WINTER 2017

biosupply trends

QUARTERLY

SPECIAL FOCUS:
INTEGRATED CARE

Therapeutic Discoveries

Lighting the Way to Treating More Patients

WHAT'S BEHIND THE RISE IN
IVIG Demand

HEALTHCARE CRISIS 2030:
Caring for Aging Baby Boomers

INTERVENTIONS IN
Adult Cancer Cachexia

Gene Therapy for SCID p.46

8 Critical Steps

Purchasing

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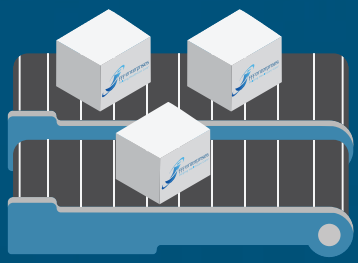

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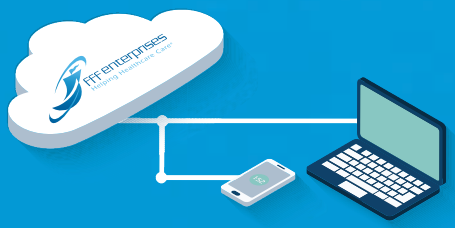

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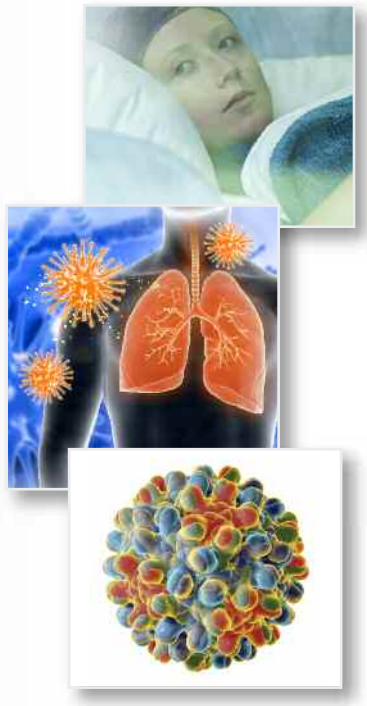

Up Front

BioTrends Watch

BioFocus

BioSources

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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Discoveries in Treatment and Illness Prevention

Increases in chronic illnesses and comorbidities affecting a growing number of populations for whom prevention and treatment are oftentimes puzzling are shaping scientific advancements. Scientists are making discoveries that are leading to prevention and better treatments. And, clinicians are discovering new approaches to improving delivery of health services so clients receive a continuum of preventive and curative services.

Indeed, scientific discovery is an important element in determining for whom a particular therapy is appropriate. This has been especially true over the past several decades for intravenous immune globulin (IVIG) therapy. As our article "Going Up: What's Behind the Growth in IVIG Demand" explains, IVIG treatment in the U.S. has grown 5 percent annually since the 1990s, with approved indications accounting for only one-third of its usage. The reason: While it has been observed to work in treating immune-mediated conditions, IVIG has also, inexplicably, been shown to have therapeutic effects for a growing number of other conditions, most predominantly autoimmune disorders. And, a host of additional ongoing clinical studies are beginning to shed light on how IVIG may help many more patients in the future.

Scientific research is also contributing to the treatment of a skyrocketing number of patients with cancer who succumb to cachexia, which is implicated in 20 percent to 30 percent of their deaths. As noted in our article "Interventions in the Treatment and Prevention of Adult Cancer Cachexia," studies are starting to better explain the causes of cancer cachexia, one of which is the administration of chemotherapy, which prevents treatment of the cancer itself. Thankfully, researchers from across the world are focusing their efforts on developing promising pharmacologic, nutrition and exercise treatment options, which may help prolong cancer patients' lives.

Gene therapy is on the forefront of prolonging lives of patients with many different diseases. In this issue, we look at how it is finally helping to save infants born with severe combined immunodeficiency (SCID). "Toward the Ultimate Cure: Gene Therapy for Severe Combined Immunodeficiency" highlights research that shows how the more than 75 percent of babies born with SCID who don't have an HLA-identical sibling donor can now survive.

On the other end of the spectrum, populations continuing to grow and age put clinicians at the leading edge of dealing with an increased number of age-related illnesses. This is especially true today for the baby boomer generation with members 65 and older forecast to increase by 73 percent in the next decade and a half. In our article "Health Crisis 2030," we look at the types of illnesses that will affect this generation, most notably dementia and other chronic conditions, and the healthcare paradigm shift needed to promote patient-centered care coordination.

Healthcare professionals also play a critical role in curtailing the rising opioid addiction epidemic, which has resulted in an unprecedented number of overdose deaths. Our article "Opioid Addiction: Is There a Solution?" shows there may be hope. Fortunately, government and healthcare organizations are collaborating to develop prescribing guidelines, and clinicians and patients are recognizing that treatment may require a combination of drug-related and recovery program options.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly* that includes many more articles on prevention and treatment discoveries, and find it both relevant and helpful to your practice.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

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

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CMS Adopts Four Options to Comply with MACRA

In response to concerns by physicians and other clinicians about their readiness to comply with the Medicare Access and CHIP Reauthorization Act (MACRA), which began Jan. 1, the Centers for Medicare and Medicaid Services (CMS) has revised implementation requirements by adopting four options that will allow providers to choose the level and pace at which they comply. The first option allows providers to avoid a negative payment adjustment in order to ease providers into broader participation. The second option allows providers to submit data for a reduced number of days, with their first performance period beginning later than Jan. 1 while still qualifying for a small payment if data is submitted about how the practice is using technology and improving. The third option, which is for practices that are ready, is to begin on Jan. 1 within the provisions of the Act. And, the final option is to participate in an advanced alternative payment model such as a Medicare Shared Savings accountable care organization.

"The action that the administration announced today will help give physicians a fair shot in the first year of MACRA implementation. This is the flexibility that physicians were seeking all along," said Andrew Gurman, MD, president of the American Medical Association. ❖

HHS Selects Physician Groups for Cancer Care Initiative

The U.S. Department of Health and Human Services (HHS) has selected nearly 200 physician group practices and 17 health insurance companies to participate in a care delivery model that supports and encourages higher quality and more coordinated cancer care. The Medicare arm of the Oncology Care Model, which began July 1, 2016, and runs through June 30, 2021, includes more than 3,200 oncologists and will cover approximately 155,000 Medicare beneficiaries.

This is one of the first Centers for Medicaid and Medicare Services (CMS) physician-led specialty care models that encourages practices to improve care and lower costs through episodic and performance-based payments that reward high-quality patient care. Under the model, physician practices may receive performance-based payments for episodes of care surrounding chemotherapy administration, as well as a monthly care management payment for each beneficiary, with an emphasis on person-centered care.

Practices participating in the model will provide treatment following nationally recognized guidelines that include enhanced services such as coordinating appointments with providers within and outside the oncology practice to ensure timely delivery of diagnostic and treatment services; providing 24/7 access to care when needed; arranging for diagnostic scans and follow-up with other members of the medical team such as surgeons, radiation oncologists and other specialists that support the beneficiary through their cancer treatment; making sure data from scans, blood test results and other tests are received in advance of patient appointments so that patients don't need to schedule additional visits; and providing access to additional patient resources such as emotional support groups, pain management services and clinical trials.

"CMS is thrilled with how many physician groups chose to be a part of the Oncology Care Model," said Patrick Conway, MD, MSc, principal deputy administrator and chief medical officer. "We have nearly doubled the number of participants that we anticipated. It's clear that oncology physicians recognize the importance of this new performance-based, episode-based payment approach to cancer care. As a practicing physician and son of a Medicare beneficiary who died from cancer, I know the importance of well-coordinated care focused on the patient's needs." ❖

CMS Finalizes ACO Cost Target Changes

In June, the Centers for Medicare and Medicaid Services (CMS) finalized changes to how it evaluates whether Medicare accountable care organizations (ACOs) are saving money. The changes came in response to complaints that the program was harder for efficient providers because they had to compete against their own success. To combat this, one change adjusts cost benchmarks based on regional rather than national spending data when an ACO signs up for a second or subsequent three-year contract period.

Another change encourages ACOs to switch to more aggressive tracks. Currently, 434 ACOs are in tracks that allow them to earn bonuses for meeting cost and quality targets without risking penalties if they fall short. Under this change, ACOs are allowed to extend their initial agreement for one year before taking on financial risk. In addition, ACOs now have up to four years to challenge the initial determination of shared savings or shared losses.

"Today's changes will encourage more physicians to improve patient care by joining ACOs, while also refining how the program measures success so that current participants are better rewarded for quality," said CMS acting Administrator Andy Slavitt.

CMS will phase in the changes for ACOs entering contract periods beginning on or after Jan. 1, 2017. However, ACOs that entered the program in 2012 or 2013 won't be able to take advantage of the new benchmarking change until they enter a new agreement in 2019. ❖

HHS Issues Final Rule to Overhaul Managed Medicaid

In the first overhaul of managed care in Medicaid and the Children's Health Insurance Program (CHIP), the Department of Health and Human Services (HHS) issued a final rule in an effort to deliver better care, smarter spending and healthier people. The rule will affect Medicaid managed care plans and the beneficiaries enrolled in them, including low-income children and families, pregnant women, elderly and individuals with disabilities.

The final rule has four goals: 1) supporting states' efforts to advance delivery system reform and improvements in quality of care for Medicaid and CHIP beneficiaries; 2) strengthening the consumer experience

of care and key consumer projections; 3) strengthening program integrity by improving accountability and transparency; and 4) aligning rules across health insurance coverage programs to improve efficiency and help consumers who are transitioning between sources of coverage. In addition, the rule establishes Medicaid's first Quality Rating System and clarifies states' authority to enter into contracts that pay plans for quality or encourage participation in alternative payment models and other delivery system reform efforts. And, it establishes network adequacy standards in Medicaid and CHIP managed care for key types of providers, while leaving states flexibility to set the actual standards.

Provisions of the rule will be implemented in phases over the next three years, starting on July 1, 2017. More information about the rule can be found at www.medicaid.gov/medicaid-chip-program-information/by-topics/delivery-systems/managed-care/managed-care-site.html. ❖

HHS Awards Millions to Improve Healthcare

In June, the Department of Health and Human Services (HHS) awarded nearly $156 million in funding to support 420 health centers in 47 states, the District of Columbia and Puerto Rico to increase access to integrated oral healthcare services and to improve oral health outcomes for Health Center Program patients. The funding will provide enough money to hire approximately 1,600 new dentists, dental hygienists, assistants, aides and technicians to treat nearly 785,000 new patients.

Then, in September, HHS awarded more than $87 million for IT enhancements in 1,310 health centers in every U.S. state, the District of Columbia, Puerto Rico, the Virgin Islands and the Pacific Basin. The funding will support health information technology enhancements to accelerate health centers' transition to value-based models of care, improve efforts to share and use information to support better decisions, and increase engagement in delivery system transformation. To support those goals, all purchases or upgrades of electronic health record systems made with the funding must use technology that is certified by the Office of the National Coordination for Health Information Technology. ❖

Bundled Payments

With the fiscal year 2017 inpatient prospective payment system and outpatient prospective payment system (OPPS) rules implemented Oct. 1 and Jan. 1, respectively, virtually all payers are steadily and quickly marching forward. And, since many payers model the Centers for Medicare and Medicaid Services (CMS) reimbursement program, understanding the changes is crucial. This column focuses on bundling, or packaging payments, under the new rules. CMS defines bundling as an all-inclusive Medicare payment for common tests, procedures and drugs, rather than paying for the components separately. Bundling comes into play in several scenarios, and it has been a part of CMS' payment strategy for several years.

> "Bundled shared-risk arrangements become high-risk propositions if care coordination, clinical protocols and information systems are not aligned across all providers and sites of care."

Bundles range from simple ones involving packaging of payment, to very complex models crossing over many service lines and patient care locations. To be successful, bundled payment models depend on the hospital's ability to create tight networks of post-acute care locations and doctors who provide quality care. Bundled shared-risk arrangements become high-risk propositions if care coordination, clinical protocols and information systems are not aligned across all providers and sites of care. In all cases, hospitals are responsible for paying for the bundles, with payments dependent on the data fed into claims, IT and analytics systems. Therefore, awareness of who is responsible for what and how bundled payments are divided/allocated to cost centers at facilities is essential. And, because bundled payments are based on cumulated claims data, telling patients' stories completely and accurately with correct International Statistical Classification of Diseases and Related Health Problems (ICD)-10, current procedural terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes is one of the most vital steps for preparing bundled payments.

CMS Mandatory Bundled Payment Programs: Defined Episodes of Care

Bundled payments for knee and hip replacements. On April 1, 2016, CMS changed the way it pays hospitals for knee and hip replacements "because they are the most commonly performed Medicare inpatient surgeries and are expected to continue to grow as the population ages."[1] This mandatory program for 67 select geographic markets currently includes major replacement for lower joint and surgical hip/femur fracture treatment, with expansion to other conditions such as surgical hip and femur fracture episodes being evaluated. Under the program, Medicare either penalizes hospitals by requiring them to partly repay the government if patients get avoidable infections and/or have other complications. Or, it rewards them with extra payments that are determined based on a composite quality score if patients do well. In addition, surgeries are treated as one complete service instead of a collection of services, which means hospitals bear the risk and are held accountable for care while patients are in post-acute facilities and for up to 90 days after discharge.

Cardiac care bundles. CMS has proposed mandatory bundled payments for cardiac care beginning July 1.[2] The proposal, to be phased in over a five-year period in 98 randomly selected metropolitan areas across the country, would hold hospitals accountable for the cost and quality of care for acute myocardial infarction and coronary artery bypass graft episodes in patients both during their hospital stay and for the first 90 days after discharge. Similar to the joint replacement program, a composite quality score would determine savings eligibility and lowered discount rates.

It should be noted that there may be overlap in required hospital participation in both programs.

Observation Patients: Packaged Payment

The Notice of Observation Treatment and Implication for Care Eligibility Act (H.R. 876) requires hospitals to provide Medicare beneficiaries who receive more than 24 hours of outpatient observation services with easy-to-understand written

notification and a related verbal explanation at discharge or within 36 hours, whichever is sooner, that states why they are receiving outpatient observation care and the potential financial implications. Unfortunately, this rarely happens, and most patients are shocked when they receive their medical bills. Medicare covers outpatient care expenses only if the inpatient stay is at least three consecutive days, not counting observation days. Therefore, those admitted for observation often must cover the cost if they need additional care at a skilled nursing facility.

In addition, the act creates a new observation comprehensive ambulatory payment classification (C-APC). Virtually all associated services (emergency room visit, labs, radiology, infusions and injections) are included in this proposed payment of $2,111 with a new status indicator, J2.[3]

CMS Policy Packaged Drugs, Biologicals and Radiopharmaceuticals

CMS has finalized its proposal to continue the C-APC payment methodology made effective in 2015 that makes a single, all-inclusive prospective payment based on the cost of all individually reported codes packaged into the C-APC. These codes may include those for the provision of the primary service and all adjunctive services that support the primary service. While CMS is continuing to pay for the codes reported, payment is not separate for each, but is instead bundled into the packaged payment for the C-APC.

From a pharmacy perspective, those that are packaged, regardless of cost, include diagnostic radiopharmaceuticals; contrast agents; stress agents; anesthesia drugs; drugs, biologicals and radiopharmaceuticals that function as supplies when used in a diagnostic test or procedure; and drugs and biologicals that function as supplies when used in a surgical procedure.

This year, CMS has proposed 25 new C-APCs within 12 clinical families be paid under the policy created by the Notice of Observation Treatment and Implication for Care Eligibility Act discussed above. These packaged payments will include ancillary services that are integral, supportive or adjunctive to, or dependent on, a primary service, with a proposed payment of $2,111 and the new status indicator, J2.[3]

CMS Packaged Drugs Based on Cost

Each year, the OPPS sets a threshold and packages some non-pass-through drugs based on cost into the APC or service payment covering the visit in which they were administered. The threshold for 2017 rose to $110 per day from $95 per day in 2016. This means CMS will not pay separately for drugs costing less than $110 per day, but will reimburse them in a packaged payment. While CMS will pay separate fees for the administration of these drugs even if they are not separately paid for, intravenous (IV) drug administration fees are not paid if no drug is billed. All drugs and biologicals must be ordered, documented as given and billed for even if they are not separately payable. This is crucial because claims ask for reimbursement and provide data. Missing drug data leads to an erroneous assumption none was given and to a misrepresentation of actual treatment and its cost.

Drug Administration Fees

Although the drug administration fee packaging category is one of the first defined by CMS, it remains one of the least understood. Services included in the CPT IV drug administration codes are use of local anesthesia; starting the IV; accessing the IV, catheter or port; routine tubing, syringe and supplies; preparation of drug; flushing at completion; and hydration fluid.

Several changes to the 42 HCPCS codes that describe drug administration services are proposed, ranging from negligible changes of less than 1 percent to a 95 percent increase for three codes (96360, 96373, 96374) and a 43 percent decrease for two codes (96401, 96411).

A Philosophical Shift

The philosophical shift in healthcare payment reform is moving away from fee-for-service to a variety of models, including bundled payments that pay for value. An underlying theme is collaboration between providers and service locations with open communication and sharing of information. As costs rise astronomically for both routine maintenance medications and new specialty drugs, including immunotherapy and biologic classes, the payer also rises to a new level of importance. As we enter 2017 and a new outpatient payment year, bundling is an issue all facilities must monitor. ❖

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.

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1. CMS Proposes Major Initiative for Hip and Knee Replacements. U.S. Department of Health and Human Services press release, July 9, 2016. Accessed at goo.gl/ZurYux.
2. Medicare Program; Advancing Care Coordination Through Episode Payment Models (EPMs); Cardiac Rehabilitation Incentive Payment Model; and Changes to the Comprehensive Care for Joint Replacement Model (CJR). Centers for Medicare & Medicaid Services Proposed Rule. Accessed at tinyurl.com/zf6tta8.
3. Department of Health and Human Services. *Federal Register*, Vol. 80, No. 130, July 8, 2015. Accessed at tinyurl.com/npbzwf5.

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.

Medicines

FDA Approves Sandoz's Erelzi as Biosimilar to Amgen's Enbrel

The U.S. Food and Drug Administration (FDA) has approved Erelzi (etanercept-szzs), the first biosimilar etanercept, for all indications included in the reference product's label, including rheumatoid arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis and polyarticular juvenile idiopathic arthritis. This is the third of four biosimilars approved in the U.S. and the second manufactured by Sandoz.

FDA approval is based on a comprehensive package of analytical, nonclinical and clinical data confirming that Erelzi is highly similar to the U.S.-licensed reference product, Amgen's Enbrel. Clinical studies included four comparative pharmacokinetic studies in 216 healthy volunteers and a confirmatory efficacy and safety similarity study in 531 patients with chronic plaque psoriasis. Extrapolation to all indications approved for use on the reference product label is on the basis that the Sandoz biosimilar etanercept and the reference product are essentially the same.

"We continue to increase patient access to key treatment options by expanding our offering of biosimilars, which helps to reduce costs within the healthcare system," said Carol Lynch, global head of biopharmaceuticals for Sandoz. "Sandoz is proud to have developed two of the [four] biosimilars that are currently FDA-approved, which further demonstrates our commitment to U.S. patients in a growing number of therapeutic areas. We are committed to bringing Erelzi to the U.S. market as soon as possible."

An application for Sandoz biosimilar etanercept was accepted by the European Medicines Agency in the fourth quarter of 2015 and is currently undergoing review. ❖

FDA Approves Sandoz Erelzi to Treat Multiple Inflammatory Diseases. Sandoz press release, Aug. 30, 2016. Accessed at www.sandoz.com/media_center/press_releases_news/global_news/2016-08-30-fda-approves-sandoz-erelzi.shtml.

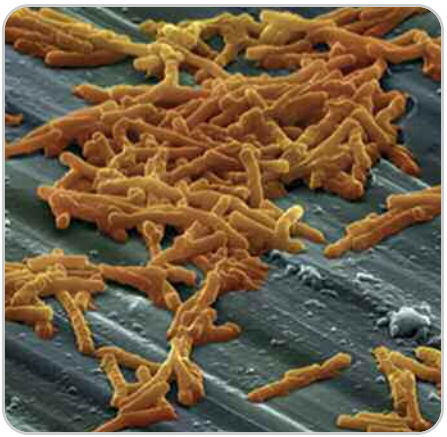
Medicines

Approval Recommended for Zinplava to Prevent Recurrence of C. Diff

In October, the U.S. Food and Drug Administration approved bezlotoxumab (Zinplava, Merck) to prevent the recurrence of Clostridium difficile (C. diff) infection (CDI) in patients aged 18 years and older. The recommendation was given despite the fact that Cheryl Dixon, PhD, a statistical reviewer at the FDA's Center for Drug Evaluation and Research, disagreed with Merck's analysis of the study end points. According to Dixon, there was "concern as to whether the efficacy of bezlotoxumab for the prevention of CDI recurrence has been adequately demonstrated." Instead, in a 10-5 vote with one abstention, the FDA's Antimicrobial Drugs Advisory Committee found that Merck "provided substantial evidence of safety and effectiveness" that a novel treatment — a human immunoglobulin G monoclonal antibody — prevented CDI recurrence.

The disagreement concerned the primary end points of the phase III MODIFY I and MODIFY II studies. FDA reviewers wrote that global cure rate would be a more relevant endpoint than infection recurrence rates, which were the primary endpoints of both MODIFY studies.

The Centers for Disease Control and Prevention (CDC) has declared C. diff an urgent public health threat, causing an estimated 500,000 infections in the U.S. in 2011, 29,000 of whom died within 30 days of initial diagnosis. About 83,000 patients who develop CDI experience at least one recurrence. Antibiotic therapy is the standard of care for CDI, but it does not prevent recurrence of the disease. In fact, 40 percent of patients who have a recurrence experience another, and after two recurrences, the likelihood of an additional episode increases as high as 65 percent, said Donnette Staas, PhD, director of regulatory affairs at Merck. Bezlotoxumab, which is not an antibiotic,



binds to the C. diff toxin B and would be given with standard-of-care antibiotics that are used to treat C. diff. It could be given as a single infusion any time during antibiotic therapy.

FDA is not bound by the committee's recommendation but takes its guidance into consideration for its review. ❖

Medicines

Vaccine for Lung Cancer Approved for Clinical Trial

A lung cancer vaccine developed in Cuba has been approved by the U.S. Food and Drug Administration (FDA) for a clinical trial at Roswell Park Cancer Institute in Buffalo, N.Y. The three-year trial of CimaVax, a form of immunotherapy, began in November and was expected to involve between 60 and 90 adult patients with stage IIIB or stage IV non-small cell lung cancer. It will be tested in combination with Opdivo, an immunotherapy drug, which is already approved in the U.S., to see if pairing improves effectiveness.

