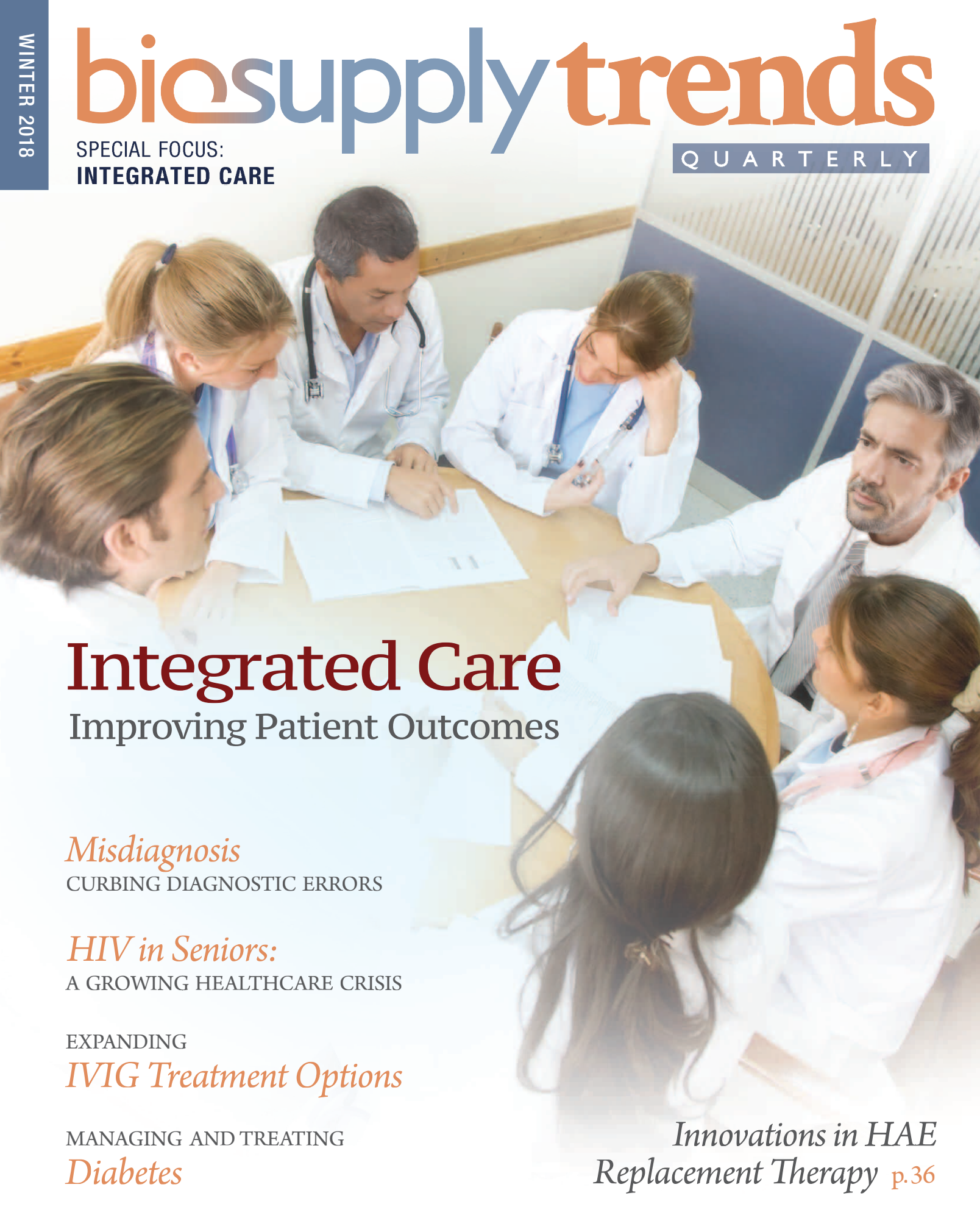
WINTER 2018

biosupply trends

QUARTERLY

SPECIAL FOCUS:
INTEGRATED CARE



Integrated Care

Improving Patient Outcomes

Misdiagnosis
CURBING DIAGNOSTIC ERRORS

HIV in Seniors:
A GROWING HEALTHCARE CRISIS

EXPANDING
IVIG Treatment Options

MANAGING AND TREATING
Diabetes

Innovations in HAE Replacement Therapy p.36

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

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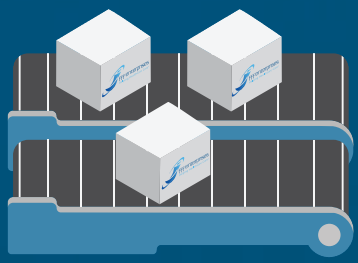

To Guaranteed Channel Integrity™

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

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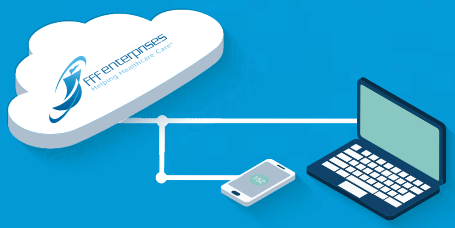

Verification

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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Since 1988

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About BioSupply Trends Quarterly

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

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Embracing Integrated Care for Improved Patient Outcomes

TODAY, INTEGRATED CARE is a worldwide trend. The World Health Organization defines integrated care as "a concept bringing together inputs, delivery, management and organization of services related to diagnosis, treatment, care, rehabilitation and health promotion. Integration is a means to improve services in relation to access, quality, user satisfaction and efficiency." Indeed, integrated care is needed now more than ever to bring together an exchange of ideas among academics, researchers, clinicians, policymakers, and users and providers of services to improve patient care. Implementation of this concept is the focus of many of the articles in this edition.

As healthcare becomes more complicated with an ever-growing number of discoveries about diseases, many of which are rare, a lack of integrated care can often result in misdiagnoses. As we point out in our article "The Misdiagnosis Dilemma," as many as 88 percent of patients who seek a second opinion receive a significantly different diagnosis, which can generate not only psychosocial health implications, but enormous economic consequences when expensive treatments are involved. The problem is caused by many factors, but the complexity of conditions and the time constraints pressuring physicians play significant roles. The key, say health experts, is education. Providers need to be open to integrating care with other physicians for second opinions in complex cases. And, insurance companies play a crucial role when recognizing that a second opinion ensures a correct diagnosis, which is always in the best interest of patient care and can curb care costs in the long run.

Current healthcare is not only more complicated, it's becoming more sophisticated, resulting in once-terminal patients living longer with diseases due to better treatments. A case in point is human immunodeficiency virus (HIV). In our article "Growing Old with HIV," we relate the increased risk of HIV for older adults, who make up more than half of all people living with HIV today, and who, increasingly, are being diagnosed at an older age due to changes in lifestyle and misperceptions about their risk of contracting the disease. This uptick in HIV among older adults creates unique challenges for healthcare professionals who may not regularly address sexual health risk behaviors with older patients. Recognition of HIV as a significant risk to older adults has resulted in improved integrated care strategies with new monitoring tools and better training for healthcare providers.

Researchers also play a critical role in the integration of care by studying the benefits of current treatments for a host of diseases that have not responded to conventional treatments and are not approved therapy by the U.S. Food and Drug Administration. As we highlight in our article "Expanding Uses of IVIG," this is increasingly true for intravenous immune globulin (IVIG) therapy. Several studies indicate IVIG may show promise in treating diseases such as lupus, multiple sclerosis, Alzheimer's, dysautonomia and infertility.

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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HHS Proposed Significant Cuts to Medicare Payments for 340B Drugs

The U.S. Department of Health and Human Services (HHS) has proposed 2018 updates to the Medicare hospital outpatient prospective payment system (OPPS) to decrease Medicare Part B payments to hospitals for 340B drugs by almost 30 percent. Under the rule, effective Jan. 1, 2018, Medicare payments for all separately payable Part B drugs dispensed to hospital outpatients, with the exception of "pass-through" drugs, vaccines and drugs identified with a to-be-established modifier indicating that the drug was not purchased at the 340B price, would be subject to a reduction in payment from average sales price (ASP) plus 6 percent to ASP minus 22.5 percent. The Centers for Medicare and Medicaid Services derived the proposed reduction from a May 2015 report to Congress from the Medicare Payment Advisory Commission in which the panel found ASP minus 22.5 percent represents the average minimum discount that 340B-participating hospitals receive for separately payable drugs under the OPPS.

According to HHS, the proposed rule is necessary to slow growth in the program shift trends of growing amounts paid by Medicare for outpatient hospital drugs and reduce Medicare beneficiary cost-sharing. Savings are estimated to be approximately $900 million in 2018 and are proposed to be implemented in a budget-neutral manner and redistributed across all other outpatient hospital services covered by Medicare through a 1.4 percent increase in Medicare payments for all other hospital outpatient services. ❖

Significant Cuts Proposed to Medicare Payments for 340B Drugs. *The National Law Review*, July 17, 2017. Accessed at www.natlawreview.com/article/significant-cuts-proposed-to-medicare-payments-340b-drugs.

New Rules Narrow ACA's Contraception Mandate

New rules issued by the U.S. Department of Health and Human Services (HHS) give employers more leeway to withhold birth control coverage on religious grounds. The rules would let a broad range of employers, including nonprofits, private firms and publicly traded companies, to stop offering free contraceptives through their health insurance plans if they have a "sincerely held religious or moral objection," according to senior HHS officials. The rules could apply to the roughly 200 entities that have participated in about 50 lawsuits over birth control coverage. However, HHS officials said that "99.9 percent of women" who currently receive birth control through the contraceptive mandate would not be affected. The rules come more than three years after the U.S. Supreme Court ruled that "closely held corporations" (in that case, Hobby Lobby) could be exempt from providing certain kinds of birth control to their employees. ❖

Nedelman M, Luhby T, Lee MJ, and Jarrett L. Trump Administration Deals Major Blow to Obamacare Birth Control Mandate. CNN, Oct. 6, 2017. Accessed at www.cnn.com/2017/10/06/health/trump-birth-control-mandate/index.html.

NIH Grants $9 Million to Children's Hospital Los Angeles for SCID Research

The National Institutes of Health's National Institute of Allergy and Infectious Diseases division has awarded nearly $9 million to researchers from Children's Center for Cancer and Blood Diseases at Children's Hospital Los Angeles (CHLA) and Boston Children's Hospital to study the lowest dose of chemotherapy needed for babies with severe combined immunodeficiency (SCID) undergoing bone marrow transplant, the standard treatment for SCID. The goal is to restore the immune system safely and effectively with less toxicity than the higher dose regimens currently in use.

The trial will be randomized for babies to receive a low or moderate dose of busulfan, a type of chemotherapy that acts to suppress the immune system in preparation for the transplant. The investigators propose that a bone marrow transplant can be performed successfully in SCID patients without the higher dose of busulfan typically used due to the patients' lack of functional T cells. "Our goal is to decrease the possible long-term effects from chemotherapy by determining the lowest doses needed to ensure T- and B-cell function in these infants, restoring normal immune systems that can last throughout their lives," said Michael Pulsipher, MD, chair of the Pediatric Blood and Marrow Transplantation Consortium, section head of bone marrow transplant at CHLA and professor of pediatrics at the Keck School of Medicine at the University of Southern California. ❖

Children's Hospital Los Angeles. Randomized Trial to Determine Most Effect, Least Toxic Treatment for Babies with SCID. Eureka Alert press release, Oct. 5, 2017. Accessed at www.eurekalert.org/pub_releases/2017-10/chla-rtt100517.php.

Congress Passes Bills Extending CHIP Funding

On Oct. 4, the House Energy and Commerce Committee and the Senate Finance Committee passed bills to extend for five years the federal funding for Children's Health Insurance Program (CHIP), which expired on Oct. 1. The bills also propose rolling back the federal enhanced match rate for CHIP by 2021. The House bill would allocate $1 billion in additional Medicaid funding for Puerto Rico and $30 million for the U.S. Virgin Islands for damage caused by hurricanes. The House bill also restores $2 billion in federal disproportionate share hospital (DSH) funding for 2018, but adds $8 billion in DSH cuts for 2026 and an additional $8 billion in cuts for 2027.

No details were given for how the Senate would fund the CHIP reauthorization, but the House bill proposes several offsets, including premium increases for higher-income Medicare recipients, changes to Medicaid rules that would make it easier for states to collect money from third-party insurers and a provision that would restrict lottery winners from receiving Medicaid for periods of time based on the size of their winnings. Ten states said that without CHIP reauthorization, they would run out of federal funds by the end of 2017, and 28 states said they will use up their money by April 2018. ❖

HRI Regulatory Center. Congress Moves to Restore Federal Funding for Children's Health Insurance Program. Accessed at www.pwc.com/us/en/health-industries/health-research-institute/hri-regulatory-center.html.

Senate Passes CHRONIC Care Act of 2017

In October, the U.S. Senate passed the Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act of 2017, which aims to improve care for seniors with chronic conditions. The Act would extend the Affordable Care Act-enacted Independence at Home (IAH) demonstration for two years and increase the number of beneficiaries that can be included in the program from 10,000 to 15,000. The IAH demonstration, which was slated to expire on Sept. 30, provides shared savings incentive payments to medical teams providing high-quality home-based care to Medicare beneficiaries with multiple chronic conditions and functional limitations.

A key provision of the Act would make the Medicare Advantage (MA) Special Needs Plan (SNP) program permanent. SNPs, which are the only type of MA plans that can limit enrollment based on patient characteristics, include plans for beneficiaries eligible for both Medicare and Medicaid (known as dual eligibles, or duals — D-SNPs), those residing in medical institutions and those with chronic illnesses (C-SNPs). This provision would require enhanced coordination between states and the federal government for D-SNPs, especially for appeal and grievance protocols, while requiring all plans to have direct contracts with the states in which they operate. And, starting in 2020, care management strategies employed by C-SNPs would be subject to heightened standards, with the Centers for Medicare and Medicaid Services required to update the list of qualifying chronic conditions every five years. In addition, the Act would expand the array of extra benefits MA plans may offer to chronically ill beneficiaries, and allow plans to use rebates to add coverage for health-related services beyond the traditional, mandatory Medicare package when premiums are below the benchmark for the region. ❖

Wynne B. The CHRONIC Care Act Passes Senate, Obstacles Remain. HealthAffairs blog, Oct. 5, 2017. Accessed at healthaffairs.org/blog/2017/10/05/the-chronic-care-act-passes-senate-obstacles-remain.

Revisiting Billing for Expensive Drug Waste

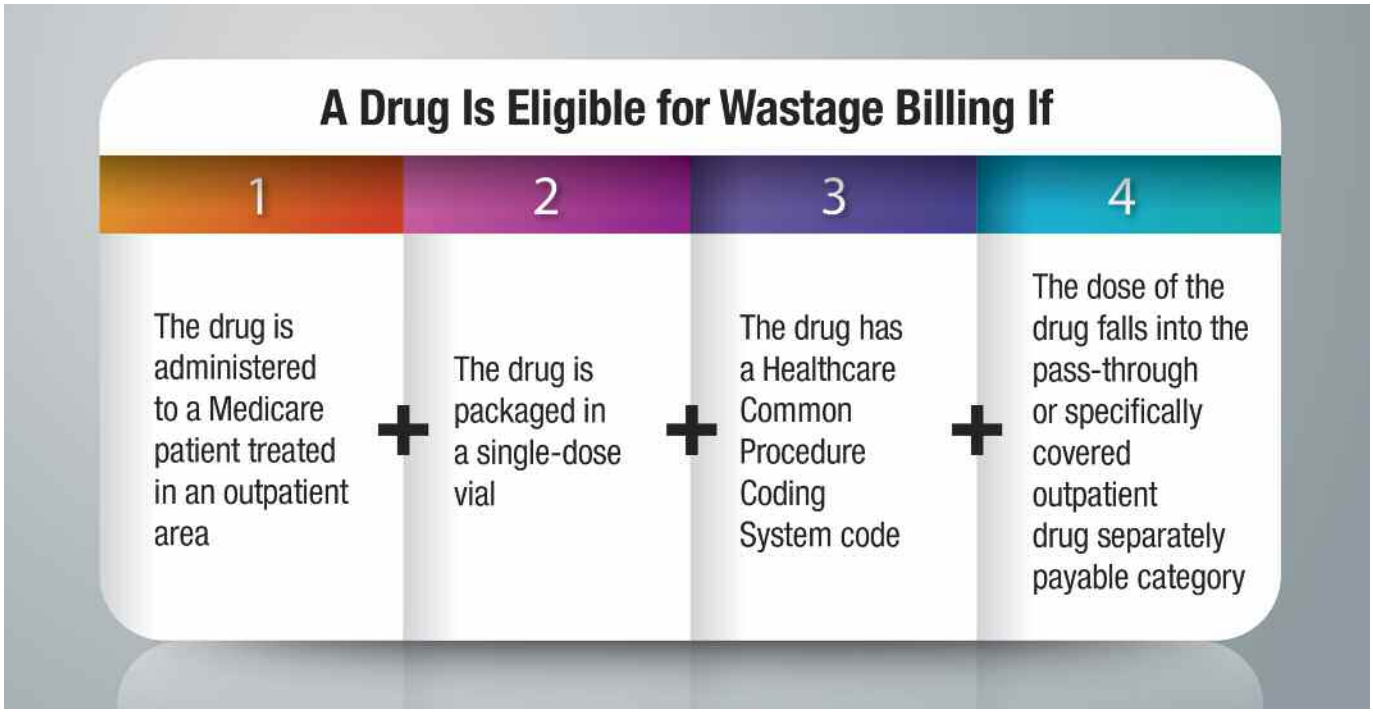
ALTHOUGH BILLING FOR drug waste sounds simple, confusion reigns for many healthcare providers, thwarting this revenue stream at many facilities. A simple test to determine whether to bill for an unused portion of drug can be answered with four questions: 1) Is the drug administered to a Medicare patient treated in an outpatient area? 2) Is the drug packaged in a single-dose vial? 3) Does the drug have a Healthcare Common Procedure Coding System code? 4) Does the dose fall into the pass-through or specifically covered outpatient drug separately payable category (versus the less-than-$120-per-day bundle or any other packaged or bundled payment category)? If the answer to all four questions is yes, drug waste should be billed. If the answer to any of these questions is no, drug waste is not billable.

Historical Perspective on Drug Waste Billing

Some of the mystery surrounding drug waste billing can be solved by understanding the payment rule history. In 2004, under the Outpatient Prospective Payment System (OPPS), Medicare ceased paying for the whole vial of a drug and moved to reimbursement of "billing units representing actual dose given." This was a financial shock to providers who then lobbied for compensation for wasted drug. In 2007, billing for expensive drug waste was introduced. Medicare doesn't mandate billing for waste, but makes it possible to recoup some money if providers choose to bill for the lost drugs. To be sure, providers must pay strict attention to the OPPS rules. In fact, the Centers for Medicare and Medicaid Services (CMS) encourages patient scheduling to ensure drugs are used efficiently. If the remainder of a single-dose vial must be discarded after the drug is administered, the program covers both the amount administered and discarded.

Providers Lag in Drug Waste Billing

Unfortunately, many providers fail to bill for drug waste. Low implementation of waste billing is a result of a combination of factors, including knowledge gaps, a perceived low return, perceived resource constraints (too much complex work for the resulting yield), lack of IT systems support for the required level of automation and documentation in the outpatient area, a business risk assessment (the fear that a change in billing might lead to scrutiny) or some other set of circumstances.



Regardless of the rationale, the decision not to bill for outpatient drug waste is hurting everyone — especially now that bundled payment models are in vogue. Bundled payment calculations are based on "big data," including the history of payment for separately payable medications and biologics, drug administration costs and payment for waste and the myriad non-separately reimbursable products used. The decision to not implement waste billing (or to not bill for non-separately reimbursable products) paints an inaccurately low picture of the true cost of medications being included in the bundled payment.

