated with a number of common degenerative diseases of the elderly, including AD.

• Both brain and plasma levels of glycated albumin have been found to be significantly higher in persons with AD than in age-matched controls.

Plasmapheresis physically removes a portion of the patient's "old" less-functional glycated albumin, which is replaced with purified human albumin sourced from plasma collected from relatively young, healthy plasma donors. This infused replacement albumin both retains its Aβ binding capacity and appears to have no quantifiable levels of bound Aβ.

> "Investments now amounting to billions of dollars in development of failed experimental AD treatments have not deterred the drug industry from continuing the quest."

This plasma exchange procedure is repeated on a regular chronic basis, with the goal of reducing brain Aβ burden by exploiting the dynamic equilibrium between the brain and blood plasma. Each time the patient's old glycated, Aβ-saturated albumin is removed by apheresis and replaced with fresh, Aβ-binding albumin, a brain-plasma concentration gradient is created by the resulting drop in plasma Aβ concentration. Uncomplexed Aβ residing in the brain and CSF is mobilized by this new concentration gradient and transits across the BBB and into the circulating plasma until a new brain-plasma Aβ equilibrium is established. All of this is established science documented in numerous studies by Grifols collaborators and others.

Why Plasma Exchange?

Investments now amounting to billions of dollars in development of failed experimental AD treatments have not deterred the drug industry from continuing the quest. There is an urgent unmet need for effective treatments that can stabilize or meaningfully delay progression of this disease. Some 5.7 million Americans now live with AD, a number projected to increase to nearly 14 million people by 2050. Atop the enormous human toll is an estimated $277 billion national cost associated with this disease, which could rise as much as four-fold by 2050. Some 70 proposed disease-modifying agents are currently in clinical development for AD, including a number of sophisticated new anti-amyloid monoclonal antibodies and anti-aggregation agents.

Grifols' proposed mechanism of action to treat AD presents a stark contrast with all the highly targeted anti-amyloid drugs of the past and present: physical removal of neurotoxic amyloid proteins with chronic plasmapheresis and albumin replacement therapy. It is elegant in its simplicity. And therapeutic plasma exchange has a decades-long clinical track record as a safe and highly effective treatment for dozens of disorders, including many for which the circulating etiologic agent removed by this procedure is unknown.

Next Steps

While the top-line AMBAR study findings are highly encouraging, there is a long list of would-be AD treatments for which strong preliminary efficacy signals observed in Phase II trials could not be replicated in larger pivotal studies. "More research is needed in a larger study so we know if this is an effective procedure for the treatment of Alzheimer's dementia," said Alzheimer's Association Scientific Director Maria Carrillo, PhD.

At the conclusion of his presentation of AMBAR study findings at an international research conference last October, Grifols Medical Director Antonio Páez told attendees that the company plans to sponsor a new trial to definitively answer whether the AD progression can be slowed or stabilized with plasma exchange. Stay tuned. ❖

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Dominick Spatafora, who suffers from lower motor neuron syndrome, founded the Neuropathy Action Foundation to educate patients and providers about neuropathy and empower them to become their own advocates.

Treating Neuropathy with IVIG: *A Patient's Perspective*

By Trudie Mitschang

DOMINICK SPATAFORA was just 30 years old when he was diagnosed with multifocal motor neuropathy (MMN). After overcoming a number of personal challenges concerning access to care, he became a patient advocate by founding the Neuropathy Action Foundation (NAF). Today, he works actively to educate patients and providers on topics related to neuropathy diagnosis and treatment.

Neuropathy is not one single disease, but several types of conditions resulting from damage to one or more of an individual's peripheral nerves. Diagnosis is based primarily on symptoms and medical history, coupled with various medical tests performed by a neurologist. While treatment varies based on diagnosis, in the case of immune-mediated neuropathies like Dominick's, the use of intravenous immune globulin (IVIG) is a preferred option.

BSTQ: Tell us about your symptoms prior to diagnosis.

