SPRING 2016

biosupply trends QUARTERLY

Special Focus: **SAFETY**

BLOOD PROTEIN THERAPEUTICS
IT ALL STARTS WITH THE PLASMA

The "Reproducibility Crisis" in Study Validation

Zoonotic Diseases: A Global Health Challenge

Hepatitis C: Is There Hope?

How Patient Stories Affect Caregiving

Myths and Facts: Venomous Snakebites

A Therapeutic Renaissance for Bleeding Disorder Patients — Page 50

8 Critical Steps

Purchasing

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Storage

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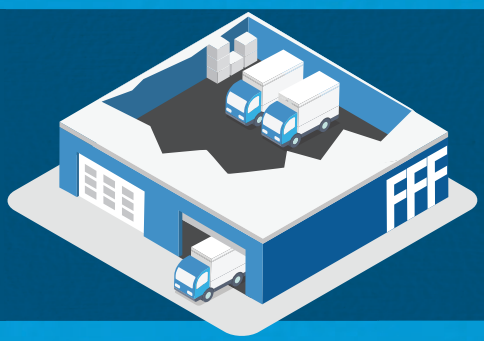

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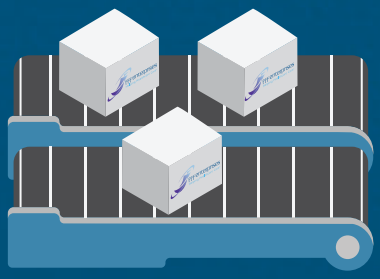

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Since 1988

To Guaranteed Channel Integrity™

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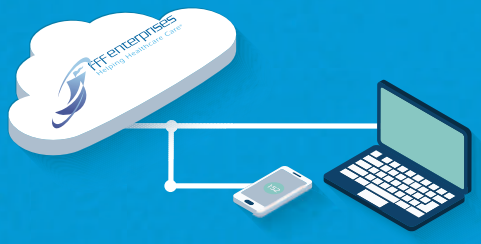

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Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

FFF enterprises
Helping Healthcare Care®

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Spring 2016

Features

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Up Front

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BioFocus

BioSources

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Patient Safety Is a Collective Responsibility

THE WORLD HEALTH Organization has deemed patient safety an endemic concern — one that our organization shares and addresses by putting patients first to ensure the safety and availability of critical-care medications we supply. But, we are just one of the key stakeholders, which include government agencies, manufacturers, healthcare providers and others, all working collectively to safely care for patients.

One sterling example of this joint effort is the vigilant management of the U.S. blood supply, which is considered the safest in the world. As noted in our article "Blood Protein Therapeutics: It All Starts with the Plasma," the number of liters of human plasma from U.S. donors has increased more than 40 percent over the last five years to meet the demand for protein therapeutics, including immune globulin, hyperimmune globulins, albumin, alpha-1 proteinase inhibitor and activated prothrombin complex concentrate. Due to overlapping safeguards implemented by plasma collection facilities, manufacturers and others, the quality and safety of these lifesaving products are ensured and patient health is protected.

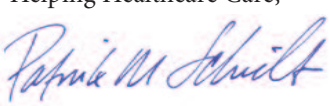
Admittedly, prior to safeguards now in place to screen blood donors, the hepatitis C virus (HCV) was transmitted through blood donations. Today, highly accurate tests detecting HCV prevent carriers from donating. Still, the disease continues to plague thousands, who, for decades, have been treated with limited effectiveness. Indeed, for those who could tolerate treatment, it resulted in just higher than a 50-percent cure rate. Until, as our article "Hope for Hep C" describes, collaboration among researchers resulted in a "miraculous" breakthrough with the development of direct-acting antiviral drugs, the first of which have already been replaced by even more effective treatments to provide cure rates as high as 99 percent. And, scientists aren't stopping there. For those few who experience treatment failure, "rescue regimens" are being developed.

Coagulation factor replacement products to treat the thousands challenged by bleeding disorders are also among the many new therapies being developed through industry collaboration. As outlined in our article "The New Therapeutic Renaissance for Patients with Rare Bleeding Disorders," where manufacturers previously focused mostly on two predominant bleeding disorders, they have now turned their attention to the more rare hereditary and acquired coagulation disorders with the development of five new factor replacement therapies. And, as innovation continues, more are on the horizon.

But the mission to improve patient safety could potentially be in jeopardy from the newly recognized threat posed by what is now known as the "reproducibility crisis." The development of medicines and therapies rests on scientific research, which relies on evidence. But recently, much research has been found to be "useless" because, when replicated, the results can't be duplicated. In our article "Irreproducible Research: The Need for Study Validation," we discuss the scientific and cultural challenges that are believed to be the culprits. Thankfully, identification of these challenges has led to changes already underway, with organizations like the National Institutes of Health and medical and academic journals, the study gatekeepers, reforming their systems.

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

Helping Healthcare Care,



Patrick M. Schmidt
Publisher

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

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CMS to Reimburse ICD-10 Mistakes for One Year

In response to concerns by providers that they won't be paid if they make minor mistakes under the transition from the ICD-9 to ICD-10 coding system, the Centers for Medicare and Medicaid Services (CMS) says it will reimburse for incorrectly coded claims for one year past the Oct. 1, 2015, deadline, as long as the erroneous code is in the same broad family as the right one.

The American Medical Association (AMA) teamed up with CMS to help make the transition easier for providers. A nationwide outreach effort to educate providers included webinars, onsite training, educational articles and calls to help physicians and other providers get up to speed before the Oct. 1 deadline. While the AMA previously supported a bill that would prohibit the U.S. Department of Health and Human Services from

replacing ICD-9 with ICD-10, an AMA spokesperson said the change is "a culmination of a vigorous effort by medicine to ask the CMS for a transition period to avoid expected disruptions during this time of tremendous change in the healthcare landscape."

CMS has also created the ICD-10 Ombudsman, as well as a host of online resources and guidance to aid the medical community. The guidance includes "Road to 10," a website that contains a countdown clock and primers for clinical documentation, clinical scenarios and other specialty-specific resources to help with implementation.

The Medicare claims processing system does not have the capability to accept ICD-9 codes for dates of services as of Sept. 30, nor is it able to accept claims for both ICD-9 and ICD-10 codes. "The coming implementation of ICD-10 will set the stage for better identification of illness and earlier warning signs of epidemics, such as Ebola or flu pandemics," said Andy Slavitt, acting administrator of CMS. ❖

HHS Announces More Funding to Improve Healthcare

The U.S. Department of Health and Human Services (HHS) has announced additional funding under the Affordable Care Act (ACA) and other programs. Under the ACA, nearly $500 million is being awarded to health centers nationwide to provide primary care services to those who need them most. The awards include approximately $350 million for 1,184 health centers to increase access to services such as medical, oral, behavioral, pharmacy and vision care. And, nearly $150 million will be awarded to 160 health centers for facility renovation, expansion or construction to increase patient or service capacity.

Also under the ACA, an additional $112 million has been awarded to help 5,000 primary care professionals in 12 states to improve the heart health of their nearly eight million patients. EvidenceNOW: Advancing Heart Health in Primary Care will make primary care practices in both urban and rural communities use the latest evidence to encourage better care, smarter spending and healthier people. The EvidenceNOW initiative establishes seven regional cooperatives composed of multidisciplinary teams of experts that will each provide quality improvement services to up to 300 small primary care practices. In addition, an eighth awardee will receive a grant to conduct an independent external evaluation of the overall EvidenceNOW initiative to study its impact on interventions on practice improvement and the delivery of cardiovascular care.

Under the Transforming Clinical Practice Initiative, 39 national and regional healthcare networks and supporting organizations will receive $685 million in awards to help equip more than 140,000 clinicians with the tools and support needed to improve quality of care, increase patients' access to information and reduce costs.

And, more than $2.2 billion in Ryan White HIV/AIDS Program grants were awarded to cities, states and local community-based organizations. The funding supports a coordinated and comprehensive system of care to ensure that more than half a million people living with and affected by HIV in the U.S. continue to have access to critical HIV healthcare, support services and essential medications. ❖

Current CMS Biosimilars Reimbursement Policy Outlined

Although there are many parameters yet to be defined, the Centers for Medicare and Medicaid Services (CMS) has published several policies on biosimilars reimbursement.

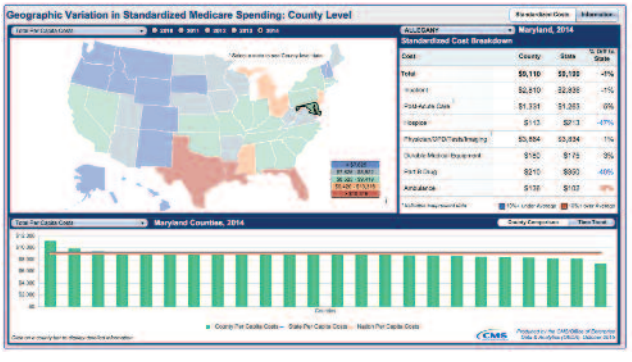
Biosimilars approved under the U.S. Food and Drug Administration's (FDA) abbreviated biosimilar pathway, as well as those deemed interchangeable, will be reimbursed at the same average sales price (ASP)-based rate (ASP plus 6 percent of the ASP of the reference product) using a single Healthcare Common Procedure Coding System (HCPCS) code. The goal is to remove financial incentives to choose an innovator product over a biosimilar, or vice versa, since providers will receive the same margin for either product. Follow-on biologics approved with a full biologics license application (BLA), which are essentially biosimilars but do not have to demonstrate biosimilarity, are eligible to receive a distinct HCPCS code and will be reimbursed based on ASP. During the initial post-launch period before ASP data are available, CMS will pay for these new biosimilars at wholesale acquisition cost (WAC) plus 6 percent of the reference product's cost.

Once a HCPCS code for a biosimilar has been created, the code will apply to all future biosimilar versions of the same reference product, but with a manufacturer-specific modifier. For example, Q5101, the code created for Zarxio (Sandoz's biosimilar of Amgen's Neupogen) will apply to all other biosimilar versions that are approved, but the HCPCS code for Zarxio must also include the modifier ZA-Novartis/Sandoz. Claims that lack the appropriate modifier will be rejected.

Under the Medicare Hospital Outpatient Prospective Payment System, coding and payment for biosimilars in hospital outpatient departments will be the same as in the physician office under Part B. CMS will post new biosimilar HCPCS codes and manufacturer-specific modifiers on its Part B biosimilars web page. ❖

CMS Creates Site that Lists Drug Use and Spending

Amid scrutiny of rising drug prices, the Centers for Medicare and Medicaid Services (CMS) has created an interactive online dashboard to allow the public and policymakers to explore the financial burden that high-expense drugs place on the Medicare program and the nation's seniors. The dashboard, which includes drugs prescribed under Medicare Part B that are administered in doctors' offices and other outpatient settings and Medicare Part D (the program's general prescription drug benefit), shows the overall spending for the top 80 drugs received by beneficiaries, along with recent trends in their prices and the number of older Americans who rely on them. Drugs were chosen for the list if they were among the top 15 in overall spending for either Medicare Part B or D, had a high level of per-patient spending or had the greatest price increases. While the data are for 2014, they compare trends in use and prices for the previous few years.