Developed by Cuba's Center for Molecular Immunology, CimaVax-EGF has been approved by a number of countries, including Paraguay and Peru. To date, more than 4,000 lung cancer patients have received the vaccine and have shown a significantly higher rate of survival, better quality of life and overall tumor stabilization. ❖

De Graaf M. A Vaccine for Lung Cancer? FDA Approves Clinical Trial for Groundbreaking Jab Created in Cuba. *DailyMail*, Oct. 27, 2016. Accessed at www.dailymail.co.uk/health/article-3879388/A-vaccine-lung-cancer-FDA-approves-clinical-trial-groundbreaking-jab-created-Cuba.html.

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Research

IDELVION Prevents Bleeds and Reduces Drug Consumption in Hemophilia B Patients

Results from the Phase III PROLONG-9FP ongoing extension clinical development program evaluating the long-term efficacy and safety of IDELVION (coagulation factor IX [recombinant], albumin fusion protein) showed that extended prophylaxis treatment regimens effectively prevented bleeds while also reducing overall IDELVION consumption. "These new data corroborate findings from the pivotal Phase III trials from PROLONG-9FP and demonstrate that IDELVION prophylaxis maintains robust efficacy and safety over time in pediatric and adult patients living with hemophilia B," said Elena Santagostino, MD, PhD, professor in the medical school of clinical and experimental hematology at the University of Milan/IRCCS Maggiore Hospital and lead investigator of the program. "Interim results from the extension study are promising and suggest that extended treatment intervals of up to 10 days and 14 days are achievable in children younger than 12 years old with hemophilia B, and even more prolonged treatment intervals of up to 21 days are conceivable for older patients."

IDELVION, manufactured by CSL Behring, was approved by the U.S. Food and Drug Administration in March, in the European Union in May and in Canada in January 2016. In the U.S., IDELVION is indicated for children and adults with hemophilia B for routine prophylaxis to prevent or reduce the frequency of bleeding episodes, on-demand control and prevention of bleeding episodes, and the perioperative management of bleeding (around the time of surgery). ❖

CSL Behring Presents Phase III Data for IDELVION for Hemophilia B at the World Federation of Hemophilia 2016 World Congress. CSL Behring press release, July 26, 2016. Accessed at finance.yahoo.com/news/csl-behring-presents-phase-iii-140000723.html.

Research

GSK's Shingles Vaccine Effective in Adults 70-Plus Years Old

A randomized Phase III study (ZOE-70) of GlaxoSmithKline's investigational shingles vaccine, Shingrix, showed 90 percent efficacy in adults aged 70 years and older that is maintained for at least four years. The high efficacy is in line with results of the ZOE-50 trial, a study in people over 50 years old that showed 97 percent efficacy.

In the randomized, observer-blind, placebo-controlled, multicenter trial that started in August 2010 in parallel with the ZOE-50 trial, more than 14,800 adults aged 70 years and older were given two doses of Shingrix intramuscularly two months apart. The primary objective was overall vaccine efficacy against shingles compared to placebo. The risk of serious adverse events, potential immune-mediated diseases or deaths observed was similar in people receiving Shingrix and placebo. The most commonly reported local adverse reaction was pain at the injection site, and the most frequently reported systemic adverse reaction was fatigue. The majority of injection site and systemic reactions occurred within seven days of vaccination, with most lasting one to three days, and generally were mild to moderate in intensity.

A pooled analysis of data from the ZOE-70 and ZOE-50 trials showed that the candidate vaccine effectively reduced the risk of subsequent chronic neuropathic pain, also known as postherpetic neuralgia (PHN), which is the most common, and often severe, complication of shingles. Shingrix was shown to be 89 percent effective in preventing PHN in people aged 70 years and older and 91 percent effective in people aged 50 years and older. ❖

GSK's Candidate Shingles Vaccine Shows High Efficacy Against Shingles and Its Complications in Adults Aged 70 Years and Over in Phase III Study Published in NEJM. GlaxoSmithKline press release, Sept. 14, 2016. Accessed at us.gsk.com/en-us/media/press-releases/2016/gsk-s-candidate-shingles-vaccine-shows-high-efficacy-against-shingles-and-its-complications-in-adults-aged-70-years-and-over-in-phase-iii-study-published-in-nejm.

Medicines

FDA Approves Amgen's Amjevita as a Biosimilar to Humira

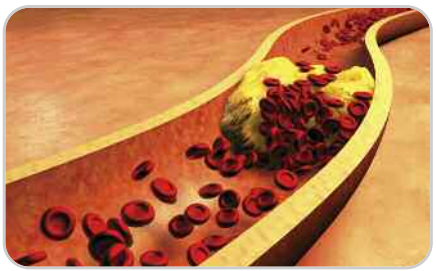
The U.S. Food and Drug Administration (FDA) has approved Amgen's Amjevita (adalimumab-atto) as a biosimilar to Humira (adalimumab) for the treatment of moderately to severe rheumatoid arthritis, active psoriatic arthritis, active ankylosing spondylitis, moderately to severely active Crohn's disease, moderately to severely active ulcerative colitis and moderate to severe plaque psoriasis. Amjevita is also indicated for moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years and older. FDA approval is based on review of evidence that demonstrates Amjevita is biosimilar to Humira. The most serious known side effects with the drug are infections and malignancies, and the most common expected adverse reactions are infections and injection site reactions.

"This is the fourth FDA-approved biosimilar," said Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research. "The biosimilar pathway is still a new frontier and one that we expect will enhance access to treatment for patients with serious medical conditions." ❖

FDA Approves Amjevita, a Biosimilar to Humira. U.S. Food and Drug Administration press release, Sept. 23, 2016. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm522243.htm.

Medicines

Sandoz Launches Generic Version of Crestor



In July, Sandoz announced the U.S. market introduction of rosuvastatin calcium tablets, a generic version of Crestor by AstraZenica Pharmaceuticals LP. In adults, rosuvastatin calcium tablets are used along with diet to lower the level of LDL, increase the level of HDL and/or lower the level of triglycerides. They are used to treat adults who cannot control their cholesterol levels by diet and exercise alone. It is not known if rosuvastatin calcium tablets are safe and effective in people with Fredrickson Type I and V dysplipidemias. Sandoz will market the tablets in 5, 10, 20 and 40 mg strengths. ❖

Sandoz Launches Generic Version of Crestor. Sandoz press release, July 21, 2016. Accessed at www.us.sandoz.com/mediacentre/news/news_20160721.shtml.

Medicines

Drug to Treat Autoimmune Hemolytic Anemia Granted FDA Orphan Drug Status

True North Therapeutics' TNT009 for the treatment of autoimmune hemolytic anemia, including cold agglutinin disease (CAD), has been granted orphan drug status by the U.S. Food and Drug Administration (FDA). TNT009 is currently in clinical development for the treatment of CAD, an autoimmune hemolytic anemia in which autoantibodies target and destroy red blood cells, causing anemia, fatigue and potentially fatal thrombosis. The prevalence of primary CAD is approximately 16 per million, and there are limited treatment options available.

TNT009 is a first-in-class monoclonal antibody that selectively inhibits the classical complement pathway by targeting C1s, a serine protease within the C1-complex in the complement pathway of the immune system, thus preventing downstream disease processes involving phagocytosis, inflammation and cell lysis. It has a unique mechanism of action and high target specificity that selectively inhibits disease processes in the classical complement pathway while maintaining the immune surveillance provided by the alternative complement pathway and lectin complement pathway.

"Receiving both U.S. and EMA [European Medicines Agency] Orphan Drug designation for TNT009 is an important milestone in the development of much-needed new treatment options for patients with CAD," said Nancy Stagliano, PhD, chief executive officer of True North. "We look forward to continuing development of TNT009 for CAD and reporting additional Phase 1b clinical data when available." ❖

True North Receives U.S. FDA Orphan Drug Status for TNT009 to Treat Haemolytic Anemia Including CAD. Pharmabiz.com, Oct. 15, 2016. Accessed at www.pharmabiz.com/NewsDetails.aspx?aid=98123&sid=2.

Research

FDA Approves First Human Trial of a Zika Vaccine

The U.S. Food and Drug Administration has approved the first human trial of an experimental Zika virus vaccine. Developed by Inovio Pharmaceuticals and GeneOne Life Science, the DNA-based vaccine known as GLS-5700 will be given to 40 people in a Phase I trial that began in July. Preclinical data from animal studies suggested that the vaccine could include a strong immune response that might protect against mosquito-transmitted Zika. The human study, however, will not test how effective the vaccine is at fighting the Zika virus. Instead, the trial will test the vaccine's safety and appropriate dosage levels. If found to be safe, larger trials of the vaccine will test its efficacy, and those will take years to complete. ❖

Mole B. First Experimental Zika Vaccine Gets Nod from FDA, Moves to Human Trials. *Ars Technica*, June 20, 2016. Accessed at arstechnica.com/science/2016/06/first-experimental-zika-vaccine-gets-nod-from-fda-moves-to-human-trials.

Research

Study Finds Influenza Vaccine's Effectiveness Can Be Improved

Research conducted at the University of Texas at Austin found that how the influenza (flu) vaccine produces antibodies to protect against disease could be used to improve the vaccine. The findings are made possible by new technology, known as Ig-Seq, that is the first and only approach able to directly identify and quantify antibodies that are present in human blood. While there are clinical tests to help determine whether a patient has antibodies that recognize a pathogen, they are not able to determine the number, molecular identities and amounts of the different antibodies that recognize the pathogen. Identifying and quantifying antibodies is important because they allow scientists to see how the vaccine stimulates the immune system to induce the production of antibodies that may then protect against infection.

During the four-year study led by a professor in the Cockrell School of Engineering and in the College of Natural Sciences, along with a team of 34 researchers from various institutions, the serum antibody repertoire in young adults before and after seasonal flu vaccination was evaluated. Researchers discovered that after vaccination, only about 40 percent of the influenza-specific antibodies were elicited directly in response to the vaccine. The remaining 60 percent were antibodies already present due to previous exposure or earlier circulating viruses or vaccines. They also discovered a new class of antibodies that are remarkably proficient in protecting laboratory mice against lethal challenge by influenza, yet unexpectedly do not block the virus from infecting cells. This last finding is important because all current metrics of influenza vaccine efficacy depend solely on the ability of serum to block infection and do not take into account the effect of antibodies that can protect against disease via alternate mechanisms. "In order to develop a better vaccine, you need to have a more precise, better understanding of the current vaccine's efficacy, and to do that, you need to identify the individual antibodies that specifically bind to influenza, understand how they protect from disease and measure how long they can persist in circulation" said Jiwon Lee, a Cockrell School chemical doctoral student and first author of the study's article.

Also during the study, the researchers investigated the relative benefits of the trivalent influenza vaccine compared with the quadrivalent vaccine, and found that about 90 percent of the antibodies elicited by one of the viruses in the trivalent vaccine also bind to the fourth virus that is now included in the newer vaccine. This raises the question of whether the adaption of the more complex quadrivalent vaccine confers an improved benefit. ❖

Flu Vaccine's Effectiveness Can Be Improved, New Findings Suggest. University of Austin, Nov. 15, 2016. Accessed at www.eurekalert.org/pub_releases/2016-11/uota-fve111516.php.

Medicines

Dusquetide Granted Orphan Drug Status to Treat Life-Threatening Immune Disorder

The U.S. Food and Drug Administration (FDA) granted orphan drug designation to dusquetide (SGX942, Soligenix) for the treatment of macrophage activation syndrome (MAS), a life-threatening complication of rheumatic disease. MAS is characterized by pancytopenia, liver insufficiency, coagulopathy and neurologic symptoms due to widespread hemophagocytosis and cytokine overproduction caused by the activation and uncontrolled proliferation of T lymphocytes and well-differentiated macrophages. MAS occurs much more frequently in patients with systemic juvenile idiopathic arthritis, but is also seen in

systemic lupus erythematosus, Kawasaki disease, adult-onset Still's disease and other vasculitis syndromes, with a mortality rate of approximately 10 percent to 20 percent.

Dusquetide is a novel innate defense regulator that acts to modulate the immune system to accelerate bacterial clearance, resolving tissue damage and controlling inflammation following exposure to bacterial pathogens, trauma, radiation and/or chemotherapy. The FDA designation was given after preclinical efficacy and safety data in animal models showed that dusquetide reduces pancytopenia and IL-12 responses and improves body weight maintenance. ❖

Eslava-Kim L. FDA Designates Dusquetide Orphan Drug for Life-Threatening Immune Disorder. MPR, Aug. 16, 2016. Accessed at www.empr.com/drugs-in-the-pipeline/investigational-muscle-protein-designated-orphan-drug-for-dmd/article/516167.

Research

Phase II Trial Launched of AAT for the Prevention of Lung Transplant Rejection

Kamada has initiated a Phase II clinical trial with its proprietary Alpha-1 Antitrypsin (AAT) for the prevention of lung transplant rejection. The trial is a randomized, open-label, single-site study of 30 lung transplant recipients to evaluate the safety and efficacy of intravenous (IV) AAT in addition to standard-of-care (SOC) versus SOC. Twenty patients will receive IV AAT treatment every other day for 14 days and then once every two weeks until week eight when they will receive monthly treatments. The 10 other patients will be treated with SOC, which includes systemic corticosteroids and immunosuppressants. Following one year of AAT treatment, there will be a one-year follow-up. The primary endpoints of the study include safety and tolerability, the incidence of acute lung transplant rejection and changes in forced expiratory volume from baseline and overall effect. Additional endpoints include various inflammatory biomarkers and functional capacity.

"Lung transplantation can be a lifesaving procedure for those with end-stage lung diseases. Unfortunately, long-term graft and patient survival are limited by both acute and chronic allograft rejection, with a median survival of just over six years. Fully one-third of all lung transplant recipients experience acute rejection in the first year, and 40 percent will develop chronic rejection within the first five years," said Professor Mordechai R. Kramer, MD, director of the Institute of Pulmonary Medicine, Rabin Medical Center, Beilinson Hospital. "Current treatment options such as immunosuppressants have limited efficacy and can have significant adverse side effects and comorbidities. Preclinical data published in *Blood* suggest that IV AAT has an immunomodulatory and anti-inflammatory mechanism of action that would support its efficacy in the prevention of lung transplant rejection."

The study is being conducted at Rabin Medical Center, Beilinson Hospital in Israel in collaboration with Baxalta, which has distribution rights to the company's IV AAT for all indications in the U.S., Canada, Australia and New Zealand. ❖

Kamada Announces Initiation of Phase 2 Clinical Trial with Intravenous Alpha-1 Antitrypsin for the Prevention of Lung Transplant Rejection. BusinessWire, April 6, 2016 Accessed at www.businesswire.com/news/home/20160406005220/en/Kamada-Announces-Initiation-Phase-2-Clinical-Trial.

Medicines

FDA Approves Cabometyx for Advanced Renal Cell Carcinoma

In April, the U.S. Food and Drug Administration approved cabozantinib (Cabometyx, Exelixis) to treat advanced renal cell carcinoma (RCC) in patients who have received prior anti-angiogenic therapy. The approval was based on a randomized study in which patients with advanced RCC who had received prior anti-angiogenic therapy received either cabozantinib 60 mg orally once daily or everolimus 10 mg orally once daily with a primary endpoint of progression-free survival among the first 375 randomized subjects. Median progression-free survival was 7.4 months and 3.8 months in the cabozantinib and everolimus arms, respectively. Median overall survival in the intent-to-treat population was 21.4 months and 16.5 months in the cabozantinib and everolimus arms, respectively. And, confirmed response rate was 17 percent in the cabozantinib arm and 3 percent in the everolimus arm. The most common adverse reactions included diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, hypertension, vomiting, weight loss and constipation. Sixty percent of patients treated with cabozantinib had at least one dose reduction while in the study. Serious adverse events, which included abdominal pain, pleural effusion, diarrhea and nausea, were reported in 40 percent of patients. ❖

Cabozantinib (Cabometyx). U.S. Food and Drug Administration press release, April 25, 2016. Accessed at www.fda.gov/Drugs/Information OnDrugs/ApprovedDrugs/ucm497483.htm.

Research

New Autoimmune Disease Treatments Could Cause Fewer Side Effects

Because many of the current treatments for autoimmune diseases leave patients at greater risk of developing other opportunistic illnesses, a research team at the University of Oxford in England has been using genetics to possibly minimize the side effects of treatment. Specifically, the team investigated how genetic variation affects the function of a protein produced by the TYK2 gene, which plays an important role in the processes that help the body fight off infection and cancer, but also promotes autoimmune diseases. They found that a single genetic variant in TYK2 has a strong protective effect that reduces its function and diminishes the activity of the immune cells that could promote disease development. These findings suggest that pharmaceutically mimicking the impact of the protective TYK2 variant could pave the way for new autoimmune disease treatments that balance the need for efficacy and safety.

"While our research indicates that TYK2 could be a good drug target for treating autoimmune diseases, drugs that block the activity of immune cells have been known to leave patients vulnerable to infections and to increase the risk of cancer," said Professor Lars Fugger of the Nuffield Department of Clinical Neurosciences at the University of Oxford. "However, by interrogating data available through the UK Biobank, the most comprehensive health study in the United Kingdom, we found that people carrying the protective TYK2 genetic variant were no more likely to have serious infections or to develop cancer than people without the variant." ❖

Study Paves the Way for New Autoimmune Disease Treatments with Fewer Side Effects. University of Oxford, Nov. 2, 2016. Accessed at www.ox.ac.uk/news/2016-11-02-study-paves-way-new-autoimmune-disease-treatments-fewer-side-effects.

Medicines

FDA Approves Vemlidy to Treat Chronic Hepatitis B Virus Infection

The U.S. Food and Drug Administration (FDA) has approved Gilead Sciences' Vemlidy (tenofovir alafenamide, TAF) 25 mg once-daily treatment for adults with chronic hepatitis B virus (HBV) infection with compensated liver disease. Approval was based upon data from two international Phase III studies (Studies 108 and 110) conducted over a 48-week period among 1,298 treatment-naive and treatment-experienced adult patients with chronic HBV infection. Study 108 treated 425 HBeAg-negative patients with either Vemlidy or Viread (an HIV drug approved to treat HBV in 2008), and Study 110 randomized and treated 837 HBeAg-positive patients with either Vemlidy or Viread. Both studies met their primary endpoint of noninferiority to Viread based on the percentage of patients with chronic hepatitis B with plasma HBV DNA levels below 29 IU/mL at 48 weeks of therapy. But, Vemlidy also demonstrated improvements in certain bone and renal laboratory parameters compared to those treated with Viread. And, patients in the Vemlidy arm experienced numerically higher rates of normalization of blood serum alanine aminotransferase levels. ❖

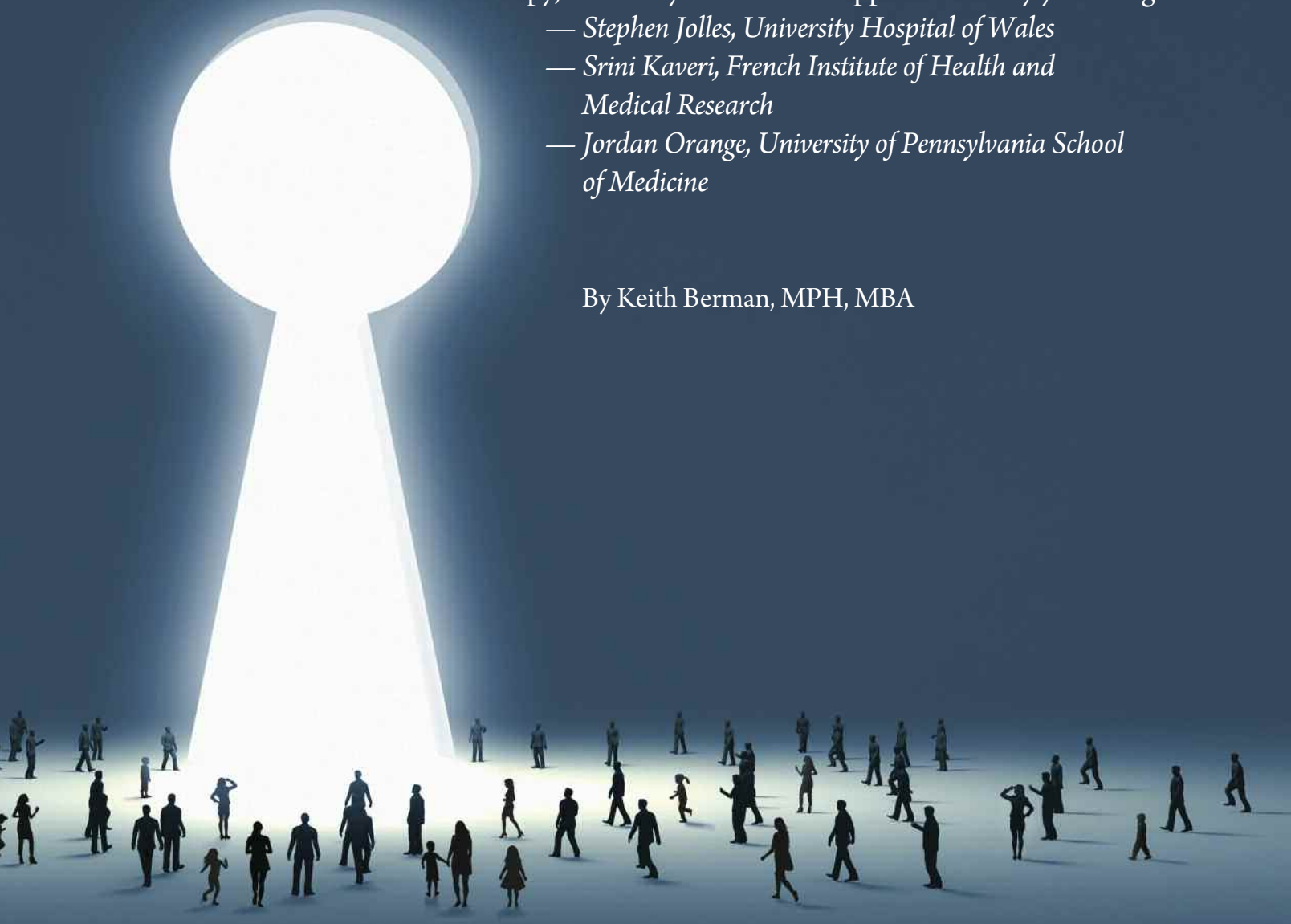
FDA Approves Vemlidy. Drugs.com, Nov. 10, 2016. Accessed at www.drugs.com/newdrugs/fda-approves-gilead-s-vemlidy-tenofovir-alafenamide-chronic-hepatitis-b-virus-infection-4452.html.