Dominick: It started with a tremor in my right hand. One day, I woke up and was unable to close my fingers together. I saw my physician who referred me to a neurologist. My very first diagnosis was Lou Gehrig's disease, and I was given three to five years to live. I refused to accept that diagnosis and sought additional opinions. After three incorrect diagnoses and a visit to the Mayo Clinic, I learned I had MMN [an immune-mediated lower motor neuron syndrome].

BSTQ: When were you first treated with IVIG?

Dominick: I was fortunate because I was immediately prescribed IVIG. It was like liquid gold — a miracle drug for me. I noticed an improvement in symptoms literally within a couple of days. IVIG not only managed my symptoms, it also prevented the disease from progressing.

BSTQ: Did your insurance plan cover treatment?

Dominick: Surprisingly, I was able to get treatment approved by my HMO. However, after being treated for about 12 months, I got a letter telling me my insurance plan would no longer cover IVIG because it was "no longer medically necessary." I spent three months fighting that decision.

BSTQ: How did you fight it?

Dominick: I was in a unique situation because I worked in government relations. I had access to the U.S. surgeon general and various elected officials who wrote letters on my behalf. I eventually received a letter from my insurance company stating I had been granted ongoing coverage for IVIG. But, the letter advised me to avoid discussing the favorable decision with other patients who would likely not be receiving the same access to care. That letter was what prompted me to found NAF. I wanted to educate patients and providers about neuropathy, empower them to become their own advocates and teach them how to stand up to any third-party payer denying them access to medication.

BSTQ: Have you ever lost coverage for IVIG?

Dominick: One of the things insurance companies bank on is the probability you will only be covered by them for a few years. The odds are high most people will change jobs every three to five years and, as a result, obtain new insurance. So, over the years, I've changed insurance, and there are constant struggles. I currently have phenomenal insurance, but every quarter, my neurologist still has to go through the prior authorization process by sending studies and filling out forms.

BSTQ: What's your treatment plan today?

Dominick: I am treated with 36 grams of IVIG at home once a month. I've recently switched products after 14 years; it was taking two-and-a-half hours for treatment, but since switching, it's taking closer to four hours since I had to slow the rate of infusion.

BSTQ: Do you think access to IVIG has improved over the years?

Dominick: I think with the advent of social media, patients are more empowered, informed and educated, and that definitely helps. The problem is health plans are continuously going out of their way to hinder access to IVIG. I also don't think there is good brand recognition with IVIG. Like any other medication, patients may have to try several brands to find the one that works for them. Without knowing there are options, a doctor may give up after the first try, and that can really be detrimental to the patient.

BSTQ: What are you most proud of in relation to NAF?

Dominick: I always quote Margaret Mead who said: "Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it's the only thing that ever has." We have that motto, and simply knowing we've helped even one patient means everything to us. ❖

Treating Neuropathy with IVIG: *A Physician's Perspective*

Dr. Todd Levine is a neurologist who specializes in immune-mediated neuropathies that are often treated with immune globulin.

TODD LEVINE, MD, is a board-certified neurologist with a subspecialty in neuromuscular diseases. He practices in Phoenix, Ariz., at Phoenix Neurological Associates (PNA). He is also the founder and director of the PNA ALS (amyotrophic lateral sclerosis) clinic and an adjunct professor of neurology at University of Kansas. In addition, Dr. Levine serves as the chairman of the neuromuscular section of the American Academy of Neurology.

BSTQ: What treatment options do you initially consider after diagnosing a neuropathy?

Dr. Levine: Treatments depend on the cause of the neuropathy. So, if it's diabetic neuropathy, we control the diabetes; if it's a toxic substance, we remove the substance; [or] if it's infectious, we treat the infection. On the other hand, if the neuropathy is caused by the immune system, we use medications to change the immune system. So, the first step is to understand the root cause before we can proceed with a treatment plan.

BSTQ: What are immune-mediated neuropathies?