The data does not list the net prices paid to manufacturers or the rebates to plans and prescription benefit management under Part D, which CMS is not permitted to disclose. Under Part B, Medicare pays 106 percent of the estimated average sales price of each drug, which reflects the average prices paid by physician offices and hospital outpatient departments, accounting for discounts and rebates. "By sharing this information and allowing people to analyze the data, we can increase the knowledge around drug spending and support efforts that are evaluating whether public dollars are being spent most effectively," said CMS Acting Administrator Andy Slavitt. ❖

Data Collection: A New Regime

An ongoing revolution in healthcare inexplicitly ties data and reimbursement with the demand for analytics that provide insight into a variety of areas — from treatment to business intelligence vital to the management of healthcare organizations and practices. The significant changes the healthcare industry experienced in 2015, ranging from reimbursement reform philosophy to coding changes inherent to the adoption of ICD-10, continue. Vital to keeping pace includes closing the gaps between areas of technology with no sector left behind. For instance, in some practices, the clinical component surges ahead, while the billing department churns out snail-mail paper bills. In hospital settings, some critical care and inpatient areas are reaping IT dollars with the latest and greatest systems, while outpatient areas are left with antiquated electronics and IT tools with limited or no interoperability.

Analytics turn data into usable information, which is not surprising as more and more data are collected in response to the mandated growth of electronic health records. What is surprising is an announcement by Andy Slavitt, acting administrator for the Centers for Medicare and Medicaid Services (CMS), on Jan. 12 confirming the Meaningful Use program will end sometime in 2016, and it will be replaced by something better. "Now that we effectively have technology in virtually every place where care is provided, we're now in the process of ending Meaningful Use and moving to a new regime culminating with the MACRA implementation," advised Slavitt. MACRA, the Medicare Access and CHIP Reauthorization Act of 2015, authorized new payment models for providers, including the Merit-Based Incentive Payment System (MIPS).

The details of this new regime are yet to be released, but the goal is to move away from rewarding providers for using technology toward achieving good patient outcomes by letting providers customize their goals so that technology is built around individual practice needs. The underlying message is that technology is essential to achieving those good patient outcomes. Slavitt emphasized the value of start-up companies, including use of open APIs (application programming interfaces) "to open the physician desktop and allow apps, analytic tools and connected technologies to get data in and out of information systems securely." CMS is "deadly serious about interoperability." "Better interoperability is necessary to close referral loops and engage patients in their care," Slavitt noted, "and data blockers will not be tolerated."

It's clear there is a need for trained professionals who know how to work with data to become an integral part of healthcare organizations to leverage the use of data and make data-based decisions. New healthcare payment reform models are based on collaboration, and the sharing of useful clinical or business data that are produced by analytics is an essential tool.

As healthcare practices launch into the 2016 payment year, the questions they should ask are: 1) Are we doing the things needed to better manage what's coming? 2) What is the impact to cost, quality and outcomes metrics of using an inadequate charge description master (CDM) with poor descriptions? 3) Does our team think of themselves as a value cycle team and make decisions that support that concept? 4) Have we elevated the priority of fixing problems, and do the CFO and finance team know what these problems are? 5) Where are the gaps, and how are we going to manage them? 6) What opportunities do they present?

At the Dec. 1 CMS Quality Conference in Baltimore, Slavitt stressed that CMS will adopt a value-based payment policy as part of an attempt at industrywide delivery system reform: "Our priority is clear: to drive a delivery system that provides better care with a smarter payment system that keeps people healthier. This means specifically that by 2018, we will reach a tipping point in our payments with over 50 percent of Medicare fee-for-service payments rewarding for quality and value and aligning Medicare Advantage and Medicaid to do the same." Slavitt also emphasized that payment policy alone is not CMS' goal: "We are not just a payer; we are an information partner.… The agency wants to turn healthcare into an information

Table 1. Suggested Areas for Review

Target Area	What to Look For	Rationale
Accuracy of drug and dose given	Is actual drug given identifiable by its NDC number and HCPCS code? Is dose correctly converted into CMS-assigned billing units?	Missing or inaccurate information paints an inaccurate treatment record; reimbursement suffers
Capture of drug waste	Options include waste billable to CMS, waste billable to other payers, waste capture that is necessary to ensure accurate accumulator totals for 340B facilities	Ignoring this waste portrays an inaccurate picture of treatment cost
Billing for all drugs administered regardless of formulary status, product cost, separate payment status, bundle status or observation status	Include all drugs, even those that are white bagged, brown bagged or provided at no or nominal cost by patient assistance programs	This ensures an accurate representation of treatment cost; it is vital to the billing of IV drug administration fees; and it shows use of a product in an eligible patient in a 340B facility
Prior authorization, LCDs and NCDs	Is there sufficient documentation in the medical record to support the ICD-10 codes required? If prior authorization has been obtained, has this been documented in an interoperable manner? Are the players involved? How can they all work together?	Lack of medical necessity is one of the most frequent reasons for payment denial. Payment denial means two things: the facility doesn't get paid and quite likely there is no record retained by the payer as to the appropriate use of that product. This is not because the choice of the product was inappropriate, but more likely because there wasn't sufficient documentation to support the use of the product

industry that supports patients and the caregivers that serve them."

As such, providers and organizations must concentrate on the importance of telling patients' stories accurately and completely in a manner that can be coded appropriately for reimbursement purposes and for contributing to the "big data pool." Their responsibility is to understand the nuances of the payment reform rules and proposals and put them into play at their facility to be a data champion. This means embracing the concept that CMS is not just a payer but a data repository and information partner. CMS, like all payers, collects a wealth of information about patients through the data that facilities send through its claims submissions.

It's important to note that there is a difference between local data warehouses at a facility level that retain data to support analytics and bigger centralized datasets that constitute the big data pool used by regulators, payers and large delivery systems. At a facility level, it's possible that everything recorded is retrievable from the data warehouse. However, only claims data currently populates CMS and most other payer databases. With this in mind, developing strategies for managing data requires a variety of tactics to ensure patients' stories are told completely and accurately.

Since the majority of healthcare payment reform centers on a shift from the inpatient to the outpatient setting and coordination among a variety of caregivers, the suggested areas for review in Table 1 are directed at that environment and refer to the Outpatient Prospective Payment System rules for 2016. These suggestions for review can be used to ensure that data management is working to support these goals. It's often a surprise what gets removed from submissions as they wend their way through the tortuous twists and turns of revenue cycle software systems. A little education will go a long way to resolving many of these issues. ❖

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

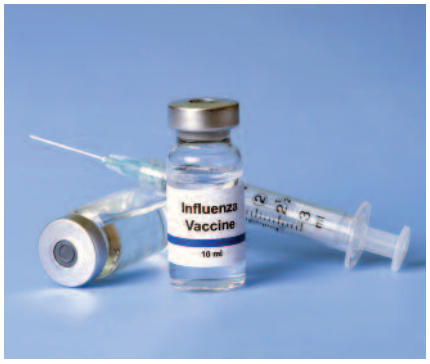
Ask Our Experts

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

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.

Vaccines

2015-16 Flu Vaccine Is Nearly 60 Percent Effective



As of the end of February, preliminary overall 2015-16 influenza vaccine effectiveness (VE) was 59 percent, according to the Centers for Disease Control and Prevention (CDC), which is comparable to past estimates for seasons when most circulating flu viruses and vaccine viruses have been similar. More specifically, based on data collected from the U.S. Flu VE Network from Nov. 2 through Feb. 12, this season's vaccine is 51 percent effective against the H1N1 viruses responsible for most flu illness this season, 76 percent effective against all influenza B viruses and 79 percent effective against the B/Yamagata lineage of B viruses. However, there is not enough data to estimate VE by age group or against H3N2 or B/Victoria lineage viruses. "This means that getting a flu vaccine this season reduced the risk of having to go to the doctor because of flu by nearly 60 percent," said Joseph Bresee, MD, chief of CDC's Epidemiology and Prevention Branch. "It's good news and underscores the importance and the benefit of both annual and ongoing vaccination efforts this season." ❖

Centers for Disease Control and Prevention. Flu Vaccine Nearly 60 Percent Effective. Accessed at www.cdc.gov/media/releases/2016/flu-vaccine-60-percent.html.

Policy

FDA Issues Guidance to Protect Blood Supply from Zika Virus

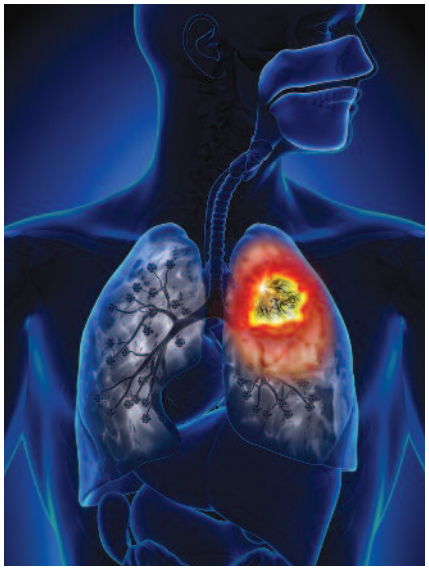
In February, the U.S. Food and Drug Administration issued a new guidance recommending the deferral of individuals from donating blood if they have been to areas with active Zika virus transmission, potentially have been exposed to the virus or have had a confirmed Zika virus infection. Specifically, in areas with active Zika virus transmission, FDA recommends that whole blood and blood components for transfusion be obtained from areas of the U.S. without active transmission. However, blood establishments may continue collecting and preparing platelets and plasma if an FDA-approved, pathogen-reduction device is used. In addition, the guidance recommends blood establishments update donor education materials with information about Zika virus signs and symptoms and ask potentially affected donors to refrain from giving blood. In areas without active Zika virus transmission, FDA recommends that donors at risk for Zika virus infection be deferred for four weeks. Individuals considered to be at risk include those who have had symptoms suggestive of

Zika virus infection during the past four weeks, those who have had sexual contact with a person who has traveled to or resided in an area with active Zika virus transmission during the prior three months, and those who have traveled to areas with active transmission of Zika virus during the past four weeks.

While there have been no reports to date of Zika virus entering the U.S. blood supply, the risk of blood transmission is considered likely based on the most current scientific evidence of how Zika virus and similar viruses (flaviviruses) are spread and recent reports of transfusion-associated infection outside of the U.S. It is also a concern because four out of five individuals infected with Zika virus do not become symptomatic. "Based on the best available evidence, we believe the new recommendations will help reduce the risk of collecting blood and blood components from donors who may be infected with the Zika virus," said Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research.

Due to recent reports of sexual transmission of Zika virus, FDA also intends to issue a guidance that will address appropriate donor deferral measures for human cells, tissues and cellular and tissue-based products. ❖

FDA Issues Recommendations to Reduce the Risk for Zika Virus Blood Transmission in the United States. U.S. Food and Drug Administration press release, Feb. 16, 2016. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm486359.htm.



Medicines

FDA Approves Keytruda to Treat Lung Cancer

In October, the U.S. Food and Drug Administration (FDA) granted accelerated approval for pembrolizumab (Keytruda, Merck & Co.) for treatment of patients with advanced (metastatic) non-small cell lung cancer (NSCLC) across all histologies whose disease has progressed on or after platinum-containing chemotherapy, as well as a targeted agent in epidermal growth factor receptor- or anaplastic lymphoma kinase-positive patients. The programmed death (PD-1) inhibitor is the second immunotherapy available for this type of tumor. It was approved along with a companion diagnostic, the PD-L1 IHC 22C3 pharmaDx test, which is the first test designed to detect PD-L1 expression in non-small cell lung tumors.