Going Up:
What's Behind the Growth in IVIG Demand

"There is still much to be learned about immunoglobulin therapy, and many more clinical applications may yet emerge."[1]

— *Stephen Jolles, University Hospital of Wales*
— *Srini Kaveri, French Institute of Health and Medical Research*
— *Jordan Orange, University of Pennsylvania School of Medicine*

By Keith Berman, MPH, MBA



LAUNCHED IN EUROPE in the late 1970s and here in the U.S. in 1981, the first intravenous immune globulin (IVIG) products transformed the lives of patients diagnosed with primary immunodeficiency (PI) disorders, freeing them from frequent painful — and usually suboptimal — doses of older intramuscular preparations. Monthly infusions of IVIG dramatically reduced severe recurring bacterial infections, hospitalizations and lost school or work days for these individuals.

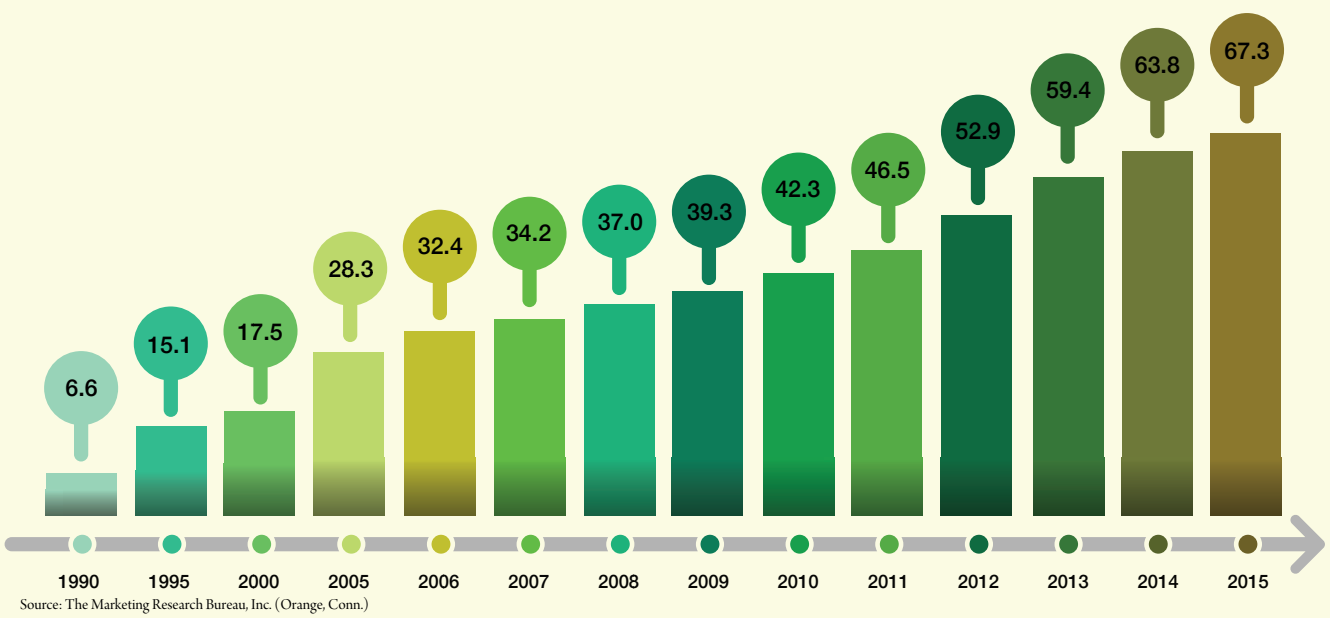
But several early IVIG products were also introduced with a second labeled indication: treatment of immune thrombocytopenic purpura (ITP). Totally unexpected, it resulted from a chance observation by Swiss investigators: When IVIG was given to a 12-year-old boy with hypogammaglobulinemia secondary to immunosuppressive therapy for severe chronic ITP, his platelet counts dramatically increased.[2,3] The Swiss and others who confirmed this finding in other ITP patients could only speculate how these IgG antibody solutions, purified from pooled plasma from thousands of healthy donors, somehow managed to block autoimmune platelet destruction. But it really didn't matter: IVIG preparations worked, they were well-tolerated, and they had fewer side effects compared to standard treatment options.

By 1990, U.S. sales of IVIG totaled about 6.6 million grams, according to Patrick Robert, whose Connecticut-based Marketing Research Bureau tracks and reports worldwide sales of human plasma-based therapeutics. Twenty-five years later, 2015 sales of IVIG and newer subcutaneous immune globulin (SCIG) products approved for PI had increased 10-fold to 67.3 million grams (Figure 1).

While PI and ITP generated most early IVIG prescribing activity, and remain important today, these two indications now account for only about one-third of total usage.

But remarkably, more than three decades after its introduction, the U.S. market for IVIG continues to grow well over 5 percent annually. While PI and ITP generated most early IVIG prescribing activity, and remain important today, these two indications now account for only about one-third of total usage.[4] Clearly something else has and continues to propel this unparalleled record of growth in market demand.

Figure 1. U.S. Sales of Polyvalent Intravenous Immune Globulin (IVIG) and Subcutaneous Immune Globulin (SCIG), 1990-2015 (in millions of grams)



Source: The Marketing Research Bureau, Inc. (Orange, Conn.)

Much Research, Many Disease Targets

Beginning with that chance ITP discovery in 1980, the "something else" has been an intense and unabated interest in the potential clinical utility of IVIG for a diverse array of difficult-to-treat immune-mediated conditions. "A striking anti-inflammatory effect of IVIG has been observed" in a number of autoimmune disorders, panelists agreed at a National Institutes of Health Consensus Development Conference in 1990, citing in particular its ability to reduce fever, neutrophil counts and acute phase reactants in Kawasaki disease.[5] "There may be multiple mechanisms of IVIG action," they suggested. Further investigations have subsequently identified a spectrum of immunoregulatory actions associated with these polyvalent IgG products that could account for their potent therapeutic effects in certain autoimmune disorders.[6,7]

Despite years of investigation, there are many immune-mediated disorders for which the effectiveness of IVIG remains uncertain or controversial.

A 1992 review article in *The New England Journal of Medicine* cited more than 35 diseases "thought to be produced by immunopathology" for which IVIG had been reported to be beneficial. Additional clinical studies have subsequently affirmed the efficacy of IVIG for some of them — Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and Kawasaki disease, for instance — while failing to conclusively document its value in others such as Sjögren's syndrome and systemic lupus erythematosus. Since 1992, literally thousands of randomized clinical trials (RCTs) and case reports have characterized the therapeutic effects of IVIG in many dozens of immune-mediated disorders. Yet to this day, little is known about how IVIG actually works across a wide range of autoimmune hematological disorders, neuropathies, myopathies, neuromuscular junction disorders, mucocutaneous blistering diseases and other immune-mediated disorders for which it is routinely prescribed (Table 1).

Table 1. Immune-Mediated Disorders for Which IVIG Is Commonly Prescribed*

Primary humoral immunodeficiency disorders

Autoimmune neuropathies
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Multifocal motor neuropathy
- Relapsing-remitting multiple sclerosis

Neuromuscular junction defects
- Myasthenia gravis exacerbations (myasthenic crisis)
- Lambert-Eaton myasthenic syndrome

Autoimmune mucocutaneous blistering disorders
- Bullous pemphigoid
- Pemphigus vulgaris and pemphigus foliaceus
- Mucous membrane pemphigoid
- Epidermolysis bullosa acquisita
- Stevens-Johnson syndrome/toxic epidermal necrolysis

Autoimmune inflammatory disorders
- Kawasaki disease
- Dermatomyositis
- Polymyositis
- Stiff person syndrome

Hematological disorders
- Immune thrombocytopenic purpura
- Neonatal alloimmune thrombocytopenia
- Post-allogeneic bone marrow transplant setting
- B cell chronic lymphocytic leukemia
- Warm antibody autoimmune hemolytic anemia
- Anti-phospholipid syndrome

Infectious diseases
- Toxic shock syndrome
- Pediatric HIV infection (prevention of bacterial infection)

Solid organ transplantation
- Densensitization of pre-renal transplant ABO incompatibility
- Acute humoral rejection of kidney allograft
- Cytomegalovirus-induced pneumonitis

*This is not intended to be an exhaustive list of disorders for which IVIG is prescribed or has been shown to be beneficial. Specific criteria usually apply to qualify for health insurance coverage.

The overall magnitude of IVIG demand is a function of that extraordinary diversity of diseases for which IVIG has been shown to be effective. But why IVIG prescriptions continue to grow — rather than having peaked and leveled off years ago like most drugs — has everything to do with what isn't known about how it works or the diseases it treats.

Unanswered Questions Limit Prescribing

Despite years of investigation, there are many immune-mediated disorders for which the effectiveness of IVIG remains uncertain or controversial. For other disorders, sufficient case reports and small case series have documented therapeutic benefit of IVIG in some patients, but critical questions remain: Are there definable parameters to help target IVIG therapy to potential responders, and minimize futile treatment? How much IVIG is required to achieve a therapeutic effect? How often should IVIG be administered? Depending on the condition, any or some combination of the following factors may be impeding efforts to answer these questions:

- A poor understanding of the pathogenesis of most immune-mediated disorders for which IVIG has been shown to be beneficial in at least some patients.
- The existence of characterized and possibly unknown disease variants, where IVIG may be effective in some but not others.
- A common lack of validated laboratory or clinical prognostic parameters to enable physicians to target IVIG therapy to the subset of patients that is likelier to respond.
- A paucity of validated laboratory parameters that may be used to guide IVIG dosage and dosing frequency.
- Typically very low disease prevalence or rarity, making the conduct of adequate dose-ranging and efficacy trials difficult or impractical.

The history of investigation of IVIG for multiple sclerosis (MS) offers an instructive example of the long and sometimes tortuous path of scientific discovery, clinical consensus and insurance coverage that ultimately reflects that consensus:

1992: IVIG dosed at 2 g/kg followed by bimonthly booster doses sharply reduces annual exacerbation rate in 10 patients with relapsing-remitting MS (RRMS)[8]

1997: IVIG is effective in monthly doses up to 2 g/kg in a randomized, placebo-controlled trial in 148 patients with RRMS[9]

2004: No clinical benefit of IVIG (1 g/kg/month) in a placebo-controlled RCT in 318 European patients with secondary progressive MS[10]

2005: An observational study of high-dose IVIG in 308 patients with RRMS documents a 69 percent reduction in the mean annualized relapse rate, similar to results of several previous RCTs evaluating IVIG for RRMS[11]

When administered at higher doses,[12] IVIG has consistently been shown to reduce the mean exacerbation rate in RRMS patients. Several other studies have confirmed, on the other hand, that IVIG has little or no therapeutic benefit for chronic progressive forms of the disease. More than a decade after the first positive studies, most health insurers now cover IVIG for RRMS as second-line therapy subject to certain criteria, typically including failure of standard MS drug treatments.[13,14,15]

Unfortunately the available clinical data still don't fully elucidate when to treat, how much to administer or which patients are likely responders or nonresponders. "IVIG therapy in RRMS has met with uncertainties that might be attributed to small patient cohorts, heterogeneity in the patients, dose of IVIG, or the duration and window of treatment," noted authors of a recent commentary.[16] And with these uncertainties about when and how to use IVIG naturally comes a hesitancy on the part of physicians to prescribe it, and insurers to agree to cover it.

> IVIG is arguably the most complex therapeutic agent of any kind in existence.

But very recently, a team of Austrian and German collaborators reported findings from a forward-thinking study whose entire purpose was to determine if genotyping and functional immune parameters can be used to predict subpopulations of RRMS patients who will benefit from IVIG from those who will not. Applying a scoring system to these biomarkers, the investigators found that IVIG responders scored either 0 or 1 (indicative of milder disease), while nonresponders scored between 7 and 9.[17]

A larger multicenter, controlled, randomized Phase IIIb trial is now in progress by the same investigators. Should this and similar studies confirm the ability to use biomarkers to prospectively predict the subpopulation of RRMS patients who will benefit from treatment, we could see much wider utilization of IVIG as a part of the standard therapeutic armamentarium to treat RRMS.

Table 2. Selected Clinical Trials Currently Evaluating IVIG[18]

Condition	Enrollment target	Estimated study completion date
Autoimmune epileptic seizures	30	August 2018
BK viremia in kidney transplant recipients	60	December 2018
Childhood encephalitis	308	February 2020
Dermatomyositis	94	March 2019
Diabetes with peripheral neuropathy/demyelination	25	February 2017
Idiopathic cardiomyopathy with high PVB19 load	50	November 2017
Intracranial hemorrhage	60	April 2018
Kidney transplant (HLA desensitization)	75	September 2018
Myasthenia gravis (corticosteroid-dependent)	60	December 2017
Myasthenia gravis exacerbation	50	June 2017
Post-polio syndrome	210	December 2018
Sickle cell disease (pain crisis)	94	July 2020
Small fiber neuropathy/demyelination	60	May 2017
Toxic shock syndrome (pediatric)	156	January 2021

More Research, Better Clinical Guidance Ahead

There are numerous clinical studies in progress (Table 2) addressing immune-mediated disorders, whose aim is to produce information both to establish efficacy and to help guide clinician decision-making about when, how much and for whom IVIG therapy is appropriate. Still other studies will be organized in the future. One by one as they are completed in coming years, the efficacy and safety of IVIG will be confirmed for more disease states. Equally important, better information will become available to guide appropriate patient selection, timing of therapy and dosing of clinical indications for which IVIG is known to work in some patients but not others.

And therein lies the answer to the mystery of why demand for IVIG continues to increase after all these years. IVIG is arguably the most complex therapeutic agent of any kind in existence. It is literally a concentrate of the largest component of the humoral immune system, whose mechanisms of action for a host of immune-mediated disorders remain poorly understood. More knowledge gleaned from well-designed clinical studies about the appropriate use of IVIG further empowers clinicians to use it and insurers to cover and pay for it.

But the challenge of organizing, funding and conducting trials in uncommon diseases that tend to be heterogeneous and little understood, with a product whose mode of action is also little understood, means that answers will continue to come slowly. Which all but assures that, for many years ahead, this slow stream of discovery will continue to light the path for IVIG to help yet more patients in need. ❖

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Interventions in the Treatment and Prevention of Adult Cancer Cachexia

Studies are shedding light on this long-misunderstood and devastating condition that may soon have approved treatments to help prolong cancer patients' lives.

By Amy Scanlin, MS

CANCER CACHEXIA is perhaps one of the most vexing of the myriad of challenges cancer patients face. Cachexia, which affects not only cancer patients but those in the end stages of other chronic diseases, causes the body's lean and fat mass to deteriorate, leading to an eventual inability to tolerate lifesaving chemotherapy due to its toxicity, thus hastening mortality. Depending on the data, cachexia affects approximately one-third to 80 percent of cancer patients and is implicated in approximately 20 percent to 30 percent of their deaths. Among its many symptoms are an extremely high metabolism, endocrine dysfunction, compromised appetite control and

impaired immune function. Cachexia is perplexing because, while its effects are devastating, its cause is only beginning to be understood, and successful treatment options are largely elusive. While simply increasing nutrient content would seem a reasonable response, it is ineffective as a unimodal therapy. In addition, many promising drug trials have shown to have negative or ineffective results. The complexity of the syndrome is a major factor, explains Vickie Baracos, PhD, specializing in palliative care medicine in the department of oncology at the University of Alberta, Cross Cancer Institute: "Nutrition support, pain and symptom management, as well as therapies to reduce excess catabolism and concurrently increase anabolism, appear to be required. Any of these alone, may have limited efficacy."

Cachexia's effects are both physical and financial, with longer inpatient stays and higher costs compared with noncachectic patients. Inpatient death rates attributed to cachexia are also higher. That being said, Dr. Baracos says the medical industry is now beginning to understand cachexia. Ten years ago, there were no Phase III clinical trials looking at cachexia, and no matter the form the current trials take, there is great learning potential. "The aim of preventing or reversing cachexia seems tangentially achievable," she explains.

Cachexia Classification

Although there is some disagreement about how cancer cachexia should be characterized, the current international consensus is that there are three clinically relevant stages:

- precachectic (less than 5 percent weight loss during the previous six months in combination with reduced food intake)
- cachectic (weight loss of greater than 5 percent)
- refractory cachexia (patients no longer responding to treatment with less than three months to live)

Currently, there are no biomarkers identified with cancer cachexia. However, researchers are looking at the complex multifactorial relationship of proinflammatory cytokines. Previously, specific inflammatory biomarkers were thought to be involved (i.e., interleukin 1 or 6, commonly known as IL-1, IL-6 and TNF-a), but more recently, they have shown to be inconsistent in some cancer cachexias. Researchers now question if IL-6 is the best predictive cytokine, particularly in advanced cancer patients, or if other cytokines such as IL-1b are better associated.[1]

When assessing and characterizing a patient's weight loss, a body mass index (BMI) of less than 20 and evidence of sarcopenia must be considered (see Defining Cancer Cachexia). And, as cachexia is explored, the severity of weight loss in relation to the rate of weight loss should be considered. This is because each patient's weight and BMI differ upon diagnosis, so looking at raw numbers in terms of weight loss or percentage of loss does not necessarily take into consideration the severity of the reduction. In addition, today's prevalence of upwardly trending body weights suggests the need to consider new definitions in cachexia weight-loss risk classifications, which also take BMI into consideration. Indeed, the international community is exploring the consideration of a revised classification of cancer cachexia in relation to treatment toxicity and mortality to gain more meaningful criteria.[2]

Causes of Cachexia

Although the specific causes of cancer cachexia are not fully understood, several studies are attempting to gain a better appreciation of contributing factors. Unfortunately, cancer cachexia is not a high priority for cancer research agencies or pharmaceutical companies, explains Dr. Baracos, so trials are difficult to fund. And, while there have been many drug trials with potential applications to cancer cachexia, the drugs' limited scope make them financially unattractive to pharmaceutical companies.

Major strides are now being made in understanding the basic biology of cancer cachexia; however, most studies involve rodent models, and there is still little known about what signals the initiation of cachexia in humans. For instance, some, but not all, cancers overproduce catabolic processes at a very intense rate.

Yet, other patients have dramatic weight loss exacerbated by not only their cancer but other lifestyle factors such as poor nutrition or an inability to care for themselves.

A common school of thought is that cachexia may be associated with the administration of chemotherapy. In one study, mice receiving five weeks of treatments for colorectal cancer exhibited MAPK-dependent muscle atrophy, mitochondrial depletion and alterations of sarcomeric units, suggesting chemotherapy potentially plays a causative role. The study also found that testing ACVR2B/Fc or MEK1 inhibitors in combination with anticancer drugs could identify those for whom strategies aimed at preventing chemotherapy-associated muscle atrophy may be helpful.[3]

Another study looked at the Pax7 muscle stem cell factor that, in normal circumstances, would develop into mature cells that bind to damaged muscle fibers to help repair them. In cancer cachexia, an overexpression of Pax7, controlled by NF-kappa B (NF-kB), inhibits the normal binding and leads to muscle wasting.[4] The researchers postulated that inhibition of Pax7 may provide an alternative therapy.

A common school of thought is that cachexia may be associated with the administration of chemotherapy.

Scientists also suspect that the gene USP19 may play a role in the development of cachexia, because studies in mice show that suppressing the gene may protect against it. Scientists are looking at two factors leading to muscle wasting: nerve loss leading to muscle atrophy (as in the case of a bedridden patient) and increased levels of cortisol. In mice in which USP19 was suppressed, muscle wasting happened much more slowly, suggesting protection against both causes of muscle wasting. If so, inhibiting the USP19 gene in the early stages of cancer could potentially have an impact on a patient's quality of life, and perhaps positively impact mortality.[5]

Researchers are also looking at the role of inflammation as a cause of white fat turning to brown fat in cancer patients. Brown fat is more calorically active, resulting in more heat production, calorie burning and organ wasting. It's possible that identifying brown fat in the early stages could predict which cancer patients will develop cachexia and benefit from preventive treatment. In mice studies, a nonsteroidal anti-inflammatory drug (NSAID) was found to be effective as preventive treatment.[6]

More recently, scientists looked at the AMP-activated protein kinase (AMPK), an enzyme that protects fat cells from energy deficiency in healthy people. They found that the inhibition of AMPK in mice with cancer caused white fat-cell wasting. Therefore, by manipulating the AMPK-stabilizing peptide (ACIP), which prevents the interaction between AMPK and the AMPK-interacting protein (CIDEA), increased fat breakdown could be halted.[7]

Treatment Options

Pharmacological treatments. There are no approved pharmacological treatments for cancer cachexia approved in the U.S. However, there are some approved in Europe. These treatments are considered palliative, and of those, progestogens (a class of steroid hormones) are considered the most effective.

Treatments for refractory cancer cachexia such as corticosteroids or progestins can provide short-term benefit. Earlier-stage therapies are "increasingly based on distinct molecular targets such as the skeletal muscle androgen receptor, myostatin, ghrelin, interleukin 6, and interleukin 1α," according to Dr. Baracos. Researchers are also assessing the success of a combination of exercise, nutritional supplementation and pharmacological intervention.[8]

The appetite stimulant Megestrol acetate (MA), approved to treat anorexia, cachexia or unexplained weight loss in patients with AIDS, and medroxyprogesterone acetate (MPA), used to treat breast, womb and kidney cancers, are showing promise for helping to improve cancer patients' nutritional status. MA is the most widely used drug for treating cancer cachexia. In clinical trials, patients showed a decreased level of IL-1, IL-6 and TNF-α after MA or MPA treatment.[9] While the mechanism by which these work against cancer cachexia is not fully understood, it is thought to be similar to corticosteroids: They may stimulate appetite and regulate the synthesis of and release of cytokines. MA and MPA have also shown to be effective in increasing body weight, primarily through water and fat mass. Unfortunately, they do not appear to be effective against increasing muscle mass.[10]

More than 100 randomized clinical trials have been conducted of potential therapies for cancer cachexia. Unfortunately, many have produced either negative results or they were not approved for treatment in the U.S. Part of the problem is a lack of consensus on what exactly should be tested. To demonstrate reversal or prevention of cancer cachexia, explains Dr. Baracos, the first endpoint is proof using dual energy X-ray or some other highly precise measure. The second endpoint must demonstrate the benefits of the therapy. However, because there is no clear guidance on what trials should be looking for, the challenge is defining

exactly what success looks like. Examples of this are four Phase III trials. Two trials assessed treatment with anamorelin, a novel, orally active, selective ghrelin receptor, to improve lean body mass and handgrip strength. And, two assessed treatment with enobosarm, an investigational selective androgen receptor modulator, to improve lean body mass and power and speed via stair climbing. While all showed significant improvements in lean muscle mass, they did not improve strength.