Dr. Levine: Immune-mediated neuropathies can be subdivided into different groups based on the type of nerve that is damaged: motor, sensory, motor and sensory, or autonomic. They are diagnosed based on characteristic changes on nerve conduction studies, or abnormalities in blood tests, spinal taps or nerve biopsies. At times, it can be difficult to be certain a neuropathy is caused by the immune system. In these cases, doctors may opt for a short trial of a therapy designed to treat immune neuropathies. If patients respond, then it is likely their neuropathy is immune-mediated. Should patients fail to respond to the first trial of therapy, it is still possible they have an immune-mediated neuropathy.

BSTQ: Can you give us an overview of the use of intravenous immune globulin (IVIG) to treat various neuropathies?

Dr. Levine: According to a guideline issued by the American Academy of Neurology, IVIG has been identified as an effective treatment for certain disorders of the nerves and muscles, including Guillain-Barré syndrome (GBS) and a form of neuropathy called chronic inflammatory demyelinating polyneuropathy (CIDP). IVIG is a type of immunotherapy that fights the misdirected immune system. Immune globulins are proteins in human blood that likely link themselves with antibodies or other substances directed at the nerves. According to the guideline, strong evidence shows IVIG effectively treats GBS, a rare disorder in which the body's immune system attacks the peripheral nervous system, causing tingling and weakness in the arms and legs. Strong evidence also shows that long-term use of IVIG can help treat CIDP, which is the chronic counterpart of GBS and can affect nerves in the arms and legs and other parts of the body.

BSTQ: When is IVIG therapy a better alternative than other treatment options for neuropathy?

Dr. Levine: That's difficult to answer. Even in the best clinical trials of CIDP, only 50 percent improve with IVIG. Other options like steroids, plasmapheresis or immunosuppressive agents can be helpful. I like to say that everyone's immune system is different, so the path to an effective treatment plan is often filled with trial and error.

BSTQ: How exactly does IG work to alleviate symptoms of neuropathy?

Dr. Levine: There are many different theories. I explain it to patients in a way that makes sense to me. IGs are antibodies from other people that block the bad antibodies in a patient's system from damaging the nerves. But, it is important to understand we have nothing to help nerves grow. We can lessen the disease, but the patient's own body has to grow the nerves on its own. So being healthy, eating well and exercise are all also very important aspects of any effective treatment plan.

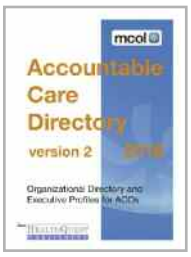
BSTQ: One subcutaneous IG (SCIG) product was recently approved to treat CIDP, and another is being considered. What benefits do you believe these offer?

Dr. Levine: SCIG generally lessens the side effects patients experience from IVIG treatments and can be easier to manage. Overall, patients will experience fewer headaches, fevers, rashes, etc. The effectiveness of IVIG and SCIG seems to be the same, but for most patients, SCIG can result in more needle sticks per month (depending on the dose of IG they are receiving and the brand). Another advantage of SCIG is that it gives patients more freedom so they are not tied to an infusion center or a nurse. In addition, many patients enjoy the sense of independence they gain from being able to manage their treatment on their own. ❖

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

The Accountable Care Directory 2018, Version 2

Author: MCOL HealthQuest Publishers



This directory, a resource for accountable care organization (ACO) stakeholders and others monitoring the industry, incorporates extensive updates and is available as a softcover book or in electronic PDF format. It encompasses an organizational directory of 795 selected ACOs, indicating next generation, standard MSSP, MSSP AIM, MSSP SNF waiver and MSSP advanced models and applicable tracks and start dates for Medicare ACOs as of the date of publication, plus a wide range of ACOs serving selected commercial and other populations. Contact and summary information is provided for each organization, along with a listing of key individuals with leadership or operational involvement, of which 4,048 of these are listed with direct phone and email contact information when available. Also included are executive profiles providing contact and biographical information for 245 executives and thought leaders involved with ACOs representing a wide range of organizations, including provider organizations, health plans, research organizations, solutions providers and others. Indexes for convenient navigation and reference are organized six different ways.