How to Bill for Drug Waste

Preparation for drug billing in outpatient clinics and treatment areas must match what's billed and charted in the electronic health record. Here are the steps to implement and/or review when going forward with billing for drug waste:

1) Determine which drugs are going to be waste candidates. Each drug reimbursed by Medicare under OPPS has been assigned a status indicator (SI). Only those with SI G or SI K are eligible for waste billing, and only when a single-dose vial, ampule and/or syringe is used. SI G indicates the drug has pass-through status and will be paid for separately as indicated by statute. SI K indicates the drug is a separately covered item that costs more than $120 per day as defined by the current 2018 OPPS rules. Simply looking at the drugs on your formulary and choosing only the ones with these two status indicators will produce a manageable first-draft listing of waste candidates. Further narrow this list by removing all products that are not in single-dose packaging. Next, select the products from this list that your outpatient departments will benefit most from waste billing. For example, you may decide to identify only a handful of expensive agents in the infusion clinic or specialty outpatient clinics for wastage billing.

2) Create a charge description number (CDM) for the selected drug and a corresponding pharmacy drug master description for the drug waste. For example, drug A CDM #123456 and drug A waste CDM# 123457. This allows a clear pathway to be created as part of drug order entry. The actual amount of the drug used will be entered, as well as the actual amount of the drug wasted. Both of these entries will appear on the medication administration record (as required), and both will proceed to billing on the same day (also as required). By using this dual drug order entry, you will have created the required documentation for both the dose of drug administered and the waste in the electronic medical record.

3) When determining drug waste, convert the dose administered into billing units, and round up to the next whole billing unit as needed. The balance of the drug from the single-dose vial will be considered waste, and should also be converted into billing units. This can be done automatically with a crosswalk built into your system, or it may be done manually with each order entry.

4) The revenue cycle team then needs to add the mandatory JW modifier code to the drug waste billed to differentiate it from the dose of the drug administered.

5) Develop policies and procedures for wastage billing, and orient your staff, including the nursing and revenue cycle teams. Stress that in the CMS world, you cannot ever bill for more than the total amount of drug in the single-dose vial. ❖

Notes

1) The Medicare Claims Processing Manual, Chapter 17, Section 40, provides policy detailing the use of the JW modifier for discarded Part B drugs and biologicals.
2) The official instruction, CR9603, issued to Medicare Administrative Contractors regarding the JW modifier change is available at www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R3538CP.pdf.
3) To access quarterly average sales price tables, go to www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2017ASPFiles.html. Focus on the ASP crosswalks (NDC to HCPCS).

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.

ASK OUR EXPERTS

Have a reimbursement question? Our experts are ready to answer them. Email us at editor@BSTQuarterly.com.

Update to Reimbursement FAQs Fall 2017 Column

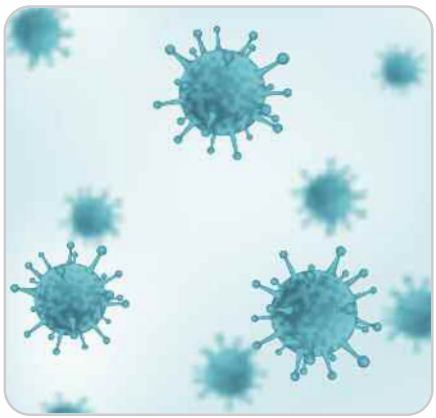
On Nov. 1, the Centers for Medicare and Medicaid released its final Outpatient Prospective Payment System (OPPS) rule with few changes from the proposed bill's language reported in this column in the fall issue. The enormous price reduction in payment for 340B SI K drugs used in the OPPS environment is going forward as planned at average sales price minus 22.5%. However, the logistic of identifying the affected drugs has changed: Effective Jan. 1, a modifier (JG) is required on SI K drugs purchased at 340B price and administered to Medicare outpatients.

Editor's Note: The content of this column is intended to provide a general guide to the subject matter. Specialist advice should be sought about your specific circumstances.

Research

Study Shows Impact of Age and Pre-Existing Influenza Immune Responses in Older and Younger Adults

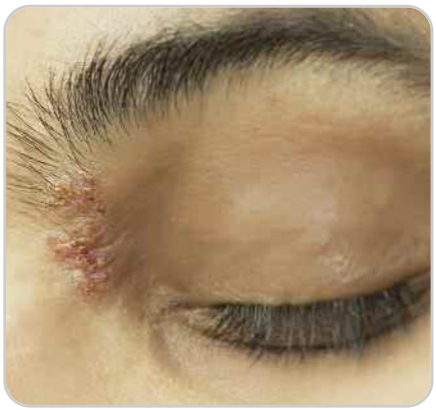
In an effort to understand how current influenza vaccines are influenced by pre-existing immunity in people of different ages, researchers vaccinated volunteers ages 18 years to 85 years with split, inactivated Fluzone influenza vaccine in four consecutive seasons from 2013 to 2016, and assessed the impact of repeated vaccination on breadth and durability of antibodies as a result of vaccine strain changes. They found that, overall, both younger and older people have the ability to mount a breadth of immune responses following influenza vaccination.



Specifically, total IgG anti-hemagglutinin (HA) binding antibodies and hemagglutination-inhibition (HAI) activity increased in all age groups against both influenza A HA components in the vaccine post-vaccination (day 21). However, younger subjects maintained seroprotective titers to the vaccine strains, which resulted in higher seroconversion rates in the elderly, since the HAI titers in elderly subjects were more likely to decline prior to the next season. Young subjects had significant HAI activity against historical, as well as contemporary H1 and H3 vaccine strains from the mid-1980s to present. In contrast, elderly subjects had HAI activity to H1 strains from all years, but were more like to have HAI activity to older strains from 1918 through the 1950s. They also had a more restricted HAI profile against H3 viruses compared to young subjects recognizing H3N2 influenza viruses from the mid-2000s to present. Vaccine recipients were then categorized by whether subjects seroconverted from a seronegative or seropositive pre-vaccination state. They found, regardless of age, immunological recall or "back-boosting" to antigenically related strains were associated with seroconversion to the vaccine strain.

According to the researchers, these findings are critical for designing the next-generation of universal or broadly protective influenza vaccines. ❖

Nunez IA, Carlock MA, Allen JD, et al. Impact of Age and Pre-Existing Influenza Immune Responses in Humans Receiving Split Inactivated Influenza Vaccine on the Induction of the Breadth of Antibodies to Influenza A Strains. *PLoS One*, 12(11): e0185666. Accessed at journals.plos.org/plosone/article?id=10.1371/journal.pone.0185666.



Medicines

FDA Approves and CDC Recommends Shingrix Vaccine to Prevent Shingles

GlaxoSmithKline (GSK) has received U.S. Food and Drug Administration approval for its Shingrix vaccine to prevent shingles (herpes zoster) in patients 50 years and older. Approval is based on positive results from Phase III trials that demonstrated efficacy against shingles greater than 90 percent across all age groups, as well as sustained efficacy over a follow-up period of four years in more than 38,000 patients. Shingrix also reduced overall incidence of postherpetic neuralgia, a form of chronic nerve pain and the most common health complication associated with shingles. The vaccine's risks include local or general short-duration reactogenicity, and the rates of severe adverse effects, deaths and immune-mediated diseases in the studies were proportional between treatment and placebo groups.

"Shingrix represents a significant advancement in the field of vaccinology," said Thomas Breuer, MD, senior vice president and chief medical officer of GSK vaccines. "The risk and severity of shingles increases with age as the immune system loses the ability to mount a strong and effective response to infection. Shingrix was developed specifically to overcome the age-related decline in immunity."

The day after FDA approval, the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) recommended the use of Shingrix to prevent shingles over Merck's Zostavax vaccine that is less effective, but was the only shingles vaccine on the market for over a decade. ACIP also recommended that adults who have received the older vaccine get the new one. The recommendation is awaiting formal endorsement by CDC, which normally takes a couple of months. ❖

Castles T. Shingrix Gets FDA Go-Ahead. *MD Magazine*, Oct. 20, 2017. Accessed at www.mdmag.com/medical-news/shingrix-gets-goahead-from-fda.

Kaplan S. C.D.C. Panel Recommends a New Shingles Vaccine. *The New York Times*, Oct. 25, 2017. Accessed at www.nytimes.com/2017/10/25/health/cdc-shingles-vaccine.html.

Medicines

CSL Behring's Privigen Now Approved to Treat CIDP

The U.S. Food and Drug Administration (FDA) has approved Privigen (immune globulin intravenous [human] 10% liquid) to treat adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability. Approval is based on two Phase III studies: Polyneuropathy and Treatment with Hizentra (PATH) and Privigen Impact on Mobility and Autonomy (PRIMA). In the PATH study, 73 percent of 207 CIDP patients receiving Privigen (as placebo) responded to treatment as measured by their adjusted score on the Inflammatory Neuropathy Cause and Treatment scale. In the PRIMA study, 61 percent of 28 patients responded to treatment.

"It is a priority in the care of CIDP patients to provide therapies that improve and maintain their strength and function while at the same time preventing relapses and minimizing side effects. However, current treatments do not work for all CIDP patients," said Mazen M. Dimachkie, professor and director of the neuromuscular division, executive vice chairman in the department of neurology at the University of Kansas Medical Center, and an investigator in the PATH study. "Privigen's approval by the FDA for the treatment of CIDP means that people with CIDP and their treating physicians have gained another treatment option that is safe and effective in helping improve strength and motor function, while potentially delaying disease relapse." ❖

Radke J. FDA Approves Privigen for CIDP. Rare Disease Report, Sept. 15, 2017. Accessed at www.raredr.com/news/fda-approves-privigen-for-cipd.

Medicines

FDA Approves Mavyret to Treat Adults with Chronic Hepatitis C

The U.S. Food and Drug Administration (FDA) has approved AbbieVie Inc.'s Mavyret (glecaprevir and pibrentasvir) to treat adults with chronic hepatitis C virus (HCV) genotypes 1-6 without cirrhosis or with mild cirrhosis, including patients with moderate to severe kidney disease and those who are on dialysis. Mavyret is also approved for adult patients with HCV genotype 1 infection who have been previously treated with a regimen either containing an NS5A inhibitor or an NS3/4A protease inhibitor, but not both. It is the first treatment of eight weeks duration approved for all HCV genotypes 1-6 in adult patients without cirrhosis who have not been previously treated. Standard treatment length was previously 12 weeks or more.

Approval was based on the safety and efficacy of clinical trials that enrolled approximately 2,300 adults with genotype 1, 2, 3, 4, 5 or 6 HCV infection without cirrhosis or with mild cirrhosis. Results of the trials demonstrated that between 92 percent and 100 percent of patients who received Mavyret for eight, 12 or 16 weeks duration had no virus detected in the blood 12 weeks after finishing treatment, suggesting patients' infection had been cured. The most common adverse reactions were headache, fatigue and nausea. Mavyret is not recommended in patients with moderate cirrhosis and contraindicated in patients with severe cirrhosis or those taking the drugs atazanavir and rifampin. ❖

FDA Approves Mavyret for Hepatitis C. U.S. Department of Health and Human Services press release, Aug. 4, 2017. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm570038.htm.

Medicines

FDA Approves First Subcutaneous Therapy to Treat HAE

The U.S. Food and Drug Administration (FDA) has approved CSL Behring's Haegarda (C1 esterase inhibitor subcutaneous [human]), the first and only subcutaneous therapy indicated for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescent and adult patients. Approval is based on a Phase III COMPACT (Clinical Studies for Optimal Management in Preventing Angioedema with low-volume subcutaneous C1-inhibitor replacement Therapy) trial, which showed that at the approved dose of 60 IU/kg, Haegarda reduced the median number of HAE attacks by 95 percent relative to placebo, and use of rescue medication was reduced by greater than 99 percent versus placebo.

Haegarda is a self-administered, plasma-derived concentrate of C1 esterase inhibitor injected twice subcutaneously. "The FDA approval of Haegarda is a transformational milestone for the HAE community because it addresses the primary need of patients: to effectively prevent debilitating HAE attacks," said Dr. Andrew Cuthbertson, chief scientific officer and research and development director at CSL Limited. "CSL Behring has a long heritage of delivering on its promises to the HAE community. Thanks to our clinical trial participants, we're proud to lead the community into the next era of treatment by offering the first and only subcutaneous preventive treatment option." ❖

FDA Approves HAEGARDA (C1 Esterase Inhibitor Subcutaneous [Human]), First and Only Subcutaneous Preventive Treatment for Hereditary Angioedema. PR Newswire, June 23, 2017. Accessed at www.gurufocus.com/news/535597/fda-approves-haegarda-c1-esterase-inhibitor-subcutaneous-human-first-and-only-subcutaneous-preventive-treatment-for-hereditary-angioedema.

Medicines

Cutting-Edge Pediatric Cancer Therapy Approved by FDA

Novartis' Kymriah (tisagenlecleucel) has been approved by the U.S. Food and Drug Administration (FDA) to treat pediatric acute lymphoblastic leukemia. The personalized treatment, called CAR (chimeric antigen receptor) T-cell therapy, is a cancer immunotherapy that harnesses the body's immune system by removing a person's cells, reengineering them with the drug and then replacing them into the body to attack cancer cells. According to Novartis, the one-time treatment costs $475,000; however, the company is working with the Centers for Medicare and Medicaid Services (CMS) to develop a payment system that reflects how well the drug works in a person. Under that system, CMS pays "only when pediatric and young adult patients respond to Kymriah by the end of the first month."

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," said Scott Gottlieb, FDA commissioner.

"New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses." ❖

Ramsey L. A Cancer Treatment That One Expert Called the 'Most Exciting Thing I've Seen in My Lifetime' Just Got Approved. Business Insider, Aug. 30, 2017. Accessed at finance.yahoo.com/news/cancer-treatment-one-expert-called-150713405.html?.tsrc=daily_mail&uh_test=1_10.

Medicines

New Drug Approved by FDA to Treat Acute Myelogenous Leukemia

The U.S. Food and Drug Administration has approved Agios Pharmaceuticals' Idhifa (enasidenib) to treat acute myelogenous leukemia, a cancer of the blood and bone marrow. Developed in partnership with Calgene, the pill treats the cancer in people with a certain genetic mutation in the IDH2 gene by starving cancer cells. It does this by targeting the metabolism of cancer cells to accomplish the Warburg effect, a phenomenon developed by German scientist Otto Warburg, who first observed in the early 1900s that cancer cells don't need as much oxygen to metabolize sugar as normal cells. The effect, which is estimated to occur in approximately 80 percent of cancers, targets just cancer cells, leaving healthy cells untouched. It's only been in the past decade, however, that researchers have figured out how to use the Warburg effect in treatments. ❖

Ramsay L. A Small Biotech Behind a Groundbreaking Approach to Tackling Cancer Just Got Its First Drug Approved. Business Insider, Aug. 2, 2017. Accessed at www.businessinsider.com/fda-approves-agios-pharmaceuticals-drug-targeting-cancer-cell-metabolism-2017-8.

Research

Study Shows a Positive Mood Could Boost Effectiveness of Flu Vaccine

Researchers at the University of Nottingham in England have found evidence that being in a positive mood when receiving an influenza (flu) vaccine can increase its protective effect. The study is the first to examine several psychological and behavioral factors that have been shown to affect how well vaccinations work. In this study, researchers investigated which factor or combination of factors has the greatest impact on the ability of the vaccinations to protect against disease. The investigators measured negative mood, positive mood, physical activity, diet and sleep three times a week over a six-week period in a group of 138 older adults due to have their flu vaccine. They then measured the amount of influenza antibody in the blood at four weeks and 16 weeks after vaccination. Results showed only positive mood over the six-week observational period was associated with higher levels of antibody. And, they found influences on the day of the vaccination had an even greater effect on how well it worked, accounting for between 8 percent and 14 percent of variability in antibody levels.

"Vaccinations are an incredibly effective way of reducing the likelihood of catching infectious diseases. But, their Achilles heel is that their ability to protect against disease is affected by how well an individual's immune system works," said professor Kavita Vedhara from the university's division of primary care. "We have known for many years that a number of psychological and behavioral factors such as stress, physical activity and diet influence how well the immune system works, and these factors have also been shown to influence how well vaccines protect against disease."

The study was unusual, however, because participants received the identical flu vaccine that they had the previous year. Therefore, the researchers found participants had very high levels of antibody, and therefore protection, for two out of three of the viruses present in the vaccination even before they were vaccinated. Because of this "ceiling effect," antibody levels for these two viruses were unlikely to reveal effects of psychological and behavioral factors. As a result, the researchers focused only on the one strain that was the least immunogenic (i.e., the strain with the low levels of antibody prior to vaccination). ❖

University of Nottingham. Being in a Good Mood for Your Flu Jab Boosts Its Effectiveness. ScienceDaily, Sept. 25, 2017. Accessed at www.sciencedaily.com/releases/2017/09/170925154701.htm.

Medicines

Kedrion Biopharma and Kamada Receive FDA Approval for KEDRAB

The U.S. Food and Drug Administration (FDA) has approved Kedrion Biopharma's and Kamada's KEDRAB (rabies immune globulin [human]) for passive, transient postexposure prophylaxis of rabies infection when given immediately after contact with a rabid or possibly rabid animal and administered concurrently with a full course of rabies vaccine. Prior to this approval, there were only two other human rabies immune globulin therapy options to prevent the onset of rabies in someone who may have been exposed to the deadly virus.

"The approval of KEDRAB represents the first product that Kedrion Biopharma has had a role in developing throughout its clinical development and through to commercialization in the U.S.," said Paolo Marcucci, president and CEO of Kedrion. "We are proud that our unique and advanced immune globulin purification technology was used in the development of KEDRAB, and look forward to a successful launch of the product with Kedrion Biopharma," added Amir London, Kamada's CEO. ❖

Kedrion Biopharma and Kamada Receive FDA Approval of KEDRAB for Post-Exposure Prophylaxis Against Rabies Infection. GlobeNewswire, Aug. 25, 2017. Accessed at www.nasdaq.com/press-release/kedrion-biopharma-and-kamada-receive-fda-approval-of-kedrab-for-postexposure-prophylaxis-against-20170825-00194.

Industry

CSL Behring Awards LEAD Grants to Support Patient Rights

CSL Behring has awarded three U.S. bleeding disorder patient organizations Local Empowerment for Advocacy Development (LEAD) grants to help them ensure patients' voices continue to be heard in their state capitals on legislative and public policy issues. The grants were awarded to the Great Lakes Hemophilia Foundation (GLHF), which will revitalize its grassroots advocacy program and execute its plan to lobby Wisconsin's state legislature; New York City Hemophilia Chapter (NYCHC), which will train members of the bleeding disorders community as regional advocacy captains, whose role will be to strengthen relationships and increase engagement with key local legislators; and Ohio Bleeding Disorders Council (OBDC), which will fund its 2017 Bleeding Disorders Advocacy Ambassadors program, which includes identifying engaged advocates around the state.

To qualify for LEAD grand support, a local group must be a recognized patient advocacy, nonprofit group with 501(c)(3) tax status representing individuals who use plasma/recombinant therapies to treat bleeding disorders, immune disorders, alpha-1 deficiency or other conditions. Qualifying organizations also must be currently addressing or intending to address a specific advocacy issue. "Our LEAD grant program is now in its ninth year, and the need for patient empowerment and advocacy has never been greater," said Dennis Jackman, CSL Behring's senior vice president for global healthcare policy and external affairs. "We believe our role goes beyond developing, manufacturing and delivering lifesaving medicines. We have an obligation to inform and impact public policy decisions to ensure all patients have access to the medicines and services they need." ❖

Moore C. CSL Behring LEAD Grants Support Patient Advocacy Efforts by Local Bleeding Disorder Groups. *Hemophilia News Today,* Oct. 6, 2017. Accessed at hemophilianewstoday.com/2017/10/06/csl-behring-lead-grants-support-bleeding-disorder-patient-advocacy-efforts.