In the first two randomized, double-blind Phase III trials of anamorelin (Romana 1 and 2), sponsored by Helsinn of Switzerland, results showed that over a 12-week period, "ghrelin mimic" stimulated appetite and regulated rate of energy usage in combating muscle wasting and increasing lean body mass in certain advanced non-small cell lung cancer patients; however, there was no difference in handgrip strength. Also, survival improved for those who either maintained or increased lean body mass. The results are exciting because the retention and gain of lean muscle mass in those with advanced lung cancer, without any exercise or nutrient intervention, is remarkable progress. Helsinn has requested approval of anamorelin from the European Medicines Agency (EMA), and discussions are underway with the U.S. Food and Drug Administration for further trials to gain approval in the U.S.[10]

In search of a different definition of clinical benefit, two Phase III trials (POWER 1 and POWER 2) of GTX Inc.'s enobosarm assessed the molecule's ability to treat and prevent cancer cachexia in patients with advanced small cell lung cancer. They also tested power and speed via the patient's ability to climb stairs. Enobosarm, which binds to the same receptor as testosterone, showed improvements in participants' ability to maintain or prevent loss of lean body mass in both trials; however, it showed no absolute increase in stair climbing power. After the disappointing results, GTX stopped testing enobosarm to treat cancer cachexia and is instead focusing on the possibility as a treatment for breast cancer.[10] It has been hypothesized that a higher dosage of enobosarm might have overcome the effects of the cancer and demonstrated improvement.

Another Phase IIb trial (ACT ONE) of espindolol, a combined anabolic and anticatabolic therapy, resulted in the largest efficacy rate in any placebo-controlled clinical trial in cancer-related cachexia. Results of the 16-week study, sponsored by PsiOxus Therapeutics, showed significant positive effects on fat-free mass, body weight, relevant functional measure and hand grip strength in patients with colorectal and non-small cell lung cancer, two types of cancer that have high rates of cachexia. Inspired by the results of earlier Phase III trials of enobosarm and anamorelin and a smaller study of L-carnitine supplementation, which also showed positive effects on weight loss and BMI, a Phase III trial of espindolol is being designed.[11]

According to Dr. Baracos, these trials are the closest ever to changing clinical practice: "It is an encouraging time. We are taking baby steps, but we are going forward."

The exercise effect. Exercise is being explored as a means to prevent and counter the effects of cancer cachexia. Even though fewer than 5 percent of studies have included exercise, the positive effects of activity on inflammation, muscle strength and endurance are well-documented, particularly if exercise intervention is begun soon after the cancer diagnosis.

Mild endurance exercise reduces oxidative capacity, insulin resistance and inflammatory response. In studies of patients with breast and prostate cancers, resistance exercise had positive results against cachexia. Even high-intensity resistance training showed positive results in patients undergoing chemotherapy, with an average increase in muscle strength of 41.3 percent and a body weight increase of 1 percent. While these studies had small population sizes, making it difficult to generalize the results, they do indicate a positive relationship between appropriate exercise interventions and mitigating cancer cachexia's devastating effects.[12]

Andrew Wolf, MS, ED, exercise physiologist at Miraval Spa

Defining Cancer Cachexia

- Weight loss greater than 5 percent over the past 6 months; or
- BMI less than 20 and any degree of weight loss greater than 2 percent;
- Appendicular skeletal muscle index consistent with sarcopenia (another wasting syndrome) and weight loss of more than 2 percent.

The stages of cancer cachexia agreed upon by the panel are:

- Precachexia: weight loss of less than 5 percent, along with other symptoms such as impaired glucose tolerance or anorexia
- Cachexia: Weight loss greater than 5 percent, or other symptoms and conditions consistent with the diagnostic criteria for cachexia
- Refractory cachexia: Patients experiencing cachexia who are no longer responsive to cancer treatment, have a low performance score and have a life expectancy of less than three months

in Tucson, Ariz., explains that the release of myostatin by cancer cells results in negative effects on muscle mass. However, positive results of resistance training by cancer patients are two-fold. "First, our muscles secrete less myostatin in response to the increased use of the muscles in order to produce force," he says. "Second, the muscles actively produce a chemical called decorin. What decorin can do is sequester the myostatin produced by the cancer cells and keep that downward regulation of muscle tissue from occurring. The beauty of this two-fold effect is that we can now give real cause-and-effect rationale to cancer patients instead of simply talking about correlations between resistance training and better posttreatment outcomes."

Nutritional interventions. Few oncologists fully understand cancer cachexia, and their recommendations for increased caloric intake are met with so-so results. This is because using nutrition as a unimodal mechanism against cachexia is insufficient. Nonetheless, studies show that nutritional support and increasing caloric intake in the form of liquid or solid nutritional supplements can reverse the effects of weight loss in the short term and may enable patients to live longer and benefit from cancer treatments. Yet, other studies showed that while fat mass was improved in cachectic patients receiving nutritional support, longevity was not.

Few oncologists fully understand cancer cachexia, and their recommendations for increased caloric intake are met with so-so results.

Generally encouraged are smaller, more frequent meals, which include fat and protein to support muscle synthesis, and proper hydration. In patients unable to tolerate eating, parenteral and enteral nutrition may be prescribed, although infection rates using these methods are higher. The Society for Critical Care Management and the American Society for Parenteral and Enteral Nutrition (ASPEN) recently updated their guidelines.[13] Also available is an article titled "A.S.P.E.N. Guidelines for Nutrition Support Therapy During Adult Anticancer Treatment."[14]

Because a review of randomized studies showed no real difference in either mobility or mortality post-op when comparing parenteral nutrition, enteral nutrition and oral diets, ASPEN does not recommend nutritional support for routine use in patients undergoing major cancer operations. And, after concluding no real benefit but an increased risk of infection in immunocompromised patients, it also does not recommend nutritional support to patients undergoing chemotherapy or head, neck, abdominal or pelvic radiation therapy. Studies do show there may be some pre-operative benefit to moderately or severely malnourished patients, and ASPEN does recommend nutritional support for "patients receiving active anticancer treatment who are malnourished and who are anticipated to be unable to ingest and/or absorb adequate nutrients for a prolonged period of time." There is also emerging evidence supporting the use of omega-3 fatty acids as a preserver of lean body mass in advanced cancer patients undergoing chemotherapy.

One confusion concerning nutrition and cancer care is patients' understanding of what constitutes a "healthy" diet and the possibly erroneous reporting of their own eating habits. While a diet high in fruits and vegetables has shown a positive effect in preventing a variety of cancers, those micronutrients may have little impact on those with advanced stage cancer. Still, good nutritional intake in the presence of cancer cachexia is valuable, especially when considering the costs of other treatments.[15]

It is important to note that nutritional support does not work for all cancer patients. It has had mixed results in some studies, and it has not been validated through rigorous clinical trials. For example, some studies show that while nutritional support can stabilize weight and reduce the side effects of cancer therapy, it may also have the unintended consequence of decreasing the therapy's effectiveness.

"In the case of a cancer diagnosis, the more levers that you can pull in order to tamp down harmful inflammatory responses that may accelerate or exacerbate your situation, the better," says Wolf. "Be that traditional medicine, complementary therapies, nutritional therapies or exercise, the more positives you can integrate the better. In addition, the proactive feeling that you are doing something to help yourself while letting experts help you cannot be overstated."

Multimodal therapies. Multimodal therapies combining pharmaceutical therapies, exercise and diet are being explored and have potential for great promise in treating cancer cachexia. A Phase III trial currently recruiting participants will assess exercise with activity directed by a physical therapist, nutrition directed by a registered dietician and pharmacologic interventions with NSAIDs. The Multimodal Exercise/Nutrition/Anti-Inflammatory Treatment for Cachexia trial is recruiting patients with lung cancer, pancreatic cancer or cholangiocarcinoma at multiple sites in Europe, Canada and Australia.

Hope Is on the Horizon

While cancer cachexia continues to confound researchers, some enlightening findings in the search for prevention and treatment are coming to light. From pharmacological treatments currently under investigation to exercise and nutrition, hope is on the horizon for this devastating condition.

Though the specifics on cancer cachexia are not yet well understood, the complexities and importance of this condition are evidenced by the well-deserved attention to this multifactorial syndrome. With conferences focusing on cancer cachexia (cancercachexia2016.com/index.html); the Society on Sarcopenia, Cachexia and Wasting Disorders, an international, nonprofit scientific organization devoted to increasing awareness, education and research about cachexia (society-scwd.org/scwd); and the *Journal of Cachexia Sarcopenia and Muscle* (www.jcsm.info/index.php/en/), excellent resources are available today. ❖

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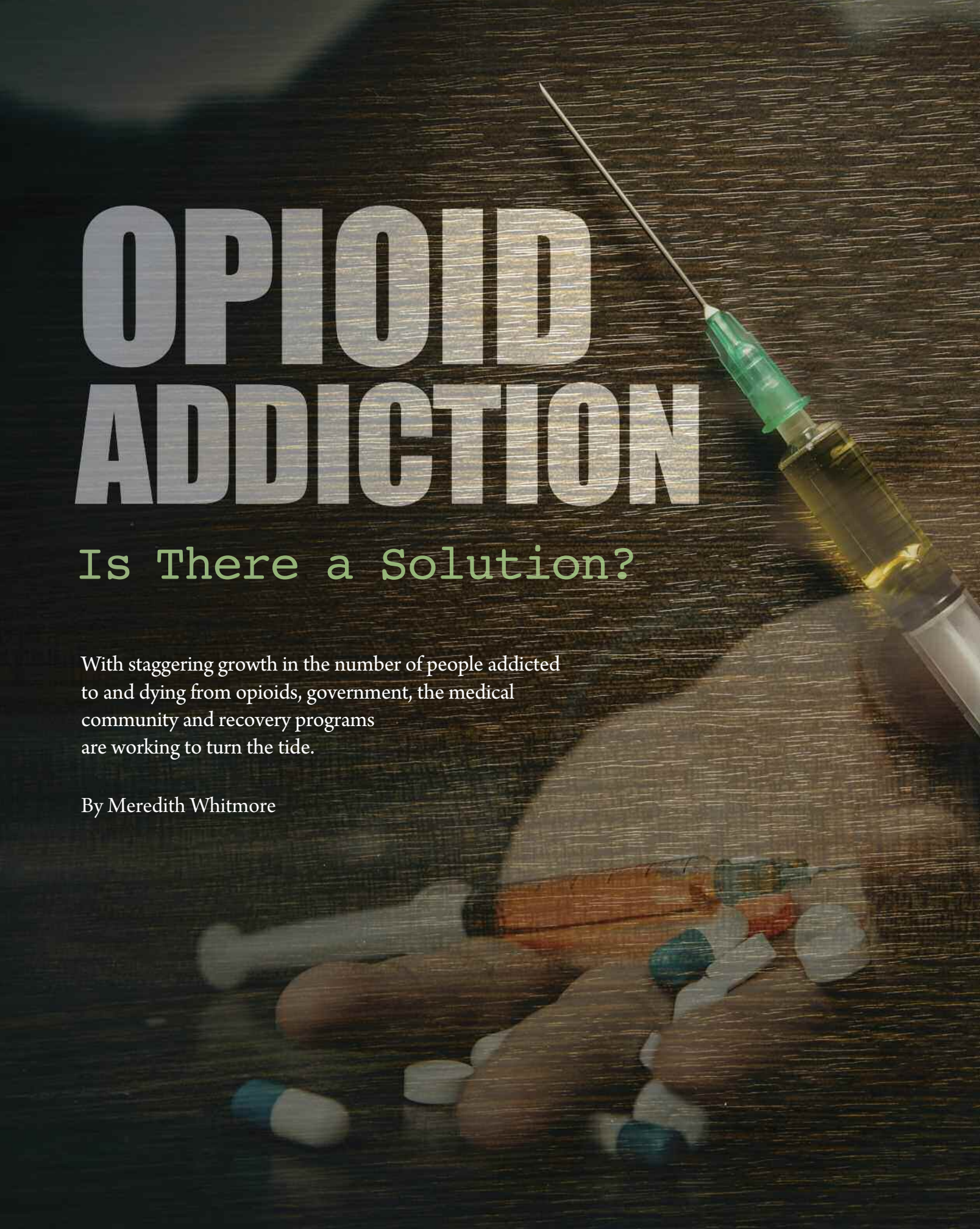


OPIOID ADDICTION

Is There a Solution?

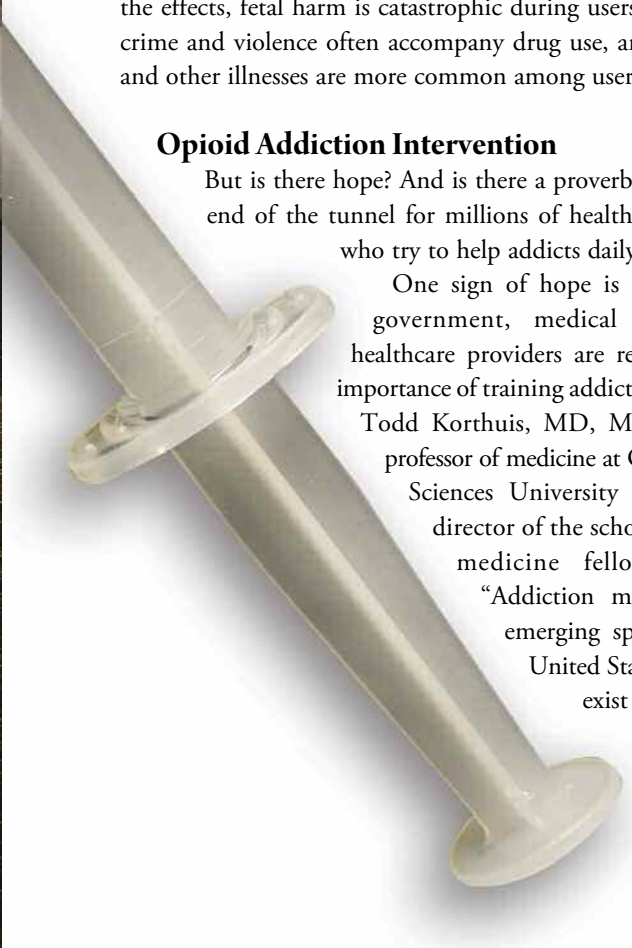
With staggering growth in the number of people addicted to and dying from opioids, government, the medical community and recovery programs are working to turn the tide.

By Meredith Whitmore

IN 2014, an unfortunate record was broken in the United States: Drug overdose deaths reached an unprecedented high, with more than 60 percent of them involving an opioid such as heroin, morphine, hydrocodone or oxycodone.[1] And in 2016, of the 21.5 million Americans age 12 years or older who suffer from opioid addiction, 1.9 million abused prescription pain relievers and 586,000 abused heroin.[2] Roughly 78 people per day die of opioid overdose in the United States,[1] and since 1999, around the time when opioids became a popular painkiller, the amount of prescription opioids sold has almost quadrupled, as have deaths from prescription opioid overdoses.[3]

Former U.S. Food and Drug Administration (FDA) commissioner David Kessler, MD, told CBS News that overprescribing opioids "has been one of the great mistakes of modern medicine. FDA has responsibility, the pharmaceutical companies have responsibility, physicians have responsibility. We didn't see these drugs for what they truly are."[4]

With these numbers and such sobering insight from a leading physician, it's easy to see that opioid addiction is a deadly and growing epidemic. The problem often seems out of control since even legally prescribed amounts of opioids can be easily and severely abused. Access is easy, and addiction can be virtually instant for some. And, the problems of drug abuse extend well beyond merely the user, because entire families are devastated by the effects, fetal harm is catastrophic during users' pregnancies, crime and violence often accompany drug use, and hepatitis C and other illnesses are more common among users.[1]



Opioid Addiction Intervention

But is there hope? And is there a proverbial light at the end of the tunnel for millions of healthcare providers who try to help addicts daily?

One sign of hope is that the U.S. government, medical schools and healthcare providers are recognizing the importance of training addiction specialists. Todd Korthuis, MD, MPH, associate professor of medicine at Oregon Health Sciences University and program director of the school's addiction medicine fellowship, says, "Addiction medicine is an emerging specialty in the United States that didn't exist 10 years ago. The idea is to train up healthcare providers from very diverse backgrounds, not just psychiatry, to be able to assess from a medical standpoint addiction issues in people who run into problems with prescription opioids. It's one thing to diagnose that someone is addicted to their pain medicine; it's quite another to treat that while you're safely managing their pain."

According to Dr. Korthuis, recent government initiatives to solve the opiate problem have also been helpful. For example, he says, the Centers for Disease Control and Prevention's (CDC) pain management guidelines "distill recent research about the negative impacts of opioid prescribing for chronic pain, both in terms of side effects and risks for patients, and also the risk at precipitating opioid use disorder and addiction issues in people who start taking them for pain." In 2016, Dr. Korthuis headed a policy meeting in Washington, D.C., on how to channel these CDC recommendations into medical training.

Overprescribing opioids "has been one of the great mistakes of modern medicine."

But, the guidelines have caused controversy. "One thing everybody is worried about with the guidelines is that they're recommending a target of no more than 90 morphine equivalents per day," Dr. Korthuis explains. "So, why 90? Because somewhere between 50 and 90 is where the risk of an unintentional overdose starts to increase. That's why people are dying of overdoses in the U.S. It's not that doctors are giving three Vicodin once a month to someone with arthritis. It's that we're giving elephant doses to people who build tolerance over time and may or may not be responding to it. We're also largely ignoring the much more evidence-based approaches such as cognitive behavioral therapy, myogenesis therapy, complementary and alternative approaches to pain management, and maximizing serotonin and norepinephrine with medications."

As doctors learn more about such alternative approaches, there is also the hope offered through various types of recovery programs and pharmaceuticals designed to ease physical dependence on opioids.

Drug-Related Treatment Options

There are medications that can assist with opioid addiction. But, do they always work?

According to Dr. Korthuis, "Medications such as methadone, Probuphine [buprenorphine] and naltrexone help decrease cravings

and help the brain reset so addicts are not driven by cravings and withdrawal symptoms. What we know is detox doesn't work on its own for opiates. The death rates and relapse rates are off the chart. Around 96 percent of people will relapse within six months after opiate detox alone. But starting on either methadone in an opiate treatment program or buprenorphine in an office-based setting decreases the risk of relapse to somewhere around 40 to 50 percent."

Chris Borgeone is a good illustration of how medication can assist recovering addicts in their transition. He hopes Probuphine will allow him to beat his dependence on pain killers and help him live a normal life without the urge to use every day. Because Probuphine is implanted in the upper arm, patients don't need to worry about missing a dose or two and potentially relapsing as a result. Borgeone told CBS News that his Probuphine implants are helping him tremendously: "I'm hoping at the end of treatment, I'll be able to move forward without any medication whatsoever."[5]

No one is immune to lapses, and SMART Recovery also teaches addicts how to deal with them.

Such drugs have been shown to help patients' social functioning and reduce the risks of overdose, contracting diseases such as hepatitis C and criminal activity.[6] How people on these medications transition to life without them is also key in their recovery. For many, a cognitive-based therapy or a 12-step program is a helpful supplement during that transition.

Nonspiritual Recovery Programs

SMART Recovery, a leading self-empowering addiction recovery support group, exists to help people recover from all types of addiction, including alcoholism, gambling, drug abuse and sexual addiction. It focuses on making addicts self-reliant, using what it calls its 4-Point Program: 1) building and maintaining motivation, 2) coping with urges, 3) managing thoughts, feelings and behaviors and 4) living a balanced life.[7]

It is not a 12-step program, which some consider one of its benefits. Instead of a step involving surrender to a higher power, it emphasizes patients' self-reliance and ways to modify their behavior. It encourages the belief that patients do have control over their choices and, ultimately, their lives.

Hank Rob, PhD, a board-certified psychologist in Portland, Ore., is an enthusiastic proponent of SMART Recovery. "The program doesn't tell people that they have to abstain, but it is a program for people who have chosen abstinence. I really want to underline that," he says. "One of its central tenants is exerting your power of choice. So, if you choose to abstain, then the program is there to help people who make that choice."

A significant difference between SMART Recovery and 12-step programs is that SMART Recovery views any spiritual aspect of healing very differently than the latter. "I think it depends on what is meant by spiritual," Dr. Rob explains. "If you take the first step of the 12 steps seriously — that you are powerless over your behavior — then you are certainly going to need something that will allow you to control yourself. If you don't start with the premise that you're powerless, then finding something that is powerful and can help you takes a different flavor. One point about SMART Recovery is not that you're powerless, but that you're not exerting your power in a way that works for you over the long term. Most people think about willpower as something that allows you to abstain. But abstaining is how you get the willpower to abstain. It's like building muscles. How do you build strong muscles? By working them out! You don't get the strength by having the muscles first."

Cognitive behavioral therapy is used extensively in SMART Recovery, which Dr. Rob says includes "accepting (not necessarily approving) and willingly being who you are instead of grudgingly being who you are or putting yourself down." Accepting others and the world in general is equally important. "If you really approach yourself and people and the world with that kind of acceptance, instead of demanding that the world be a certain way, namely your way, that itself is what I would call a spiritual transformation," he says. "And if that's what the importance of a spiritual aspect means, then I certainly agree that SMART Recovery is spiritual. But if you mean a higher power that's required because you're powerless, then that's a different kind of an idea."

"There's a lot of hope for treatment," he adds. "And, one thing we know is that change is a function of efforts to change. So, what really matters is continually making the effort to change. If you keep at it and keep at it and keep at it, eventually, you do change. The nature of habits is we do them quickly and effortlessly and without much awareness. So, if you're going to change a habit, the first thing is consciousness raising. You've got to get more aware of it."

No one is immune to lapses, and SMART Recovery also teaches addicts how to deal with them. "The only effective mechanism, since you can't get rid of that [urge to return to addictive behavior] is to learn to recognize the temptation and then refuse to go along with it," explains Dr. Rob. "SMART Recovery advocates a technique called DISARM, which stands

for 'destructive imagery self-talk and refusal method.' So, you recognize your destructive thinking and self-talk and refuse to go along with it. The more you practice this, the better you get at it. The more you give in, the better you get at that."

As for results, SMART Recovery reports that it is as effective as 12-step programs and other programs that employ cognitive behavioral therapy.[8]

12-Step Program Groups

Unlike SMART Recovery, Narcotics Anonymous (NA), like other 12-step programs, identifies itself as a spiritual fellowship. The organization offers a recovery process and peer support network that are linked together. According to NA, its success is the therapeutic value of addicts working with other addicts. In a 2015 survey, participants in NA have an average length of "cleantime" of 8.32 years.[9] Two examples of this are recovering addicts Emberlee and Judith (NA prohibits its members from revealing last names).

After two suicide attempts and multiple attempts to stop using, Emberlee claims she would not have recovered without the steps. "I am sober today," she says. "I never thought that was possible. The 12 steps is where I found hope. I had to do something, and I'd heard for so many years that the only thing that worked was doing the 12-step program. And it did. The difference is that there are steps. I was told it's not a drug problem, it's a thinking problem. For me, addiction is entirely a thinking problem. Until I understood that I needed to change my way of thinking, I continued to revert back to drugs. I thought that was my solution. I'm not saying that drugs aren't addicting, because they are. But without a 12-step program, I would always go back to drugs. And without being institutionalized, I didn't know how to stop, and I couldn't stop. I literally was physically dependent on an opioid to get up out of bed in the morning."