The approval is based in part on data from the KEYNOTE-001 trial that led to the drug being granted a breakthrough therapy designation by FDA in October 2014. Results of that trial show that pembrolizumab had an overall response rate of nearly 20 percent among 495 previously treated-naive patients with advanced or metastatic NSCLC. The overall response rate was 45.2 percent among a cohort of patients with high PD-L1-expressing NSCLC. The median duration of response exceeded one year in all responders regardless of the degree of PD-L1 expression. And, median overall survival was 12 months for all patients, 9.3 months for previously treated patients and 16.2 months for previously untreated patients. The most common adverse effects included fatigue, decreased appetite, shortness of breath or impaired breathing, and cough. The drug also has the potential to cause severe immune-mediated adverse effects.

Pembrolizumab had been previously granted FDA approval for use in advanced melanoma. ❖

Research

New Type of Sound Wave May Allow for Inhalable Vaccines

A new form of hybridized sound waves developed by Australian researchers may allow drugs and vaccines to be delivered to the body through a nebulizer in a fine mist inhaled into the lungs. The new sound waves, called "surface-reflected bulk waves," combine two existing types — bulk waves (much like a carpet being shaken from one end to the other) and surface waves (like waves rolling across the surface of the ocean without affecting the depths) — that create a powerful wave with high frequencies but low amplitudes. The combined power of the surface and bulk waves means that drugs can be administered at a rate of up to 5.0 ml per minute rather than around 0.2 ml per minute. "It's basically 'yelling' at the liquid so it vibrates, breaking it down into vapor," said Amgad Rezk from Royal Melbourne Institute of Technology (RMIT). "We have used the new sound waves to slash the time required for inhaling vaccines through the nebulizer device from 30 minutes to as little as 30 seconds." The scientists are using a new device called HYDRA, built to take advantage of the new waves, to convert electricity passing through a piezoelectric chip into vibrating sound waves that are then used to break the liquid drugs into a spray. HYDRA in turn improves the effectiveness of the advanced nebulizer in use at RMIT.

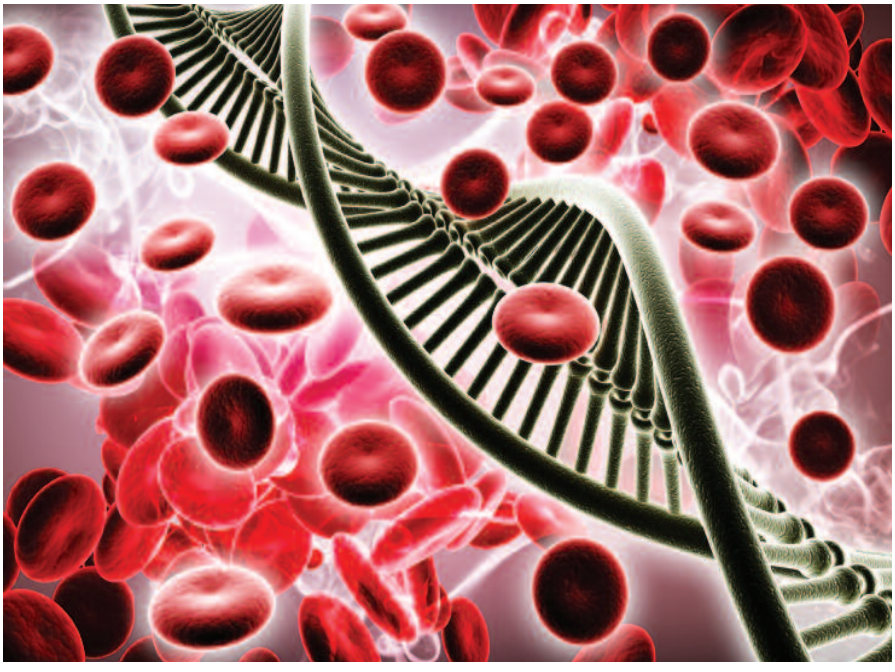
What's more, the new sound waves are gentle enough to be used in biomedical applications. "Our work also opens up the possibility of using stem cells more efficiently for treating lung disease, enabling us to nebulize stem cells straight into a specific site within the lung to repair damaged tissue," adds Rezk. "This is a real game-changer for stem cell treatment in the lungs."

The work was published in the journal *Advanced Materials*. ❖

Nield D. Newly Discovered Type of Sound Wave Allows for Inhalable Vaccines. Science Alert, Jan. 8, 2016. Accessed at www.sciencealert.com/a-newly-discovered-type-of-sound-wave-could-lead-to-needle-free-vaccines.

Research

New Gene Therapy Could Be Safe, Effective for Hemophilia B Patients



A new kind of gene therapy tested in animals could be safe and effective for human patients with hemophilia B, according to a multi-year, ongoing study. In the study, the researchers developed a way to use a lentivirus, which is a large retrovirus, to deliver factor IX genes to the livers of three dogs with naturally occurring hemophilia. The researchers removed the genes involved in viral replication, a process that turned the virus into a vector. They then injected the viral vectors directly into the liver or intravenously, and after more than three years, the dogs experienced zero or one serious bleeding event each year. Before the therapy, the dogs experienced an average of five spontaneous bleeding events that required clinical treatment. And, importantly, the researchers detected no harmful effects. "The result was stunning," said Timothy Nichols, MD, director of the Francis Owen Blood Research Laboratory at the University of North Carolina School of Medicine and co-senior author of the study's paper, which was published in *Science Translational Medicine*. "Just a small amount of new factor IX necessary for proper clotting produced a major reduction in bleeding events."

With gene therapy, doctors can give hemophilia patients a one-time dose of new clotting genes instead of a lifetime of multiple injections of recombinant factor IX that, until very recently, had to be given several times a week. A new U.S. Food and Drug Administration-approved hemophilia treatment requires only once or twice monthly injections indefinitely. This new gene therapy would involve a single injection and could potentially save money while providing a long-term solution to a lifelong condition. A major potential advantage of it is the use of lentiviral vectors, to which most people do not have antibodies that would reject them and make the therapy less effective. In human clinical studies, approximately 40 percent of the potential participants screened for a different kind of viral vector — called adeno-associated viral (AAV) vectors — have antibodies that preclude them from entering AAV trials for hemophilia gene therapy treatment. Therefore, more people could potentially benefit from the lentivirus gene therapy approach. Lentivirus vectors are so large that they can carry larger loads, namely the factor IX genes that people with hemophilia B lack (an approach that also could be used for hemophilia A where the factor VIII gene is considerably larger).

To further demonstrate the safety of this new hemophilia treatment, the researchers used three different strains of mice that were highly susceptible to developing complications such as malignancies when introduced to lentiviruses. They found no harmful effects, which they attribute to the lentiviral vector making it safe.

Before testing this gene therapy approach in human trials, the researchers hope to increase the potency of the therapy to decrease spontaneous bleeding even more, while also keeping the therapy safe. Before the treatment, the hemophilia dogs had no sign of factor IX production. After, they exhibited between 1 percent and 3 percent of the production found in normal dogs, a slight increase enough to substantially decrease bleed events. However, the researchers think it would be best if they could boost factor IX production to between 5 percent and 10 percent of normal while remaining safe. ❖

University of North Carolina School of Medicine. Drug Discovery Gives Hope to Halting Progression of Alzheimer's Disease. *Medical Science News*, March 12, 2015. Accessed at www.news-medical.net/news/20150312/Study-New-gene-therapy-safe-effective-for-patients-with-hemophilia-B.aspx.

Medicines

FDA Approves Adynovate to Treat Hemophilia A

The U.S. Food and Drug Administration (FDA) has approved Baxalta's Adynovate (antihemophilic factor [recombinant] PEGylated) for use in adults and adolescents aged 12 years and older with hemophilia A. Adynovate is approved for on-demand treatment and control of bleeding episodes, as well as prophylaxis. Consisting of the full-length coagulation factor VIII molecule (historically known as antihemophilic factor) linked to other molecules known as polyethylene glycol (PEGylated), it is modified to have longer circulating half-life and potentially requires fewer injections than unmodified antihemophilic factor when used to reduce the frequency of bleeding.

FDA approval of Adynovate was based in part on a Phase III clinical trial of patients aged 12 years to 65 years who were assigned to either twice-weekly prophylaxis (40-50 IU/kg) or on-demand treatment (10-60 IU/kg) with the drug. The study found that previously treated patients in a twice-weekly prophylaxis arm had 95 percent fewer annual bleeds compared with those treated on demand (median annual bleed rate was 1.9 vs. 41.5, respectively). During the study, 38 percent of prophylaxis-treated patients experienced zero bleeds, and 57 percent of patients experienced zero joint bleeds based on six months of prophylaxis. Nearly all patients (98 percent) on prophylaxis with Adynovate did not have a dose adjustment in the study, and nearly all bleeding episodes (96 percent) were controlled with one or two infusions of the drug. Common adverse reactions reported in the trial were headache and nausea. ❖

Research

Engineered Protein Controls Bleeding in Severe VWD

Results of a Phase III study show that BAX 111, a highly purified recombinant von Willebrand factor (rVWF) analog manufactured by Baxalta, appeared safe and effective for treatment of bleeding episodes in patients with severe von Willebrand's disease (VWD).

In the study, 37 patients were assigned to one of four arms composed of rVWF (50 IU/kg or 80 IU/kg) with or without rVIII (Advate, Baxalta). Most patients also received as-needed treatment with rVWF of 40 IU/kg to 60 IU/kg for regular bleeding episodes and up to 80 IU/kg for major bleeds. Overall, 22 patients experienced 192 bleeding episodes (122 minor bleeds, 61 moderate bleeds and 7 major bleeds). A single infusion proved effective for 81.8 percent of bleeding episodes. Using a four-point scale, the researchers rated 96.9 percent of bleed control as excellent. One-hundred percent of patients achieved treatment success, defined as a mean efficacy rating of less than 2.5. Eight adverse events occurred, including two serious adverse events (chest discomfort and increased heart rate without cardiac symptomatology) that occurred concurrently in one patient. However, no thrombotic events or severe allergic reactions occurred. And, the researchers did not detect the development of any VWF or FVIII inhibitors, anti-VWF-binding antibodies or antibodies against host-cell proteins. ❖

Gill JC, et al. Engineered Protein Safely, Effectively Controls Bleeding in Severe von Willebrand's Disease. *Blood*, 2015;doi:10. 1182/blood-2015-02-629873.

Medicines

FDA Approves Boosted Flu Vaccine for Older Adults

The U.S. Food and Drug Administration (FDA) has approved Fluad (Seqirus), an influenza vaccine that contains the adjuvant MF59, in hopes of better protecting individuals over age 65 who typically have a poor immune response to vaccines. It is the first flu vaccine to include a compound that helps stimulate the immune system so that a vaccine is more effective. MF59 is an oil-in-water mixture that includes squalene, an oily nutrient produced by the liver, and some preservatives. When mixed with vaccines, MF59 increases the number of immune system cells that are stimulated. "Immunizing individuals in this age group is especially important because they bear the greatest burden of severe influenza disease and account for the majority of influenza-related hospitalizations and deaths," said Dr. Karen Midthun from FDA. The vaccine, manufactured by newly formed Seqirus, a global company created by bioCSL and the influenza vaccines business formerly owned by Novartis, should be available for the 2016-2017 influenza season. ❖

Research

ProMetic Completes First Dosing in Plasminogen Deficiency Patients

In its Phase I clinical trial, ProMetic Life Sciences successfully completed its first round of IV plasminogen dosing in plasminogen deficiency patients, which was found to be safe and very well tolerated with no drug-related adverse events. The company will now proceed with the administration of a higher dose in order to complete the pharmacokinetic profile of the drug before year-end as planned. The clinical program will then cross over to Phase II and III in which plasminogen patients will be administered multiple doses to define the optimal treatment regimen to achieve the primary end point. The U.S. Food and Drug Administration has agreed to an accelerated regulatory approval pathway given the rarity of the condition and the unmet medical need.