Research

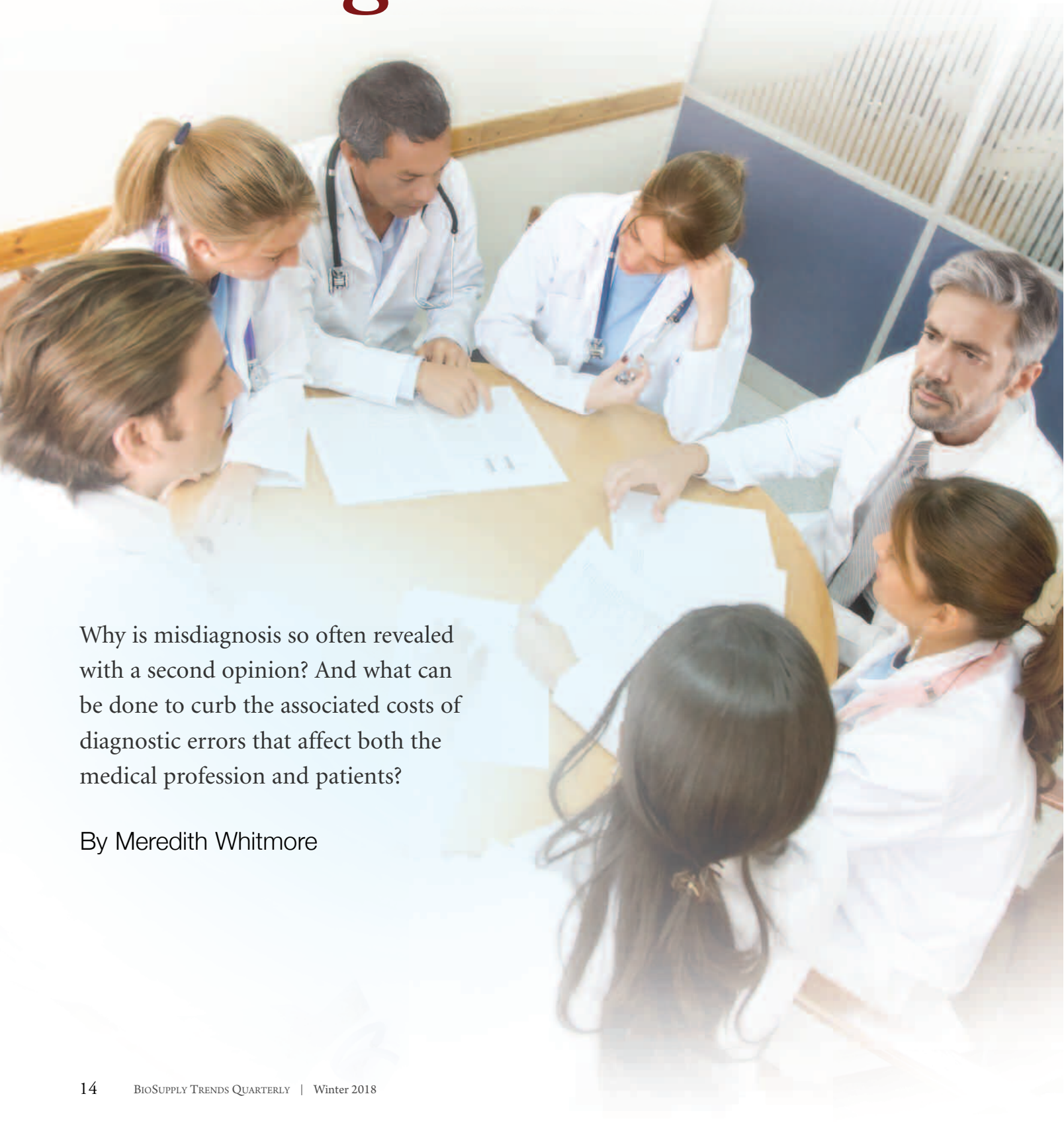
Clinical Trial of Universal Flu Vaccine Is a Success

Scientists at the National Institutes of Health (NIH), Frederick National Laboratory for Cancer Research and the University of Melbourne in Australia tested a new universal flu vaccine that produced good immunity against several different strains of influenza viruses. In the study, the research team looked at antibodies from 40 healthy adults who had been vaccinated against group two H7N9 or group one H5N1 flu strains, and found that B cells in people immunized with the group two vaccine were broadly reactive to viral proteins in both group one and group two hemagglutinin subtypes. According to the researchers, the results suggest that vaccines against the stem hemagglutinin proteins of group two viruses could be more effective at inducing widespread immunity than those against group one hemagglutinin stem proteins, or the current subtype specific vaccines.

The next studies will confirm whether an initial vaccination with group one or group two proteins is more effective for developing the most broadly reactive antibodies, and they will include evaluation of vaccine in young children who haven't received the flu vaccine previously and don't have pre-existing antibodies to confuse results. The researchers will also continue evaluating their universal vaccine in a larger number of people. If the current vaccine proves safe in Phase I clinical trials, the next steps will be Phase II and III clinical trials to test its effectiveness and to monitor side effects. ❖

Wood S. First Success in Long Search for Universal Flu Vaccine. Invisiverse, July 19, 2017. Accessed at www.invisiverse.com/news/first-success-long-search-for-universal-flu-vaccine-0178826.

The Misdiagnosis Dilemma



Why is misdiagnosis so often revealed with a second opinion? And what can be done to curb the associated costs of diagnostic errors that affect both the medical profession and patients?

By Meredith Whitmore

PATIENTS RELY ON healthcare providers' knowledge and skill to diagnose medical issues and properly treat them. Much of the time, diagnoses are well-considered and correct. But, sometimes, they come into question, and patients seek a second opinion. And, other times, doctors are not entirely sure about their diagnoses, perhaps due to a lack of specific equipment or facilities that could aid them, which can be especially true when diagnosing rare conditions.

Misdiagnoses are revealed more often than one might expect at tertiary referral hospitals. A 2017 Mayo Clinic study found as many as 88 percent of patients who seek a second opinion are given a new diagnosis that often differs greatly from that of the referring physician. In other words, only 12 percent of these patients' original diagnoses are confirmed.[1] "It's a very complex problem," says Robert Lohr, MD, a coauthor of the study and an assistant professor of medicine in the division of hospital internal medicine at Mayo Clinic in Rochester, Minn.[2] So complex and important is the issue of misdiagnosis, in fact, that the Institute of Medicine called the need to study it a "moral, professional and public health imperative."[3,4] Justifiably, it's important for healthcare professionals to consider the costs to the medical profession, the public and, especially, patients in the event of a misdiagnosis. A second opinion leading to a correct diagnosis could help patients avoid unnecessary treatment, stress and financial expense. It could also bring them and their families relief if the original diagnoses were more serious.

The Plight of Physicians

According to Dr. Lohr, their study focused on primary care physicians and patients they referred into their general internal medicine division for a variety of reasons. "These were not just physicians, but also nurse practitioners and physician assistants," he says. "We don't know what went into the decision to make the referral, and there are a lot of reasons that can go into that. Certainly, the provider can throw up their hands and say, 'Gee, I don't know what to do next, we need some help.' Or, they may have tried a lot of things, and they're just getting nowhere. The patient may even say they're getting nowhere and request to go someplace else. Or, it may be, and I think this is very often the case in primary care, that the complexity of the problem appears to be more than they can handle in the very short time frame that most primary care physicians are working under. They're seeing a patient every 10 to 15 minutes. Some problems take much longer than that to sort out. So, about one in five of the patients who were referred received a pretty different diagnosis.

"They simply don't have the time, the resources or even, in some cases, the technology to hone in on some of these problems. It really all boils down, in the long run, to having the time to do a thorough history and a physical. That is the basis from which everything else is generated. If you have the time to do that, and you have the time to think about it, you can usually go down a proper diagnostic pathway. If that isn't working, you regroup and maybe go in a little bit different direction. But, if you don't have the time, or it's something that you need more laboratory or radiologic evaluation for, then patients have to be referred.

"The broader issue, though, really has to do with the level of experience new physicians have. Less-experienced physicians tend to cast very broad nets and, in general, do a lot of evaluation. More experienced physicians tend to hone in on things a little bit more precisely, and maybe cast a narrower net to begin with. There are problems on both sides. In the first situation, you may be doing a lot of unnecessary testing. In the latter situation, you might not be doing enough. There's a fine line in between, but I think the bottom line is whether you're experienced and have the time, or inexperienced and have the time. To evaluate the patient, you need to be able to shift gears. If the direction that you're going doesn't seem to be correct, then you need to regroup or ask for some assistance."[2]

A 2017 Mayo Clinic study found as many as 88 percent of patients who seek a second opinion are given a new diagnosis that often differs greatly from that of the referring physician.

Dennis Bourdette, MD, FAAN, FANA, professor and chairman of the department of neurology at Oregon Health and Science University (OHSU), agrees: "I think a lot of physicians have heavy workloads, so it's almost a hassle to think more about difficult patients. It seems to me it's personality, too. Some of the neurologists who don't refer patients for second opinions are

actually people I know because they trained with us, which is shocking. My opinion is that it's an ego thing with them. Some doctors get offended if a patient asks for a second opinion. If I have a patient who wants to get a second opinion, I'm more than willing to refer them out of our system. I do think part of it can be a lack of humility. To work up a patient as an academician and not know what the diagnosis is, and then say, 'I'm going to send you to Mayo Clinic and have them figure out the diagnosis,' well, that can be a humbling experience. I prefer to think I've done my job as a physician, to make sure patients get appropriately diagnosed. If I have to get help from another physician, so be it. The bottom line is providing good care to our patients."[5]

"Depending on the nature of the misdiagnosis and the type of problem that the patient has, misdiagnosis has serious psychosocial health and economic implications."

The Costs of Misdiagnosis

Dr. Bourdette is all too familiar with the pitfalls of misdiagnosis. Notably, he and his colleagues have conducted studies regarding the misdiagnosis of multiple sclerosis, a disease he is an expert in treating. "Depending on the nature of the misdiagnosis and the type of problem that the patient has," he explains, "misdiagnosis has serious psychosocial health and economic implications. Consider multiple sclerosis [MS]. We have these very expensive medicines which are generally safe, but some of them have serious and even life-threatening complications. The cost of these medicines, which are not curative but life-long for a diagnosis of MS, are running about $80,000 a year now. So, if someone is misdiagnosed with MS, and they're put on an $80,000-a-year medication, it doesn't take very many misdiagnoses for that to have a huge economic impact — not to mention the impact on the patient being mistreated rather than treated for what they actually have."

Dr. Bourdette adds that insurance companies often make obtaining a second opinion quite difficult for patients. This is a potentially serious problem for everyone because, "a colleague within the same system is much less likely to question a diagnosis than someone outside the system. It's just human nature, unless you've got a nonjudgmental, supportive situation in which physicians discuss challenging cases." According to him, the MS misdiagnosis rate at OHSU is roughly 5 percent. "Some of the patients we see have seen a neurologist in the community and [have] either been told they have MS or probably have MS, and we determine that they do not have MS," he says. "I think misdiagnosis is a real problem that is not currently being addressed in an adequate fashion."[5]

Curbing the Misdiagnosis Problem

To curb the misdiagnosis problem, Dr. Bourdette says education is key: "I think the insurance companies should be interested when we're talking about diagnoses that have significant costs that come with the therapy. Frankly, to avoid a 5 percent misdiagnosis error with MS alone, not to mention equally expensive diseases, it would actually pay the insurance companies to get a second opinion before approving placement of a patient on disease-modifying therapy. If there was a commitment to doing this for certain indications in particular, when there are significant interventions that are either costly or potentially harmful, that maybe a second opinion should be required."

Dr. Bourdette is quick to add that second opinions can also be performed remotely for many disorders, and usually less expensively. For example, he does roughly 30 of these consults a year. "Typically, I'm seeing someone who may have MS, or has MS or related disorders, and there's a treatment decision being made," he explains. "So the physicians provide a case summary and imaging, like an MRI scan. Then there's a series of questions they want answered. There's a pretty rapid turnaround. My experience with that is I'm often either reassuring the patient that the diagnosis is correct and the recommended therapies are correct, or I've raised questions about the diagnosis and alternative diagnoses and alternative approaches for treatment. There are different ways to get a second opinion. Not everyone can fly to the Mayo Clinic for that. But, again, depending on the disorder and what the implications are, getting a second opinion is useful. I think this is an important, unrecognized and not widely discussed problem."[5]

Dr. Lohr has similar thoughts about how to curb the problem of misdiagnosis, but he adds, "If a patient comes in for a 10- or 15-minute appointment, but this is clearly going to go beyond that and it isn't an emergency, it's prudent to say, 'We've got to have more time.' Then, schedule the patient when you can devote the time the diagnosis deserves. I think a difficulty is when that isn't done. Doctors often think they must see a certain number of patients, and they've got to figure out a diagnosis in 15 minutes. That can tend to get physicians into some trouble

because they're not taking the time that's needed. I think being current and recognizing when more time is needed is key. And if you truly don't have the time, then refer the patient to somebody who does. Referral centers, whether at Mayo or any academic referral center, expect to see complex patients, so we don't have to see patients in 15 minutes. Primary care physicians do, but if you're in more of the referral part of the practice, you do get more time."[2]

Praise Where Praise Is Due

Dr. Lohr wants healthcare professionals to understand he does not think those who refer patients for a second opinion are doing a poor job. Instead, he feels concern for doctors who might assume he's being critical. The Mayo Clinic study "has generated a fair amount of media attention since its publication," he explains. "One of the things I have been asked is whether I, as the consulting physician, look down upon or think doctors who are making the referrals aren't doing their jobs well. There's nothing that could be further from the truth. They are working extremely hard, doing the best they can, but, again, with somewhat constrained time and occasionally resources. The vast majority of the time, they're hitting the mark right and are right on. Primary care physicians work very hard [and have] enormous time constraints on them, not just from the standpoint of seeing a lot of patients. But, there are time-motion studies that suggest for every hour you spend seeing patients face to face, there are two hours of paperwork generated by that. So they have a lot of responsibility. But, there are situations where another set of eyes and ears can be helpful."[2]

Misdiagnoses are a dreaded, yet largely unspoken problem in many clinics and hospitals across the country. Dr. Bourdette sums up a possible solution: "If more attention is called to it, we'll start seeing more interest in the problem. And I think insurance companies should actually be very concerned about this."[5] ❖

MEREDITH WHITMORE is an English professor and freelance journalist in the Northwest.

References

1. Young EZ. Mayo Clinic Researchers Demonstrate Value of Second Opinions. Mayo Clinic, April 4, 2017. Accessed at newsnetwork.mayoclinic.org/discussion/mayo-clinic-researchers-demonstrate-value-of-second-opinions.
2. Interview with Robert Lohr, MD, Mayo Clinic, Rochester, Minn.
3. Singh H and Graber ML. Improving Diagnosis in Health Care: The Next Imperative for Patient Safety. *New England Journal of Medicine*, 2015; 373:2493-2495. Accessed at www.ncbi.nlm.nih.gov/pubmed/26559457.
4. The National Academies of Sciences Engineering Medicine. Diagnostic Error in Health Care Consensus Study. Accessed at www.nationalacademies.org/hmd/Activities/Quality/DiagnosticErrorHealthCare.aspx.
5. Interview with Dennis Bourdette, MD, Oregon Health and Science University, Portland, Ore.

Growing Old with HIV

Private and public healthcare challenges grow as an aging population grapples with the ramifications of increasing numbers of HIV-positive senior citizens.

By Trudie Mitschang

IT'S BEEN 30 years since the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) epidemic first made headlines. In the ensuing years, medical breakthroughs and strides in HIV treatment and management have resulted in diagnosed individuals living longer and relatively healthy lives. As a result, the HIV-positive population that just decades ago was not expected to survive is aging into senior citizen status at an alarming rate, creating unique challenges for healthcare providers and public health officials. Actually, not all individuals over age 55 who are living with HIV contracted the disease when they were younger; many new cases are occurring in an aging population that remains sexually active and HIV-ignorant. According to data presented at the 125th Annual Convention of the American Psychological Association, older adults make up almost half of all people living with HIV. And these numbers are on the rise.[1]

Information presented at the 2016 White House AIDS and Aging Meeting stressed that misperceptions about risk have contributed to the uptick in HIV diagnoses: "Older age is not a safety net that protects people from getting HIV. Many issues surrounding older adults will only increase as our country faces the continuing graying of our nation's HIV epidemic."[2]

Perceptions and Lifestyle Increase Risk Factors

Longer lifespans, rising divorce rates and lack of education are all factors in the rising HIV rates among seniors. A recent Medscape article noted that older adults who are sexually active may be at higher risk of contracting the virus, in part because as a population they are overlooked when it comes to HIV education and prevention: "The lack of information about HIV risk directed to older adults is compounded by the fact that HIV risk exists in a context of secrecy, especially later in life."[3] In addition, certain behaviors, such as older men intentionally hiding sexual orientation, extramarital sex, sex with commercial sex workers and substance abuse involving needles, create a perfect storm of vulnerability and denial.

Infection risk may also be increased by an aging and potentially compromised immune system or other age-related health conditions. "HIV is still perceived as a young person's disease, so healthcare providers may not regularly address sexual health and risk behaviors with their older patients," says Mark Brennan-Ing, PhD, director for research and evaluation at the AIDS Community Research Initiative.[1]

Another influencing factor includes more effective HIV drug therapies that have allowed many who contracted the virus decades ago to survive well into their senior years. Many of these adults are managing their HIV status successfully, although they may face other health challenges related to the long-term effects of the virus and/or side effects of their medications. "The challenges of caring for the patient with HIV who is aging are similar to those of caring for other aging patients," says Dr. Brennan-Ing. "The difference is that older adults with HIV may be confronting [age-related health] issues decades earlier than their non-infected peers; older adults with HIV are much more likely to die from chronic conditions associated with aging than an AIDS-related condition."[1]

Longer lifespans, rising divorce rates and lack of education are all factors in the rising HIV rates among seniors.

Social trends such as rising divorce statistics that put older individuals back in the dating scene also contribute to HIV infection rates. In addition, the widespread availability of drugs like Viagra means seniors are much more likely to be sexually active with multiple partners, not realizing that advanced age can make them even more vulnerable to infection. Some of the age-related risks include:

- An aging immune system is less resistant to infection.
- Underlying health conditions common in older individuals can create increased vulnerability to communicable disease.
- Thinner skin as a result of aging may make it easier for the virus to enter the bloodstream.

When it comes to minimizing risk factors for HIV, knowledge is clearly power. For older adults, ignorance about risk can make them less likely to ask potential partners about HIV status, less likely to be tested themselves and reticent to broach the subject of sexual activity with their healthcare providers.

Aging Populations Experience Dual Diagnosis

Thanks to advances in research and treatment, an HIV diagnosis today does not automatically mean an AIDS diagnosis is soon to follow. However, the older one is at the time of diagnosis, the higher the probability of a dual diagnosis of HIV and AIDS, with the larger proportion of those dual diagnoses due to late-stage testing. According to the Centers for Disease Control and Prevention, as of 2014, 40 percent of those aged 55 and older already had late-stage AIDS infections at the time of their HIV diagnosis.[4] Sadly, an older person could live for years with HIV without seeking medical attention, attributing the symptoms to other age-related conditions:

- Fatigue and weight loss associated with AIDS could be interpreted as normal aging symptoms.
- AIDS-related pneumonia is sometimes mistaken for congestive heart failure in older patients.
- HIV-related dementia can be mistaken for Alzheimer's or Parkinson's disease.

In addition, some conditions, including heart disease, cancer, dementia and kidney disease, may develop earlier in patients with HIV, and HIV-positive status can also worsen conditions common to seniors, including diabetes, osteoporosis, arthritis and high blood pressure.[4]

Medicare spending for HIV has increased over the years and, in fact, the program now serves as the single largest source of federal financing for HIV care and treatment.

Counting the Health and Financial Costs

Anyone living with HIV, regardless of age, faces extremely high medical costs, with the lifetime cost of care often totaling hundreds of thousands of dollars. Medicare serves as a significant source of health coverage for people living with HIV. According to a 2016 report published in the Henry J. Kaiser Family Foundation titled "Medicare and HIV," 2016 Medicare spending on HIV totaled $10 billion and represented 51 percent of federal spending on HIV care.[5] The cost of medications makes up a bulk of that figure. The addition of the Part D prescription drug benefit for Medicare resulted in spending on HIV surpassing federal Medicaid spending.