Emberlee adds that the spiritual solution in the program is what gave her a temporary reprieve. "So as long as I stay in fit spiritual condition, I don't have to use today, and I won't use today," she explains. "But it requires me to take action every single day to do something for my recovery, to work a step, to talk to another addict, to go to a meeting. It requires me to do things every single day for my recovery."

Judith, an attorney and recovering addict who now operates clean-and-sober-living facilities in the Midwest, believes that rehab is an important part of recovery, but it's not the only component. Many addicts, she says, are most vulnerable after rehab, and without a 12-step program and the support of caring people, treatment has only a 3 percent success rate.

For her, mere abstinence was insufficient as well. After 11 months of being clean and sober, without a daily program and nothing to change her unhealthy thinking, Judith says, "I was just a hair away from suicide. When I was abstinent, I could not feel meaning or fulfillment. I could not function. I would have gone back to drugs because I hadn't changed my thinking yet. And the longer I was away from the drugs, the more horrible it was. But when I finally did the 12-step program, and really worked through, completed and followed the steps, I got a connection with a higher power. Call it God, call it whatever. That's when I recovered."

Judith realizes that many people don't want to acknowledge the existence of a power greater than themselves. They want a medical or purely science-based solution. But, she firmly believes that recovery must be spiritually (but not necessarily religiously) based. "What we say is a drugs and alcohol problem is but a symptom of someone's spiritual malady," she explains. "That does not mean there is not a physical component. There very much is a physical component of addiction." The problem, she says, is that many doctors and treatment centers don't acknowledge the spiritual component. Instead, they focus only on the physical element.

An Epidemic of Hope

With addiction specialists such as Dr. Korthuis becoming better trained and more prominent, improved opioid addiction drugs such as Probuphine helping addicts to be weaned off substances, the government's dedication to ending the opioid addiction epidemic, and devoted recovering addicts who strive to help other addicts successfully navigate recovery programs, there are hopeful solutions to opioid addiction. But no matter what form the solution, it requires hard work, daily commitment and constant support from family, friends and the medical community. For addicts who are ready to accept help, work for it and commit to it, there is great hope. ❖

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Healthcare Crisis

By Trudie Mitschang

Meeting the future healthcare needs of aging baby boomers will require tackling the rise of chronic illness, addressing the impact of Alzheimer's disease and reinventing care models to address the needs of a graying America.

APPROXIMATELY 75 MILLION Americans make up the demographic known as the baby boomer generation. The U.S. Census Bureau categorizes baby boomers as individuals born between 1946 and 1964, and if you do the math, it turns out that nearly three million of them will hit retirement age every year for the next two decades. By 2030, that means the number of Americans 65 and older will climb to more than 71 million, up from about 41 million in 2011, a 73 percent increase, according to U.S. Census Bureau estimates.[1] The question on many minds is: What influence will this aging demographic have on our nation's public health, social services and healthcare systems? The answer: a staggering one. "This is the most powerful force operating in our health system right now, this generational change," says Jeff Goldsmith, president of Health Futures Inc., Charlottesville, Va. "So far, the growth in the number of senior citizen boomers has been incremental, and its impact on healthcare has been overshadowed by federal reform and budget battles. People aren't paying much attention."[1]

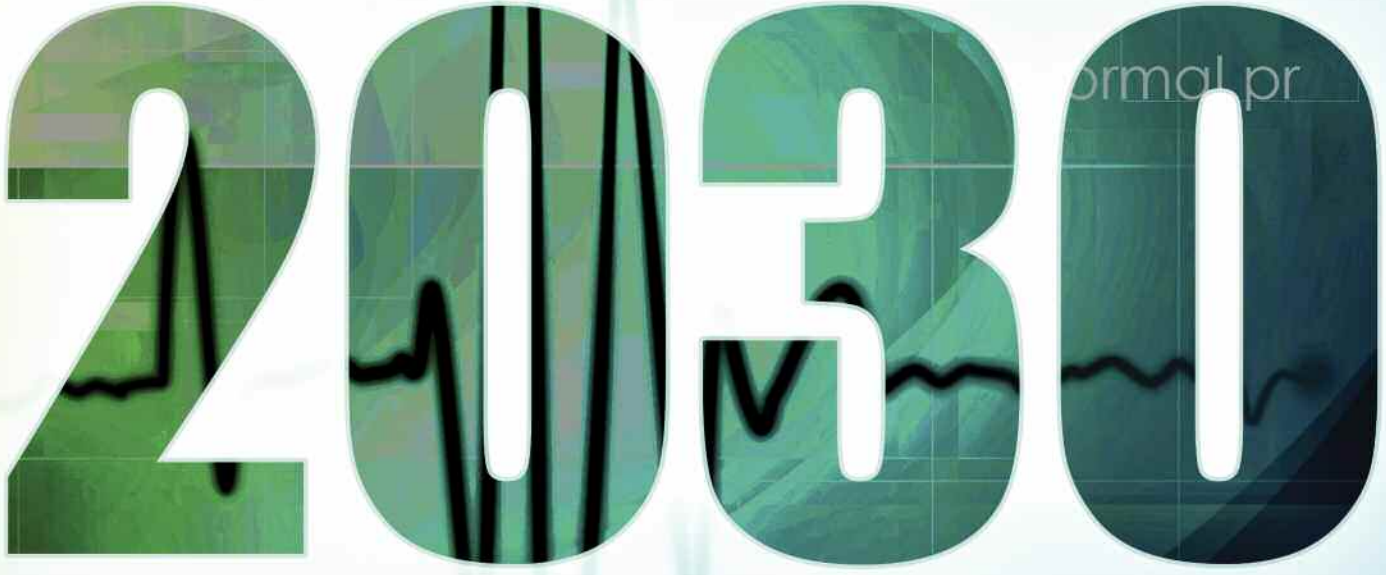
Addressing the Chronic Illness Crisis

While today's seniors are living longer than previous generations, they are not necessarily aging well. In fact, one of the biggest healthcare hurdles facing hospitals and healthcare systems during the next several decades will be the management of chronic diseases within this rapidly growing population. A joint report from First Consulting Group and the American Hospital Association, titled "When I'm 64 … How Boomers Will Change Health Care,"[2] noted the following estimates.

By 2030:

- 14 million boomers will have diabetes;
- 26 million will have arthritis;
- More than 21 million will be considered obese;
- Knee replacement surgeries will increase 800 percent; and
- Hospital admissions among boomers will increase more than 100 percent, totaling half of all admissions in America.

Experts agree that the chronic illness crisis among aging Americans presents one of the biggest challenges to an already taxed healthcare system. According to *Baby Boomer* magazine, two-thirds of this aging population are expected to have as many as five chronic diseases by age 65.[3] Clearly, a multipronged approach will be needed to prepare physicians for this onslaught of patients and the resulting avalanche of prescription medications and treatment plans.



To address the rising concern, the American Medical Association has established a policy requiring all physicians with older patients to be competent in geriatrics. This policy applies to physicians at all levels, including undergraduates, residents and practicing physicians. In addition, the American Association of Medical Colleges has developed programs for medical students covering 26 geriatric competencies, including being able to explain the impact of age-related changes on drug selection and dosage; diagnosing dementia; and talking with patients and families about palliative care.[3] Similar competencies in geriatrics are in development for residents in the fields of surgery, family medicine, internal medicine and emergency medicine, and for other specialists involved in treating older patients.

When patients present with multiple chronic illnesses, it puts a strain not only on healthcare providers, but on Medicare. As the founder and president of the Alliance for Aging Research, Daniel Perry, explained, "The reality is most elderly people do not have one disease on their death certificates." He notes that elderly patients often receive care from more than one specialist, as well as a primary care provider, but the current healthcare system in the U.S. does not support coordination and collaboration between providers in different fields. "We don't have a healthcare system that is well-designed to diagnose, assess, prevent, postpone and treat the multiple chronic conditions that accompany the aging process," Perry says.[2]

Preparing for the Dementia Dilemma

A 2015 study conducted by the Lewin Group in Falls Church, Va., for the Alzheimer's Association offered dire predictions for onset of Alzheimer's disease (AD) in baby boomers. According to the study, more than 28 million future seniors could be diagnosed with AD by 2050, accounting for nearly 25 percent of Medicare spending by 2040. The study also predicts that the prevalence of AD in baby boomers will rise from 1.2 percent in 2020, when most will be in their 60s and 70s, to an astonishing 50.1 percent in 2050, when these individuals reach their mid-80s and older. By 2040, more than twice as many baby boomers will have AD (10.3 million) than the equivalent age group had in 2015 (4.7 million).[4]

Experts agree that the chronic illness crisis among aging Americans presents one of the biggest challenges to an already taxed healthcare system.

"The risk of Alzheimer's increases with age, and as baby boomers get older — because of the size of the generation — the number of people developing the disease will rise to levels far beyond anything we've seen. The size of this generation is the major factor here," says Christine Bredfeldt, PhD, from the Lewin Group. "The study is important because it is based on an updated model that charts the trajectory and economic impact of Alzheimer's based on the rate of new diagnoses, the number of people who will be living with the disease and the cost of medical and long-term care between now and 2050."[4]

The findings of the study speak to the urgency of addressing

future Medicare costs for this at-risk population. Predictions estimate the cost of caring for more than 10 million AD patients could consume nearly 25 percent of Medicare spending. That number represents the longer-expected lifespan of the boomer generation coupled with the progressive nature of the disease, resulting in the widespread need for long-term or nursing home care.

A new study launched in September titled the "Alzheimer's Prevention Initiative Generation Study" is unique because it specifically targets baby boomers as study enrollees, focusing on individuals who are 60 years to 75 years of age and currently showing no signs of cognitive impairment. Enrollees are also those who inherited two copies of the e4 type of the apolipoprotein E (APOE) gene, the major genetic risk factor for developing AD at older ages.[5] The goal of the study is to test whether either or both of two investigational compounds — an active immunotherapy and an oral medication — compared to placebo might prevent or delay the emergence of AD symptoms in people who are at particularly high risk for developing the disease at older ages because of their genetic profile. "Even if this research only results in our ability to delay the onset of Alzheimer's disease by five years, the impact could be enormous," says Pierre Tariot, MD, director of the Banner Alzheimer's Institute (BAI) and coprincipal investigator for the study. "Some estimates indicate that even a short delay could reduce the number of Alzheimer's cases by 50 percent. That's quite a legacy for baby boomers to leave future generations."[6]

More than 28 million future seniors could be diagnosed with AD by 2050, accounting for nearly 25 percent of Medicare spending by 2040.

The five-year study is sponsored by Novartis, a Swiss pharmaceutical company, and Amgen, a biotechnology company based in Thousand Oaks, Calif., in collaboration with BAI, and with funding from the National Institute on Aging, as well as the Alzheimer's Association, Fidelity Biosciences Research Initiative, GHR Foundation and Banner Alzheimer's Foundation.

Training the Next Generation of Geriatric Physicians

Like older adolescents aging out of pediatric care, aging baby boomers will also need to transition from their current general practitioners to physicians with expertise in geriatrics. According to some estimates, there are currently only 7,000 certified geriatricians in the U.S. — far too few for the coming wave of senior citizens. To address this, four academic medical centers that are leaders in geriatric care — the Icahn School of Medicine at Mount Sinai, the Johns Hopkins University School of Medicine, Duke University School of Medicine and the University of California, Los Angeles (UCLA) School of Medicine — formed a consortium to provide geriatric training to physicians who teach in medical schools and residency programs.[7]

Known as the Faculty Development to Advance Geriatric Education, or FD-AGE, the program doesn't aim to create new geriatricians; rather, its goal is to teach physician-educators from all specialties how to address the complex issues involved in the care of older adults. The hope is that they will go back to their home institutions and pass on what they have learned. "The FD-AGE program is a recognition that most older people won't be cared for by a geriatrician," says Rosanne Leipzig, professor of geriatrics and palliative medicine at the Icahn School of Medicine and a consortium leader.[7]

Ethan Cumbler, MD, an associate professor of medicine at the University of Colorado who specializes in the practice of hospital medicine, set up the only hospital unit specializing in the care of the elderly in Colorado after taking part in the FD-AGE program at UCLA in 2007 and 2008. When teaching other physicians, Dr. Cumbler stresses that treating elderly patients requires a holistic approach that takes into consideration all of their physiological, psychological, economic and social issues.[7]

In addition to training the next generation of providers, models of care will need to evolve to address a rapidly aging population. The white paper "Retooling for an Aging America: Building the Healthcare Workforce"[8] addresses this need, explaining that the current healthcare system often fails to provide high-quality care to older adults, in part because services are often delivered by many different providers with limited or no collaboration. For example, in the current "pay-for-service" healthcare environment, a patient managing several chronic diseases is likely seeing an equal number of specialists requiring multiple office visits.

"Chronically ill Medicare beneficiaries often see multiple physicians — all working within their own silo — with no one physician responsible for all care. In our fractured delivery system, no one physician takes responsibility for guidelines-based care, and health information is most often not shared among these silos," state Michael O. Fleming, MD, and Tara Trahan Haney, MPA, in a PubMed report.[9] According to the authors, in the absence of a care coordinator, there is often a breakdown in communication between the patient and the physician team:

"In many instances, a patient is admitted to the hospital, but the primary care physician never knows about the event or any medication changes that resulted, thereby increasing the chances of a readmission."

With the rise of chronic illness within baby boomer patients, hospital admission and readmission represent a significant expense for Medicare. According to research published in the *New England Journal of Medicine*, one in five Medicare patients ended up back in the hospital less than 30 days after discharge in 2003 and 2004.[10] And, while many hospital readmissions are unavoidable, experts believe that hospitals can engage in several activities to lower their rate of readmissions and related costs. In 2012, the Centers for Medicare and Medicaid Services (CMS) launched the Medicare Hospital Readmission Reduction Program as part of the Affordable Care Act. The program fines certain hospitals for excessive rates of readmissions for Medicare patients with specified conditions. Early evidence suggests that the program is showing signs of success.[10]

Reinventing Care Models for an Aging Population

As we look to the future, the healthcare community has a unique opportunity to adopt a new approach to healthcare delivery, one that promotes patient-centered care coordination, from the first diagnosis of a chronic illness throughout the continuum of care. While many innovative models of care show promise, implementation to date has been minimal. What is clear is there is not a one-size-fits-all approach that can meet the changing and diverse needs of an aging patient population.

Experts suggest there will need to be a paradigm shift when it comes to identifying the healthcare team as a whole, which will likely expand to include everyone involved in a patient's care, from healthcare professionals, direct care workers and nonprofessional caregivers (including family and friends) to the patients themselves. Giving each of these stakeholders access to the data, knowledge and tools needed to provide high-quality care can be accomplished using a variety of assistive technologies, remote monitoring systems and mobile health, potentially reducing the need for in-office care. Health information technologies and remote monitoring systems, for example, can allow for more healthcare to take place in the home care setting to improve communication among all caregivers and enable providers to make more efficient use of their time.

An article in *Today's Geriatric Medicine* titled "Remote Monitoring in Geriatric Care" notes that the success of passive monitoring stems from its ability to collect data continuously and alert caregivers in real time of any changes or fluctuations. Although proven to be a valuable tool, remote monitoring use remains inconsistent throughout the industry as the regulatory environment becomes increasingly complex. In 2014, CMS drafted a provision to cover remote monitoring for managing chronic care, although reimbursements are limited to certain providers, conditions and types of remote patient monitoring. However, as adoption increases and providers demonstrate its value, CMS could begin to incentivize monitoring as a pay-for-performance measure — a move that could be mutually beneficial to both providers and the aging baby boomers whose long-term quality of life may very well hang in the balance.[11]

Beyond technology, new comprehensive care facilities may also address the needs of aging adults, including specialized acute care for the elderly units in hospitals and resident facilities that offer a spectrum of medical assistance, from assisted living through advanced dementia care.

For more than seven decades, the baby boomer generation has influenced everything from marketing and economic trends to the country's political climate. As they step into their golden years, this highly opinionated and vocal demographic will likely be the key driver when it comes to future healthcare trends as well. "A lot of people strongly believe that baby boomers in particular are going to receive a lot of their care in the future over the Internet, over the phone," says Richard Birkel, senior vice president for the Center for Healthy Aging and director, self-care management alliance at the National Council on Aging, a nonprofit service and advocacy group. "Healthcare is going to have a significant e-health component. It does already, but nothing like we're going to see in the next five to 10 years, and I think baby boomers are going to be leaders in that area."[1] ❖

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

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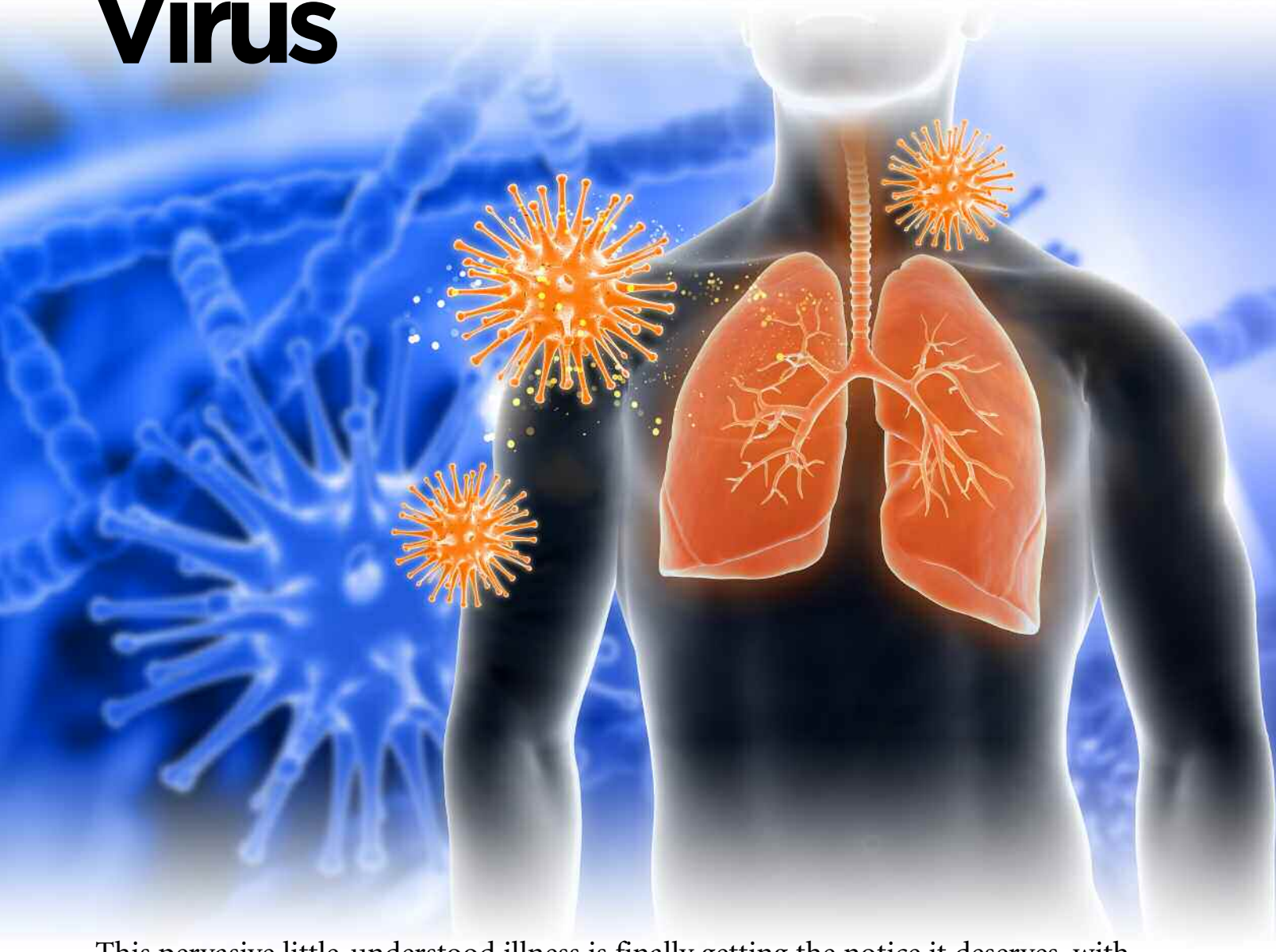
Update on **Respiratory Syncytial Virus**



This pervasive little-understood illness is finally getting the notice it deserves, with current attention focusing on better understanding and prevention.

By Ronale Tucker Rhodes, MS

WITH THE HIGH prevalence of respiratory syncytial virus (RSV) in the U.S. and globally, it's a wonder this sometimes-deadly illness isn't better known or more talked about. RSV is recognized as one of the most common causes of childhood illness.[1] It is the most common cause of lower respiratory tract infections in children, with most infants infected before 1 year of age and virtually all children infected by 2 years of age.[2] Depending on the source, there are between 57,000[2] to 120,000[3] children under 5 years of age in the U.S. requiring hospitalization each year due to RSV, resulting in approximately 4,500 deaths.[4] But RSV also affects adults, especially older adults and those with compromised immune systems. In adults over age 65 years, RSV results in approximately 177,000 hospitalizations and 14,000 deaths.[2]

RSV is a very highly contagious illness spread via respiratory secretions through contact with infected people or contaminated objects or surfaces.[3] Discovered in 1956, RSV is a member of the family Paramyxoviridae and the subfamily Pneumovirinae. The enveloped RNA virus has two main types (subgroups A and B) and many subtypes (strains); however, the clinical significance of the different strains remains unclear.[1,5] What is clear is that this pervasive illness is avoidable, despite there is still no vaccine to prevent it. Therefore, with little awareness of RSV and how to prevent it, government and other healthcare entities are prioritizing research to better understand it and to develop a preventive vaccine.

Causes of RSV

Because there are many different strains, no one has full immunity to RSV, and some people have many RSV infections throughout life.[5] In the U.S. and other countries with similar climates, RSV infections generally occur during the fall, winter and spring, but that can vary from year to year.[6]

Those infected with RSV are usually contagious for between three days and eight days, although some infants and people with weakened immune systems can be contagious for as long as four weeks.[7] The incubation period ranges from two days to eight days, but usually is between four days and six days.[5]

RSV spreads easily in crowded areas such as child care facilities, preschools and nursing homes through both direct and indirect contact with infected persons. Infection can occur when infectious particles make contact with mucous membranes of the eyes, mouth or nose, and even through the inhalation of secretory respiratory droplets. And, because infectious particles can survive for more than six hours on objects and surfaces, infection can occur by touching them and rubbing the eyes, nose or mouth.[5]

Symptoms and Progression of RSV

Symptoms of RSV in adults and older, healthy children are typically mild and mimic the common cold. In most infants, symptoms are similar to a bad cold with fever, prominent runny nose and nasal congestion lasting between one week and two weeks. Some babies and young children also develop symptoms of bronchiolitis or pneumonia.[3] In very young infants, irritability, decreased activity and breathing difficulties may be the only symptoms, but infection without symptoms is rare among infants.[8,9]

Those at increased risk of severe and, sometimes, life-threatening RSV infections include:[10]

- infants younger than 6 months old;
- younger children, especially under 1 year of age, who were born prematurely or who have an underlying condition such as congenital heart or lung disease;
- children with weakened immune systems such as those undergoing chemotherapy or transplantation;
- infants in crowded child care settings;
- older adults;
- adults with asthma, congestive heart failure or chronic obstructive pulmonary disease; and
- people with immunodeficiency disorders, certain transplanted organs, leukemia or HIV/AIDS.