Plasminogen is a naturally occurring protein that is synthesized by the liver and circulates in the blood. Activated plasminogen, plasmin, is a fundamental component of the fibrinolytic system and is the main enzyme involved in the lysis of blood clots and clearance of extravasated fibrin, making it vital in wound healing, cell migration, tissue remodeling, angiogenesis and embryogenesis. The most common condition associated with plasminogen deficiency is ligneous conjunctivitis, which is characterized by thick, woody growths on the conjunctiva of the eye, and if left untreated can lead to blindness. ❖

ProMetic Successfully Completes First Dosing in Plasminogen Deficient Patients. ProMetic Press Release, Aug. 10, 2015. Accessed at www.prometic.com/en/news-events/press-release-prometic-successfully-completes-first-dosing-923.php?y=2015.

Medicines

Newly Approved Drug Reverses Effects of Neuromuscular Blocking Drugs Used During Surgery

In December, the U.S. Food and Drug Administration (FDA) approved Merck and Co.'s Bridion (sugammadex) injection to reverse the effects of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide, neuromuscular blocking drugs used in certain types of surgery in adults to cause temporary paralysis by interfering with the transmission of nerve impulses to the muscle. Rocuronium bromide and vecuronium bromide are used to paralyze the vocal cords when patients require an artificial airway or breathing tube for surgery, a process called tracheal intubation; to prevent patients from moving during surgery when they are receiving general anesthesia; and to prevent the body from breathing automatically when a patient has been placed on a ventilator. "Bridion provides a new treatment option that may help patients recover sooner from medications used for intubation and ventilation during surgery," said Sharon Hertz, MD, director of the division of anesthesia, analgesia and addiction products in FDA's Center for Drug Evaluation and Research. "This drug enables medical personnel to reverse the effects of neuromuscular blocking drugs and restore spontaneous breathing after surgery."

FDA approved Bridion after its evaluation in three Phase III clinical trials involving 456 participants. In the trials, return to recovery time was faster overall for the Bridion treatment groups compared with the comparator groups, with most participants recovering within five minutes of routine use of Bridion. Due to concerns of anaphylaxis and hypersensitivity reactions, Bridion was further evaluated in a randomized, double-blind, parallel-group, repeat-dose trial. Of the 299 participants treated with Bridion, one person had an anaphylactic reaction. The most common adverse reactions reported in clinical trials included vomiting, low blood pressure, pain, headache and nausea. ❖

U.S. Food and Drug Administration. FDA Approves Bridion to Reverse Effects of Neuromuscular Blocking Drugs Used During Surgery. Press release, Dec. 15, 2015. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm477512.htm.first-dosing-923.php?y=2015.

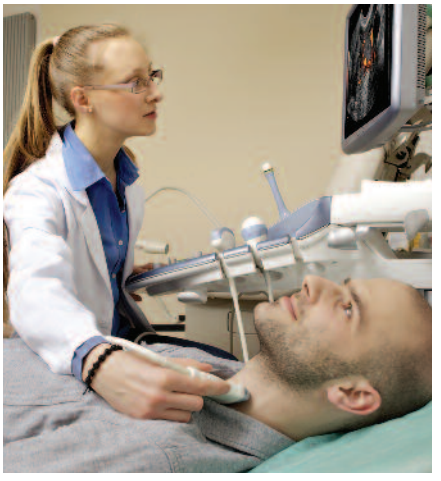
Research

Cancer-Causing Gene Found in Plasma May Help Predict Outcomes for Patients

University of Cincinnati researchers have discovered that a human cancer-causing gene, called DEK, can be detected in the plasma of head and neck cancer patients, which may help doctors understand how a person's immune system could be used to treat cancer or predict outcomes in patients. In the study, researchers collected whole blood from either patients with newly diagnosed and untreated head and neck cancer or normal healthy participants who were the same age. Plasma was separated from the samples, and an ELISA test was administered. Plasma DEK levels were compared to normal control levels, tumor stage, age and smoking status, as well as to inflammatory markers in the plasma and tissue that can signify cancer.

"We found that DEK was present in the plasma of both healthy control subjects and those with head and neck cancer," said Trisha Wise-Draper, MD, PhD, assistant professor in the division of hematology oncology at the UC college of Medicine, a member of both the Cincinnati Cancer Center and UC Cancer Institute, and principal investor on the study. "Overall, DEK was decreased in head and neck cancer patients compared to healthy patients, but it was inversely correlated with IL-6, which is secreted by T cells (white blood cells that play a role in immunity) and triggers an immune response, in the plasma. The immune system's reaction to the tumor also appeared to be linked with high DEK plasma levels. So, although DEK presence is increased in head and neck cancer tissue, plasma DEK levels are decreased in patients when compared with healthy individuals and are further decreased in patients with advanced cancers."

According to Dr. Wise-Draper, these findings, along with DEK's link with IL-6 levels, suggests that high DEK levels may mean better outcomes for patients. "Furthermore, high DEK levels in the plasma may predict better immunotherapy in terms of cancer treatment," she says. "Further analyses are ongoing to determine whether DEK levels predict response to various treatments, correlate with the body's immune response and whether DEK presence in the serum will predict remaining disease or early relapse. This information will be important to verify DEK plasma measurements as a clinically useful test and may give insight to future personalized and targeted treatment strategies for head and neck cancer." ❖



University of Cincinnati Academic Health Center. Cancer-Causing Gene Found in Plasma May Help Predict Outcomes for Patients. *Science Newsline Medicine*, Feb. 18, 2016. Accessed at www.sciencenewsline.com/news/2016021817340038.html.

Research

Biomarker Found in CIDP Patients Who Don't Respond to IVIG Therapy

A recent study has discovered a biomarker in chronic inflammatory demyelinating polyneuropathy (CIDP) patients that explains why they don't respond to intravenous immune globulin (IVIG) therapy. In the study, researchers used immunocytochemical methods to identify antibodies to the paranodal protein neurofascin 155 (NF155) in four of 61 patients with CIDP. All of the patients had disabling (modified Rankin Scale scores of 4), predominantly distal weakness that was refractory to treatment with IVIG. Two of the patients were identified from a local sample of 53 patients with CIDP. The other two patients were from a national pool of eight patients with previously identified CIDP refractory to IVIG. Disabling tremor and ataxia was present in three of the four patients.

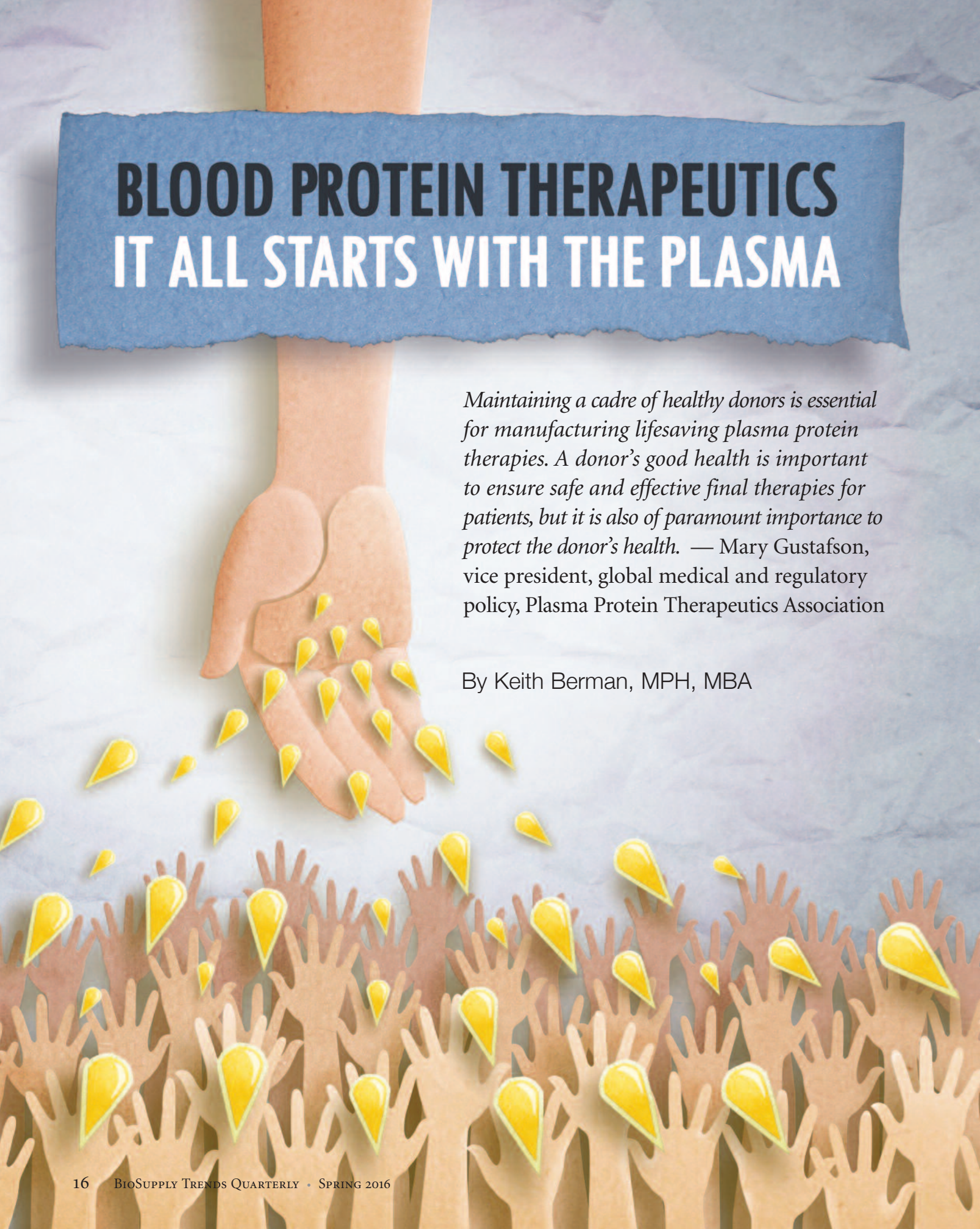
Currently, there are no biomarkers that predict response to therapy reliably. While most CIDP patients improve with IVIG, a small subset remain refractory and need other immunosuppressive treatments. Therefore, identifying the antibodies to components of the peripheral nerve associated with specific phenotypes would be an important aid in optimizing treatment.