Medicare spending for HIV has increased over the years and, in fact, the program now serves as the single largest source of federal financing for HIV care and treatment.[5] HIV patients under age 65 often qualify for Medicare because of their disability status, while a growing share of the HIV population is over age 65 and already aged into the program. Other sources of financial support for patients include Medicaid and state or community assistance programs, AIDS Drug Assistance Programs (ADAP) and other low-income subsidies.[5]

Evaluating the Emotional Toll

The mental health landscape for older adults living with HIV is complex, with the population five times more likely to experience depression than those of a similar age who do not have the virus. One study found 27 percent of HIV-infected older adults had considered suicide, while a 2010 study found 39 percent of HIV-infected older adults exhibited symptoms of major depressive disorder.[6]

Compared to their younger counterparts, HIV-positive older adults have a lower survival rate following an AIDS diagnosis and fewer social supports to help navigate the daunting task of disease care and management. Not surprisingly, all people living with HIV are at increased risk of developing mood, cognitive or anxiety disorders, and depression's ramifications can extend beyond emotional health, often leading to decreased levels of medication compliance. In a *U.S. News and World Report* article citing the psychological effects of HIV, Sheryl Catz, PhD, a clinical psychologist and professor who researches HIV, health behavior and chronic disease management, states, "We did find across the board that people who were depressed had a more difficult time with their [medication] adherence."[7]

Social isolation and post-diagnosis rejection by family and even partners can compound the overwhelming feelings of loss associated with a positive HIV diagnosis. While there is no one-size-fits-all coping strategy, finding a support group or at least one trusted individual who can serve as a confidant can help alleviate some of the stigma and shame associated with HIV. "I'm a big believer [that], psychologically, it is important people not be entirely isolated with their HIV diagnosis and they are not living entirely alone with it," said Robert Remien, PhD, a professor of clinical psychology and director of the HIV Center for Clinical and Behavioral Studies at Columbia University. "We never recommend people disclose or not disclose," adds Dr. Catz. "But we do see a tremendous burden lifted off people when they have a network of [supporters] who are aware of their status."[7]

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Reference: 1. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med.* 2017;376(12):1131-1139.

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----------WARNINGS AND PRECAUTIONS----------
- Severe hypersensitivity reactions may occur. In case of severe hypersensitivity, discontinue HAEGARDA administration and institute appropriate treatment. Epinephrine should be immediately available for treatment of severe hypersensitivity reaction.
- At the recommended subcutaneous (S.C.) dose, a causal relationship between thromboembolic events (TEEs) and the use of HAEGARDA has not been established. However, thrombosis has occurred in treatment attempts with high doses of C1-INH intravenous (I.V.) for prevention or therapy of capillary leak syndrome before, during or after cardiac surgery (unapproved indication and dose).
- Because HAEGARDA is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

----------ADVERSE REACTIONS----------
- Adverse reactions occurring in more than 4% of subjects treated with HAEGARDA were injection site reaction, hypersensitivity, nasopharyngitis and dizziness.

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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Based on October 2017 version.

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Finding a supportive community or seeking out the assistance of a psychologist or social worker can also be beneficial, especially when people are newly diagnosed and processing the short- and long-term ramifications of the diagnosis.

Identifying Improved Care Strategies

In June 2017, a new health app aimed at the aging lesbian, gay, bisexual and transgender population debuted as a service to help the HIV-positive population manage their healthcare. Developed by Sage, a British software company, the Health Storylines digital app reminds users to take their medications, helps monitor daily symptoms and allows them to share symptoms and medication information with healthcare providers. "It's incredibly user-friendly and can enhance conversations between app users, their healthcare providers and care managers," says Diosdado Gica, Sage's chief program officer.[8]

In addition to healthcare monitoring tools, better training for healthcare providers can play a critical role in helping an aging population deal with HIV. In an article published in *The Rainbow Times*, Sean Cahill, PhD, director of curriculum and policy at the National Center for Innovation HIV Care, outlines several strategies HIV and AIDS service providers can implement, including improved training regarding cultural and social sensitivities for older adults with HIV; increased screening for comorbidities, including mental health issues; addressing substance abuse issues; candid conversations about sexual activity; and proactively discussing HIV prevention and testing. "Topics such as dating and being sexually active while living with HIV, medication adherence, dealing with stigma (from family, friends, coworkers and healthcare professionals) and navigating insurance issues can provide clients with more information on pertinent issues and create a space where individuals can connect with those who are facing similar difficulties," says Dr. Cahill.[9]

Medication Breakthroughs and the Need for a Global Response

Three decades ago, no one could have imagined that HIV would one day be categorized as a geriatric disease. Yet by 2030, it is estimated more than 70 percent of people with HIV will be over age 50.[10] While the numbers are daunting, new medications in the pipeline may make treating this population easier. Current research is focused on a long-term injectable, which might be preferable for older patients who struggle to manage complicated medication regimens. And, a new two-drug HIV treatment currently under U.S. Food and Drug Administration review for potential 2018 release could offer a more streamlined approach to care, replacing the multiple medication treatment plans that are common today.

While research has made tremendous strides in addressing the spread of HIV/AIDS, for healthcare providers and public health officials, the task at hand is centered on educating individuals who have been largely ignored by outreach efforts. Confronting the lingering stigmas associated with HIV and ageism, targeting funding efforts toward the needs of this population, and taking a more proactive approach to HIV testing and prevention programs can help a generation of current and future patients lead longer, healthier and more productive lives. "With the demographic shift toward older adults in the HIV population globally, and the elusiveness of a cure, addressing the care needs of this aging population is paramount," says Dr. Brennan-Ing. "The aging of the HIV epidemic will be very challenging, but provides the opportunity to mount a global response that will address the needs of this population across regions and settings."[11] ❖

In addition to healthcare monitoring tools, better training for healthcare providers can play a critical role in helping an aging population deal with HIV.

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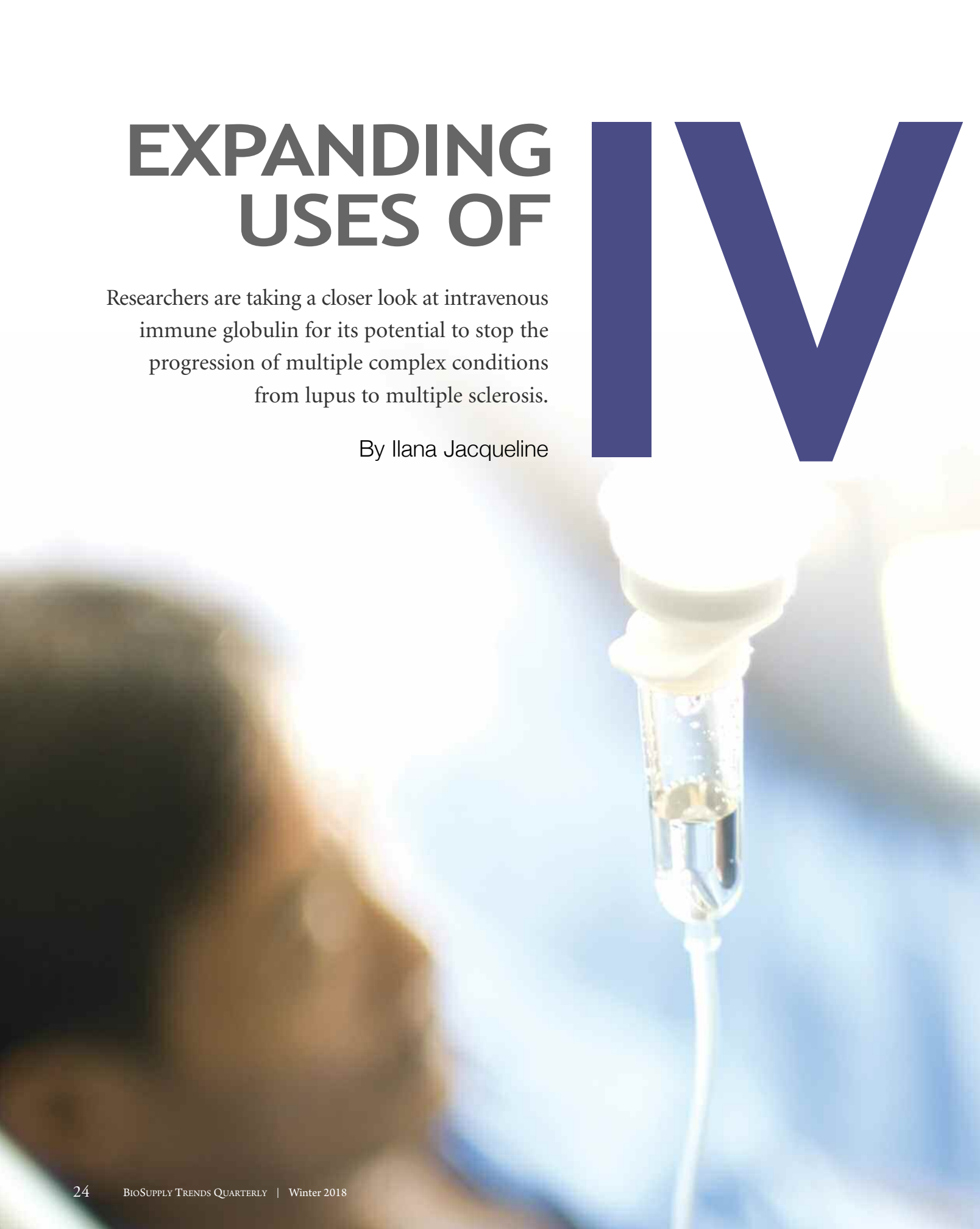
References

1. Brennan-Ing M. Q&A: Treating Older Adults with HIV. *Healio Infections Disease News*, Sept. 18, 2017. Accessed at www.healio.com/infectious-disease/hiv-aids/news/online/%7Bee1b16c9-ff82-4e5c-9e7d-8d253b881bed%7D/qa-treating-older-adults-with-hiv.
2. Aging in Stride. Seniors and HIV/AIDS: The Statistics Might Surprise You. Accessed at aginginstride.enewsworks.com/en/12/articles/263/Seniors-and-HIVAIDS-the-Statistics-Might-Surprise-You.htm.
3. Linsk NL. HIV Among Older Adults: Age-Specific Issues in Prevention and Treatment. *AIDS Readiness*, 2000;10(7). Accessed at www.medscape.com/viewarticle/410303_2.
4. Centers for Disease Control and Prevention. HIV Among People Aged 50 and Over. Accessed at www.cdc.gov/hiv/group/age/olderamericans/index.html.
5. Kaiser Family Foundation. Medicare and HIV. Accessed at www.kff.org/hivaids/fact-sheet/medicare-and-hiv.
6. Heckman TG. Introduction to Current Issues on HIV/AIDS in Older Adults. *Psychology and AIDS Exchange Newsletter*, January 2014. Accessed at www.apa.org/pi/aids/resources/exchange/2014/01/introduction.aspx.
7. Webster H. Living with the Psychological Effects of HIV. *U.S. News and World Report*, Jan. 2, 2015. Accessed at health.usnews.com/health-news/patient-advice/articles/2015/01/02/living-with-the-psychological-affects-of-hiv.
8. Mintz L. New Health App Launched by SAGE for LGBT Seniors to Help Ageing HIV-Positive Population. *Pink News*, June 9, 2017. Accessed at www.pinknews.co.uk/2017/06/09/new-health-app-launched-by-sage-for-lgbt-seniors-to-help-ageing-hiv-positive-population.
9. Cahill T. Improving the Health of Seniors Living with HIV. *The Rainbow Times*, Oct. 10, 2017. Accessed at www.therainbowtimesmass.com/improving-health-seniors-living-with-hiv.
10. Kramer L. Growing Old with HIV After Decades of Drug Success. CNBC, Feb. 14, 2017. Accessed at www.cnbc.com/2017/02/14/the-new-hiv-challenge-treating-the-disease-as-a-geriatric-condition.
11. Older Adults with HIV: An Overlooked Population? American Psychological Association, Aug. 4, 2017. Accessed at www.sciencedaily.com/releases/2017/08/170804100408.htm.

EXPANDING USES OF IV

Researchers are taking a closer look at intravenous immune globulin for its potential to stop the progression of multiple complex conditions from lupus to multiple sclerosis.

By Ilana Jacqueline



IG

THE LIST OF conditions that intravenous immune globulin (IVIG) may potentially treat has grown exponentially since its first use to treat primary immunodeficiency disease (PI) in 1952. It is known IVIG protects against infections, modulates the immune system and reduces inflammation,[1] but it's not entirely understood why it works, not only for diseases it is approved to treat, but for many others that have failed to respond to conventional treatments.

To date, the U.S. Food and Drug Administration (FDA) has approved IVIG for only six indications: PI, idiopathic thombocytopenic purpura, multifocal motor neuropathy, B-cell chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy. And, while the most frequent prescribers of IVIG therapy have been immunologists, today, specialists in neurology, nephrology, rheumatology, dermatology and hematology have all found clinical uses for the treatment.[2] As a matter of fact, it is believed, and in some instances medical evidence has shown, that IVIG may be beneficial for treating many off-label indications, which, according to past estimates, represent 50 percent to 80 percent of total IVIG use.[3] These indications include a host of complex medical conditions, including lupus, multiple sclerosis (MS), Alzheimer's disease, dysautonomia, infertility and many others.

The IVIG Process

The manufacture of IVIG starts with plasma donations. In the United States alone, there were more than 38 million donations of plasma collected in 2016, according to the Plasma Protein Therapeutics Association (PPTA),[4] more than double the 15 million donations collected just one decade ago. Worldwide, the total annual demand for plasma by pharmaceutical companies that manufacture plasma-based therapies is about 38 million liters.[5] To meet this growing demand, most of the world's plasma is collected in about 400 plasma donation centers scattered throughout the U.S., with some of it exported to other countries.

Once collected, plasma — 92 percent water and 8 percent proteins — must go through a fractionation process that separates and collects the individual proteins, of which 64 percent are albumin, 20 percent are immune globulin, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others such as antithrombin, protein C, C1 esterase inhibitor, etc.

As part of the industry's voluntary international standards program for manufacturers, known as the Quality Standards of Excellence, Assurance and Leadership (QSEAL), all plasma is held in inventory for 60 days before it can enter the manufacturing process. This allows for rigorous testing to identify, retrieve and destruct plasma donation from donors who are disqualified for various reasons such as having received a tattoo or piercing at the time of the original donation or failing to report foreign travel.[6]

While the most frequent prescribers of IVIG therapy have been immunologists, today, specialists in neurology, nephrology, rheumatology, dermatology and hematology have all found clinical uses for the treatment.

Once the plasma is released from inventory, it is ready for fractionation. During the fractionation process, plasma is pooled from multiple donations, purified and processed in a specific order to extract specific plasma proteins that have a proven health benefit. The steps and regulations required to collect donated plasma and complete the manufacturing process that ultimately results in the final therapies takes between seven and

nine months. Between weeks 0 and 4, the plasma is collected. Then, between weeks 4 and 12, it is batched and transported to the fractionation plant, where it is stored from weeks 12 through 16. During this period, "it is the combination of time, temperature, pH and alcohol concentration [that] allows the extraction of the specific therapeutic proteins." At that point, the plasma is inspected and released for production. Production occurs between weeks 20 and 24. Then, between weeks 24 and 28, internal testing of the therapeutic proteins takes place, and the therapies are then released by FDA and shipped between weeks 28 and 32 to the wholesalers and end users.[6]

The IVIG Challenge

In the U.S., there are currently six companies — BPL, CSL Behring, Grifols, Kedrion, Octapharma and Shire — that manufacture and market IVIG products. These include Carimune NF, Flebogamma 5% DIF, Flebogamma 10% DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammaplex, Gamunex-C, Octagam 5%, Octagam 10% and Privigen.

The half-life of IVIG is between three to four weeks, and the cost can be more than $100,000 annually.

With a half-life between three to four weeks and costs exceeding $100,000 annually, IVIG for off-label (unapproved by FDA) treatment is frequently a burden for providers to present enough scientific evidence to gain approval for the cost of treatment. For those fortunate enough to be treated with IVIG off-label, results are often not instantaneous, but often take several months and several infusions before any benefits are quantified, which can cause disruption in therapy. This was the case for Cece Collins, a patient with dysautonomia who did not respond to typical treatment options. "My doctor has championed the use of IVIG for me, but the insurance process has still been a nightmare," says Collins. "We had to have mountains of documentation, including research articles. The medical director at the institution where I'm receiving treatment wants me to submit a review of my progress after every four infusions. But I won't see results until I have at least six solid months of continuous treatment. Gaps in coverage mean that I'm only on my fourth dose, and I was just rejected from the next round of infusions."

The process has been frustrating for both Collins and her physician who have had to manage her rapid decline. Unfortunately, the relevant studies have not been enough for insurance to provide continuity of care and to keep her stabilized.

IVIG Possibilities

Despite the challenges, many diseases are being studied for off-label IVIG treatment with varying results. Following is a brief review of a select few.

Lupus. An autoimmune disease that can cause damage to skin, joints and organs, lupus is a chronic condition thought to be caused by a combination of a person's hormones, environment and genetics. The Lupus Foundation of America estimates 1.5 million Americans and at least five million people worldwide suffer from a form of lupus. The disease strikes mostly women of childbearing age, and can cause symptoms of hair loss, extreme fatigue, stroke, rashes and chronic pain.[7]

FDA has approved the use of corticosteroids, antimalarial drugs, monoclonal antibody belimumab (Benlysta), Acthar injections and aspirin to treat lupus. However, because of these powerful immune-suppressing treatments, some patients experience lower antibody levels that can leave them vulnerable to infection. Treating these infections is a primary benefit of IVIG. However, IVIG can also help boost abnormally low platelet or low red blood cell counts. And, the use of IVIG can prevent a patient's white blood cells from destroying platelets, which can cause autoimmune thrombocytopenia and autoimmune hemolytic anemia.

While IVIG is not a first-line treatment for lupus since it is time-consuming and expensive, for some patients, it may be their only hope at successful disease management. A 2015 study at the University of California, Irvine, tested the efficacy of IVIG in lupus erythematosus patients that yielded positive results. In the study, 15 patients were administered 500 mg/kg of IVIG per day on consecutive days up to a total of 2 g/kg per month for three months. IVIG was then discontinued, and the subjects were monitored for an additional six months for a possible relapse. Study results showed IVIG monotherapy achieved rapid and persistent decrease in disease activity, steady improvement of patients' quality of life, low relapse rate and mild nature and short duration of relapses. In addition, since healing was maintained for months after treatment, the researchers concluded it is possible that "IVIG triggered molecular events mediating the therapeutic action of IVIG that continued to unfold after the end of therapy."[8]

MS. An autoimmune disease that impacts the central nervous system, MS often impairs the spinal cord, optic nerves and brain. This chronic, lifelong condition is progressive, meaning it can intensify over time and, in some patients, may become disabling. There is no cure for MS, but there are treatments available to help patients manage symptoms. These include corticosteroids to help reduce inflammation and disease-modifying drugs such as Betaseron, Axonex, Extavia and Plegridy.

While IVIG does not appear to slow the progression of MS, treatments may lengthen the time between relapses for those with relapsing-remitting MS. Doctors have also prescribed IVIG for patients with severe relapses that have not responded to corticosteroids.

In a 2008 meta-analysis of six clinical trials, researchers found results were consistent. While IVIG was well-tolerated, the studies could not substantiate a beneficial effect of IVIG in the studied doses, and the utility of IVIG for relapsing-remitting MS was still in question. However, the results did prove that IVIG can be considered as an alternative therapeutic option, second-line therapy or adjuvant therapy considering its positive beneficial effects.[9]

Alzheimer's disease. Though Alzheimer's disease affects an estimated 5.5 million Americans and is the sixth-leading cause of death in the United States, its cause and cure have eluded scientists since its discovery by German physician Alois Alzheimer in 1906. This fatal progressive disease, which is the most common form of dementia, destroys brain cells and causes challenges with brain function and memory loss.