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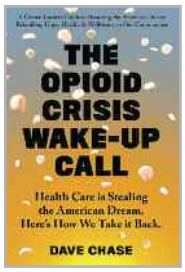
The Opioid Crisis Wake-Up Call

Author: Dave Chase



In *The Opioid Crisis Wake-Up Call*, Dave Chase explores the already-existing solutions to the largest public health crisis in 100 years, updating and expanding on the content and themes from his 2017 best-seller *The CEO's Guide to Restoring the American Dream*. In this book, he defines what real change requires throughout all facets of U.S. healthcare — from the demands on employers to use their market power to force change, to the role of policymakers, community organizers, insurers and pharmaceutical manufacturers in solving their own part of the problem.

healthrosetta.org/wake-up-call

ICD-10-CM Expert for Physicians 2019 with Guidelines 1st Edition

Author: Optum360

Developed specifically to meet the needs of physicians, the Optum360 codebook contains the complete ICD-10-CM code set, which is the cornerstone for establishing medical necessity, determining coverage and ensuring appropriate reimbursement. Included are a new symbol in the tabular for codes associated with Centers for Medicare and Medicaid Services (CMS) quality payment program measures and a symbol to identify codes associated with CMS hierarchical condition categories used in risk adjustment coding. Supplementary appendixes available only in the expert edition include pharmacology listings, Z codes for long-term use of drugs and associated drug names, and Z codes used only as primary diagnosis.

www.amazon.com/ICD-10-CM-2019-Physicians-Expert-Guidelines/dp/1622544285/ref=sr_1_4?s=books&ie=UTF8&qid=1539013626&sr=1-4&keywords=physician+books

Top Trends in Drug and Device Advertising and Promotion

Author: U.S. Food and Drug Administration

This report covers six areas regulators give the most attention concerning drug and device advertising and promotion: 1) Consistent communication: Three factors that ensure communications are consistent with a product's approved labeling, 2) Direct-to-consumer advertising: Use of distracting visuals, competing superimposed images and lively music that can minimize the required presentation of risk information, 3) Risk disclosure: How much information needs to be presented and how, 4) Payer communications: Disseminating healthcare economic information to payers postapproval, 5) Preapproval promotion: A new safe harbor for communicating information about investigational products to payers and 6) Transparency: Making it clear that a communication is sponsored advertising.

www.fdanews.com/products/56085?hittrk=BTTDDAP-18906TB2-K-rrhodes%40igliving.com&utm_campaign=Products%3A%20BTTDDAP%3A%20Top%20Trends%20in%20Drug%20and%20Device%20Advertising&utm_source=hs_email&utm_medium=email&utm_content=65690473&_hsenc=p2ANqtz-_IG9-QEJuP2_PdGXlWR-amM01sQAVeTHGvV8SgKyqr2tLOLyAOpj-xRQXHFDT9PzeDnXlPh5gvnG8un9z7M2gLUgtuUA&_hsmi=65690473

Improved Social and Behavioral Scores Following IVIG Therapy Suggest a Neuroimmune Etiology in Some Children with Autism

A number of case reports have documented the efficacy of intravenous immune globulin (IVIG) in children with autoimmune encephalopathy (AIE), and several studies have described improvements in autism-related characteristics following IVIG therapy. Now, in the largest case series of children with autism spectrum disorder (ASD) treated with IVIG, researchers identified brain-targeted autoantibodies in children with ASD. In the study, 82 children were screened for specific blood autoantibodies or other markers associated with AIE of which 49 of those whose autism-related behavioral and other symptoms were recommended a trial of IVIG.

Thirty-one children received varying monthly doses of IVIG, with the majority receiving 2.0 grams per kilogram of body weight or more. The majority of parents (90 percent) reported some improvement, with 71 percent reporting improvements in two or more symptoms. Statistically significant improvement was documented for the subset of patients whose caregivers completed the Aberrant Behavior Checklist (ABC) and/or Social Responsiveness Scale (SRS) questionnaires. The antidopamine D2L receptor antibody, anti-tubulin antibody and ratio of antidopamine D2L to D1 receptor antibodies were related to changes in the ABC. Changes in the Cunningham autoantibody panel predicted SRS, ABC and parent survey-based treatment responses with good accuracy. Adverse effects of IVIG administration were common (62 percent) but mostly limited to the treatment period; only two (6 percent) patients discontinued IVIG because of adverse effects.