The study was published in the March 11, 2015, issue of *Neurology*. ❖

BLOOD PROTEIN THERAPEUTICS
IT ALL STARTS WITH THE PLASMA

Maintaining a cadre of healthy donors is essential for manufacturing lifesaving plasma protein therapies. A donor's good health is important to ensure safe and effective final therapies for patients, but it is also of paramount importance to protect the donor's health. — Mary Gustafson, vice president, global medical and regulatory policy, Plasma Protein Therapeutics Association

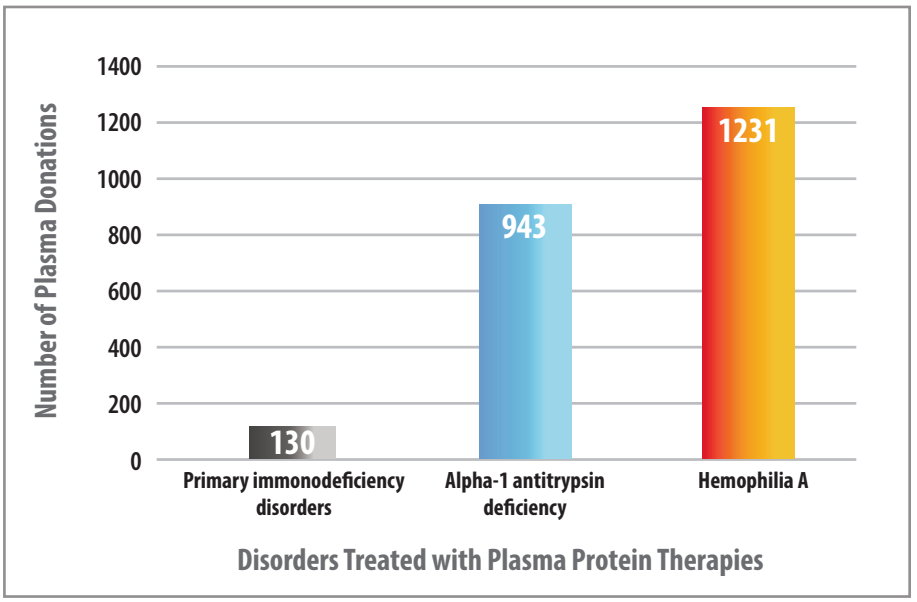
By Keith Berman, MPH, MBA



Most adults have learned at some point that blood is important because red blood cells carry oxygen to our vital organs and tissues, and white blood cells help fight infections. And thanks in part to growing appeals for platelet donors, some also appreciate that there is a specialized type of blood cell that stops bleeding. But far fewer lay people are aware that hundreds of proteins, performing important or life-critical functions, are constantly circulating in the straw-colored liquid plasma that comprises around 60 percent of human blood.

Today, a relative handful of these proteins are purified from donor human plasma and prescribed to treat persons with hereditary or other deficiencies: immune globulins that combat infectious diseases and regulate immunity, albumin responsible for maintaining blood pressure and a host of other functions, a number of clotting factors essential for normal hemostasis, alpha-1 antitrypsin that protects pulmonary elastic tissue against the destructive activity of the enzyme elastase.

Figure 1. Number of Plasma Donations Needed to Support One Year of Therapy for a Single Patient



Source: Plasma Protein Therapeutics Association

The Growing Need for Plasma and Plasma Donors

Beyond the fact that they are both sourced from human donors, a vast gulf separates the typical needs of a patient who requires red cell or platelet transfusions and one who requires most plasma protein therapies. As little as one or perhaps a few whole blood or apheresis donors can cover a single patient's typically acute, short-term platelet or red cell transfusion requirements. But for individuals reliant on most plasma protein therapies, the formula is turned on its head: Treatment is frequently chronic or lifelong. Literally hundreds of individual plasma donations are required to purify enough treatment to meet the annual requirements of an adult who needs immune globulin, clotting factor or alpha-1 antitrypsin therapy (Figure 1).

Coupled with the large number of plasma donations to treat a single patient is a growing U.S. and international patient market, as more people are diagnosed and prescribed treatment. Where once plasma donors were recruited in order to make enough albumin to meet hospital needs, demand for intravenous and subcutaneous IgG immune globulin (IVIG and SCIG) therapies now dictates the requirement for donated plasma — the result of 30 years of continuous growth in global usage (Table 1). Between 2000 and 2014, combined demand for IVIG and SCIG grew nearly 8 percent annually on average, necessitating a similar pace of recruitment of plasma donors and collections. Over the most recently reported 10-year period, U.S. plasma collections have increased nearly three-fold, from 10.4 million in 2005 to 32.5 million in 2014 (Table 2).

An automated plasmapheresis procedure is used to collect an average of about 750 mL of plasma* during a donation session that typically lasts one to one-and-a-half hours, for which donors are compensated for their time. All cellular components are returned to the donor, sometimes along with sterile saline to maintain blood volume. More than 480 U.S. Food and Drug Administration (FDA)-licensed centers throughout the U.S. are engaged in plasma collection activity, according to the Marketing Research Bureau.

With this vast and ever-expanding plasma collection enterprise comes a two-fold responsibility for industry: 1) to assure the quality and safety of this critical raw material and 2) to safeguard the health of the plasma donor.

* Referred to as "source plasma." According to the Marketing Research Bureau, source plasma accounted for nearly 95 percent of the total volume of plasma directed for further manufacture into plasma protein therapeutics in 2014; the balance was "recovered plasma" from whole blood donations.

Ensuring High Plasma Quality

While both U.S., Canadian and European government authorities license and regulate all plasma collection activities, in the early 1990s, the industry resolved to go beyond those requirements by instituting additional rigorous standards for certification of plasma collection centers under the Plasma Protein Therapeutics Association's International Quality Plasma Program (IQPP).

In addition to defining standards for collection center management that encompass the facility itself, quality assurance and personnel education and training, IQPP sets donor qualification, management and health standards. The following are among the key requirements to become a qualified donor:

• Potential donors must pass two separate medical screenings to assure that they are in good health.

• Donated plasma from potential donors is collected and tested on two different collection dates using highly sensitive assays for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV); no plasma is released for processing or "fractionation" until testing results from the second donation come back nonreactive.

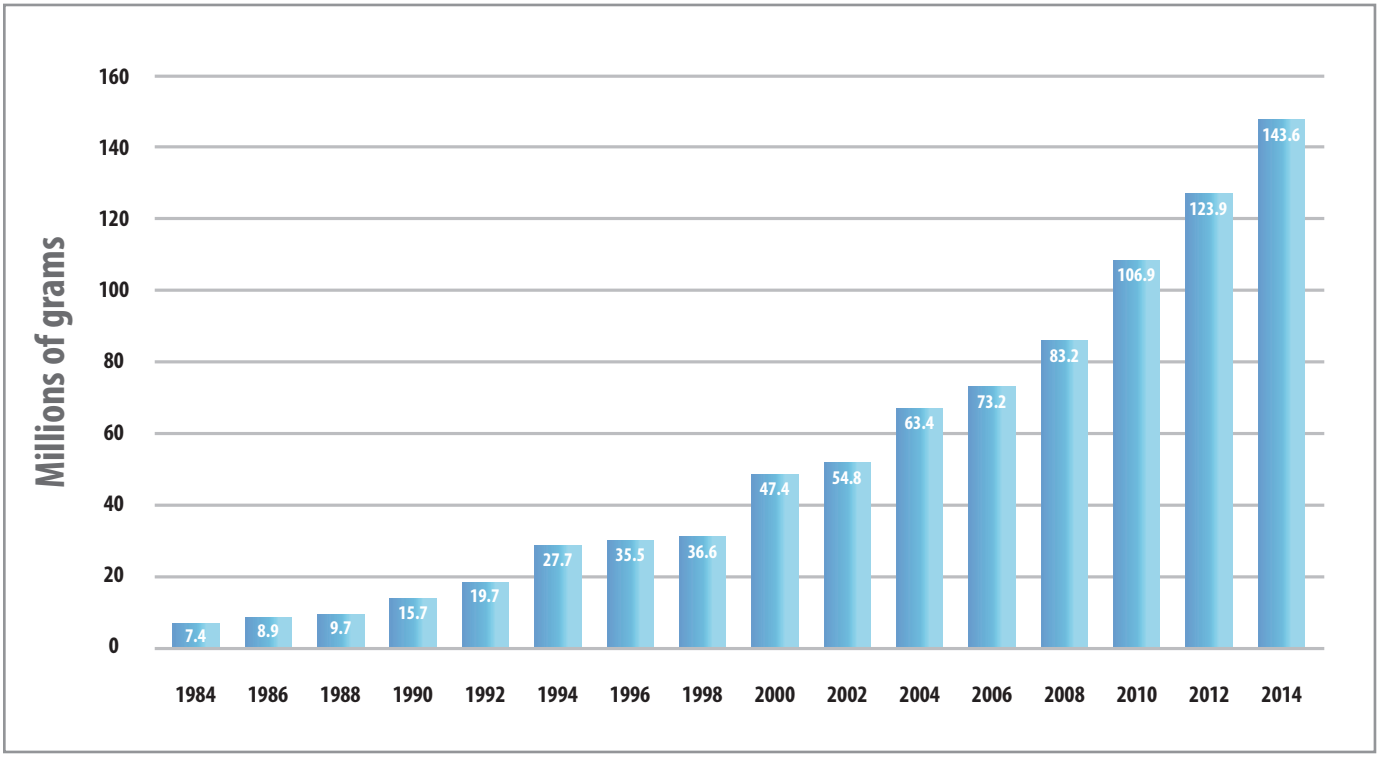
• If a first-time donor does not return to donate a second time within six months, that donor loses his/her qualified donor status and must qualify again; plasma from a one-time plasma donor — even when all test results are nonreactive — cannot be used to manufacture products.

• All new donors are checked against the National Donor Deferral Registry database, which includes persons permanently deferred from donating plasma at any IQPP–certified plasma collection center due to positive test results for HIV, HBV or HCV.

Additionally, an IQPP community-based donor standard only allows donors who permanently reside within the defined donor recruitment area of the plasma collection center to donate at that center. This standard has been shown to help maintain a steady and reliable donor population and supply of quality plasma.

In the 1980s, to assure that therapeutic plasma derivatives do not transmit viral or other infections, FDA regulators and industry implemented a "tripod" of safety measures: donor screening, pathogen testing and pathogen inactivation and removal steps during processing.[1] The IQPP donor management standards have proven to be integral to the success of both the donor screening and pathogen testing elements of the safety "tripod." Last year marked a very significant safety milestone for the plasma products industry and the patients it serves: Two decades and many millions of doses of IG, albumin, clotting factors and other licensed plasma-based therapeutics

Table 1. Worldwide Demand for Intravenous and Subcutaneous Immune Globulin Products (IVIG/SCIG), 1984-2014



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

have been administered to U.S. patients without a single report of infection transmission.**

Protecting Plasma Donor Health

As it is for volunteer whole blood and apheresis platelet and red cell donors, a paramount priority is to ensure that the collection process does not in any way compromise the health of the plasma donor. Toward this end, federal regulations relating to donors of source plasma require:

• An appropriate medical history and examination of the donor by qualified medical staff, certifying that the donor is in good health.

• Temperature not to exceed 37.5 degrees Celsius (99.5 degrees Fahrenheit) and body weight equal or greater than 110 pounds on the day of the procedure.

• Systolic and diastolic blood pressures between 90 mmHg and 180 mmHg and 50 mmHg and 100 mmHg, respectively, with a regular pulse between 50 and 100 beats per minute.