IVIG therapy for Alzheimer's was thought to be very promising in its early stages. In 2009, the Alzheimer's Association reported studies of medical records of 847 people who received IVIG treatments versus those of nearly 85,000 people who did not. The studies showed people who received IVIG had a 42 percent lower risk of developing Alzheimer's disease over four years.[10]

Discouragingly, in 2013, a more formalized study called GAP (Gammaglobuin Alzheimer's Partnership) was conducted by the Alzheimer's Disease Cooperative Study (ADCS), the National Institute of Aging and Baxter International. The Phase III trial measured the progress of 390 patients in 45 centers in the United States and Canada, and after 18 months of treatment, it failed to prove efficacy in reducing cognitive decline and stabilizing existing functional abilities in patients.[11]

However, while most studies found on clinicaltrials.gov have either been completed or terminated, there are currently two active studies not currently recruiting, and another that began in December 2015 and is currently recruiting that is evaluating the effect of IVIG on brain scans for research purposes only (not for medical treatment). The study is broken down into three parts in which patients receive a single dose or placebo, multiple doses or placebo for up to 24 weeks and multiple doses or placebo for up to 72 weeks.[12]

Interestingly, a new study posted on Oct. 24 purports to determine if changes in brain amyloid levels are evident three months after infusion of 0.4 g/kg of IVIG every 14 days times five infusions. While the study was not yet recruiting at the time of this writing, it is estimated to be completed by June 2018.[13]

Dysautonomia. Presenting in several forms, including postural orthostatic tachycardia syndrome, neurocardiogenic syncope and multiple system atrophy, dysautonomia is an umbrella term used to describe the dysfunction of the autonomic nervous system. It is not a rare condition, as it is estimated to affect (in some form) more than 70 million people worldwide, according to Dysautonomia International. The condition can occur secondary to diseases like diabetes, rheumatoid arthritis, celiac disease, Parkinson's and Sjögren's syndrome.

While IVIG does not appear to slow the progression of MS, treatments may lengthen the time between relapses for those with relapsing-remitting MS.

Treatments for dysautonomia are varied. There is no cure, but patients may improve with treatment for an underlying cause of the disease. Treatment is often prescribed per symptom and can include responses to combat orthostatic hypotension. Patients are instructed to elevate the head of their bed, eat a high-sodium diet and can be prescribed drugs such as fludrocortisone and midodrine. Doctors are also exploring the use of intravenous saline therapy.

Jill Schofield, MD, a researcher on the topic of antiphospholipid syndrome and the use of IVIG in refractory autoimmune dysautonomia patients, describes these patients as having an underlying autoimmune disease, a family history of autoimmune disease and progressive worsening of dysautonomia symptoms over time, despite typical treatment. She has been prescribing a unique dose of IVIG to these patients: high-dose (1 to 2 gm/kg monthly) given slowly with aggressive hydration to reduce the risk of aseptic meningitis and thrombosis. On average, 88 percent of patients have responded to treatment within 5.7 weeks. "IVIG is highly efficacious in patients with refractory autoimmune dysautonomias," says Dr. Schofield. "And, it is a fairly safe and well-tolerated treatment in these patients when given with pre- and sometimes post-hydration." Dr. Schofield plans to release the results of her findings later this year.

Infertility. Pregnancy and autoimmune conditions can lead to a multitude of complications, including miscarriages. It is not understood why IVIG works for women with recurrent pregnancy loss, but it has been found to lower the incidence of miscarriage. One theory is that IVIG combats natural killer (NK) cells. Women who have never given birth and have high levels of NK cells in their peripheral blood have higher chances of pregnancy loss.[14]

With infertility affecting nearly 12 percent of women in the United States, it can be troubling to many who find themselves excluded from what some physicians feel is an ineffective treatment with a high price tag. The American Society for Reproductive Medicine and the American Congress of Obstetricians and Gynecologists claimed that after reviewing five studies in the 1990s, IVIG simply did not show enough evidence to suggest it could treat or prevent miscarriages. Still, some doctors vouch for its impact, and many fertility clinics still offer the treatment to couples in distress, as long as they're willing to pay for it out of pocket.[15]

Alzahra Hospital Tabriz in Iran is currently recruiting for a study on immunomodulatory effects of IVIG on pregnancy rate or patients with recurrent pregnancy loss. A similar study on unexplained primary recurrent miscarriage and the use of IVIG is being conducted in Tokyo.[16]

Other disease states. There are currently more than 90 clinical trials recruiting patients to study the use of IVIG in different conditions, including:

- Small fiber neuropathy
- Kawasaki disease
- Chronic inflammatory demyelinating polyneuropathy
- Influenza
- Toxic shock syndrome
- Autoimmune epilepsy
- Spinocerebellar ataxia
- Demyelination in diabetes mellitus
- Sickle cell disease
- Post-polio syndrome
- Graft-versus-host disease
- Antibody positive psychosis
- Idiopathic inflammatory myopathy
- Sarcoidosis
- Dermatomyositis
- Myasthenia gravis
- Alloimmune thrombocytopenia

Looking Forward

Numerous researchers believe IVIG holds promise for treating many more diseases than those currently FDA-approved. And, clinical trials are key to uncovering its potential. According to Lilly Stairs, who serves on the board of the American Autoimmune Related Diseases Association and heads patient advocacy at Clara Health, patient participation in clinical trials is what truly makes or breaks awareness, availability and coverage of a new treatment. "Patients are key stakeholders in the clinical trials process and absolutely have the power to both improve and expedite them," explains Stairs. "When sponsor companies include patients in the clinical trials design process, it exponentially improves enrollment, speed and outcomes because the trial is tailor-made to accommodate the needs of the patient."

To help in expediting the process, it is critical that physicians make patients aware of clinical trials and the power of breakthrough research. "We need to work together to demystify clinical trials, which are often stigmatized and considered a 'last resort,'" adds Stairs. "All patients deserve to know that clinical trials are a treatment option and can provide access to cutting-edge therapies. Greater awareness and participation will result in faster enrollment and, ultimately, a quicker pathway to approval." ❖

There are currently more than 90 clinical trials recruiting patients to study the use of IVIG in different conditions.

ILANA JACQUELINE is a 27-year-old dysautonomia and primary immune deficiency disease patient from South Florida who has been writing professionally since 2004.

References

1. Orange JS, Hossny EM, Weiler CR, et al. Use of Intravenous Immunoglobulin in Human Disease. *Journal of Allergy and Clinical Immunology*, 2006;117: S525-53. Accessed at www.jacionline.org/article/S0091-6749(06)00178-3/pdf.
2. Jolles S, Sewell WAC, and Misbah SA. Clinical Uses of Intravenous Immunoglobulin. *Clinical & Experimental Immunology*, 2005 Oct; 142(1): 1–11. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC1809480.
3. U.S. Department of Health and Human Services. Analysis of Supply, Distribution, Demand and Access Issues Associated with Immune Globulin Intravenous (IGIV) Executive Summary, February 2007. Accessed at aspe.hhs.gov/sp/reports/2007/IGIV/execsum.htm.
4. Plasma Protein Therapeutics Association. United States Total Collections 2007-2016. Accessed at www.pptaglobal.org/images/Data/Plasma_Collection/Total_Yearly_Collections_2007_-_2016.pdf.
5. Bult JM. Meeting the Needs of Plasma Protein Therapies. Presentation at the APEC Policy Dialogue and Workshop on Attaining a Safe and Sustainable Blood Supply Chain, Manila, The Philippines, Oct. 1, 2014. Accessed at www.pptaglobal.org/images/presentations/2014/BULT_-_APEC_WORKSHOP_MANILA_Compatibility_Mode.pdf.
6. Rhodes RT and McFalls K. The Drivers Behind Plasma Protein Therapies. *BioSupply Trends Quarterly*, January 2010. Accessed at www.bstquarterly.com/archived_issues.aspx.
7. Lupus Foundation of America. Lupus Facts and Statistics. Accessed at resources.lupus.org/entry/facts-and-statistics.
8. Ky C, Swasdibutra B, Khademi S, Desaim S, and Grando SA. Efficacy of Intravenous Immunoglobulin Monotherapy in Patients with Cutaneous Lupus Erythematosus: Results of Proof-of-Concept Study. *Dermatology Reports*, 2015; volume 7:5804. Accessed at www.researchgate.net/publication/275586096_Efficacy_of_Intravenous_Immunoglobulin_Monotherapy_in_Patients_with_Cutaneous_Lupus_Erythematosus_Results_of_Proof-of-Concept_Study.
9. Olyaeemanesh O, Rahmani M, Goudarzi R, and Rahimdel A. Safety and Effectiveness Assessment of Intravenous Immunoglobulin in the Treatment of Relapsing-Remitting Multiple Sclerosis: A Meta-Analysis. *Medical Journal of the Islamic Republic of Iran*, 2016; 30: 336. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC4898867.
10. Perspectives in Alzheimer's Science. Immunotherapy Could Offer Protection Against Alzheimer's Disease. *Neurology*, July 2009. Accessed at www.alz.org/research/downloads/Timeline.pdf.
11. Jeffery S. IVIG Fails in Phase 3 for Alzheimer's. Medscape Neurology, May 7, 2013. Accessed at www.medscape.com/viewarticle/803724.
12. Clinicaltrials.gov. A Study of LY3002813 in Participants With Memory Damage Due to Alzheimer's Disease (AD) or AD. Accessed at clinicaltrials.gov/ct2/show/NCT02624778?term=intravenous+immune+globulin&cond=Alzheimer+Disease&draw=2&rank=12.
13. Clinicaltrials.gov. Effect of IVIG on Cerebral and Retinal Amyloid in Mild Cognitive Impairment Due to Alzheimer Disease. Accessed at clinicaltrials.gov/ct2/show/NCT03319810?term=intravenous+immune+globulin&cond=Alzheimer+Disease&draw=5&rank=7.
14. Sapir T, Carp H, and Shoenfeld Y. IVIG as Treatment for Recurrent Pregnancy Loss (RPL). *Harefuah*, 2005 Jun;144(6):415-20, 454, 453. Accessed at www.ncbi.nlm.nih.gov/pubmed/15999561.
15. Lee SM. Infertile Couples Turn to Disputed Therapy. SF Gate, Feb. 23, 2013. Accessed at www.sfgate.com/health/article/Infertile-couples-turn-to-disputed-therapy-4303518.php.
16. ClinicalTrials.gov. Immunodulatory Effects of IVig on Pregnancy Rate of Patient with Recurrent Pregnancy Loss. Accessed at clinicaltrials.gov/ct2/show/NCT03174951.

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Update on

For the many different types of diabetes, there are no cures yet, but a host of successful treatments available, with myriad more being studied.

By Jim Trageser

ONE OF THE earliest diseases described in classical antiquity, diabetes has been a human malady throughout written history. The Egyptian physician Hesy-Ra wrote of a condition of too-frequent urination in 1552 B.C. The term "diabetes" — meaning "to siphon" — was first used in 250 B.C. by Apollonious of Memphis, an ancient Greek physician.[1] Four hundred years later, Greek physician Aretaeus described the condition as "the melting down of flesh and limbs into urine." By the Middle Ages, the disease was formally known as diabetes mellitus (the Latin word for honey added to indicate the urine of patients was known to be sweet after it was observed ants were attracted to the urine of diabetics).[2]

In 1776, English physician Matthew Dobson noted there were two types of diabetics: those who perished in as little as five weeks, and those who lasted for decades, but were never cured.[1] His was the first classification of diabetes into types 1 and 2. In 1889, the first major advance in understanding and treating diabetes occurred when two doctors in Strasbourg, France,

discovered that removing the pancreas from a dog led to symptoms of diabetes. Just over a decade later, German researcher Georg Zuelzer found injecting extract from the pancreas eased the symptoms of diabetes.[2] Then, in 1922, Canadian physician

Diabetes

Frederick Banting successfully treated a diabetic dog with insulin extracted from another dog,[2] for which he shared the Nobel Prize in Medicine with John James Rickard Macleod, in whose laboratory the work was done.[3] Soon after, a higher-quality insulin was extracted from cattle and made commercially available. The first synthetic insulin was produced in 1978.[4]

More than three millennia after diabetes was first described, we understand the mechanisms of the disease, and we can use insulin to stop it from killing patients in the short term. But, we still don't have a cure or an effective way to prevent its onset. It remains a serious, debilitating disease that shortens lifespans and negatively impacts a patient's quality of life.

What Is Diabetes?

Diabetes mellitus is any condition in which there is too much sugar in the bloodstream.[5] It is generally caused by the pancreas not producing enough insulin, a protein used to stimulate the passage of glucose from the blood into the cells of surrounding tissues. In some cases, it is caused by insulin resistance, which occurs when the tissues of the body are unresponsive to the presence of insulin and, therefore, unable to extract glucose from the blood.

The Centers for Disease Control and Prevention (CDC) estimates 29 million (approximately 9 percent) Americans have some form of diabetes, and up to one-quarter of them are not yet diagnosed. More than one-third of adult Americans have prediabetes, 90 percent of whom are unaware of it.[6] Further, a 2011 study published in the British journal *The Lancet* found rates of diabetes are rising across the globe.

The vast majority of patients (CDC estimates between 90 percent and 95 percent) with diabetes will develop the version known as type 2.[7] Although less severe than type 1 because the pancreas still makes insulin, just not enough, and the body is less efficient at using it,[8] type 2 diabetes generally manifests during adulthood and can be treated with diet and exercise in its early stages.

Type 1 diabetes is an autoimmune disease that occurs when the body's immune system mistakenly attacks the pancreas, destroying the beta cells that produce insulin.[9] Typically appearing during childhood or adolescence, it is fatal within weeks if left untreated.

Even rarer than type 1 diabetes is a handful of other variants of the disease:

- Gestational diabetes: Expectant mothers may develop diabetes that goes away after delivery.[10] Patients who have had gestational diabetes are at higher risk of developing type 2 diabetes later in life, as is the unborn child.
- Neonatal diabetes mellitus: With this rare condition (one in every 100,000 to 500,000), the baby develops diabetes in the first six months of life. In about half of these cases, the condition is permanent.[11] When the condition persists, it is called permanent neonatal diabetes mellitus. In the other half whose condition subsides, it is known as transient neonatal diabetes mellitus.
- Maturity-onset diabetes of the young (MODY): This form of diabetes is hereditary and is caused by one of a handful of mutations that prevent the pancreas from producing enough insulin.[11]
- Cystic-fibrosis-related diabetes: Patients with cystic fibrosis often develop diabetes when the thick mucus the body produces in response to the disease causes scarring of the pancreas, interfering with production of insulin.[12]
- Diabetes can also manifest as a symptom or complication of other diseases, ranging from Cushing's syndrome to hemochromatosis, pancreatic cancer and hyperthyroidism.[13]

While the discovery that insulin can be used to manage the disease changed the prognosis of type 1 diabetes from one of imminent death to a chronic disease, mortality rates for diabetics remain much higher than for the general population. Even when being successfully managed with insulin, diet and exercise, diabetes continues to exact a toll on the circulatory system, nervous system, kidneys and eyes.[14] It is the leading cause of both amputation and adult-onset blindness in the U.S.[6]

Diabetes was the seventh-leading cause of death in the U.S. in 2015 (79,835 deaths were attributed primarily to diabetes), and was listed as a contributing cause of death on another 252,806 death certificates.[15] It is generally thought that types 1 and 2

diabetes shorten lifespan by about 20 years and 10 years, respectively.[16] However, some recent studies show modern treatment regimens may be significantly lowering mortality.[17]

The Centers for Disease Control and Prevention estimates 29 million (approximately 9 percent) Americans have some form of diabetes, and up to one-quarter of them are not yet diagnosed.

Causes of Diabetes

Researchers do not yet fully understand how or why most cases of diabetes develop. Type 1 diabetes has been shown to be an autoimmune disorder, but the specific triggers — whether environmental or reaction to an infection — are not yet fully known. Type 2 diabetes, accounting for the vast majority of diabetes cases, is thought to be the result of several factors, from genes to lifestyle.[13] It is the least understood manifestation of the disease.

Researchers believe gestational diabetes is caused by a combination of hormonal changes during pregnancy, genetic predisposition and overall health factors.[13] MODY and neonatal diabetes mellitus are both monogenic forms of the disease caused when a single gene mutation prevents the body from producing or reacting appropriately to insulin.

In rare instances when diabetes is the result of another disease, such as with cystic fibrosis-related diabetes, the underlying health issue is the immediate cause. These include:

- Cancer of or physical trauma to the pancreas, negatively impacting its ability to produce insulin;
- Cushing's syndrome causing the body to produce too much cortisone, which lessens the ability of the liver and skeletal muscles to respond to insulin;[18]
- Acromegaly (a disorder caused when the pituitary produces too much growth hormone), which overstimulates production of insulin and, in rare cases, induces insulin resistance;
- Hemochromatosis (a disorder caused when the body stores too much iron), which can cause organ damage, including to the pancreas; and
- Certain drugs that can either harm the beta cells that produce insulin in the pancreas, or disrupt insulin's normal activity in the body. These include niacin (vitamin B3), diuretics, anti-seizure drugs, psychiatric drugs, drugs that treat HIV, pentamidine, anti-rejection medications and glucocorticoids.[13]

Symptoms and Progression of Diabetes

Since the term "diabetes" is used to describe high blood sugar and not its underlying cause, all forms of diabetes will have similar symptoms. However, symptoms of type 1 diabetes typically manifest over a course of weeks, while type 2 diabetes may take years to become noticeable. Symptoms often include:[13]

- Frequent urination
- Increased thirst
- Hunger pangs
- Fatigue
- Numbness or tingling in the extremities
- Sores that will not heal
- Sudden weight loss
- Blurred vision

Even properly treated, diabetes is a progressive disease. Over time, the risks of complications include:[14]

- Cardiovascular disease: High levels of glucose in the bloodstream cause damage to blood vessels over time. Diabetics have a higher risk of experiencing a heart attack or stroke.
- Kidney disease: The same blood vessel damage that can cause cardiovascular disease can also damage the kidneys, up to and including kidney failure requiring dialysis or transplant.
- Nerve damage: Damage to the capillaries that feed nerves can lead to loss of feeling in the hands and feet (and ultimately tissue damage that may require amputation to prevent infection), as well as problems with digestion. Men may suffer erectile dysfunction.
- Impaired vision: Deteriorating blood vessels can lead to a damaged retina. Diabetics are also at higher risk of cataracts and glaucoma.
- Impaired hearing: Blood vessel damage can affect the inner ear.

Side effects of gestational diabetes may include preeclampsia in the mother, and excess growth and low blood sugar in the developing child, as well as an increased risk for the child to develop type 2 diabetes later in life.[14]

Symptoms for the above side effects and complications will manifest as the diabetes progresses, and will be consistent with those diseases.

Diagnosing Diabetes

The American Diabetes Association recommends screening the following individuals for diabetes and prediabetes, with or without symptoms:[19]

• Everyone 45 and older, with a retest every three years, and
• Anyone with a body mass index above 25 if they have any additional risk factors, including a sedentary lifestyle, high blood pressure, high cholesterol, a history of ovarian cysts or having delivered a baby that weighed more than 9 pounds.

Prediabetes is defined as having a higher-than-normal blood sugar count, but not as high as full-blown type 2 diabetes.

Certain ethnic groups have a higher incidence of diabetes, including African Americans, Alaskan natives, native Americans, Asian Americans, Latinos and Pacific Islanders (including Hawaiians).[13]

Hyperthyroidism, an autoimmune disease, is another risk factor. Indeed, any time a patient is dealing with an autoimmune disease, he or she is at a higher risk for developing other autoimmune diseases. And, while no causal link between hyperthyroidism and type 1 diabetes has yet been discovered, there is a high correlation.[20]

All pregnant women should be tested for gestational diabetes, rechecked throughout pregnancy and checked after giving birth to ensure blood sugar levels have returned to normal levels.[21]

A diabetes diagnosis can be made using the glycated hemoglobin (A1C) blood test, which measures a patient's average blood sugar level. For pregnant patients and those with a nonstandard version of hemoglobin in whom the A1C test may not be accurate, other blood sugar tests can be performed.

Treating Diabetes

The first course of treatment for every case of diabetes is to institute a healthy diet and maintain regular exercise. Depending on the type of diabetes, this may be augmented with daily glucose testing and insulin. Other medications may also be used to help manage symptoms of associated conditions such as high blood pressure or cholesterol.