The investigators believe findings from this open-label case series provides evidence supporting a neuroimmune subgroup in patients with ASD.

Connery K, Tippett M, Delhey LM, et al. Intravenous immunoglobulin for the treatment of autoimmune encephalopathy in children with autism. Transl Psychiatry *2018 Aug 10;8(1):148.*

Neonatal Fc Receptor Antagonist Efgartigimod Sustainably Reduces Circulating IgG Level in Humans

Observing that management of severe antibody-mediated autoimmune diseases with intravenous immune globulin (IVIG) and plasma exchange therapy can be associated with serious adverse events or a substantial burden on patients, investigators from the Belgian biotechnology company argenx and U.S. collaborators conducted a Phase I clinical study to assess a novel modified antibody Fc fragment (efgartigimod) that reduces the circulating IgG level by blocking neonatal Fc receptor-mediated IgG recycling.

This randomized, double-blind, placebo-controlled first-in-human study was conducted in 62 healthy volunteers to explore single and multiple ascending intravenous doses of this Fc receptor antagonist. The study objectives were to assess safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity. Findings from this study were compared with the pharmacodynamics profile elicited by efgartigimod in cynomolgus monkeys.

Efgartigimod treatment resulted in a rapid and specific clearance of serum IgG levels in both cynomolgus monkeys and healthy volunteers. In humans, a single administration of efgartigimod reduced IgG levels by up to 50 percent, while multiple dosing further lowered IgG levels on average by 75 percent. Approximately eight weeks following the last administration, IgG levels returned to baseline. Efgartigimod did not alter the homeostasis of albumin or immunoglobulin classes other than IgG. No serious adverse events related to efgartigimod were observed.

The investigators concluded efgartigimod is "safe and results in a specific, profound and sustained reduction of serum IgG levels," and proposed this therapeutic approach warrants further evaluation in IgG-driven autoimmune diseases.

Ulrichts P, Guglietta A, Dreier T, et al. Neonatal Fc receptor antagonist efgartigimod safely and sustainably reduces IgGs in humans. J Clin Invest *2018 Oct 1;128(10):4372-86.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective January 1, 2019, through March 31, 2019

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	CARIMUNE NF	CSL Behring	J1566	$86.22	$84.84
	FLEBOGAMMA	Grifols	J1572	$68.79	$67.69
	GAMMAGARD SD	Shire	J1566	$86.22	$84.84
	GAMMAPLEX	BPL	J1557	$91.78	$90.31
	OCTAGAM	Octapharma	J1568	$70.94	$69.80
	PRIVIGEN	CSL Behring	J1459	$80.64	$79.34
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$84.45	$83.10
	GAMMAKED	Kedrion	J1561	$80.23	$78.94
	GAMUNEX-C	Grifols	J1561	$80.23	$78.94
SCIG	CUVITRU	Shire	J1555	$136.05	$133.87
	HIZENTRA	CSL Behring	J1559	$101.12	$99.50
	HYQVIA	Shire	J1575	$141.78	$139.51

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

Calculate your reimbursement online at www.FFFenterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	CARIMUNE NF Lyophilized	CSL Behring	PI, ITP	6 g, 12 g
	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	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)	Shire	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
	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Shire	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	CUVITRU Liquid, 20%	Shire	PI	1 g, 2 g, 4 g, 8 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g
	HYQVIA Liquid, 10%	Shire	PI	2.5 g, 5 g, 10 g, 20 g, 30 g

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

2018–2019 Influenza Vaccine

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

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	5 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	5 years and older	90688
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	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST (LAIV4)	MEDIMMUNE	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* 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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