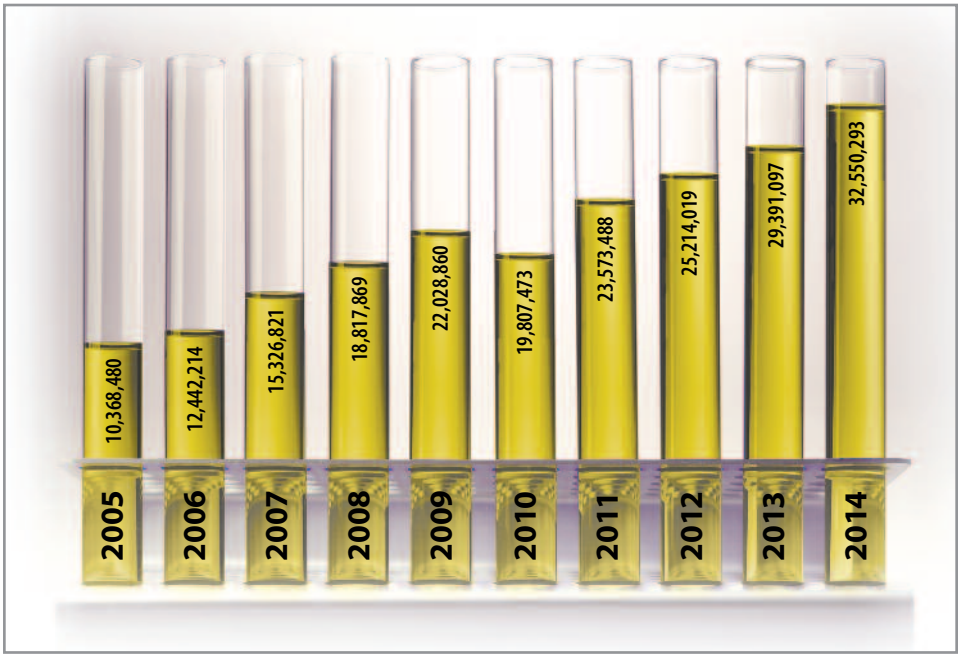
• Hemoglobin greater than or equal to 13.0 gm/dL (39 percent hematocrit) in males and greater than 12.5 gm/dL (38 percent hematocrit) in females.

• Total plasma protein of no less than 6.0 grams per 100 mL of blood; the donor is deferred if total plasma protein drops below this standard, and can donate again only when it returns to an acceptable level.

Plasma collection center medical staff must defer any donor or prospective donor found to have a medical condition that would place the donor at risk from the plasmapheresis procedure. Plasma donors are weighed at each donation visit to accurately calculate the appropriate plasma volume to be collected based on a weight-specific nomogram.

Plasma may be donated up to two times weekly, with a minimum of two days between donation visits. This allows adequate recovery of circulating plasma protein levels. Very infrequently, a plasma donor may misunderstand the reasons for limiting the number of times he or she can donate per week and attempt to "cross donate" more often than is allowed at a different plasma collection center. Measures in the IQPP Cross Donation Management Standard are in place to protect the health of the donor by minimizing the risk of cross donation.

Table 2. U.S. Plasma Collections for Manufacture into Therapeutics, 2005 – 2014



Source: Plasma Protein Therapeutics Association

The plasmapheresis procedure separates the donor's plasma from whole blood using a sterile, pyrogen-free, single-use donor set and sterile, pyrogen-free anticoagulant solution. Blood is collected, the plasma separated and the cellular components returned to the donor using aseptic methods. All IQPP-certified centers have processes in place to monitor, manage and record any donor adverse events that might occur. Adverse events occur very infrequently, are usually minor and include vasovagal reactions (e.g., hypotension, lightheadedness and nausea), reactions to citrate used as an anticoagulant (e.g., perioral tingling and metallic taste), allergic reactions and itching or hematoma at the venipuncture site. Overall adverse event rates in donors giving plasma by apheresis are significantly lower than for whole blood donors and also appear to be lower than for donors giving platelets or white blood cells by apheresis.[2,3]

Other studies examining the safety of regular long-term plasma donation demonstrate that it is safe. Parameters of humoral and cellular immunity in plasma donors are normal

** In 1995, a single production lot of a factor VIII concentrate was implicated in the infection of three hemophilia A patients (*MMWR* 1996 Jan 19;45[2]:29-32). The FDA is not aware of a definitive cause of that contamination event (personal communication, R. Chapelle, FDA/CBER).

and not different from nondonors. Similarly, there are no signs of iron store depletion or increased cardiovascular risk associated with long-term plasma donation.[4]

Donors Who Feel Well Come Back

Finally, there is mutual self-interest in assuring that a qualified donor stays in peak health and thus minimize risks of donation-related side effects. The donor who feels well after the procedure is one who is less likely to skip donation visits or entirely drop out. The plasma collection center benefits when it doesn't have to recruit and qualify new replacement donors.

Thus, donors receive basic education about how to optimize their health, as well as specific tips to prepare for the donation visit. They are encouraged to eat healthy meals that include foods high in protein and iron, avoid smoking (or stop smoking 30 minutes prior to donation to avoid changes in heart rate and blood pressure that could result in a deferment), and get at least seven to nine hours of sleep. On the night before and the day of the plasmapheresis procedure, donors are reminded to drink plenty of water or juice to assure that the body is well-hydrated and reduce the risk of side effects, including light-headedness. For the same reason, they are advised to avoid drinking alcoholic beverages, which can cause dehydration.

The plasma donor is the first vital part of the process to produce safe and effective plasma protein therapeutics. Fully aware of the need for even more donors tomorrow, next year and into the future, the industry can be counted on to make the safety and health of its plasma donors its first priority. ❖

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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Irreproducible Research: The Need for Study Validation

Changes are needed in the way scientific research is currently conducted to ensure its legitimacy and efficacy.

By Jim Trageser

Modern science is facing what could be the gravest threat to its remarkable run of success — a run that extends from the beginning of the Scientific Revolution some four and a half centuries ago. The issue is the "reproducibility crisis" in which a significant percentage of scientific studies are unable to be reproduced by others, not only undermining their value but also threatening the public's faith in scientific research as a whole.

Many explanations are being offered as both the popular and academic press take an increasingly skeptical look at the issue. The size of the problem is not yet clearly known, nor even agreed upon. Nor are the root causes or potential solutions matters even close to consensus. But what nobody seems to be disputing is the reality that a huge swath of scientific research — including that being conducted in many medical fields — is basically useless. More ominously, it is also not widely disputed that the reproducibility crisis threatens the very foundations of the scientific culture in the West, upon which rests modern medicine.

Many science and medical writers are warning that the reproducibility crisis undercuts the very premise of the scientific method: the idea that science is ultimately based on facts that can be proven through observation and/or experimentation. If much of that experimentation is so flawed as to prove nothing, or if the analysis of the observations is statistically meaningless, then our science is far less efficient and effective than we have all believed.

How It's Supposed to Work

Everyone working in the medical sciences is well aware of how the scientific method works: Let the evidence guide you where it will. Either a drug works against a disease, or it does not. A treatment leads to improvement, or it does not.

A properly designed study will account for all outside influences, and it will compare a control group vs. a study group. Further, in most reputable journals, no studies can be published until they've been reviewed by other experts in the same discipline. This "peer review" process is designed to be the main defense against fraud and incompetence. These peers should be reviewing a study to ensure it was properly configured to account for all variables so that the experiments truly indicate whether the drug or treatment being tested is effective. They should also be weighing whether any conclusions tied to the study are truly reflective of the evidence offered.

But it is this entire process that is under heightened scrutiny as hundreds, and potentially thousands or more, of research papers are being found wanting in one respect or another.

The Scientific Challenges

In the last few years, researchers from a variety of disciplines discovered that while reviewing previous work in their fields, they were unable to get the same results as reported in published papers. Either primary research or statistical conclusions drawn from existing research were found to be impossible to reproduce. Some researchers have been worried about this phenomenon for a while, even if the issue is only now gaining traction in the academic press.

The advocacy nonprofit *Public Library of Science (PLOS)* published an article 11 years ago arguing that statistical claims associated with research results were often invalid or misleading. Its author, John P. A. Ioannidis, a statistician and physician on faculty at Stanford, argues that most often it is not fraud that leads to bad studies, but the research culture itself. His belief is that out-and-out fraud is but a small sliver of bad research; instead, secrecy and misapplication of statistics theory are the main culprits.[1] (Outright fraud is easier to detect and confront than systemic bias. There is even an entire website devoted to reporting on retraction of studies at retractionwatch.com.) Roger Peng, associate professor in the department of biostatistics at Johns Hopkins Bloomberg School of Public Health, backs up Ioannidis' assertion that statistics illiteracy clouds far too many conclusions drawn from research.[2]

Statistical error may come from not understanding how to properly account for anomalies that arise during the course of an experiment. For instance, *PLOS* is conducting an analysis of how researchers account (or fail to account) for rodents that die from seemingly unrelated issues during the course of medical experiments.[3] An earlier review of experiments that utilized rodents found a significant number had a smaller number of test subjects at the conclusion of the research than at the beginning, with no accounting for this discrepancy.

Beyond errors that escape peer review are the pressures associated with the highly competitive, cutthroat world of academic research in the United States and Western Europe. With every faculty member and tenure-track adjunct having to conduct original research in order to get or keep a job in their chosen field — or simply to finish their doctorate program — the pressure to conduct original research is enormous. As noted in 2013 by Fiona Fidler and Ascelin Gordon on the Phys.org website, "There can be little doubt that the 'publish or perish' research environment fuels this fire. Funding bodies and academic journals that value 'novelty' over replication deserve blame too."[4]

In the last few years, researchers from a variety of disciplines discovered that while reviewing previous work in their fields, they were unable to get the same results as reported in published papers.

The growing number of participants in science and academia only adds to these pressures. There are far more working-class and middle-class students qualifying for and being accepted into four-year universities today than was true a half-century ago — a 300 percent increase in the number of college and university students in the United States, far outstripping population growth.[5] The United States alone has gone from turning out an average of 545 science and engineering doctorates a year in the 1920s to more than 27,000 in 2010.[6]

While this growth has provided an undoubted burst of democratization to what was formerly a preserve of the rich, we now also have more and more researchers fighting for grant money and tenure-track positions, increasing competitive pressures. Just in the years from 1997 to 2011, funding requests

to the National Institutes of Health doubled, from 31,000 research grant applications to 62,000.[6]

The result of more people competing for the same resources is probably predictable. Chris Chambers, professor of psychology and neuroscience at Cardiff University in Britain, said "significance chasing" — aiming for the highest perceived level of interest in order to attract more attention and funding — is inadvertently leading to bad research.[7] (Ironically, his March 2015 comments came at a conference at University College London just a week before BioMed Central, a major publisher of medical journals, announced the retraction of 43 published papers for reasons of peer review fraud.[8] It was a BioMed Central blog that quoted his comments made at the conference.)