Those with type 1 diabetes will require insulin to regulate their blood sugar since their pancreas is not producing any insulin. Insulin use requires a testing kit so patients can monitor their blood sugar levels on a daily or more frequent basis and adjust the insulin doses accordingly.[22]

Type 2 diabetes and gestational diabetes patients are often able to control their disease with diet and exercise alone. However, over time, these patients are more likely to require insulin. And, if the expectant mother's blood sugar can't be regulated successfully with diet and exercise, insulin may be prescribed.

A healthy diet — one low in processed sugars and trans fats — can help the body self-regulate blood pressure and cholesterol, and prevent swings in blood sugar levels.[22] Combining a dietary plan with regular exercise can also help maintain a healthy weight, which will help slow the onset of any complications. Since exercise helps the body move more sugar from the bloodstream to muscle cells, regular exercise increases the body's efficiency by encouraging more insulin production and by making the body more receptive to insulin.[23]

Some patients may be prescribed drugs to promote more insulin production or slow the liver's production of glucose. Metformin is usually the first drug prescribed for type 2 diabetes to slow the production of glucose. It may also be used for those with prediabetes to reduce the risk of developing diabetes.[23]

In very rare cases, a pancreatic transplant may be called for if patients with type 1 diabetes cannot be successfully managed with insulin. However, due to the side effects of the lifelong anti-rejection drugs, this is typically only recommended when a kidney transplant is already scheduled.[23]

Neonatal diabetes can be treated with insulin or glibenclamide, which promotes the production of more insulin in the pancreas.[24] For those whose diabetes is the result of another underlying issue, treatment will have to be coordinated with treatment of the original condition. However, controlling blood sugar levels is critical no matter the original cause.

Preventing Diabetes

CDC estimates fully a third of adults have prediabetes. Healthy meals, regular exercise and weight control are the best methods for reducing the risk of developing full-blown type 2 diabetes.[25] And, there is some evidence that metformin may further reduce the risk, but this remains under study. CDC has launched the National Diabetes Prevention Program (www.cdc.gov/diabetes/prevention/index.html), which provides a host of materials physicians can use when treating patients.

Researchers do not yet fully understand how or why most cases of diabetes develop.

There is no way to prevent type 1 diabetes or any type of diabetes with a genetic cause. However, the risk of developing gestational diabetes can be reduced with the same methods used for prediabetes. For instances of diabetes caused by other conditions, controlling those diseases remains the best course for reducing the risk of developing diabetes as a complication.

Ongoing Research

Given how widespread diabetes is and the serious complications arising from it, it is no surprise there are thousands of ongoing studies looking at prevention, treatment and cures. ClinicalTrials.gov listed more than 12,000 diabetes-related studies either recently completed or ongoing as of early fall 2017.

Among the more interesting studies is a potential vaccine entering clinical trials in 2018 that would target an enterovirus thought to play a critical role in triggering type 1 diabetes in children.[26] And, a possible cure for type 1 diabetes is the goal of a study looking at whether a combination of the anti-rejection drug anti-thymocyte globulin and the anti-cancer drug pegylated G-CSF can help restore insulin production.[27]

Given how widespread diabetes is and the serious complications arising from it, it is no surprise there are thousands of ongoing studies looking at prevention, treatment and cures.

Hundreds of new approaches to treatment are also being studied:

A Brazilian study is looking at whether regular exercise can restore blood vessel performance.[28] And, a U.S. study is investigating whether an electronic device can use visible light to measure biomarkers in the skin to diagnose diabetes without the need to draw blood.[29]

Intravenous immune globulin (IVIG) is being studied to see if it can relieve symptoms of diabetes-related neuropathy (nerve disease). The University of Toronto was recruiting volunteers at press time for a study of the efficacy of IVIG in treating peripheral neuropathy in diabetics.[30] A 2010 study conducted at Nagoya University in Japan showed patients with multifocal diabetic neuropathy gained significant pain relief with IVIG therapy (however, those with symmetric neuropathy did not).[31] And, a team at the University of Verona in Italy found that IVIG was effective in quickly relieving pain in patients with diabetic lumbosacral radiculoplexus neuropathy.[32]

A California pharmaceutical company is studying their proposed new drug, Sotagliflozin (or LX4211), to see if it can help lower insulin resistance.[33]

Also under review are the efficacy of public education campaigns and better training for medical professionals.

Looking Ahead

Although diabetes was one of the first diseases identified in history, having been with us since biblical times, there is no cure or vaccine for the disease yet. While promising leads are in the pipeline that will hopefully bring new treatments and perhaps even a cure, for now, physicians will continue to work with patients to construct healthy approaches to managing the disease, minimizing its complications and extending a high quality of life for as many years as possible. ❖

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References

1. Defeat Diabetes Foundation. Diabetes ABCs. Accessed at www.defeatdiabetes.org/diabetes-history.
2. McCoy K. The History of Diabetes. Everyday Health. Accessed at www.everydayhealth.com/diabetes/understanding/diabetes-mellitus-through-time.aspx.
3. NobelPrize.org. John Macleod — Facts. Accessed at www.nobelprize.org/nobel_prizes/medicine/laureates/1923/macleod-facts.html.
4. American Diabetes Association. The History of a Wonderful Thing We Call Insulin, Aug. 21, 2012. Accessed at diabetesstopshere.org/2012/08/21/the-history-of-a-wonderful-thing-we-call-insulin.
5. WebMD. Diabetes Health Center. Accessed at www.webmd.com/diabetes/default.htm.
6. Centers for Disease Control and Prevention. Diabetes at a Glance 2016. Accessed at www.cdc.gov/chronicdisease/resources/publications/aag/pdf/2016/diabetes-aag.pdf.
7. Danaei G, Finucane M, Lu Y, et al. National, Regional, and Global Trends in Fasting Plasma Glucose and Diabetes Prevalence Since 1980. *The Lancet*, July 2, 2011. Accessed at www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60679-X/fulltext.
8. MedlinePlus. Diabetes. Accessed at medlineplus.gov/diabetes.html.
9. Diabetes.co.uk. Differences Between Type 1 and Type 2. Accessed at www.diabetes.co.uk/difference-between-type1-and-type2-diabetes.html.
10. National Institute of Diabetes and Digestive and Kidney Diseases. What Is Diabetes? Accessed at www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes.
11. National Institute of Diabetes and Digestive and Kidney Diseases. Monogenic Forms of Diabetes. Accessed at www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/monogenic-neonatal-mellitus-mody.
12. Cystic Fibrosis Foundation. Cystic Fibrosis-Related Diabetes. Accessed at www.cff.org/Life-With-CF/Daily-Life/Cystic-Fibrosis-related-Diabetes.
13. National Institute of Diabetes and Digestive and Kidney Diseases. Symptoms and Causes of Diabetes. Accessed at www.niddk.nih.gov/health-information/diabetes/overview/symptoms-causes.
14. Mayo Clinic. Diabetes Complications. Accessed at www.mayoclinic.org/diseases-conditions/diabetes/basics/complications/con-20033091.
15. American Diabetes Association. Statistics About Diabetes. Accessed at www.diabetes.org/diabetes-basics/statistics/?referrer=https://www.google.com.
16. Diabetes.co.uk. Diabetes Life Expectancy. Accessed at www.diabetes.co.uk/diabetes-life-expectancy.html.
17. Gregg E, Cheng Y, Saydah S, et al. Trends in Death Rates Among U.S. Adults with and without Diabetes Between 1997 and 2006. *Diabetes Care*, June 2012. Accessed at care.diabetesjournals.org/content/35/6/1252.
18. Pivonello R, De Leo M, Vitale P, et al. Pathophysiology of Diabetes Mellitus in Cushing's Syndrome. *Neuroendocrinology*, September 2010. Accessed at www.ncbi.nlm.nih.gov/pubmed/20829623.
19. Mayo Clinic. Diabetes Tests and Diagnosis. Accessed at www.mayoclinic.org/diseases-conditions/diabetes/basics/tests-diagnosis/con-20033091.
20. Almekinder E. The Relationship Between Diabetes and Thyroid Disorder. The Diabetes Council. Accessed at www.thediabetescouncil.com/the-relationship-between-diabetes-and-thyroid-disorder.
21. Mayo Clinic. Gestational Diabetes Symptoms and Causes. Accessed at www.mayoclinic.org/diseases-conditions/gestational-diabetes/symptoms-causes/dxc-20317176.
22. National Institute of Diabetes and Digestive and Kidney Diseases. Managing Diabetes. Accessed at www.niddk.nih.gov/health-information/diabetes/overview/managing-diabetes.
23. Mayo Clinic. Diabetes Treatments and Drugs. Accessed at www.mayoclinic.org/diseases-conditions/diabetes/basics/treatment/con-20033091.
24. Diabetes.co.uk. Neonatal Diabetes. Accessed at www.diabetes.co.uk/neonatal-diabetes.html.
25. Mayo Clinic. Diabetes Prevention. Accessed at www.mayoclinic.org/diseases-conditions/diabetes/basics/prevention/con-20033091.
26. Hankaniemiab M, Laitinen O, et al. Optimized Production and Purification of Coxsackievirus B1 Vaccine and Its Preclinical Evaluation in a Mouse Model. *Vaccine*, June 27, 2017. Accessed at www.sciencedirect.com/science/article/pii/S0264410X17307053.
27. ClinicalTrials.gov. Reversing Type 1 Diabetes After It Is Established. Accessed at clinicaltrials.gov/ct2/show/results/NCT01106157.
28. ClinicalTrials.gov. Effect of Physical Exercise on Endothelial Function in Patients with Type 2 Diabetes Mellitus. Accessed at clinicaltrials.gov/ct2/show/NCT01983007.
29. ClinicalTrials.gov. Evaluation of a Noninvasive Diabetes Screening Device in Subjects at Risk for Diabetes. Accessed at clinicaltrials.gov/ct2/show/NCT01080157.
30. ClinicalTrials.gov. IVIg for Demyelination in Diabetes Mellitus. Accessed at clinicaltrials.gov/ct2/show/NCT02372149.
31. Kawagashira Y, Watanabe H, et al. Differential Response to Intravenous Immunoglobulin (IVIg) Therapy Among Multifocal and Polyneuropathy Types of Painful Diabetic Neuropathy. *Journal of Clinical Neuroscience*, August 2010. Accessed at www.ncbi.nlm.nih.gov/pubmed/20627580.
32. Tamburin S and Zanette G. Intravenous Immunoglobulin for the Treatment of Diabetic Lumbosacral Radiculoplexus Neuropathy. *Pain Medicine*, November 2009. Accessed at www.ncbi.nlm.nih.gov/pubmed/19788714.
33. ClinicalTrials.gov. Safety and Efficacy of LX4211 with Metformin in Type 2 Diabetes Patients with Inadequate Glycemic Control on Metformin. Accessed at clinicaltrials.gov/ct2/show/NCT01376557.

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Replacement Therapy for Hereditary Angioedema: *Innovations Define a New Standard of Care*

By Keith Berman, MPH, MBA

LIVING WITH HEREDITARY angioedema (HAE) is a painful, disabling and often frightening experience. This rare autosomal dominant disorder, characterized by a deficiency (type I) or a dysfunction (type II) of the C1 inhibitor protein, manifests as recurrent acute attacks of localized edema, usually affecting the skin or the respiratory or gastrointestinal tracts. While the frequency, severity and localization of these angioedema attacks varies widely from one individual to the next, at least 50 percent of patients experience a life-threatening laryngeal attack caused by asphyxiation due to upper airway obstruction.[1]

Historically, HAE treatment options were few and limited by dose-related toxicity. But the recent approvals of a number of effective new treatments have dramatically improved the prognosis for the roughly one in 50,000 people affected by this disorder (Figure 1).

The Roles of C1 Inhibitor

Also referred to as C1 esterase inhibitor, C1 inhibitor (C1-INH) is a key inhibitor of coagulation factors XIa and XIIa, complement component C1 and plasma kallikrein. Through multiple complex pathways, C1-INH modulates the extent of increased microvascular permeability and edema that normally occurs during an inflammatory reaction. In particular, C1-INH acts to regulate the conversion of prekallikrein to

Figure 1. C1 Inhibitor and Synthetic Peptide Products Approved to Treat or Prevent Hereditary Angioedema Attacks

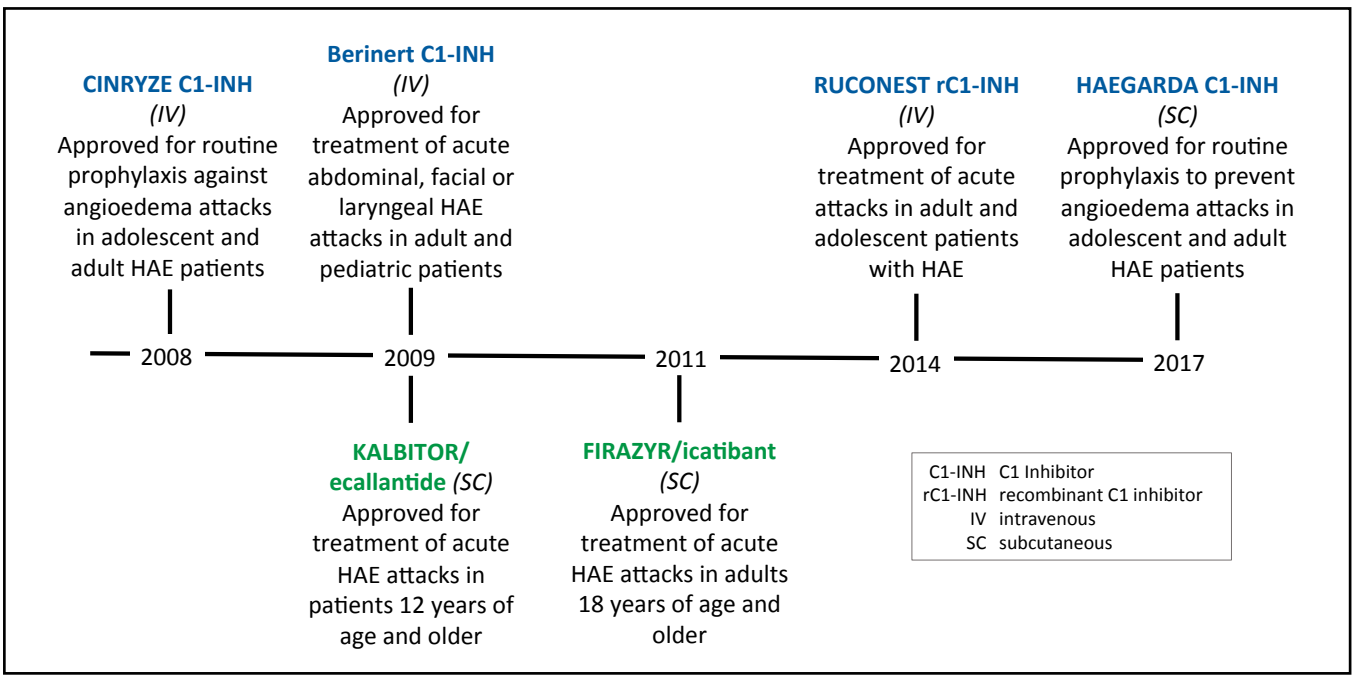
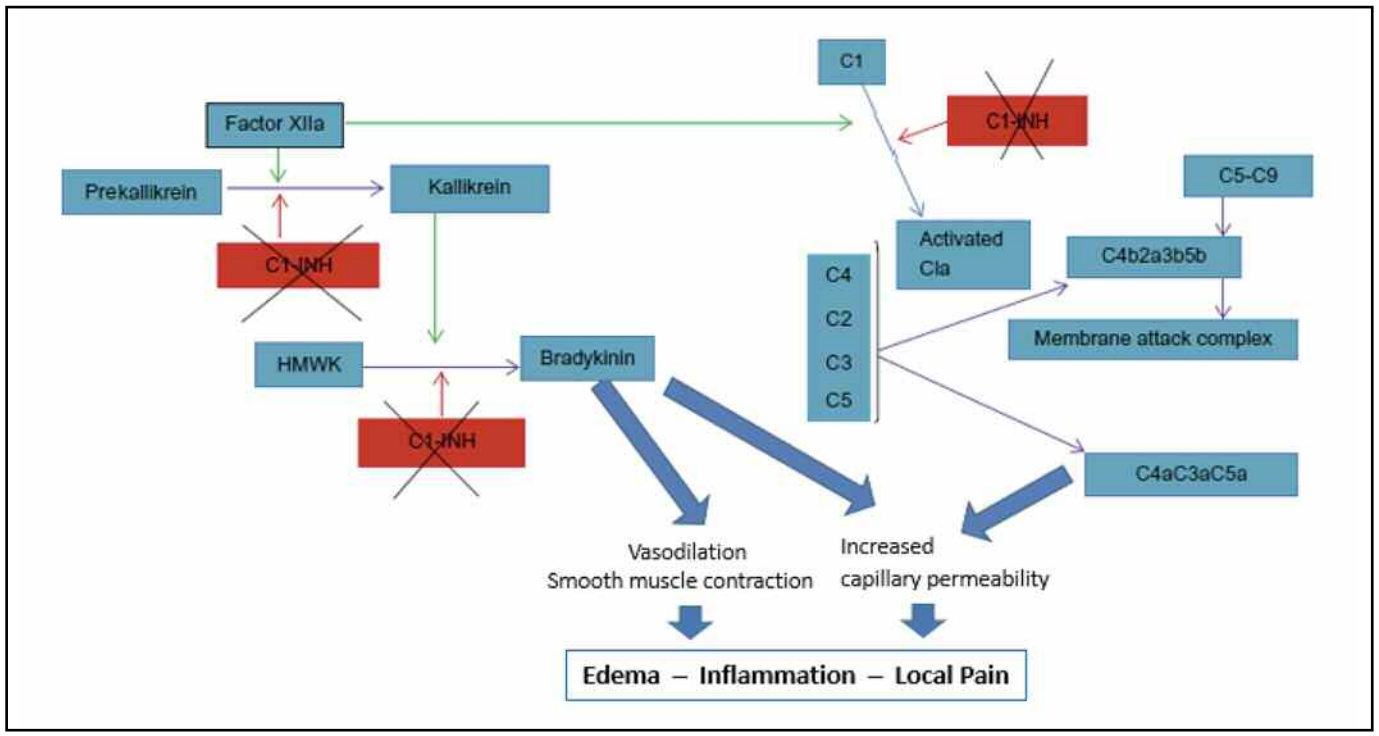


Figure 2. Hereditary Angioedema: Dysregulation of Coagulation, Contact and Complement Cascades Due to Deficit of Normal C1 Inhibitor Production

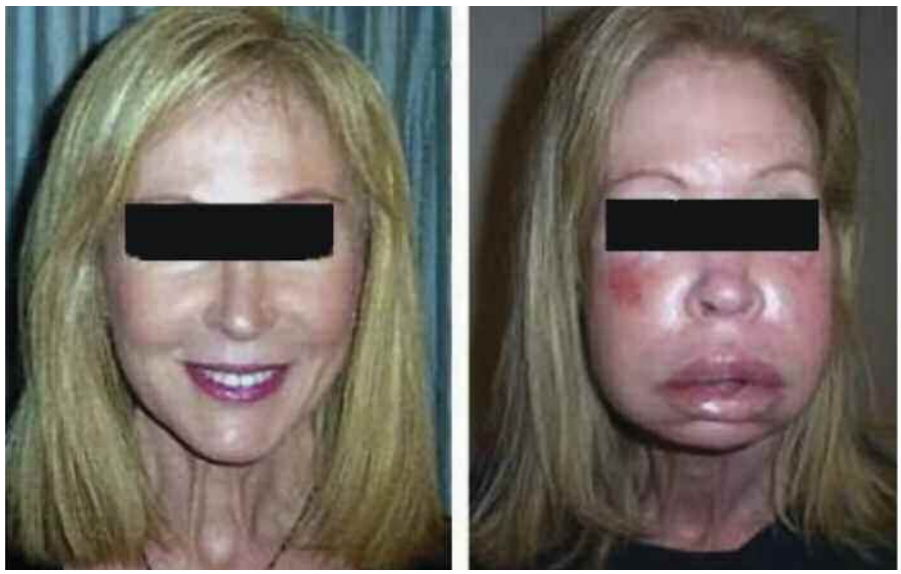


Adapted from Ghazi A, Grant JA. *Biologics* 2013;7:103-13.

kallikrein, which in turn limits production of bradykinin, a powerful vasodilator thought to be responsible for the characteristic symptoms of localized swelling, inflammation and pain associated with HAE attacks.