Because there are many different strains, no one has full immunity to RSV, and some people have many RSV infections throughout life.

Complications that typically happen with those who are more at risk of severe RSV infections include hospitalization, pneumonia or bronchiolitis, middle ear infection (mostly in infants and young children), asthma (developing later in life) and recurring infections.[11]

The majority of children hospitalized for RSV are under 6 months old. When hospitalized, they most commonly require supplemental oxygen, IV fluids and pulmonary inhalation therapy.[3] In a study of adult patients hospitalized with laboratory-confirmed RSV infection, pneumonia was found in 42.3 percent, bacterial superinfection in 12.5 percent and cardiovascular

complications in 14.3 percent. Additionally, 11.1 percent developed respiratory failure requiring ventilator support. All-cause mortality at 30 days and 60 days was 9.1 percent and 11.9 percent, respectively, with pneumonia the most common cause of death.[12]

Preventing RSV

Without a vaccine yet available to prevent RSV, individuals need to be aware of steps they can take to avoid infection and passing on infection. Of course, it isn't always possible to prevent the spread of RSV since it is often spread during the early stages of illness prior to the development of severe symptoms.

Frequent handwashing and not sharing cups, glasses or utensils can decrease the spread of RSV. Those experiencing cold-like symptoms should cover their coughs and sneezes, wash hands frequently and correctly (with soap and water for 20 seconds), avoid sharing cups and eating utensils, refrain from kissing others and clean contaminated surfaces such as doorknobs. Interaction with children at high risk for developing severe disease should also be avoided.

Hospitals and doctor offices can play a role by paying strict attention to contact precautions such as handwashing and wearing gowns and gloves.[3,7]

> The majority of children hospitalized for RSV are under 6 months old.

Previously, RSV immune globulin intravenous was available as passive immunization to protect against RSV infection. However, it is no longer being manufactured.[13] In 1998, though, the U.S. Food and Drug Administration approved palivizumab (Synagis) to help prevent severe RSV; it is given as a monthly injection during RSV season. According to the American Academy of Pediatrics guidelines, the following are candidates for palivizumab prophylaxis:[13]

- infants younger than 24 months who have hemodynamically significant congenital heart disease (cyanotic or acyanotic lesions) or who have chronic lung disease and are off oxygen or pulmonary medications for less than 6 months at the start of RSV season;
- premature infants born at 28 weeks' gestational age or less who are younger than 1 year old at the start of RSV season (once treatment is initiated, it should continue throughout the season and not stop at 1 year of age);
- premature infants born at 29 weeks' to 32 weeks' gestational age who are younger than 6 months old at the start of RSV season (once treatment is initiated, it should continue throughout the season and not stop at age 6 months); and
- infants born at 32 weeks' to 35 weeks' gestational age who are younger than 3 months old at the start of or during RSV season and who either attend child care or have one or more siblings or other children younger than 5 years old living permanently in the same household (prophylaxis should be provided only until age 3 months).

It should be noted that palivizumab is prescribed only for high-risk infants to help prevent severe RSV infection. And, it's expensive, so insurance companies often have strict guidelines that limit for whom they will pay for the medication.[3]

Diagnosing RSV

Nonspecific lab tests for children who experience nonsevere symptoms include complete blood count, serum electrolyte concentrations, urinalysis and oxygen saturation. For therapeutic diagnosis, specific tests include cell culture, antigen-revealing techniques, polymerase chain reaction (PCR) assay and molecular probes.[13]

Cell culture is typically supplemental to antigen detection tests since the latter's sensitivity generally ranges from 80 percent to 90 percent. And, while antigen detection tests are generally reliable in young children, they are less useful in older children and adults. It's also recommended that, for optimal results, experienced lab technicians be consulted for cell culture because of its thermolability. Reverse transcription-PCR (RT-PCR) assays, which often exceed the sensitivity of antigen detection methods, should be considered when testing older children and adults because they may have low viral loads in their respiratory specimens.[8]

Treating RSV

The mainstay therapy for RSV is supportive care such as acetaminophen to treat fever and, in cases of bacterial complication, an antibiotic.[14] While corticosteroids are sometimes prescribed, clinical data doesn't support their use to treat RSV.[13]

For severe cases of RSV, hospitalization may be needed to provide intravenous fluids and humidified oxygen. Infants and children may need mechanical ventilation to ease breathing.[13] Pharmacologic therapies include bronchodilators such as albuterol (ProAir HFA, Proventil-HFA, Ventolin HFA) to relieve wheezing, alpha agonists, a nebulized form of ribavirin (Virazole) and an injection of epinephrine or a form of epinephrine that can be inhaled through a nebulizer.[14]

Ongoing Research

As of this writing, there are 21 open studies investigating treatments for and potential vaccines to prevent RSV in infants and older adults.[15]

Outside of these trials, one important area of research centers on identifying which infants are at greater risk of severe RSV infection so that they are treated more aggressively. In recent years, scientists have made significant progress in better understanding adult lung diseases by studying lung tissue. However, because infants are so fragile, attempting to obtain lung samples is unsafe. But, a recent study conducted at the University of Rochester Medical Center (URMC), which could lead to much more precise diagnosis of RSV and other infant lung diseases, found that cells from an infant's nose are remarkably similar to those found in the lungs. Nasal cells can be captured through a simple swab of the nostril. "An infant with RSV could potentially have their nasal cells tested to determine if they are among the small group that will develop a severe response that might require hospitalization," said Thomas Mariani, PhD, professor of pediatrics at URMC. "Additionally, we could potentially use this method to examine other at-risk infants such as those born prematurely who face a greater risk for lung disease throughout life and identify which of those children should be treated more aggressively."[16]

While developing a vaccine that would prevent RSV in all people is what is ultimately needed, despite repeated efforts, no vaccine has yet been effective. Interestingly, though, scientists at Vanderbilt University Medical Center (VUMC) working with colleagues in California and Pennsylvania believe they have discovered why the virus has been so difficult to neutralize. They found that competition among antibodies for binding the same viral site can interfere with effective neutralization of the virus. Using palivizumab (the drug licensed to prevent serious RSV complications in high-risk infants), which targets the antigenic site II of the RSV F protein that fuses the viral particle to its target cell in the lung, they found that the target cell undergoes a dramatic structural rearrangement and reveals another, previously concealed binding site next to site II. In essence, the neutralizing antibody essentially binds to the new site instead of the target site. According to the researchers, the answer may be to design a vaccine strategy that identifies and produces neutralizing monoclonal antibodies that target only site II and not the entire F protein.[17]

Today, two RSV fusion (F) nanoparticle vaccines, both manufactured by Novovax, are in Phase III clinical trials.[18]

Looking Ahead

Understanding and preventing RSV is a priority. In August 2015, the National Institutes of Health launched a new study to help understand infection in healthy adults to aid development of RSV medicines and vaccines. The study will enroll up to 60 healthy men and nonpregnant women ages 18 years to 50 years who will receive a drop of liquid containing RSV in each nostril and remain hospitalized in isolation for one to two weeks, during which time they will be monitored for development and progression of disease. Results are expected sometime in 2017.[19]

Today is an exciting time as vaccines progress in clinical trials to protect against RSV. In June, the Advisory Committee on Immunization Practices' RSV Vaccines Working Group presented an update that outlined the status of preventive measures against RSV, as well as its goals in relation to adults aged 60 years and older and those with underlying medical conditions. The update points out how much progress has been made since 2003, when only one live-attenuated vaccine was in Phase I trials, to the one now approved for high-risk infants, and the 11 others in clinical trials, four of which are in Phase II and III trials.[18]

With nearly 19,000 deaths each year due to RSV, it can only be hoped that this illness will one day be much less prevalent, if not eliminated altogether. ❖

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

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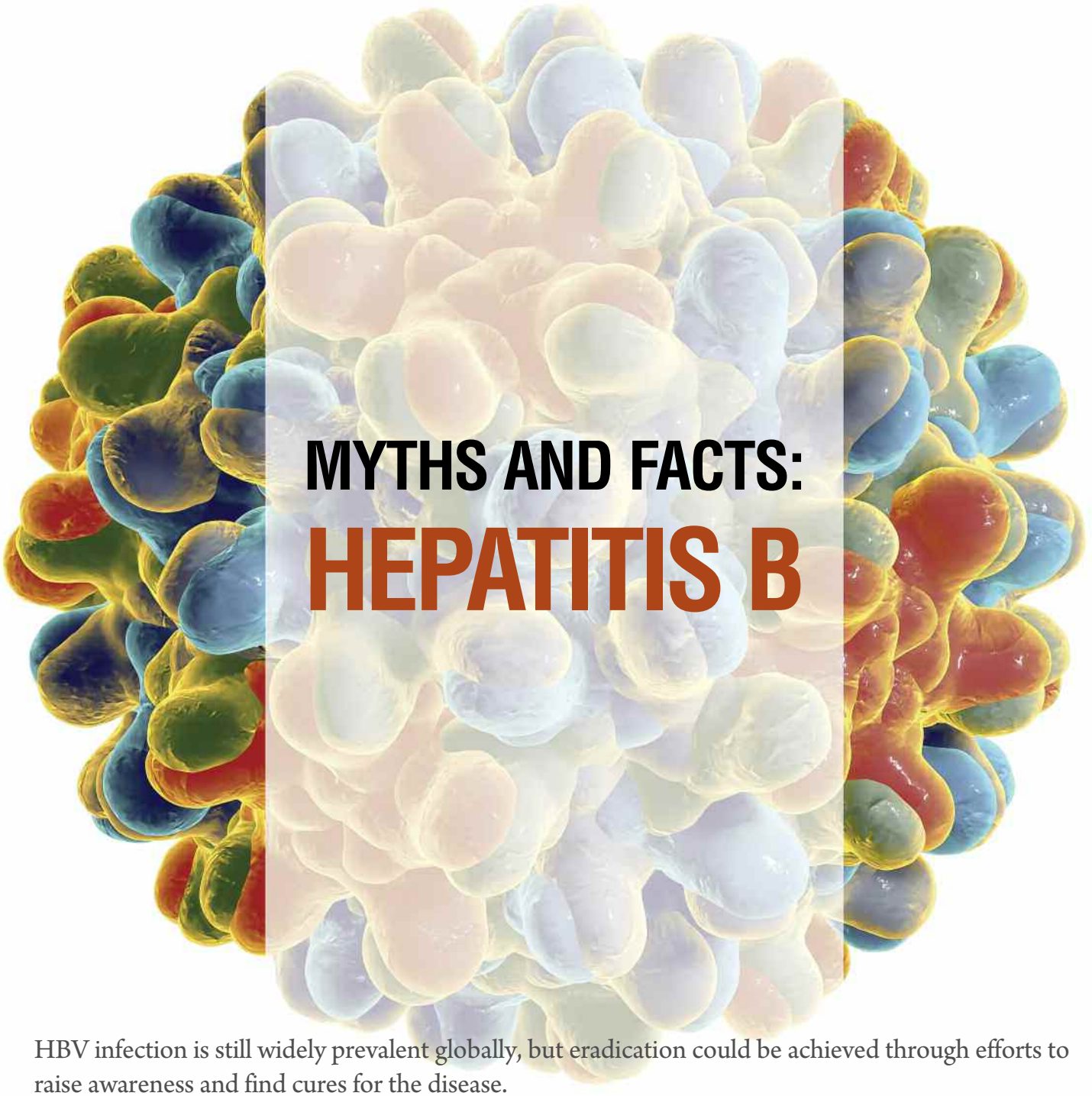

MYTHS AND FACTS: HEPATITIS B

HBV infection is still widely prevalent globally, but eradication could be achieved through efforts to raise awareness and find cures for the disease.

Ronale Tucker Rhodes, MS

IN 2016, MORE than 650 patients at a hospital in Melbourne, Australia, were believed to be at risk of contracting hepatitis B after coming into direct contact with an infected healthcare worker. Letters mailed by the health department to notify the patients recommended a blood test to determine if they had been infected. Newspaper reports about the risk of contracting the "deadly" virus created a scare, with one woman reportedly saying "she had been crying and shaking ever since she received the health department letter."[1] Scares have also occurred in the U.S., including one in 2009 when five patients tested positive after visiting the same doctor's office in New Jersey,[2] and another in 2013, when 420 patients were notified by the Tulsa (Okla.) Health Department that they had potentially been exposed to the virus after being treated at a dentist's office where health investigators found sterilization, staffing and other infractions.[3]

Hepatitis B is but one of the many strains of hepatitis, ranging from A to G, with types A, B and C the most common. While hepatitis has been around for centuries, it wasn't until the 1940s when doctors discovered the virus responsible for it.[4] Hepatitis B was officially recognized in 1967 when Baruch Blumberg, MD, and his team, while studying hemophiliac patients who had received multiple blood transfusions, identified an unusual antigen from a blood sample of an Australian Aborigine. They later determined that antigen was the cause of hepatitis B, a discovery for which Dr. Blumberg was awarded the Nobel Prize for Medicine in 1976. Just two years later, he and his colleague, Irving Millman, MD, invented the hepatitis B vaccine and the diagnostic test for hepatitis B.[5]

Hepatitis B virus (HBV) infects the liver and can cause liver inflammation called "hepatitis."[6] It is estimated to have infected two billion people throughout the world, 400 million of whom have chronic hepatitis B, making it one of the most common human pathogens.[7] In 2014 in the U.S., there were an estimated 19,200 new infections, with an overall incident rate of 0.9 cases per 100,000 people, and an estimated 850,000 to 2.2 million total cases (depending on the study) of chronic HBV infection.[8,9] Hepatitis B is widespread and can be deadly, which makes the facts surrounding the disease paramount to reducing its spread.

Separating Myth from Fact

Myth: Hepatitis B is a rare disease.

Fact: Hepatitis B is one of the most common infectious diseases in the world, having infected more than one-third of the global population.[10]

Myth: Only people who are suspected of being exposed to HBV should be tested.

Fact: Anyone is capable of contracting hepatitis B. People who are suspected of being exposed should definitely be tested. The Centers for Disease Control and Prevention (CDC) specifically recommends the following individuals be tested even if it is not suspected they have been exposed to HBV: all pregnant women; persons born in regions with intermediate or high rates of hepatitis B; U.S.-born persons not vaccinated as infants whose parents were born in regions with high rates of hepatitis B; men who have sex with men; injection drug users; patients with elevated liver enzymes of unknown etiology; hemodialysis patients; persons needing immunosuppressive or cytotoxic therapy; HIV-infected persons; and donors of blood, plasma, organs, tissues or semen.[8]

The basic test for HBV infection is called the Hepatitis B Core IgM Antibody test, which will indicate the serological markers (Table 1) that show whether an individual is immune to, susceptible to or infected with HBV.[11]

Table 1. Serological Markers of HBV Infection Identified with the Hepatitis B Core IgM Antibody Test[11]

- Hepatitis B surface antigen (HBsAg): A protein on the surface of HBV; it can be detected in high levels in serum during acute or chronic HBV infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- Hepatitis B surface antibody (anti-HBs): The presence of anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develop in a person who has been successfully vaccinated against hepatitis B.
- Total hepatitis B core antibody (anti-HBc): Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with HBV in an undefined time frame.
- IgM antibody to hepatitis B core antigen (IgM anti-HBc): Positivity indicates recent infection with HBV (≤6 months). Its presence indicates acute infection.
- Hepatitis B e antigen (HBeAg): A secreted product of the nucleocapsid gene of HBV that is found in serum during acute and chronic hepatitis B. Its presence indicates that the virus is replicating and the infected person has high levels of HBV.
- Hepatitis B e antibody (HBeAb or anti-HBe): Produced by the immune system temporarily during acute HBV infection or consistently during or after a burst in viral replication. Spontaneous conversion from e antigen to e antibody (a change known as seroconversion) is a predictor of long-term clearance of HBV in patients undergoing antiviral therapy and indicates lower levels of HBV.

Myth: The incidence of HBV infections has been increasing.

Fact: Actually, CDC reports that acute hepatitis B has been declining in incidence since 1990 mainly due to effective vaccination strategies, with the number of reported cases remaining stable since 2009. Chronic HBV infection, on the other hand, remains a major public health challenge. More than one-half of chronic HBV infections are among Asians and Pacific Islanders, and 71.3 percent are among persons born outside of the U.S. In addition, approximately 47 percent to 70 percent of those with HBV infection living in the U.S. were born in other countries.[12]

Myth: Hepatitis B can be inherited.

Fact: Yes and no. While hepatitis B can't be inherited from parents, pregnant women infected with HBV can spread the virus to their babies during childbirth.[12]

Myth: Hepatitis B can be contracted by eating contaminated food or by kissing.

Fact: The only way hepatitis B can be spread is by coming into contact with blood, semen and vaginal secretions. The most common causes of transmission include unprotected sexual contact, sharing needles among injection drug users and reuse of contaminated needles and syringes. Other causes of transmission include sharing of razor blades or toothbrushes. In the U.S. and Canada, the virus is rarely transmitted via blood transfusions since donated blood is routinely screened for hepatitis B.[6]

Myth: People with hepatitis B have very obvious symptoms.

Fact: People can live with hepatitis B for decades without having any symptoms or feeling sick. It is estimated that only 30 percent of people who are infected with the virus show any signs or symptoms.[12] And, two out of three Asian-Americans with hepatitis B don't know they are infected.[13] Those who do show symptoms usually do so within 90 days after exposure. Symptoms may include jaundice, dark-colored urine, tan-colored stools, mild fever, excessive tiredness, poor appetite, abdominal pain, nausea and vomiting.[10,14]

Myth: Hepatitis B affects all persons the same.

Fact: The natural course of hepatitis B differs from one person to another. When individuals are initially infected, they have acute hepatitis B infection. During the acute phase, 90 percent of adults' immune systems will successfully fight it, clearing the infection within six months, healing the liver completely and becoming immune to hepatitis B infection for the rest of their lives. Not as fortunate, 10 percent of adults' immune systems are unable to fight the virus, and they develop chronic hepatitis B infection, meaning they will have it for the rest of their lives. In babies, the percentages are reversed; only 10 percent clear the infection, while the remaining 90 percent develop chronic hepatitis B infection.

In those with chronic hepatitis B infection, the liver becomes

inflamed and scarred over the years, but the speed at which that takes place varies between people. Some will not have a problem during their lifetime, while others will develop severe liver scarring (cirrhosis) within 20 years.[15] Left untreated, nearly one in four people with chronic hepatitis B develops serious liver problems, even liver cancer.[13] Indeed, hepatitis B is the main cause of liver cancer.[14] And, it is a leading cause of cancer deaths among Asian-Americans.[13]

Myth: People with hepatitis B will likely develop other strains of hepatitis.

Fact: It's not possible for hepatitis B to develop into another strain of hepatitis because each is caused by its individual strain. For instance, hepatitis A is caused by the hepatitis A virus, and so on. However, sometimes people with hepatitis B also get hepatitis D.[12]

In observance of World Hepatitis Day 2016, the Hepatitis B Foundation partnered with Eiger BioPharmaceuticals, a developer of therapeutics for hepatitis D, to launch a first-of-

its-kind hepatitis D disease awareness and testing program. Hepatitis D is the deadliest form of viral hepatitis that occurs only in people already infected with hepatitis B since the D virus needs the B virus to survive. "Hepatitis delta is the most severe form of viral hepatitis, yet many patients suffering from chronic hepatitis B are unaware of their risk for co-infection with hepatitis delta virus," said Robert Gish, MD, medical director of the Hepatitis B Foundation. It is hoped that expanded testing will enable patients and their healthcare providers to better understand disease progression and clinical management outcomes.[16]

Myth: There is no reliable protection against HBV infection.

Fact: Controlled clinical trials show that the hepatitis B vaccine provides greater than 90 percent protection from acute and chronic infection in infants, children and adults immunized before being exposed to the virus.[17] And, immunologic memory provided by the vaccine remains intact for at least 20 years among healthy individuals who initiate the vaccine on or after 6 months of age. Studies also show that the vaccine provides long-term protection against clinical illness and chronic HBV infection even though antibody levels might become low or decline below detectable levels.[11]

Table 2. CDC Hepatitis B Vaccination Recommendations[8]

- All infants at birth
- Older children who have not previously been vaccinated
- Susceptible sex partners of infected persons
- Persons with multiple sex partners
- Persons seeking evaluation or treatment for an STD
- Men who have sex with men
- Injection drug users
- Susceptible household contacts of infected persons
- Healthcare and public safety workers exposed to blood on the job
- Persons with chronic liver disease, including HCV-infected persons with chronic liver disease
- Persons with HIV infection
- Persons with end-stage renal disease, including pre-dialysis, hemodialysis, peritoneal dialysis and home dialysis patients
- Residents and staff of facilities for developmentally disabled persons
- Travelers to regions with intermediate or high rates of hepatitis B (HBsAg prevalence of ≥2%)
- Unvaccinated adults with diabetes mellitus ages 19–59 (for those aged ≥60 years, at the discretion of clinician)
- Anyone else seeking long-term protection

Hepatitis B is one of the most common infectious diseases in the world, having infected more than one-third of the global population.

Currently, there are two single-antigen and two combination vaccines available in the U.S. Single-antigen vaccines, which protect against only hepatitis B virus, include Engerix-B (GlaxoSmithKline) and Recombivax (Merck), both of which can be administered to infants and adults. Combination vaccines include Pediarix (GlaxoSmithKline), which protects against hepatitis B, diphtheria, tetanus, pertussis and inactivated poliovirus, and Twinrix (GlaxoSmithKline), which protects against both hepatitis A and B. Pediarix is for children only, ages 6 weeks through 7 years. Twinrix is recommended only for persons aged 18 years or older who are at increased risk for both hepatitis A and B infections.[11]

Both CDC and the American Academy of Pediatrics recommend that all children receive the hepatitis B vaccine starting at birth. CDC also recommends the vaccine for people who are at increased risk of contracting HBV (Table 2).[8]

The recommended vaccine schedule for both children and adults is three intramuscular injections, with the second and third doses administered one month and six months, respectively, after the first dose. Infants born to HBV-infected mothers require the vaccine and hepatitis B immune globulin within 12 hours of birth to protect them from infection. And, because the vaccine contains no live virus, it is safe during pregnancy and lactation, as well as in immunocompromised persons.[11]

Myth: Hepatitis B can be treated.