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The anonymous "Neuroskeptic" blogger for *Discover* magazine, as well as one of his regular readers responding in the comments section of his post, wonders if the fact that most academic and scientific journals publish only "significant" results doesn't also add to the pressure through what Neuroskeptic refers to as "publication bias." Neuroskeptic also worries about "p-hacking," often referred to as data dredging, in which existing data is automatically (via computer algorithms) searched for statistical anomalies. Rather than searching for evidence to back up or dispute an existing hypothesis, the patterns themselves are the subject of the search — and once found, hypotheses are then developed to explain them.[9]

All of these different pressures — to get published, to stand out from other researchers, to secure funding — are likely introducing unintended bias into the conclusions reached, if not the very research itself. And yet, just as the ability to reproduce a study would seem to be more important than ever, these same pressures faced by academics are leading many of them to show great reluctance to share details of their research. This protects their intellectual work, but also makes it near impossible for others to replicate their work. As Fidler and Gordon pointed out in their Phys.org commentary, "Data sharing and other procedures outlined here can be time-consuming and currently provide little academic reward."[4]

The Cultural Challenge

Coverage of these issues has begun leaking over to the mainstream press. The first big waves in the media came in 2012 when pharmaceutical researchers C. Glenn Begley and Lee Ellis dove into 53 supposedly groundbreaking oncology studies from 2001 to 2011, and could only reproduce 11 percent.[10] Drug companies took notice, as they were pouring billions of dollars in private research money into new studies designed to build on the results of earlier — suddenly questionable — studies.

More reports about irreproducible research followed in the popular media. *Time* magazine weighed in on the issue in 2014,[11] as did *Wired*.[12] Last July, the popular science blog I09 published a piece titled "Half of Biomedical Research Studies Don't Stand Up to Scrutiny."[13] *Smithsonian* magazine addressed it earlier this year.[14]

These reports might not sound as ominous as the more rigorous scientific papers, but public support for the sciences is essential to preserving or even increasing government funding of research. Most funding for basic scientific research comes from governments, with grants awarded based on a combination of past success and the potential for gains in new knowledge.

It is a shared cultural belief in the ability of science to provide important advances in our understanding of the universe, and apply those new insights in ways that improve our quality of life, that makes it possible for the government to invest heavily in scientific research — particularly medical research. Threaten that belief in the legitimacy and efficacy of scientific research, and you threaten public funding. Without voter support for government funding, said funding cannot survive — particularly in democratic systems, and certainly not at the levels to which we have become accustomed.

Finding Solutions

It is likely that further study of the issue is needed before a consensus emerges on the scope and nature of the problem. And without a broader consensus, it will be difficult to change the overarching culture of scientific research (including the disinclination to full disclosure of study parameters).

Still, changes in the way research is conducted — or at least funded and published — are already underway. The National Institutes of Health (NIH) has beefed up its grant application

process, requiring more explanation of the science behind the proposed study and more rigorous efforts to eliminate variables.[15] This, of course, applies only to medical studies, but the NIH standards will encourage other government agencies to at least take notice.

As gatekeepers of information about studies, many medical and academic journals are changing the way they accept papers for publication. *PLOS* now requires full disclosure of all data before it will publish any research studies.[16] And *Nature* magazine is offering data repository agreements to encourage public sharing of research data among its contributors.[17] *Nature* has gone so far as to devote an entire online hub to the topic at www.nature.com/news/reproducibility-1.17552.

And the debate on what else ought to be done continues. Neuroskeptic proposes peer review of research studies before they even begin, with journals committing to publishing the results no matter what they are.[18] Peng, the Johns Hopkins biostatistician, is proposing enhanced instruction in statistics for budding researchers in all scientific disciplines to improve the quality of conclusions reached from study results.[19] Fidler and Gordon suggest a reproducibility index, which they argue would require more sober statistical analysis of research results. They also propose that researchers share their computer code — their search algorithms — along with the data used in the study being reported on, so that others can provide a true "apples-to-apples" comparison.[4]

It will likely take a combination of all these proposals to begin changing the culture of medical and scientific research. But with so many billions of dollars at stake in both private and public research funds, the current uproar over the "reproducibility crisis" is unlikely to lessen until system reforms are put in place. ❖

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Zoonotic Diseases:
An Emerging Global Health Challenge

Although noncommunicable diseases are the leading cause of morbidity and mortality in most developed nations, infectious diseases, particularly those transmitted through contact with animals, remain a major public health concern.

By Trudie Mitschang

In the early 1960s, vaccines for viral diseases such as measles, mumps, rubella and polio promised to control and potentially eradicate these and other highly contagious infections. Even smallpox, a disease caused by the variola virus that was responsible for the deaths of between 300 million and 500 million people during the 20th century, showed signs of succumbing to an intense global immunization campaign. In the wake of such promising advances, Australian virologist and Nobel Prize winner Macfarlane Burnet made the following statement: "There may be some wholly unexpected emergence of a new and dangerous infectious disease, but nothing of the sort that has marked the past fifty years."[1]

Unfortunately, that prediction has proven to be only partly true, as evidenced by a host of new, unexpected infectious diseases, including a plethora of zoonotic diseases and epidemics that could offer only a glimpse of potential deadly pandemics to come. The emergence of the MERS virus in Saudi Arabia, a new killer strain of bird flu in China and an unprecedented Ebola outbreak in West Africa have all highlighted the scientific community's failure to pinpoint the source or identify the means to stop the impending wave of viral threats.

"Research in all of the epidemics we have faced over the past decade has been woeful," said Jeremy Farrar, director of the Wellcome Trust global health foundation and an expert on infectious diseases.[2] "The world is at risk because there are huge gaps in our knowledge base. We don't now have a vaccine for SARS if it came back tomorrow; we don't know how to treat MERS; it took us six to nine months before we started clinical trials of vaccines for Ebola and in the meantime almost 12,000 people lost their lives; and during the H1N1 pandemic, the number of people randomized into clinical studies was very close to zero."

An Escalating Concern

Over the last 15 years, the world has witnessed more than 15 deadly zoonotic or vector-borne global outbreaks, and since 1980, more than 87 new zoonotic and/or vector-borne diseases have been discovered. Some estimates state that approximately 75 percent of newly emerging infectious diseases are zoonoses.[3]

By definition, any disease or infection that is naturally transmissible from vertebrate animals to humans and vice-versa is classified as a zoonosis. According to the Pan American Health Organization publication *Zoonoses and Communicable Diseases Common to Man and Animals*, zoonoses have been recognized for many centuries, and over 200 have been described. They are caused by all types of pathogenic agents, including bacteria, parasites, fungi and viruses.[4]

Reducing public health risks from zoonoses and other health threats at the human-animal-ecosystems interface is a complex challenge at best, says the World Health Organization (WHO). Management and reduction risks must take into account the myriad interactions among humans, animals and the various environments they live in, and any long-range plan will require communication and collaboration among all the sectors responsible for human health, animal health and the environment. In other words, multiple stakeholders must commit to making the identification and eradication of zoonotic diseases a top priority.

WHO is engaging in an ever-increasing number of cross-sectoral activities to address many of these health threats, including existing and emerging zoonoses[4] in four major categories:

• *Bacterial threats.* Every year, millions of people get sick because of foodborne zoonoses such as Salmonellosis and Campylobacteriosis. These types of illnesses can cause fever, diarrhea, abdominal pain, malaise and nausea. Other bacterial zoonoses include anthrax, brucellosis, infection by verotoxigenic Escherichia coli, leptospirosis, plague, Q fever, shigellosis and tularaemia.

• *Parasites.* In Latin America alone, 100 out of 100,000 inhabitants suffer from a parasite infection called cysticercosis/ taeniasis found in swine that is linked to seizures headache and many other symptoms. Other parasitic zoonoses include trematodosis, echinococcosis/hydatidosis, toxoplasmosis and trichinellosis.

• *Viruses.* Rabies is a well-known disease found in carnivores and bats that is mainly transmissible to humans by bites. An estimated 55,000 people, mainly children, die of rabies each year. Other viral zoonoses include avian influenza, Crimean-Congo hemorrhagic fever, Ebola and Rift Valley fever.

• *Fungi.* Dermatophytoses are superficial mycoses that may be acquired from infected animals and affect the skin, hair and nails of humans, causing itching, redness, scaling and hair loss. Another mycotic infection that can be zoonotic is sporotrichosis.

The Ebola Outbreak: What We Have Learned

The 2014 Ebola outbreak in West Africa dramatically raised awareness of the global burden of infectious diseases and raised questions about the preparedness of public health systems. It was documented as the worst outbreak of this virus in history. In Guinea, Sierra Leone and Liberia, the three countries most affected by the outbreak, about 70 percent of those infected have died.[5]

Although the research is ongoing, speculation regarding Ebola's origins has yet to produce a conclusive answer. The first known human cases of Ebola occurred in 1976 during two simultaneous outbreaks in Sudan and the Democratic Republic of the Congo, according to WHO.[6] Nearly 20 years later, in 2005, researchers looking for the reservoir of Ebola sampled more than 1,000 small animals in the Central African nations of Gabon and the Republic of the Congo, which experienced outbreaks of Ebola. They tested 679 bats, 222 birds and 129 small terrestrial vertebrates. The only animals found to harbor the Ebola virus were bats, and researchers have found Ebola virus RNA in at least three species of fruit bats. That made the animals — commonly hunted and eaten in Guinea — a top contender as the source of the disease.[7]

Some estimates state that approximately 75 percent of newly emerging infectious diseases are zoonoses.

In October 2014, panic ensued when a New York doctor returning from a humanitarian mission in West Africa tested positive for the Ebola virus. Later that year, two nurses from Dallas also tested positive for the virus. All three were quickly quarantined and have since recovered from the illness. Despite the hysteria driven by media coverage, public health officials believe the likelihood of a widespread Ebola outbreak in the U.S. is minimal. According to Dr. William Schaffner, a professor of preventive medicine and infectious diseases at Vanderbilt University Medical Center in Nashville, Tenn., if Ebola were to become widespread in the U.S., the mortality rate from the virus would likely be significantly lower than in Africa. "The death rate would be lower in the U.S.," said Schaffner in an interview with *Live Science*. "Everybody believes we could move it down from 50 percent to 30 percent, or perhaps even

lower than that. If they had available the kinds of supportive care that we're able to provide in the United States — in our hospitals and, particularly, in our intensive care units — the survival rate (in Africa) would be much higher."[8]

Ebola is not the only viral illness making headlines in recent years. In February, the public scrambled to understand the implications of the Zika virus after WHO designated it as an international public health emergency because of the suspected relationship between Zika and a rise in cases of a rare congenital condition called microcephaly in Brazil. Officials at the Centers for Disease Control and Prevention (CDC) have urged pregnant women against travel to about two dozen countries, mostly in the Caribbean and Latin America, where the outbreak is growing. Zika is a mosquito-transmitted infection related to dengue, yellow fever and West Nile virus. Although it was discovered in the Zika forest in Uganda in 1947 and is common in Africa and Asia, it did not begin spreading widely in the Western Hemisphere until May 2015.[9]

The 2014 Ebola outbreak in West Africa dramatically raised awareness of the global burden of infectious diseases and raised questions about the preparedness of public health systems.

Epidemic, Endemic or Pandemic: Understanding Key Terminology

Three terms are used in epidemiology — the study of the spread, causes and consequences of disease — to describe disease distribution:

• *Epidemic* is a widespread increase in the observed rates of disease in a given population. Diseases such as mumps, measles and cholera can become epidemics, depending on a range of factors.

• *Endemic* is a consistently heightened rate of disease observed in and associated with a given population over time. For example, malaria is endemic in a number of tropical zones in the world.

• *Pandemic* is a sudden increase in the observed rates of disease across many populations globally. The most infamous is the 1918-19 flu pandemic, which killed 675,000 people in the United States and millions around the globe.