Conversely, low functional C1-INH levels permit the unchecked generation of bradykinin, anaphylatoxins and chemotaxins that induce and perpetuate the vasodilation, smooth muscle contraction and increased capillary permeability (Figure 2) that are thought to account for painful swelling involving the extremities, gut tract, larynx and face (Figure 3) in persons with HAE. While angioedema attacks usually occur spontaneously with no clear causal factor, emotional stress, local tissue trauma, menstruation, infections and use of certain medications are all known to trigger attacks.

Figure 3. A Hereditary Angioedema Attack with Severe Facial Edema



Source: www.medvestnik.by/ru/diagnose/view/nasledstvennyj-r-angionevroticheskij-otek-nao-11562-2014.

Historical HAE Management

Until recently, management of HAE was largely limited to long-term prophylactic treatment with attenuated androgens (e.g., danazol and stanozolol), which reduce the number and severity of angioedema attacks by boosting endogenous biosynthesis of C1-INH, or with antifibrinolytic drugs (e.g. epsilon

aminocaproic acid), whose mechanism of action is unknown.

Unfortunately, chronic administration of therapeutic doses of attenuated androgens is frequently associated with hepatotoxicity, virilization and an array of other dose-related side effects that many patients cannot tolerate.[2,3] Further, attenuated androgens are not useful in the acute treatment of angioedema attacks. Prophylaxis with antifibrinolytic agents has proven not to be reliably effective.[4,5]

> In addition to the licensure of several C1-INH concentrates, FDA approved two other novel treatments for acute attacks in HAE patients from 2009 to 2011.

In 1980, European and U.S. investigators published reports of the successful use of C1-INH concentrates purified from human plasma to treat acute episodes of angioedema in HAE patients.[6,7] But while C1-INH was soon adopted as a standard therapy in Germany and elsewhere in Europe, it remained unavailable in the U.S. for the next three decades.

C1 Inhibitor Approved to Treat HAE Attacks

In 2009, the U.S. Food and Drug Administration (FDA) approved CSL Behring's C1-INH concentrate, Berinert, for the treatment of acute abdominal or facial HAE attacks in adults and adolescents,* based on safety and efficacy findings from a placebo-controlled, double-blind, randomized prospective clinical study in 125 subjects.[8] At least 70 percent of subjects in both the Berinert and placebo groups were suffering from abdominal attacks at baseline.

In subjects treated with 20 IU/kg body weight of Berinert for any acute attack, the median time to onset of symptom relief was significantly reduced compared to placebo treatment. The reduction in time to onset of relief was most pronounced in severe attacks: 0.5 hour versus 13.5 hours. In the subset of subjects experiencing abdominal attacks, the median time to start of relief of the last symptom (e.g., pain, nausea, vomiting, cramps and diarrhea) present at baseline to improve was one hour for Berinert group subjects, compared to 24 hours for placebo group subjects.[1]

In 2012, FDA approved a label expansion that allows for self-administration of Berinert with appropriate training, translating into an opportunity for much faster relief of symptoms. "Once the early signs of an HAE attack begin to emerge, any delay in starting treatment can increase the severity of that attack … and can lead to a patient needing to be hospitalized," noted study investigator Bruce Zuraw, MD. "However, if a patient self-administers therapy as soon as symptoms begin to appear, these problems can usually be averted."

Self-administration at the onset of an abdominal or facial HAE attack resulted in a median onset of relief of just 48 minutes, versus more than four hours for the placebo group. In an extension study, self-administration of Berinert to treat potentially life-threatening laryngeal attacks provided a median onset of relief of just 15 minutes; based on these findings, FDA also approved Berinert for laryngeal attacks in addition to facial and abdominal attacks.[9]

But in patients with underlying risk factors, such as presence of an indwelling catheter, prior history of thrombosis, underlying atherosclerosis and immobility, there have been reports of serious arterial and venous thromboembolic events following administration of Berinert and other C1-INH products. As such, physicians are advised to weigh the benefits of treatment of HAE attacks against the risks of thromboembolic events in patients with underlying risk factors.[2]

Short-Acting Peptides Approved to Treat HAE Attacks

In addition to the licensure of several C1-INH concentrates, FDA approved two other novel treatments for acute attacks in HAE patients from 2009 to 2011: KALBITOR (ecallantide) and

**In 2016, the labeled indication for Berinert was expanded to include treatment of acute HAE attacks in children under 12 years of age; Berinert is the only HAE treatment currently indicated for use in pediatric patients.*

FIRAZYR (icatibant). By different mechanisms of action, these agents respectively act to inhibit the production or the activity of bradykinin, the primary mediator of painful, edematous HAE attacks.

KALBITOR, a 60-amino-acid recombinant peptide produced in yeast cells, selectively inhibits plasma kallikrein. Through its direct interference with kallikrein, KALBITOR reduces swelling and inflammation by inhibiting the conversion of high molecular weight kininogen to bradykinin. A pair of randomized, double-blind, placebo-controlled trials evaluated the safety and efficacy of subcutaneous delivery of 30 mg of the product for treatment of acute HAE attacks in a total of 168 adult and adolescent patients. In both trials, KALBITOR significantly reduced attack severity from baseline to four hours posttreatment. Of 187 HAE patients treated with subcutaneous KALBITOR, five (3 percent) experienced anaphylaxis, usually within one hour of administration. As symptoms of potentially life-threatening anaphylaxis are similar to acute HAE symptoms, prescribers are cautioned to closely monitor patients for any signs of a serious allergic reaction. About 20 percent of patients seroconverted with anti-ecallantide antibodies, the rate increasing with exposure over time. Other common side effects included headache, nausea, fatigue, diarrhea and upper respiratory tract infection.[10]

FIRAZYR is a selective bradykinin B2 receptor antagonist, with a binding affinity similar to bradykinin. This synthetic short-acting decapeptide competitively inhibits bradykinin from binding the B2 receptor on target cells, interfering with its vasodilatory action that results in swelling, inflammation and pain. If the response is deemed inadequate or if symptoms recur after the initial 30 mg subcutaneous dose, up to two additional doses may be administered in a 24-hour period. In a randomized, placebo-controlled, double-blind study of 98 adult patients with HAE who developed moderate to severe cutaneous or abdominal attacks, the median time to a 50 percent reduction in symptoms following FIRAZYR treatment was 2.0 hours (95% confidence interval [CI], 1.5 to 3.0 hours) versus 19.8 hours (95% CI, 6.1 to 26.3 hours) following placebo treatment (P<0.001). Near-complete symptom relief was attained in a median of eight and 36 hours, respectively, for the two treatment groups.[11]

> Optimal HAE management is treatment to prevent painful and disabling HAE attacks from occurring in the first place, or at least to reduce the number and severity of breakthrough attacks that occur.

Unlike KALBITOR, which must be administered by a qualified healthcare professional due to a risk of anaphylaxis, FIRAZYR can be safely self-administered by properly trained patients upon recognition of symptoms of an HAE attack. The advantage of self-administration is plainly evident: It shortens delay to initiation of treatment, limiting the severity of acute attacks, including potentially life-threatening laryngeal attacks.

Intravenous C1 Inhibitor Prophylaxis for HAE

Optimal HAE management is treatment to prevent painful and disabling HAE attacks from occurring in the first place, or at least to reduce the number and severity of breakthrough attacks that occur. The most obvious solution for patients with severe disease is chronic replacement of absent or dysfunctional endogenous C1-INH with regular infusions of C1-INH concentrate.

Routine prophylaxis with a human C1-INH was finally evaluated a decade ago in a study of 22 subjects, who were randomly assigned to receive intravenous injections of saline placebo or 1,000 units of Shire's CINRYZE C1-INH product every three to four days for 12 weeks. Patients were then crossed over to the alternative treatment for a second 12-week evaluation period.[12]

Mean attack rates for all 22 subjects during the two 12-week crossover periods were 6.26 and 12.73 for the C1-INH and placebo treatments, respectively. This difference of 6.47 attacks was highly significant (95% CI, 4.21 to 8.73; P<0.001). Further, the mean attack severity score (on a 3-point scale with 1 indicating mild, 2 moderate and 3 severe) was significantly lower with C1-INH prophylaxis than with placebo (1.3 ± 0.85 versus 1.9 ± 0.85; P<0.001). The

total duration of attacks was likewise significantly shorter with C1-INH prophylaxis than with placebo (2.1 ± 1.13 versus 3.4 ± 1.39 days; P<0.002). Half as many subjects on C1-INH prophylaxis required open-label rescue therapy for HAE attacks as those receiving placebo. Common nonserious reactions with CINRYZE administration included headache, nausea, rash and vomiting.

Based on these and other findings, FDA approved CINRYZE in 2008 for routine prophylaxis against HAE attacks. With appropriate training, CINRYZE can now be self-administered by patients.

But as with Berinert administration, there is a risk of thromboembolic events with this intravenously infused product. In an open-label trial that further investigated prophylactic use of CINRYZE in 146 HAE patients, five serious thromboembolic events were reported (myocardial infarction, deep vein thrombosis, pulmonary embolism and two cerebrovascular accident events) — all in patients with underlying risk factors.[13]

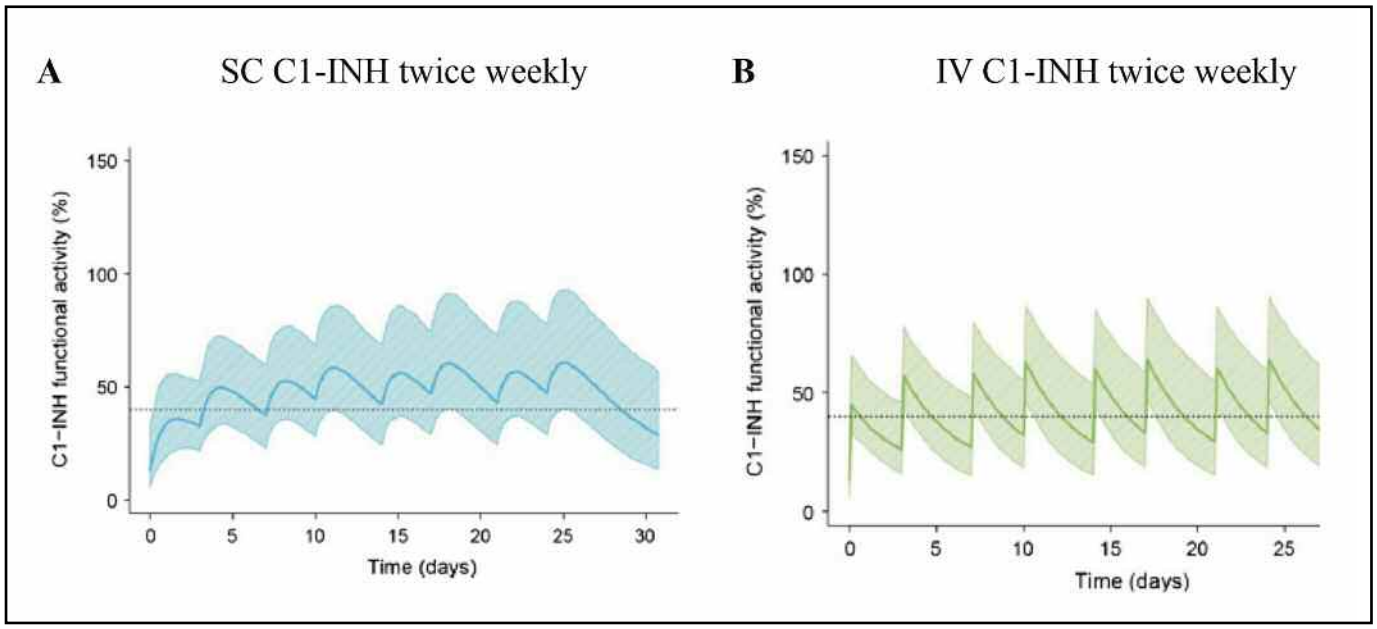
Three years ago, a third C1-INH replacement therapy option became available when FDA approved Pharming's novel recombinant human C1-INH product, brand named RUCONEST, for treatment of acute HAE attacks in adults and adolescents. Purified from the milk of transgenic rabbits, intravenous RUCONEST administration at 50 IU/kg results in accelerated and sustained relief of symptoms of HAE attacks, despite a much shorter elimination half-life than human plasma-derived C1-INH concentrates.[14]

Subcutaneous C1 Inhibitor Prophylaxis for HAE

In nonaffected individuals, circulating C1-INH is naturally maintained at a physiologic, steady-state level. This is not the case with periodic intravenous infusion of a C1-INH concentrate. With a half-life of around 20 hours, the pharmacokinetic profile for twice-weekly intravenous administration of C1-INH exhibits a pronounced saw-tooth pattern, with high peaks following infusion, dropping over several days to much lower trough levels just preceding the next infusion (Figure 4A).[15]

At a clinically safe therapeutic dose of 1,000 IU, the C1-INH trough level consistently dips below the minimum therapeutic target of 40 percent of normal C1-INH functional activity, the apparent lower threshold for protection against angioedema attacks. Unsurprisingly, a recent study found that, in patients who received twice-weekly intravenous C1-INH prophylaxis, breakthrough angioedema attacks tended to occur shortly before the next scheduled infusion.[16] Additionally, technical difficulties with regular venous access often requires the use of indwelling venous catheters, which introduces

Figure 4. Modeled C1 Inhibitor Functional Activity With Biweekly Intravenous (IV) or Subcutaneous (SC) Administration of Therapeutic Doses



Based on pharmacokinetic data with biweekly IV administration of 1,000 IU Berinert and 3,000 IU HAEGARDA. Dashed black lines represent minimum therapeutic target of 40% C1-INH functional activity. Solid lines represent median functional activity, and shaded areas represent 5th and 95th percentiles.
Adapted from Zuraw BL, Cicardi M, Longhurst HJ, et al. *Allergy* 2015;70:1319-28.

infection and other risks.

Subcutaneous administration, on the other hand, reduces the "peak-to-trough ratio" and results in more consistent, sustained and higher trough values (Figure 4B). With this understanding, a multinational research team conducted a prospective, randomized, double-blind, crossover, placebo-controlled Phase III trial to evaluate prophylactic treatment with a self-administered subcutaneous delivery form of a new C1-INH product developed by CSL Behring.[17] Over consecutive 16-week periods, two groups of 45 patients self-administered placebo and C1-INH twice-weekly at a dose of either 40 IU/kg or 60 IU/kg.

The results were unprecedented. The median reduction in the number of attacks versus placebo was 88.6 percent with a 40 IU dose. There was an even higher 95.1 percent reduction with a 60 IU dose; overall, patients in the 60 IU/kg group had half as many attacks as those in the 40 IU/kg group. Fully 40 percent of patients in the higher-dose group did not experience any attacks over the 16-week treatment period, as compared with no patient who received placebo.

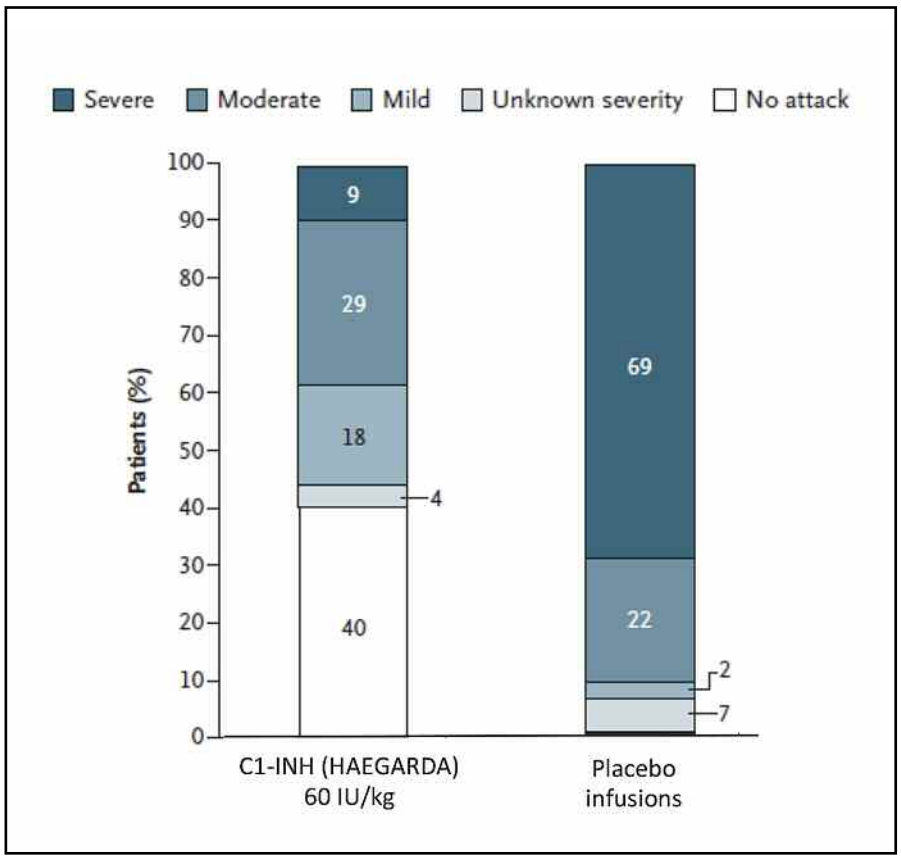
> "The approvals of six new treatments over the last nine years have transformed the management of HAE."

Additionally, the average severity of HAE attacks was dramatically lower with subcutaneous C1-INH prophylaxis than placebo treatment (Figure 5). During their C1-INH treatment period with either dose, just 13 patients had a total of 52 severe attacks, while 64 patients receiving placebo-period treatment had a total of 252 severe attacks. During the 40 IU and 60 IU C1-INH treatment periods, five and zero patients, respectively, experienced a laryngeal attack, compared to 25 patients during placebo treatment. In the 60 IU group, the use of rescue medication to treat attacks was reduced 10-fold during the C1-INH treatment period compared to the placebo treatment period (0.32 vs. 3.89 per month). There were no reported thromboembolic events or any other treatment-related serious adverse events in either C1-INH-dose group.

In June 2017, FDA approved CSL Behring's novel subcutaneous C1-INH product, brand named HAEGARDA, for routine prophylaxis to prevent HAE attacks in adult and adolescent patients.

Separately, Shire recently announced positive topline efficacy and safety results from a Phase III trial evaluating a more convenient liquid form of its own new

Figure 5. Maximum Severity of HAE Attacks During Prophylactic Treatment: Self-Administered Subcutaneous C1 Inhibitor (HAEGARDA) Versus Placebo



Adapted from Longhurst HJ, Cicardi M, Craig T, et al. *New Engl J Med* 2017;376:1131-40.

> ***The options for treatment of HAE have undergone a dramatic change... We now have safe, specific, and effective medications for both on-demand and prophylactic treatment of HAE.***
>
> ***— US Hereditary Angioedema Association Medical Advisory Board Recommendations for the Management of HAE Due to C1 Inhibitor Deficiency.***[19]

subcutaneously administered C1-INH (SHP616 Liquid). Overall, 78 percent of patients experienced a 50 percent or greater reduction in the HAE attack rate compared to placebo; 38 percent of patients were attack-free during their SHP616 Liquid treatment period, compared to 9 percent during the placebo period. No thromboembolic events or other treatment-related serious adverse events were reported.[18]

CSL Behring is sponsoring an extension study with HAEGARDA to investigate whether individual dosing adjustments can further improve treatment response in patients who continue to experience breakthrough attacks. If approved, Shire's new liquid, ready-to-use C1-INH product will be a welcomed advance for patients who must now follow multiple steps to reconstitute the product with supplied diluent and a transfer set. Additional approvals of C1-INH products for treatment of children are also anticipated in the near future.

> "Additional approvals of C1-INH products for treatment of children are also anticipated in the near future."