Fact: Generally, there is no treatment for acute hepatitis B because it usually resolves in a matter of weeks. In this case, individuals are advised to get plenty of rest, adequate nutrition and fluids. In severe cases, some people need to be hospitalized.[18]

Treatment for chronic hepatitis B includes antiviral drugs and regular monitoring for signs of liver disease progression.

Table 3. FDA-Approved Antiviral Drugs to Treat Chronic HBV Infection[19]

Brand Name	Generic Name	Manufacturer	Indication
Baraclude	Entecavir	Bristol-Myers Squibb	Patients with evidence of active viral replication
Epivir HBV	Lamivudine	GlaxoSmithKline	Patients with hepatitis B viral replication and active liver inflammation
Hepsera	Adefovir dipivoxil	Gilead Sciences	Patients 12 years of age
Intron A	Interferon alpha-2b	Schering	Patients 1 year of age or older with compensated liver disease
Pegasys	Peginterferon alpha-2a	Roche	Adult patients with HBeAg positive and HBeAg negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation
Tyzeka	Telbivudine	Novartis	Adult patients with evidence of viral replication and either evidence of persistent elevations in serum amino transferases or histologically active disease
Viread	Tenofovir	Gilead Sciences	Adults

Currently, there are seven FDA-approved antiviral drugs to treat chronic HBV infection (Table 3):[19]

In 2015, the World Health Organization issued its first hepatitis B treatment guidelines that cover the full spectrum of care, from determining who needs treatment, to what medicines to use and how to monitor people long-term (Table 4).[20]

Myth: Hepatitis B can be cured.

Fact: Acute hepatitis B usually cures itself when the body kills the virus. There is, however, no cure for chronic hepatitis B, only treatment, although medicines may lower virus levels in the body to an undetectable level.[21] There may be hope for a cure in the future, though.

In April 2015, Australian scientists reported on a study in which they used an experimental U.S.-created cancer drug to cure hundreds of mice suffering from chronic hepatitis B. The drug, birinapant, has been tested in more than 350 Americans, but it is still in clinical testing. "Birinapant enabled the destruction of hepatitis B-infected liver cells while leaving normal cells unharmed," said Marc Pellegrini, who led the team at Melbourne's Walter and Eliza Hall Institute. "Excitingly, when birinapant was administered in combination with the current antiviral drug entecavir, the infection was cleared twice as fast compared with birinapant alone."

According to Pellegrini, the drug restores apoptosis, a biological mechanism that clears damaged cells. "Normally, [healthy] liver cells would respond to infection by switching on a signal that tells the cell to destroy itself for the greater good, preventing further infection," he explains. "However, our research showed that the virus commandeers the liver cells' internal communications,

Table 4. World Health Organization Hepatitis B Treatment Guidelines Key Recommendations[20]

1) Use of a few simple noninvasive tests (aspartate aminotransferase-to-platelet ratio index and transient elastrography) to assess the stage of liver disease to help identify who needs treatment

2) Prioritizing treatment for those with the most advanced stage of liver disease

3) Use of two safe and highly effective medicines — tenofovir or entecavir — because they have a very low risk of developing drug resistance, are easy to take as one pill once a day and have few side effects

4) Regular monitoring using simple tests for early detection of liver cancer to assess whether treatment is working and if treatment can be stopped

telling the cells to ignore the infection and stay alive. Birinapant flips the cell survival 'switch' used by the virus, causing the infected cell to die."

Birinapant, developed by Tetralogic, has been undergoing medical tests since 2009 and is currently in Phase II trials. Human clinical trials of birinapant in combination with entecavir are currently underway in Melbourne, Perth and Adelaide.[22]

Also working toward a cure, the Hepatitis B Foundation, announced in January its successful completion of its "Nobel Challenge" campaign that raised more than $3 million to further its mission to eliminate the deadly hepatitis B virus. Funds will support the efforts of its nonprofit research arm, the Baruch S. Blumberg Institute, to accelerate the pace of research in pursuit of a cure for hepatitis B. In March, the Institute recruited a team of nationally renowned scientists to focus exclusively on research to develop a cure for hepatitis B.

According to the Foundation, "Blumberg researchers are building on recent discoveries that have heightened the momentum around finding a cure for hepatitis B and liver cancer: new screening methods to search for effective drugs; new ways to treat hepatitis B using different approaches to shut down the virus; a new blood biomarker that aids in the early detection of liver cancer; and a promising drug that selectively kills liver cancer cells in animal studies." The researchers, according to Timothy Block, PhD, president and co-founder of the Hepatitis B Foundation, "are among the first, if not the only group, to identify a small molecule that inhibits hepatitis B virus cccDNA formation. This is significant because inhibition of cccDNA is considered essential in achieving a complete cure." The scientists hope their breakthrough discoveries will result in human clinical trials within the next three years.[23,24]

Dispelling the Myths Now

On July 28, World Hepatitis Day was celebrated with the theme "elimination." According to the World Health Organization (WHO), 2016 is a pivotal year for viral hepatitis with WHO member states adopting an elimination strategy for the disease.[25] The initiative, which was introduced at the 69th World Health Assembly in May, is the first global health sector strategy on viral hepatitis and includes goals for the elimination of viral hepatitis as a public health threat by 2030.[26]

According to CDC's Division of Viral Hepatitis, the National Academies of Sciences, Engineering and Medicine Health and Medicine Division (formerly the Institute of Medicine) released a report that explores the barriers to eliminating the public health problem of hepatitis B and hepatitis C in the U.S., and reaffirms that hepatitis elimination can be achieved with the right resources, commitment and strategy. Its follow-up (Phase II) report, due to be released in early 2017, is expected to include specific recommendations and targets for elimination.

On July 28, World Hepatitis Day was celebrated with the theme "elimination."

Until these efforts come to fruition, with roughly one-third of the global population infected with HBV, heightening awareness and eliminating the myths surrounding hepatitis B are the best measures for limiting this deadly disease. ❖

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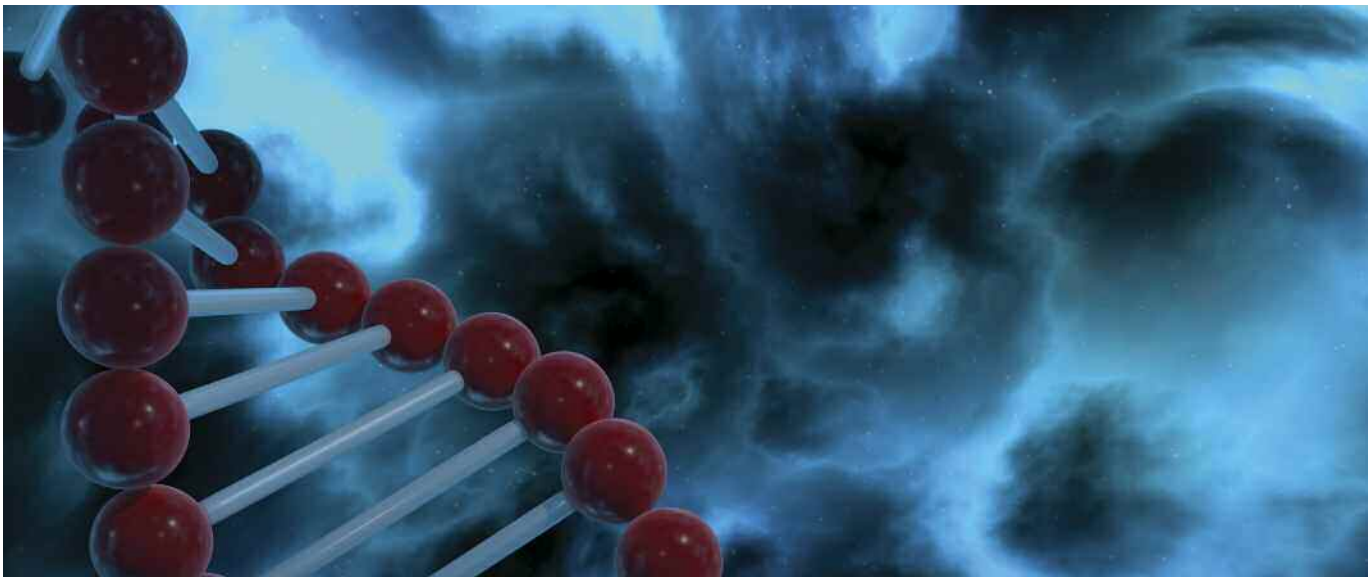
Toward the Ultimate Cure: *Gene Therapy for Severe Combined Immunodeficiency*

By Keith Berman, MPH, MBA



PRIOR TO THE successful use of hematopoietic stem cell transplantation (HSCT) to reconstitute the immune system, profound derangements of both cellular and humoral immunity in newborns born with severe combined immunodeficiency (SCID) were always fatal in infancy. Clinical experience accumulated over the last two decades has helped refine HSCT therapy and, thus, improve the odds of long-term survival for children born with this extremely rare genetic disorder. It is now apparent, for example, that for certain patients, the likelihood of long-term survival improves with a less intensive myeloablative conditioning regimen, or no conditioning at all. It's now well-documented that survival odds are much better in SCID infants diagnosed and transplanted in the first three-and-a-half months after birth, or who are fortunate enough not to have experienced an infection prior to their procedure.[1] This understanding of the importance of very early transplantation was a major impetus for universal newborn SCID screening with the T-cell excision circle (TREC) assay, which is now in place or is being implemented in 47 states.[2]

But the predominant factor that influences long-term survival is outside anyone's control: the availability (or nonavailability) of blood-forming hematopoietic stem cells (HSCs) from an HLA-identical sibling donor. For SCID infants with a matched sibling bone marrow or peripheral blood stem cell donor, the prospects for long-term survival are now edging toward 100 percent.[1] Unfortunately, less than 25 percent of patients have a matched sibling donor.[3]

SCID patients for whom only a matched unrelated or haploidentical HSC donor is available face far higher risks of life-threatening complications and death. Many continue to suffer severe recurrent infections due to only partial engraftment and incomplete restoration of immunity. HSCT will fail to adequately restore B-cell immunity in as many as one-half of these patients, necessitating chronic antibody replacement therapy with intravenous immune globulin (IVIG). Repeated breakthrough infections and complications of HSCT, including graft-versus-host disease, can

cause cumulative damage to the lungs and other vital organs. Many of these children experience failure to thrive and cognitive deficits. More than one in four will succumb within the first five years after HSCT.[1]

The one remaining therapeutic option has been the dream of clinicians for decades: to treat the disorder by correcting it at its most fundamental genetic level, with gene therapy.

The Infancy of Gene Therapy

By the 1980s, genetic flaws causing the two most common forms of SCID had been identified and fully characterized:

• ADA-SCID: A defective gene encoding adenosine deaminase (ADA) results in a deficiency of this metabolic enzyme, which is critical for lymphocyte differentiation and growth.

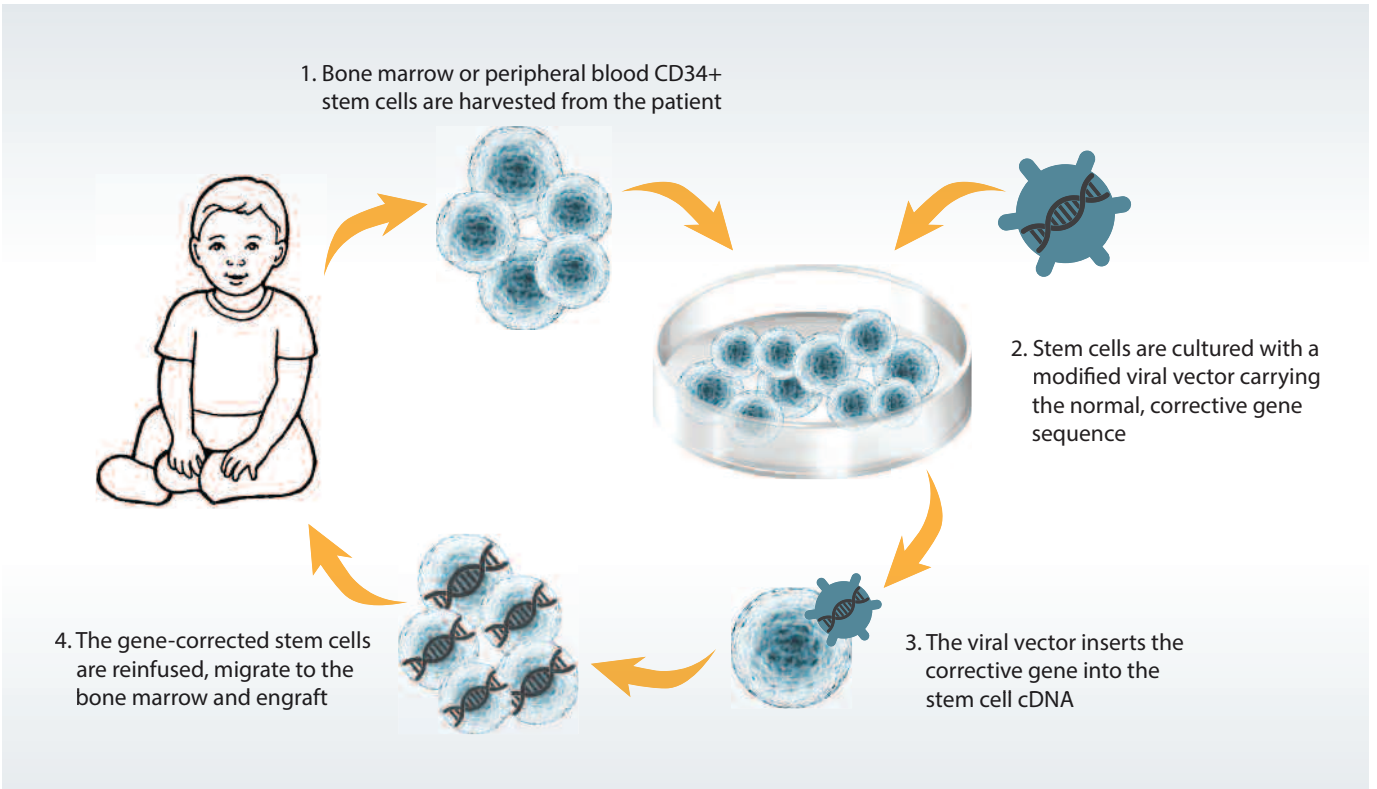
• SCID-X1: A defective gene on the X chromosome that encodes the common gamma chain of the interleukin-2 (IL-2) receptor (IL2RG) results in profound disruption of the development of T lymphocytes and natural killer (NK) cells.

In a handful of cutting-edge laboratories here and in Europe, techniques were developed to exploit the ability of gamma-retroviruses to ferry and insert normal copies of the affected genes directly into the DNA of CD34+ lymphocytes collected and purified from the patient's own bone marrow or blood circulation. The idea was to expand these gene-corrected cells ex vivo and reinfuse them into the patient, to find their way into the bone marrow space and differentiate into the T and B lymphocytes and NK cells that mediate immune function (Figure 1).

On Sept. 14, 1990, after much testing in animal models, U.S. investigators at the National Institutes of Health initiated the world's first human gene therapy trial in a 4-year-old U.S. girl with ADA-SCID.[4] Shortly thereafter, Italian investigators at the San Raffaele Telethon Institute for Gene Therapy initiated their own trial, employing different gamma-retrovirus vectors to insert the normal ADA gene into defective CD34+ lymphocytes harvested from patients with ADA-SCID.[5]

In simultaneous reports published five years later in the journal *Science*, the Italian and U.S. teams announced highly encouraging findings in a total of four ADA-SCID patients who had previously been supported with exogenous ADA replacement therapy.[6,7] The T cell and NK cell counts normalized in all patients, as did a number of cellular and humoral

Figure 1. Schematic Representation of a Gene Therapy Procedure for SCID



immune responses. ADA gene expression persisted in the two U.S. patients at four-year follow-up. At that point, it appeared that the dream might soon become reality.

Protocol Change Transforms ADA-SCID Gene Therapy

Unfortunately, it soon became evident that the initial engraftment of retrovirus- and ADA gene-transduced T lymphocytes did not sustain itself sufficiently over the long term; the small proportion of genetically corrected HSCs that did engraft failed to provide adequate protection against severe infections. Fortunately, later experimentation demonstrated that mild cytoreductive "conditioning" with low-dose busulfan or similar agents, essentially making room in the bone marrow for the reinfused gene-corrected CD34+ lymphocytes, was highly effective in facilitating immune reconstitution.

In 2002, the San Raffaele Telethon team was the first to describe sustained engraftment of genetically engineered HSCs using nonmyeloablative conditioning, with long-term increases in T-cell counts, normalization of T-cell function and restoration of a robust humoral response to vaccine challenges in two ADA-SCID patients.[8] Seven years later, this same team reported the outcomes of gene therapy using autologous CD34+ bone marrow cells transduced with a gamma-retroviral vector in 10 children with ADA-SCID and no available HLA-identical sibling donor: All 10 patients were alive after a median of 4.0 years (range 1.8 to 8.0) with stable engraftment of HSCs. Nine of the 10 had normalization of T-cell function, and five no longer required IVIG replacement therapy. "Effective protection against infections and improvement in physical development has made a normal lifestyle possible," the investigators reported.[9] Other gene therapy research teams in Europe and the U.S. have published similar results with different ADA-SCID gene therapy protocols using a conditioning regimen and conventional gamma-retroviral vectors to insert normal copies of the ADA gene into CD34+ HSCs.[10,11]

New findings published this year by an international consortium again led by San Raffaele Telethon confirm 100 percent long-term survival in 18 consecutive ADA-SCID patients receiving gene therapy, with normalization of T-cell populations, reduced need for IVIG replacement and a 10-fold mean reduction in severe infection rates.[12] Further, in contrast to other severe primary immunodeficiency disorders treated with gene therapy, no cases of retrovirus-mediated insertional mutagenesis have been identified in any of the roughly 60 ADA-SCID patients treated to date.

A landmark event in May 2016 marked the culmination of a 25-year journey by these investigators, their clinical collaborators on three continents and the courageous families that agreed to participate. Acting on a recommendation by the European Medicines Agency — Europe's equivalent of the U.S. Food and Drug Administration (FDA) — the European Commission approved Strimvelis (autologous CD34+ cells transduced to express ADA) for the treatment of patients with ADA-SCID for whom no suitable HLA-matched related stem cell donor is available. It is the world's first licensed corrective childhood gene therapy.

Strimvelis will be marketed in European Union countries by GlaxoSmithKline, which also collaborated in its final stages of development. This individually customized treatment for ADA-SCID fulfills the promise of gene therapy: to essentially cure the more than three-quarters of ADA-SCID children who do not have a suitable donor for HSCT.

Gene Therapy for SCID-X1: Full Stop to Full Speed Ahead

Concurrent with preliminary ADA-SCID trials in the early 1990s, other investigators were actively testing similar gene therapy protocols to treat male children with X-linked severe combined immunodeficiency (SCID-X1) and a poor HSCT prognosis. SCID-X1 is the predominant disease variant, accounting for 50 percent to 60 percent of all SCID cases. Preclinical studies confirmed that gamma-retroviral vectors effectively inserted the healthy gene for IL2RG into harvested CD34+ cells. A decade later, after incorporating the mild nonmyeloablative conditioning that produced durable engraftment in ADA-SCID gene therapy trials, small published SCID-X1 patient series documented persisting normalized T, B and NK cell counts and restored immune functions.[13,14]

But a shocking and unexpected setback put a halt to progress in SCID-X1 gene therapy: Five of the first 20 patients treated in these trials developed T-cell leukemia between two and five years after their procedure. In all cases, evidence pointed to aberrant activation of nearby oncogenes triggered by a powerful oncogene "enhancer" element within the gamma-retroviral vector.

Investigators immediately set about developing safer gene transfer vectors. Two types are now being evaluated in clinical trials with encouraging efficacy results and, thus far, without any evidence of a leukemogenic effect. One is modified gamma-retrovirus vectors entirely devoid of enhancer sequences,[15] and the second is novel "self-inactivating" lentiviral vectors designed to have a reduced risk of activating oncogenes.[16] Extended patient accrual and follow-up will be necessary to establish whether these alternative vectors prove to be safe in current SCID-X1 gene therapy trials, as well as in ongoing trials evaluating

Table 1. Active U.S. Gene Therapy Trials for Primary Immunodeficiency Disorders

Disorder	Sponsor	Study Title	ClinicalTrial.gov identifier
Adenosine Deaminase-Dependent SCID (ADA-SCID)	Donald Kohn, MD/ National Institutes of Health	Autologous Transplant of EFS-ADA Modified Bone Marrow Cells for ADA-Deficient Immunodeficiency (SCID)	NCT01852071
X-Linked SCID (SCID-X1)	David Williams, MD/ Boston Children's Hospital	Gene Transfer for SCID-X1 Using a Self-Inactivating Gammaretroviral Vector	NCT01129544
	St. Jude Children's Research Hospital/ NHLBI	Gene Transfer for Severe Combined Immunodeficiency in Newly Diagnosed Infants (LVXSCID-ND)	NCT01512888
	National Institute of Allergy and Infectious Diseases (NIAID)	Lentiviral Gene Transfer for Treatment of Children Older Than 2 Years of Age With X-Linked Severe Combined Immunodeficiency (XSCID)	NCT01306019
Chronic Granulomatous Disease (CGD)	NIAID/Genethon	Study of Gene Therapy Using a Lentiviral Vector to Treat X-Linked Chronic Granulomatous Disease	NCT02234934
Wiskott-Aldrich Syndrome (WAS)	David Williams, MD/ Boston Children's Hospital	Pilot and Feasibility Study of Hematopoietic Stem Cell Gene Transfer for Wiskott-Aldrich Syndrome	NCT01410825

gene therapy for two other primary immunodeficiency disorders — Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD) — in which earlier use of gamma-retroviral vectors was also associated with fatal acute leukemia (Table 1).

On the Horizon: More Approvals for More Uses

Past challenges of long-term engraftment of gene-corrected progenitor cells and vector-associated leukemia risks appear to have been resolved. All evidence now suggests that gene therapy is largely curative for most patients with ADA-SCID and SCID-X1, without the risks of complications and graft failure associated with matched unrelated or haploidentical HSCT.

Additional findings from six currently ongoing gene therapy clinical trials[17] will be of value to further optimize patient outcomes. All evidence suggests that it is now only a matter of time before gene therapy protocols for these two rare genetic disorders — and potentially CGD, WAS and other life-threatening primary immunodeficiencies — secure FDA approval for commercialization.

Meanwhile, what has been learned about how to optimize the safety and efficacy of gene therapy from experience with SCID patients has helped researchers to design better gene therapy vectors and clinical protocols for far more common genetic disorders, including, for example, sickle cell disease, beta-thalassemia and hemophilia A and B. Thanks to this pioneering SCID research, thousands of patients with these debilitating disorders may not need to wait so long for potentially curative gene therapy: All three are currently the subjects of active clinical trials. ❖

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. Since 1989, he has also served as editor of *International Blood/ Plasma News*, a blood products industry newsletter.