More Treatment Innovations in the Pipeline

The approvals of six new treatments over the last nine years have transformed the management of HAE. But the collaboration between industry and the clinical research community continues with several active initiatives that promise to further

Like hemophilia and primary humoral immunodeficiency disorders, HAE is a rare genetic disease for which replacement therapy with concentrates purified from donor plasma provides safe and highly effective treatment. Looking forward, we can expect more new human plasma-based products that effectively treat other rare genetic disorders with simple replacement of a deficient or dysfunctional blood protein. ❖

KEITH BERMAN, MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. He also serves as editor of *International Blood/Plasma News*, a blood products industry newsletter.

References

1. Gompels MM, Lock RJ, Abinum M, et al. C1 inhibitor deficiency: consensus document. *Clin Exp Immunol* 2005 Mar;139(3):379-94.
2. Gelfand JA, Sherins RJ, Alling DW, et al. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N Engl J Med* 1976;295:1444-8.
3. Cicardi M, Bergamaschini L, Tucci A, et al. Morphologic evaluation of the liver in hereditary angioedema patients on long-term treatment with androgen derivatives. *J Allergy Clin Immunol* 1983;72:294-8.
4. Frank MM, Sergent JS, Kane MA, et al. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double blind study. *N Engl J Med* 1972;286:808-12.
5. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: A broad review for clinicians. *Arch Int Med* 2001 Nov 12;161:2417-29.
6. Gadek JE, Hosea SW, Galfand JA, et al. Replacement therapy in hereditary angioedema. Successful treatment of acute episodes of angioedema with partly purified C1 inhibitor. *N Engl J Med* 1980;302;542-6.
7. Agostoni A, Bergmaschini L, Martignoni G, et al. Treatment of acute attacks of hereditary angioedema with C1-inhibitor concentrate. *Ann Allergy* 1980;44:299-301.
8. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol* 2009 Oct;124(4):801-8.
9. Berinert. CSL Behring: Full Prescribing Information, revised 9/2016. Accessed at labeling.cslbehring.com/PI/US/Berinert/EN/Berinert-Prescribing-Information.pdf.
10. KALBITOR (ecallantide). Shire: Full Prescribing Information, revised 3/2015. Accessed at www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf.
11. FIRAZYR (icatibant). Shire: Full Prescribing Information, revised 12/2015. Accessed at pi.shirecontent.com/PI/PDFs/Firazyr_USA_ENG.pdf.
12. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *New Engl J Med* 2010 Aug 5;363:513-22.
13. CINRYZE. Shire: Full Prescribing Information, revised 12/2016. Accessed at pi.shirecontent.com/PI/PDFs/Cinryze_USA_ENG.pdf
14. Bernstein JA, Relan A, Harper JR, et al. Sustained response of recombinant human C1 esterase inhibitor for acute treatment of hereditary angioedema attacks. *Ann Allergy Asthma Immunol* 2017 Apr;118(4):452-5.
15. Zuraw BL, Cicardi M, Longhurst JH, et al. Phase II study results of a replacement therapy for hereditary angioedema with subcutaneous C1-inhibitor concentrate. *Allergy* 2015 Oct;70(10):1319-28.
16. Aygören-Pürsün E, Martinexz-Saguer I, Longhurst HJ, et al. C1 inhibitor for routine prophylaxis in patients with hereditary angioedema: interim results from a European Registry study. *J Allergy Clin Immunol* 2016;137:Ab251 (abstract).
17. Longhurst H, Cicardi M, Craig T, et al. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *New Engl J Med* 2017 Mar 23;376(12):1131-40.
18. Shire's Investigational Subcutaneous C1 esterase inhibitor (C1 INH [Human]) Liquid for Injection (SHP616) Significantly Reduces Hereditary Angioedema Monthly Attack Rate Versus Placebo in a Phase 3 Pivotal Trial (news release). Accessed at www.shire.com/en/newsroom/2017/september/cwabkg.
19. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 Recommendations for the Management of Hereditary Angioedema Due to C1 Inhibitor Deficiency. *J Allergy Clin Immunol Pract* 2013 Sep-Oct;1(5):458-67.

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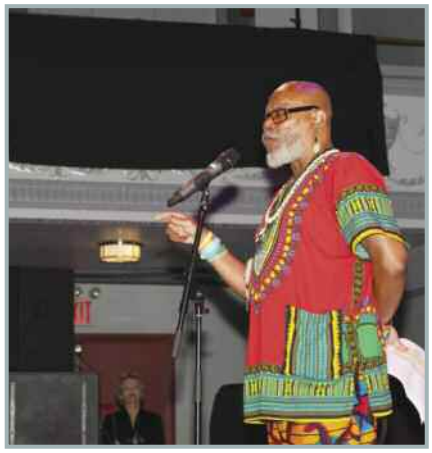


Reginald Brown was diagnosed with HIV 31 years ago and told he had two years to live. Today, he is healthy due to the lifesaving cocktail made available in 1997.

HIV in Older Adults:
A Patient's Perspective

By Trudie Mitschang

AS A COMMUNITY organizer, activist and gender nonconformist, Reginald Brown, MEd, is as outspoken as he is passionate about issues surrounding social justice and healthcare reform. The Kansas City, Kan., native graduated from the University of Kansas in 1975, and went on to teach dance and choreography in Mexico City, Amsterdam, Berlin and Athens. Brown was back in the States for a visit when he was originally diagnosed with human immunodeficiency virus (HIV), and at the time, doctors gave him two years to live. That was 31 years ago, and today, this unstoppable 65-year-old is living proof that medical breakthroughs and treatment-plan compliance make it possible to survive and even thrive with what was once a universally fatal virus.

BSTQ: Tell us about your HIV diagnosis.

Brown: I was diagnosed on Aug. 15, 1986. Although I had been living and working in Athens, Greece, I was home visiting my parents in Kansas City. Doctors told me I had two years to live, and I remember feeling like I had been punched in the stomach. When I got back to my parents' house, I immediately called an 800 support number I'd been given. I was relieved because I was talking to someone who was also HIV-positive. Today, I consider myself very fortunate because I have had no AIDS-related illnesses and have been noninfectious for 14 years thanks to the antiretroviral cocktail I take.

BSTQ: How did your HIV diagnosis impact your quality of life?

Brown: In a strange way, my diagnosis was a triple blessing. For one thing, I didn't have to worry anymore about contracting HIV. It forced me to prioritize my life and focus on what was important. It also taught me to live in the moment and appreciate life.

BSTQ: What is your treatment plan?

Brown: I take four antiretrovirals twice a day. I see my doctor every six months unless there is an issue that needs addressing. I take one pill for depression and see my psychiatrist every three months. I also take baby aspirin, Claritin for my sinuses and four cholesterol pills daily.

BSTQ: How is your health overall?

Brown: I am healthy, and my T cells are higher than they have ever been. The only issue is my high cholesterol, which may be the result of my HIV cocktail, the HIV itself or my eating habits.

BSTQ: Tell me about your relationship with your healthcare providers. Do you feel your issues are understood and addressed?

Brown: I have had three primary care physicians since my diagnosis. I was with John Montana, MD, from 1991 until 2004, when he passed away. Dr. Dalton was his backup and took over the practice. Dr. Dalton left the clinic in May last year, so now I have Dr. Sarpel. I had a fantastic relationship with my previous doctors and look forward to the same with Dr. Sarpel. It is of the utmost importance that my primary care physician is someone who I know and can question and discuss my treatment plan.

BSTQ: Are you a part of any support group?

Brown: I participated in the Friends in Deed 40 over 40 long-term survivors eight-week course because I learned there are many long-term survivors and thrivers. I took the course because I answered an email seeking 40 men over 40 who were diagnosed before 1997, the year when the lifesaving cocktail became available.

BSTQ: How do you pay for your medications, and have you had financial difficulty due to the high cost of care?

Brown: All of my medication is covered by Medicaid, and my healthcare is covered by Medicare, both of which predate the Affordable Care Act. If they cut Medicaid, my quality of life will deteriorate, which is why I've been active in "Kill the Bill" protest activities in my area.

BSTQ: How do you maintain a positive attitude?

Brown: My spirituality allows me to find a blessing in every situation. I may not be able to control what happens to me, but I can choose how I respond to it! I have determined to live no matter what because death is inevitable. I refuse to waste time being consumed by it because I am too busy living. I am still living and creating my dreams every day by the grace and mercy of my ancestors and Creator. ❖

HIV in Older Adults:
A Scientist's Perspective

MARK BRENNAN-ING, PhD, is a senior research scientist at the Brookdale Center for Healthy Aging at Hunter College, City University of New York, and an adjunct professor at the New York University Rory Meyers College of Nursing. Dr. Brennan-Ing's research focuses on psychosocial issues affecting persons living with HIV and older sexual and gender minority adults. He is past president of the State Society on Aging of New York, a fellow of the Gerontological Society of America (GSA), and past board member of the New York Association on HIV Over Fifty. He was the principal convener for GSA's HIV/AIDS and Aging interest group, a member of the American Society on Aging's LGBT Aging Information Network Leadership Council, and 2016 chair of the American Psychological Association's Committee on Sexual Orientation and Gender Diversity. Dr. Brennan-Ing was the lead editor on the seminal book on aging with HIV published in 2009 titled *Older Adults with HIV: An In-Depth Examination of an Emerging Population*, and the 2016 volume of *HIV and Aging: Interdisciplinary Topics in Gerontology and Geriatrics*.

BSTQ: What physical, psychological and social impacts does HIV have on older adults?

Dr. Brennan-Ing: Biologically, HIV causes changes in the immune system and is associated with chronic inflammation, both of which are associated with greater incidence of age-related comorbidities that exacerbate declines in immune function associated with aging (i.e., immunosenescence). Psychologically, people aging with HIV have much higher rates of depression compared with noninfected adults, which is associated with treatment nonadherence and greater functional disability. Socially, older adults with HIV often lack the informal social support networks of family and friends that most other older adults rely on for caregiving and other types of assistance needed to remain independent in the community. Unfortunately, there are very few programs and services available from government, healthcare providers and community-based agencies that address the unique needs of the older HIV-positive adult.

BSTQ: What specific health issues challenge older adults living with HIV?

Dr. Brennan-Ing: The challenges of caring for the patient with HIV who is aging are similar to those of caring for other aging patients. The difference is the older adult with HIV may be confronting these issues decades earlier than their noninfected peers. The older person with HIV frequently experiences multiple comorbid conditions, leading to a greater burden of disease than among those without HIV. In fact, older people with HIV are much more likely to die from chronic conditions associated with aging than an AIDS-related condition. High levels of multimorbidity can also lead to numerous prescribed medications in addition to HIV treatment, which can result in polypharmacy and harmful drug interactions. Physicians can successfully address these issues by incorporating geriatric care principles into their practice such as using multidisciplinary care teams, involving patients and their significant others in developing a care plan, focusing on functional ability rather than trying to treat every symptom that the patient is experiencing, and employing palliative care when necessary.

BSTQ: How do age-related stigmas affect older adults living with HIV?

Dr. Brennan-Ing: HIV is still perceived as a young person's disease, and so healthcare providers may not address sexual health and risk behaviors with older patients. Nearly one in five new HIV infections in the U.S. are detected in those aged 50 years and older. And, the older you are at time of HIV diagnosis, the more likely you are to receive a dual diagnosis of HIV and AIDS. Likewise, for the person who has grown older with HIV, internalized ageism may put them at risk for poorer physical and mental health outcomes. For example, an older person with internalized ageism may ignore signs and symptoms of disease they perceive to be a "normal" part of aging, and forgo potentially helpful or even lifesaving medical treatment.

BSTQ: What advice do you have for clinicians who treat older adults living with HIV?

Dr. Brennan-Ing: Although most of the scientific literature focuses on the problems and pathologies of the older person with HIV, we need to also be mindful that many of these individuals are long-term survivors who have successfully coped and adapted to living with this once-terminal disease. There is resilience in this population, and providers should leverage the important personal and social resources that have allowed the HIV-positive adult to face the challenges of aging to maximize clinical outcomes and a decent quality of life. ❖

BeMedWise.org

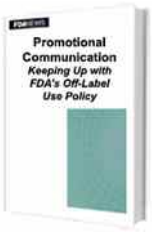
Author: National Council on Patient Information and Education (NCPIE)

NCPIE has redesigned its website to help pharmacists better deal with medication nonadherence that often leads to unnecessary disease progression, disease complications, lower quality of life and possible premature death and more serious illnesses. BeMedWise.org provides pharmacists with tips, checklists and toolkits specifically for parents, older adults, caregivers, teen influencers, the general public and others. For instance, the section on medications for older adults explains the specific ways pharmacists can help, in addition to talking to patients about their medications.

BeMedWise.org

Promotional Communication: Keeping Up with FDA's Off-Label Use Policy

Author: U.S. Food and Drug Administration (FDA)



This report explores the draft guidances and other FDA activity on the subject of promotional communication, explaining what companies must do to stay on the right side of the agency's new policies and how to take advantage of the opportunities they present. Sections include: 1) How FDA's amendments to the "intended use" regulation has changed the landscape; 2) What "consistent communications" means versus "on-label and off-label communications"; 3) The "three-factor test" for consistent communications and how it is it applied in practice; 4) How to evaluate consistent communications as "scientifically appropriate and statistically sound"; 5) What's the real-life scope of the new safe harbor for preapproval communications with payers; and 6) How the context of communications should ensure adequate disclosure of information (e.g., study designs, limitations, disclaimers, etc.).

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Merit-Based Incentive Payment System (MIPS) Online Resources

Author: Centers for Medicare and Medicaid (CMS)

CMS has added three online resources to assist physicians participating in MIPS. The MIPS Participation Fact Sheet answers some frequently asked queries about who can participate and how the rules apply to clinicians who provide healthcare in rural health clinics, federally qualified health centers and critical-access hospitals, and it explains exemptions for certain clinicians. The MIPS Improvement Activities Fact Sheet provides a discussion of the four performance categories that will affect Medicare payments: quality, clinical practice improvement activities, use of certified electronic health record technology and resource use. It also lists the nine subcategories of improvement activities from which physicians can choose, such as population management, beneficiary engagement and integration of behavioral and mental health, and then explains how to submit improvement activities, including details about reporting criteria. The third is a list of CMS-approved qualified registries, including the registry name, contact information and a breakdown of costs and services offered, as well as which reporting options, performance categories, quality measures and electronic clinical quality measures are supported for each registry option. qpp.cms.gov

The 21st Century Take on Observational Studies: Using Real-World Evidence in the New Millennium

Author: U.S. Food and Drug Administration (FDA)

This guide provides information about the opportunities and pitfalls observational studies can offer. The report looks at the growing trend toward observational research and how provisions in the 21st Century Cures Act create even more incentives to rely on real-world evidence in the development of medical products. It covers: 1) The evolution of patient-focused research; 2) How observational studies can be used in the preapproval and postmarket stages; 3) The potential for saving time and money; 4) New data sources that make observational studies a viable alternative to clinical trials; and 5) How drug- and devicemakers view observational research and how they are using it.

www.fdanews.com/products/5502

Subcutaneous Prophylaxis with Bispecific Monoclonal Antibody Reduces Bleeding Rate in Hemophilia A and Inhibitors

Findings from a multinational Phase III study involving 109 male participants with hemophilia A and inhibitors showed that once-weekly subcutaneous prophylactic administration of an investigational bispecific humanized monoclonal antibody (emicizumab; ACE910) was associated with a significantly lower rate of bleeding events than no prophylaxis. Emicizumab bridges activated factor IX and factor X to restore the function of activated factor VIII, which is deficient in persons with hemophilia A.

Participants receiving episodic treatment with bypassing agents before trial entry were randomly assigned in a 2:1 ratio to receive subcutaneous emicizumab at a dose of 3.0 mg/kg for four weeks, followed by 1.5 mg/kg thereafter (group A) or no emicizumab prophylaxis (group B). Participants who had previously received prophylactic treatment with bypassing agents — recombinant factor VIIa (NovoSeven) or activated prothrombin complex concentrate (FEIBA) or both — were assigned to emicizumab prophylaxis in group C. The primary endpoint was the difference in the rate of treated bleeding events over a period of at least 24 weeks.

The annualized bleeding rate (ABR) was 2.9 events among 35 group A participants assigned to emicizumab prophylaxis, compared to 23.3 events among 18 group B participants assigned to no prophylaxis, representing a significant difference of 87 percent favoring emicizumab prophylaxis (P<0.001).

Twenty-four participants in group C experienced a significantly lower ABR with emicizumab prophylaxis (3.3 events) than with previous bypassing-agent prophylaxis (15.7 events), a rate reduction of 79 percent (P<0.001).

Additional studies are being conducted by co-developers Hoffman-La Roche and Chugai Pharmaceutical to evaluate the pharmacokinetics, safety and efficacy of emicizumab in children with hemophilia A and inhibitors, as well as the feasibility of reduced frequency of prophylactic injections.

Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. New Engl J Med *2017 Aug 31;377(9):809-18.*

Subcutaneous Immunoglobulin Well-Tolerated and Effective in Mild to Moderate Exacerbations of Myasthenia Gravis

Canadian investigators at the University of Alberta evaluated the use of self-administered subcutaneous immune globulin (SCIG) in a prospective, open-label, Phase III crossover trial in adult patients with myasthenia gravis (MG) experiencing mild to moderate worsening of symptoms. Patients self-infused 2 g/kg of SCIG over a period of four weeks. The primary endpoint was change in quantitative MG (QMG) score from baseline to study end at six weeks. Secondary endpoints, including change in manual muscle testing (MMT), MG activities of daily living (MG-ADL) and MG composite (MGC) scores, as well as occurrence of adverse events and tolerability, were assessed.

Twenty-two of 23 patients completed the study. The QMG score decreased from 14.9 ± 4.1 to 9.8 ± 5.6, the MMT score decreased from 16.8 ± 0.5 to 5.2 ± 4.5, the MG-ADL score decreased from 9.5 ± 3.0 to 4.6 ± 3.0, and the MGC score decreased from 17.4 ± 5.0 TO 5.6 ± 4.5 (all results P<0.0001). Common adverse events included headache and injection site reactions. No serious adverse events occurred during the study.

The investigators concluded that SCIG is well-tolerated, safe and effective in mild to moderate MG exacerbations, but acknowledged that "comparative safety and efficacy must be established with randomized controlled trials."

Beecher G, Anderson D, Siddiqi ZA. Subcutaneous immunoglobulin in myasthenia gravis exacerbation: A prospective, open-label trial. Neurology *2017 Sep 12;89(11):1135-41.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective Jan. 1, 2018, through March 31, 2018

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	CARIMUNE NF	CSL Behring	J1566	$68.83	$67.73
	FLEBOGAMMA	Grifols	J1572	$67.31	$66.23
	GAMMAGARD SD	Shire	J1566	$68.83	$67.73
	GAMMAPLEX	BPL	J1557	$77.62	$76.37
	OCTAGAM	Octapharma	J1568	$71.18	$70.04
	PRIVIGEN	CSL Behring	J1459	$76.96	$75.73
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$76.60	$75.37
	GAMMAKED	Kedrion	J1561	$81.41	$80.10
	GAMUNEX-C	Grifols	J1561	$81.41	$80.10
SCIG	CUVITRU	Shire	J1555	$137.89	$135.68
	HIZENTRA	CSL Behring	J1559	$98.31	$96.73
	HYQVIA	Shire	J1575	$140.63	$ 138.37

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

** CUVITRU does not yet have Medicare rates.

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	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	3 years 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	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

* Age indication per package insert is ≥5 years; however, the Advisory Committee on Immunization Practices recommends Afluria not be used in children aged 6 months through 8 years because of increased reports of febrile reactions in this age group. If no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5-8 years who has a medical condition that increases the child's risk for influenza complications, Afluria can be used; however, providers should discuss with the parents or caregivers the benefits and risks of influenza vaccination with Afluria before administering this vaccine.

Afluria may be used in persons aged ≥9 years.

** 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.

*** For the Advisory Committee on Immunization Practices' latest intranasal influenza vacccine recommendations, please visit www.cdc.gov/vaccines/acip/index.html.

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