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Psoriatic arthritis can be a difficult diagnosis to manage. Julie Cerrone, who has lived with the disease since age 10, has learned to not only survive but thrive, and now helps others do the same.

Psoriatic Arthritis: *A Patient's Perspective*

By Trudie Mitschang

IT BEGAN AS a twinge in her left knee. A 10-year-old softball player, Julie Cerrone underwent painful knee surgery after being diagnosed with a torn meniscus. Seventeen years later, after enduring multiple surgeries and misdiagnoses, she learned the injury she sustained at age 10 was caused by the underlying inflammation associated with psoriatic arthritis.

Psoriatic arthritis is a chronic inflammatory autoimmune condition that causes joint pain, stiffness and swelling. Because the symptoms aren't always obvious, it is commonly misdiagnosed, as Cerrone learned the hard way. She recalls spending much of her childhood enduring physical therapy or using a brace or crutches for mobility as doctors attempted to figure out what was wrong with her.

A Painful Road to Diagnosis

Although ill for much of her life, Cerrone's symptoms disappeared for a few years after high school but returned with a vengeance after college. As a young information technology consultant, Cerrone struggled to cope with a challenging career and a chronic illness. "It was a very strenuous job," she says. "I would fly out on business Monday and not come home until Friday." As the stress mounted, Cerrone started feeling worn down, and the pain down her leg returned. "If I moved even a little, the pain would be agonizing."

The next three years were filled with confusion and misdiagnoses — from sciatica to a thickening of her synovial tissue, the latter of which led to two back-to-back knee surgeries in 2012. Then, in December of that year, things came to a head. "My leg swelled up so much I couldn't even put pants on," she says. Frustrated, Cerrone referenced a health diary her mother had used to record her symptoms and injuries from the time she was an infant. Seeing a pattern, she brought the information to her rheumatologist, who ultimately diagnosed her with a severe case of psoriatic arthritis, along with complex regional pain syndrome and avascular necrosis in her femur bone.

Looking back, Cerrone believes her early experience with physicians and the resulting frustration ultimately helped her to become her own healthcare advocate. "So much pressure is put on doctors to tell us everything we need to do to get better. But if you learn as much as you can about psoriatic arthritis on your own and are vigilant about your symptoms, you can go a long way toward helping yourself," she says. "I feel as though I get more concrete answers from my doctors now because I've become more knowledgeable and am more prepared to ask the right questions."

From Health-Challenged to Health Coach

Once she received her diagnosis, Cerrone's doctors put her on methotrexate and Humira (adalimumab), a TNF inhibitor. While she says both medications helped, she also credits other components of her treatment plan for her symptom relief, including eliminating gluten and red meat from her diet and alternative treatments such as yoga and water therapy. "I actually spent a year tracking every single one of my symptoms," Cerrone says. "I recently presented all my tracking methods, from food, relationships and activity levels, to sleep patterns, moods and emotions, at Stanford Medicine X. I was able to identify my specific triggers, which led me to my ultimate treatment plan."

Despite her arduous journey to diagnosis and the many setbacks along the way, getting the right diagnosis and treatment plan has allowed Cerrone to become an expert in managing psoriatic arthritis. A born optimist, she now refers to her condition as a blessing in disguise: "It gave me a chance to start a career helping others."

Today, Cerrone makes her living as a certified holistic health coach, yoga instructor and WEGO Health patient influencer and network director. She has been blogging about living with psoriatic arthritis for several years, developing a loyal following. "Whether it's through health coaching, through my blog, through a yoga class or working with the amazing patient influencers at WEGO Health," Cerrone says, "I'm always striving to help patients realize they still can live their best life despite any diagnosis." ❖

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

Psoriatic Arthritis:
A Physician's Perspective

DAFNA GLADMAN, MD, is a rheumatologist at the Toronto Western Hospital and senior scientist at the Krembil Research Institute in Toronto, Ontario, Canada. For close to 40 years, Dr. Gladman has built a career in rheumatology focused on finding answers about psoriatic arthritis. She was the recipient of the Verna Wright Prize for outstanding contribution to the field of psoriatic arthritis presented by the International Psoriatic Arthritis Group in Naples, Italy.

BSTQ: Tell us about your background and research in psoriatic arthritis (PsA).

Dr. Gladman: I have been working in the area of PsA since 1978, when I started the Psoriatic Arthritis Clinic at Women's College Hospital. It became a program when other researchers joined me in the early 1980s. The PsA program moved with me, first to the Wellesley Hospital and then in 1995 to the Toronto Western Hospital. Our research has demonstrated that PsA is more severe and more common than previously recognized; we identified predictors for progression of clinical and radiological damage, as well as mortality. We have identified genetic factors for susceptibility and disease expression. We have also investigated patient reported outcomes and comorbidities in these patients.

BSTQ: What are the symptoms of PsA?

Dr. Gladman: PsA is an inflammatory form of arthritis. As such, patients present with pain and stiffness in the joints, which may be swollen and occasionally have a red discoloration. Patients may have swollen "sausage digits" called dactylitis, as well as inflammation at the insertion of tendons and ligaments into bone, called enthesitis. Enthesitis most often affects the insertion of ligaments and tendons into the ankle bone (Achilles and plantar fascia). About half the patients have arthritis in the back (spondylitis), which may or may not be symptomatic.

BSTQ: How is PsA typically diagnosed?

Dr. Gladman: PsA is diagnosed clinically based on the presence of psoriasis and/or nail changes and the symptoms provided by the patients coupled with a physical examination. Laboratory tests are often done to rule out other forms of arthritis. X-rays may be very helpful as they show specific changes that help confirm the diagnosis.

BSTQ: How does PsA differ from rheumatoid arthritis (RA)?

Dr. Gladman: Both PsA and RA are inflammatory forms of arthritis. While RA can occur together with psoriasis, nail lesions are more common in patients with PsA. PsA affects men and women equally, while RA affects women three times more often than men. RA affects the first row of knuckles, whereas PsA affects the end row in 53 percent of patients. Also, dactylitis and enthesitis are not features of RA, and patients with RA do not have spondylitis. On the other hand, patients with PsA do not have rheumatoid nodules or the other extra-articular features of RA.

BSTQ: Is PsA hereditary?

Dr. Gladman: Yes. Relatives of patients with PsA are 30 times more likely to have PsA than the general population. We (and others) have identified a number of genetic factors, and are now working on epigenetic factors.

BSTQ: You've been working to develop screening tools for earlier diagnosis. Tell us about that.

Dr. Gladman: We have developed a screening tool for PsA called the ToPAS (Toronto Psoriatic Arthritis Screen), and have modified it as ToPAS2. These instruments can identify PsA among patients with or without psoriasis and have worked very well in our center, as well as in Turkey. We are currently testing whether the ToPAS2 can screen for psoriasis in the general population.

BSTQ: Are there any promising treatments for PsA on the horizon?

Dr. Gladman: There are lots of new therapies for PsA. Since 2000, when the first anti-TNF agent etanercept became available, we now have four additional anti-TNF agents, including infliximab, adalimumab, golimumab and certolizumab. In addition, we have the anti-IL12/23 agent ustekinumab, and more recently, anti-IL17 agents, including secukinumab and ixekizumab. We also have one oral agent, the PDE4 inhibitor apremilast, available for PsA. The JAK inhibitor tofacitinib, which is already approved for RA, has been proven effective for PsA and will likely be approved in the near future. ❖

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

Countering Vaccine Hesitancy

Author: Kathryn M. Edwards, Jesse M. Hackell, The Committee on Infectious Diseases and The Committee on Practice and Ambulatory Medicine

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

This clinical report provides information about addressing parental concerns about vaccination, referred to as vaccine hesitancy, which emerged to depolarize the "pro" versus "anti" vaccination alignment and to express the spectrum of parental attitudes toward vaccines. It covers statistics related to vaccine acceptance and refusal, vaccine testing and safety, historical vaccine opposition, current vaccine exemptions, factors involved in vaccine acceptance, parents' varied concerns about vaccines and how they should be addressed, and the role that pediatricians play. It also emphasizes that the current vaccine schedule is the only recommended schedule, proposes that an effective communication approach is developing a trusted relationship with parents and using the presumptive delivery strategy, and covers when dismissal of patients who refuse vaccination is acceptable.

pediatrics.aappublications.org/content/138/3/e20162146

Human Albumin Factor VIII (FVIII) Market: Growth, Share, Opportunities, Competitive Analysis and Forecast, 2015-2022

Author: Research Corridor

This report studies current and future aspects of the human albumin FVIII market based upon market dynamics, key ongoing trends and segmentation analysis. It also provides a 360-degree view of the industry with geographic segmentation, statistical forecast and the competitive landscape. It discusses the marketing positioning of the major players, and concludes with a company profiles section that provides information on major developments, strategic moves and financials.

www.researchcorridor.com/human-albumin-factor-vlll-fviii-market

Pharmacy: An Introduction to the Profession

Author: American Pharmacists Association (APhA)

APhA has published its third edition of this textbook geared to student pharmacists entering their first professional year of study. The textbook presents a concise, straightforward analysis of the top pharmacy issues and forces shaping the profession. It covers key topics such as government regulation, ethics and career pathways, and it features a special chapter on communications in pharmacy by Bruce A. Berger, BSPharm, PhD, one of the field's foremost experts on interpersonal and organizational communication. Other features include learning objectives in each of the 10 chapters, a glossary of key pharmacy terms and details about pharmacy associations, internships, residencies and periodicals. Supplementing the book are online readings from the pharmacy literature selected by the authors.

ebusiness.pharmacist.com/PersonifyEbusiness/ShopAPhA/ProductDetails.aspx?productId=93334847

Adding Pediatric Studies to New Drug Development: A Guide to U.S. and EU Rules

Author: U.S. Food and Drug Administration

Under a newly released U.S. Food and Drug Administration (FDA) guidance, Pediatric Study Plans, manufacturers getting ready to submit a New Drug Application or Biologics License Application must include data on potential use of the product in pediatric populations. This report explains the requirements of both U.S. and European Union regulators to guide the process of incorporating pediatric studies into drug development. Included is how to put together a pediatric study plan; how to get a priority review voucher for the application; how to get a waiver or deferral from the pediatric requirement; the kinds of incentives regulators are offering drugmakers to conduct pediatric research; how Canada, Japan and Switzerland are addressing the pediatric research issue; and potential developments in the works.

www.fdanews.com/addingpediatricstudiestonewdrugdevelopment

Similar Efficacy with Use of Subcutaneous and Intravenous Immunoglobulin in CIDP and MMN: Meta-Analysis

Recent interest in the use of subcutaneous immunoglobulin (SCIG) in place of intravenous immunoglobulin (IVIG) for treatment of multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) prompted Canadian investigators to conduct a meta-analysis of published reports evaluating the efficacy and safety of the two IG treatment options for these chronic autoimmune neuropathies.

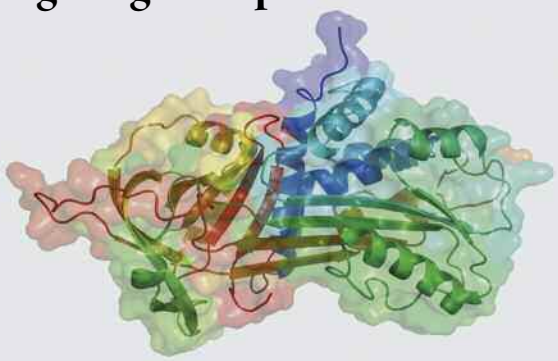
A total of eight studies comprising 50 patients with MMN and 88 patients with CIDP were included in the meta-analysis; six of the eight studies were conducted prospectively. There were no significant differences in muscle strength outcomes in MMN and CIDP with use of SCIG in lieu of IVIG. For MMN, the effect size was 0.65 (95 percent confidence interval [CI], -0.31 to 1.61) and for CIDP, the effect size was 0.84 (95 percent CI, -0.01 to 1.69). Additionally, administration of SCIG was associated with a 28 percent reduction in relative risk of moderate (e.g., fever, headache, nausea) and/or systemic adverse effects (95 percent CI, 0.11 to 0.76).

"Based on its comparable efficacy and seemingly better safety profile, SCIG could be considered as a valid alternative to IVIG

in patients with CIDP and MMN, particularly patients who experience frequent fluctuations or cannot tolerate IVIG despite adjustments to the frequency and doses of infusion," the investigators concluded.

Racosta JM, Sposato LA, Kimpinski K. Subcutaneous vs. intravenous immunoglobulin for chronic autoimmune neuropathies: a meta-analysis. Muscle Nerve *2016 Sep 20 [Epub ahead of print].*

Human Alpha-1 Antitrypsin Improves Early Posttransplant Lung Function in Pig Lung Transplant Model



Human alpha-1 antitrypsin (A1AT) has been shown to prevent pulmonary ischemia-reperfusion injury in rats. Based on this and the ability of large-animal models to provide important preclinical evidence to inform clinical trials, investigators at Toronto General Research Institute used a pig lung transplant model to determine whether human A1AT could attenuate reperfusion injury after prolonged hypothermic preservation.

Donor lungs were preserved for 24 hours at 4 degrees Celsius, followed by lung transplantation. In a randomized and blinded fashion, intravenous A1AT (240 mg/kg; n = 5) or human albumin (n = 5) was administered to lung recipients before reperfusion. Allograft gas exchange function and lung mechanics were monitored during a four-hour reperfusion period. Microscopic lung injury, inflammatory response, coagulation activity and cell death were also assessed.

Pulmonary gas exchange was significantly better during the four-hour reperfusion period in the A1AT group. Treatment with A1AT improved static pulmonary compliance, significantly reduced pulmonary edema and lung permeability, inhibited inflammatory mediators in the circulation, and reduced apoptosis in the lung allografts. Based on this evidence of improved immediate posttransplant lung function in pigs, the investigators proposed consideration of a large-animal survival model to support further advancement toward a clinical trial of A1AT to prevent primary graft dysfunction in lung transplantation.

Iskender I, Sakamoto J, Nakajima D et al. Human α-1 antitrypsin improves early post-transplant lung function: Pre-clinical studies in a pig lung transplant model. J Heart Lung Transplant *2016 Jul;35(7):913-21.*

Information Management Tool

Sylogent has formally launched Projectic, a web-based process management tool designed to visualize milestones, projects and tasks for the pharmaceutical industry. Projectic allows for repetitive structured processes to be saved as templates that are managed by key data points. It has been installed at several pharmaceutical companies to assist with study registration, clinical data disclosure and publication planning. Additional templates are being configured to assist with regulatory submissions, narrative processing and medical information. The stand-alone software is configured to import data from Excel spreadsheets or any source system. It is integrated with Sylogent's structured information platform, Syquence, and other products, including CTD Publisher, Pubstrat, Conference Authority, Journal Selector and clinicaltrials.gov.

Sylogent, (215) 504 7000, projectic.com

Insulin Pen

In July, the U.S. Food and Drug Administration cleared the InPen for marketing in the U.S. Manufactured by Companion Medical, the insulin pen connects to smartphones to help track intake, calculate dosage and manage how much insulin is in reserve. The InPen uses standard Bluetooth wireless to connect to a smartphone app that handles all the calculations, display of data and management of reminders. It automatically calculates dosage and then records both time and size of dose taken at every injection, performing many functions of an insulin pump without being an "electronic leech stuck to the skin that many find unpleasant or uncomfortable." However, the insulin dosage still has to be dialed in manually, which is a safety precaution.

Companion Medical, (858) 522-0252, www.companion-medical.com

Secure RX Printer System

The Secure RX Printer System complies with the Centers for Medicare and Medicaid Services' tamper-resistant prescription law, which took effect in October 2014. The core of the system is a modified Zebra Technologies GX420 locking barcode printer housed in a customized locking acrylic printer enclosure that provides a secure prescription printing solution. The system functions with existing EMR or prescription software and contains an integrated lock to prevent unauthorized removal of prescription media. The half-inch-thick printer enclosure can attach to a desktop or table top for additional security. With remote secure printer management, only authorized personnel can access the printer settings. A cutter and catch tray allows for printing individual prescriptions to prevent waste, and the feed button is disabled to prevent inadvertent printing of prescriptions. The printer is preconfigured for state-approved tamper-resistant direct thermal prescription paper, and the thermal printing technology doesn't require a ribbon. The TCP/IP ethernet protocol is supported. In addition, USB and serial ports are disabled, and Bluetooth and wi-fi printer options are purposely not installed.

Royce Digital Systems Inc., (888) 852-3100, www.roycedigital.com

Fully Automated Patient Monitor

The Connex Spot Monitor is a new patient monitor for physician offices. It features an easy-to-use, vivid touchscreen display and provides accurate vital signs measurement, including blood pressure averaging, spot checking, interval monitoring and custom scoring across patient populations. The device connects wirelessly to an emergency medical record (EMR) and accurately sends vitals to the patient chart from the point of care to help improve efficiency. It offers an upgradeable design and custom configurations, including a choice of thermometry and/or pulse oximetry, connectivity and mounting/mobility options. In addition, the new Accessory Power Management Stand with WhisperDrive technology features additional power backup, providing up to 17 hours of on-time, alleviating the need to charge the monitor as frequently. Features include accuracy and performance for neonate through adult patients; SureBP technology that provides blood pressure in only 15 seconds; blood pressure averaging to help ensure accurate hypertension diagnosis; Connex Scoring App on-device calculator for custom protocols like NEWS, MEWS; the ability for clinicians to safely leave the room while blood pressure averaging is running; choice of leading SpO2 technologies: Masimo, Nellcor or Nonin; partnerships with more than 90 leading EMRs, including Epic and Cerner; and a mobile stand option, including a work surface with integrated battery for extended usage.

Welch Allyn, (800) 535-6663, www.welchallyn.com/en/products/categories/patient-monitoring/vital-signs-devices/connex-spot-monitor.html

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Medicare IVIG/SCIG Reimbursement Rates

Rates are effective Jan. 1, 2017, through March 31, 2017.

Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM IVIG	Kedrion	J1556	$74.29	$73.10
CARIMUNE IVIG	CSL Behring	J1566	$64.08	$63.05
FLEBOGAMMA IVIG	Grifols	J1572	$65.36	$64.31
GAMMAGARD SD IVIG	Shire	J1566	$64.08	$63.05
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	$78.01	$76.76
OCTAGAM IVIG	Octapharma	J1568	$70.80	$69.66
PRIVIGEN IVIG	CSL Behring	J1459	$77.35	$76.11
CUVITRU SCIG	Shire	J3490 / J3590 / J7799	**	**
HIZENTRA SCIG	CSL Behring	J1559	$98.46	$96.88
HYQVIA SCIG	Shire	J1575	$129.69	$127.61
GAMMAGARD LIQUID IVIG/SCIG	Shire	J1569	$80.39	$79.10
GAMMAKED IVIG/SCIG	Kedrion	J1561	$72.88	$71.71
GAMUNEX-C IVIG/SCIG	Grifols	J1561	$72.88	$71.71

* 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.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Kedrion	IVIG: PI	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	IVIG: PI, ITP	6 g, 12 g
CUVITRU Liquid, 20%	Shire	SCIG: PI	1 g, 2 g, 4 g, 8 g
FLEBOGAMMA 5% DIF Liquid	Grifols	IVIG: PI	2.5 g, 5 g, 10 g, 20 g
FLEBOGAMMA 10% DIF Liquid			5 g, 10 g, 20 g
GAMMAGARD LIQUID 10%	Shire	IVIG: PI, MMN SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Shire	IVIG: PI, ITP, CLL, KD	5 g, 10 g
GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 5 g, 10 g, 20 g
GAMMAPLEX Liquid, 5%	Bio Products Lab	IVIG: PI, ITP	5 g, 10 g, 20 g
GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP SCIG: PI	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
HIZENTRA Liquid, 20%	CSL Behring	SCIG: PI	1 g, 2 g, 4 g, 10 g
HYQVIA Liquid, 10%	Shire	SCIG: PI	2.5 g, 5 g, 10 g, 20 g, 30 g
OCTAGAM Liquid, 5%	Octapharma	IVIG: PI	1 g, 2.5 g, 5 g, 10 g
OCTAGAM Liquid, 10%		IVIG: ITP	2 g, 5 g, 10 g, 20 g
PRIVIGEN Liquid, 10%	CSL Behring	IVIG: PI, ITP	5 g, 10 g, 20 g, 40 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

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2016-2017 Influenza Vaccine

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

Manufacturer	Product	Presentation	Age Group	Code
TRIVALENT				
SEQIRUS	AFLURIA (IIV3)	5 ML multi-dose vial	5 YEARS AND OLDER*	90658/Q2035
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUVIRIN (IIV3)	5 ML multi-dose vial	4 YEARS AND OLDER	90658/Q2037
		0.5 ML prefilled syringe, 10-BX		90656
SEQIRUS	FLUAD (aIIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90653
PROTEIN SCIENCES	FLUBLOK (RIV3)	0.5 ML single-dose vial, 10-BX	18 YEARS AND OLDER	90673
SANOFI PASTEUR	FLUZONE HIGH-DOSE (IIV3)	0.5 ML prefilled syringe, 10-BX	65 YEARS AND OLDER	90662
QUADRIVALENT				
SEQIRUS	FLUCELVAX (ccIIV4)	0.5 ML prefilled syringe, 10-BX	4 YEARS AND OLDER	90674
GSK	FLUARIX (IIV4)	0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
GSK	FLULAVAL (IIV4)	0.5 ML single-dose syringe	6 MONTHS AND OLDER	90686
		5 ML multi-dose vial	6 MONTHS AND OLDER	90688
MEDIMMUNE	FLUMIST** (LAIV4)	0.2 ML live virus intranasal spray	2-49 YEARS	90672
SANOFI PASTEUR	FLUZONE (IIV4)	5 ML multi-dose vial	6-35 MONTHS	90687
			3 YEARS AND OLDER	90688
		0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
		0.5 ML single-dose vial, 10-BX		90686
SANOFI PASTEUR	FLUZONE PEDIATRIC (IIV4)	0.25 ML prefilled syringe, 10-BX	6-35 MONTHS	90685
SANOFI PASTEUR	FLUZONE INTRADERMAL (IIV4)	0.1 ML prefilled microinjection, 10-BX	18-64 YEARS	90630

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based trivalent 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.

** As of June 22, 2016, the CDC's ACIP voted against using the live attenuated influenza vaccine (LAIV), also known as nasal spray, during the 2016-2017 flu season. According to the CDC, data from the U.S. Influenza Vaccine Effectiveness Network showed a 3 percent vaccine effectiveness (VE) in study participants between 2 years and 17 years of age. This 3 percent estimate means no protective benefit could be measured, compared to traditional flu shots (IIV), which demonstrated a 63 percent VE against any flu virus among children 2 years to 17 years of age.

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