It's important to note that the term "outbreak" can refer to an epidemic or pandemic. Epidemiologists' ability to define a disease distribution as epidemic, endemic or pandemic allows health workers, clinicians and policy makers to set local and global priorities for controlling illness and promoting health throughout a population level.

Defining and examining the global distribution of infectious diseases, in both time and location, is a major research priority. A 2014 study published in the *Journal of the Royal Society Interface* examines the global changes in the frequency of outbreaks of infectious diseases between 1980 and 2013. In all, the dataset covered 12,102 outbreaks of 215 diseases, with 44 million individual cases in 219 countries around the world. The researchers, based at Brown University, sought to examine the relationship between the location and timing of disease outbreaks and the characteristics of outbreak sites, such as the presence of certain animals that transmit disease to humans.[10]

Among the study's findings:

• Sixty-five percent of the diseases, making up 56 percent of all outbreaks, were zoonoses. These include Ebola, HIV, the bubonic plague and Lyme disease.

• Zoonotic diseases have been becoming increasingly diverse over time, but only a small number cause the majority of outbreaks in each decade: "From 1980 to 1990, 80 percent of all zoonotic disease outbreaks were caused by only 25 percent of potential zoonoses in the dataset, and only 22 percent and 21 percent of zoonoses from 1990 to 2000 and from 2000 to 2010, respectively." (The authors caution that zoonotic disease cases may be undercounted in the nations affected the most because of limited infrastructure and health resources.)

• Other factors influencing the rise of zoonotic diseases include the fact that human populations are growing and expanding into new geographic areas, and as a result, more people live in close contact with wild and domestic animals.

• Changes in climate and land use such as deforestation and intensive farming practices and disruptions in environmental conditions and habitats provide new opportunities for diseases to pass to animals.

• International travel and trade have increased, allowing diseases to spread more quickly than at any time in history.

Collaborative Solutions: The One Health Initiative

One Health Initiative is a term that refers to the concept of multidisciplinary collaborative approaches to solving today's global and environmental health challenges. The One Health Initiative autonomous pro bono team started the One Health Initiative website in 2008, which has since been serving as a global repository for all news and information pertaining to

One Health. Organizations supporting this movement include the American Medical Association, American Veterinary Medical Association, UC Davis One Health Institute, American Society of Tropical Medicine and Hygiene, American Association of Public Health Physicians, CDC, United States Department of Agriculture, National Oceanic and Atmospheric Administration and U.S. National Environmental Health Association. Additionally, more than 850 prominent scientists, physicians and veterinarians worldwide have endorsed the initiative.

One Health was born out of, and fueled by, fear. In 2004, there was global anxiety that a zoonotic disease, highly pathogenic avian influenza (HPAI) H5N1, could lead to a pandemic rivaling, and possibly exceeding, the catastrophic Spanish flu outbreak at the end of World War I. The introduction of the One Health Initiative provided international agencies with a vehicle for interinstitutional and interdisciplinary collaboration to address the threat of emerging zoonotic diseases like H5N1, and enabled these international agencies and national authorities to work together in the search for solutions.[11]

The global response to avian influenza was launched in January 2006 against a One Health backdrop at the International Ministerial and Pledging Conference of Beijing. This led to collaboration between the European Union, U.S. and the United Nations, and five subsequent years of cooperation focused on the control of avian influenza. In 2010, the World Bank published a framework for the control of animal influenzas through the application of One Health principles. The World Bank estimated that between 2005 and 2009, $4.3 billion U.S. were pledged for the international control of HPAI,[11] giving merit and credibility to the One Health concept.

With the success of that initial collaboration under its belt, the One Health Initiative is seeking to expand its efforts to "promote, improve and defend the health and well-being of all species by enhancing cooperation and collaboration between physicians, veterinarians, [and] other scientific health and environmental professionals."[12]

According to Dr. Laura Kahn, a physician on the research staff of the Woodrow Wilson School of Public and International Affairs at Princeton University, a One Health holistic approach to the challenges posed by 21st-century life and the resulting threat of zoonotic diseases is essential: "Climate change and increasing human populations will definitely increase the need for multidisciplinary, collaborative programs. As the Earth's resources are strained with increasing demands for energy, food, shelter and water, we must anticipate that a sustainable future will require a holistic approach to human, animal and ecosystem health. A One Health approach will be critical if we hope to meet the challenges of the 21st Century and beyond."[13] ❖

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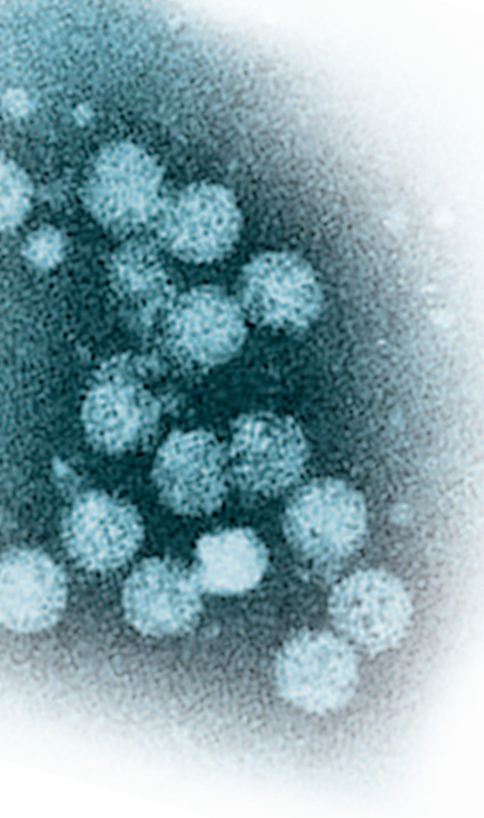

Hope for Hep C

Screening and new treatments offer a high cure rate for those affected by what was once a grave disease.

By Meredith Whitmore

When speaking with Sue Simon, it is difficult to believe she was ever ill or even discouraged. After her stage-4 hepatitis C diagnosis in 1991, the upbeat elementary school teacher faced two decades of painful, unsuccessful treatments. "I tried every interferon that came on the market," she says. "Every time a pharmaceutical company changed or tweaked a drug, I tried it."

Despite her willingness and efforts to battle the hepatitis C virus (HCV), some treatments left her even sicker. "For two years I tried maintenance treatment with interferon. It destroyed my bone marrow," she explains. "I was in the hospital for almost the whole summer in 2008 because it suppressed my immune system and I had no white count at all."

Still, she fought to beat the virus. Finally, in 2013, a clinical trial of the direct-acting antiviral drug Viekira Pak (ombitasvir/paritaprevir/ritonavir; dasabuvir) cured her. Sue will be HCV-free for the rest of her life. She never dreamed she would see the day when a virus is cured with medication, but she is now adamant about others getting tested and finding help along their own HCV journey. She has also discovered another calling as a patient advocate/writer for the HCV community. "Get tested, get treated, get cured" is her confident advice to those who have not previously considered hepatitis C but may be at risk.

Historically, such assurance has not been as available to hepatitis C patients. Optimism is, in fact, a very recent development in this virus's story.

History, Background and Epidemiology

Once called non-A or non-B hepatitis because it did not share the same serological markers of the better-known hepatitis A or hepatitis B,[1] the virus that is now known as hepatitis C was identified in 1989. Scientists suspect it existed for decades before that.[2,3]

"HCV belongs to a family of viruses called flaviviruses, which include the causative agents of yellow fever, dengue fever and West Nile encephalitis," explains Dr. Ira Jacobson, chairman of the department of medicine at Mount Sinai Beth Israel and vice chair of the department of medicine at Icahn School of Medicine at Mount Sinai. "It's spread by parenteral transmission, which means it's not spread orally, but rather requires percutaneous exposure to body fluids that contain the virus. The most common routes of transmission are, by far, exposure to contaminated blood, which is why thousands and thousands of people used to get it from blood transfusions. That was before the advent of highly accurate HCV tests developed in the early 1990s to screen blood donors. The virus is also transmitted readily among drug users who share syringes or other equipment. Perhaps about 3 to 5 percent of the time, it can be passed by mother to infant though vertical transmission. And, though it is rare in the United States, the virus has been spread on a large scale through nosocomial transmission, which is infection from a healthcare setting through unhygienic equipment. Doctors are mystified by the small percent of patients who get hepatitis C yet are without any of these risk factors."

Dr. Ype de Jong, assistant professor at Weill Cornell Medical College and a visiting assistant professor at The Rockefeller University, agrees that some cases are mysterious: "I have patients who really cannot find another risk factor other than just getting manicures [from a salon with suspected contaminated equipment]. So I think there is still some low-level infection here and there. Sometimes people get it from contaminated endoscopy equipment, but these are the stories that make the national news in this country."

The medical community is most concerned about IV drug users. "The heroin epidemic that is ongoing, mostly because we doctors have been prescribing opiates like crazy in this country, has created an iatrogenic opiate addiction," explains Dr. de Jong. "Heroin and other IV drugs are so much less expensive than opiates that there is now an enormous amount of heroin use in rural America, particularly in the rural Northeast. The Centers for Disease Control and Prevention [CDC] is afraid that these people are sharing needles, and there has been an uptick in the prevalence of hepatitis C in 2013."[4]

Even if a person has no dramatic risk factors such as drug use, everyone in the HCV community stresses the importance of being tested. "One of the biggest things is birth cohort screening — or screening according to one's birth year," explains Dr. de Jong. "There was so much drug use in the 1960s and '70s, and then injuries in Vietnam that required transfusions, that the baby boomer generation — those born between 1945 and 1965 — should be tested for hepatitis C. They believe 5 percent of the people have hepatitis C even if they're asymptomatic and have no risk factors. Everyone should still get screened."

Dr. Jacobson adds that in some areas, testing is statutory: "It is now mandatory in some states, including New York, that people born between the years 1945 and 1965 have a one-time test for hepatitis C in certain contexts, such as primary care offices or upon admission to a hospital. You're automatically supposed to have a test for hepatitis C if you haven't had one before. That's because up to two-thirds of people with hepatitis C in this country are baby boomers. And so it was decided by agencies like the CDC and the U.S. Preventive Services Task Force that an efficient way to identify the majority of as-yet undiagnosed Americans would be via birth cohort rather than risk-based screening."

Symptoms and Diagnosis

"Diagnosis almost always is a shock to patients," says Dr. Raymond Chung, director of hepatology at Massachusetts General Hospital and associate professor of medicine at Harvard Medical School. "Of the three million patients in the United States who have hepatitis C, just over half of them don't know they have it." (Some researchers put the number of undiagnosed people at closer to four million.[5])

Because most patients who suffer from HCV do not have specific symptoms, if any, many people are diagnosed when their physicians prescribe routine blood work for a physical or to diagnose another possible illness. To confirm an HCV diagnosis, doctors may run a liver biopsy in addition to blood tests.[6]

And, even though many patients are asymptomatic for decades, the virus is not dormant. "It is slowly destroying the liver, but the symptoms are not very specific, and most people just don't know they are ill," says Dr. de Jong. "Patients don't become jaundiced or have fevers or have abdominal pain from having hepatitis C. They might experience a little bit more fatigue than other people, and in very rare cases, there are complications such as skin ulcers or renal failure."

Past Treatments

"In the past, interferon-based strategies were the only treatment for this disease," says Dr. Chung. "Initially, our strategies revolved around either interferon given alone or interferon given with ribavirin, another antiviral, though weaker. That combination produced response rates in just over 50 percent of patients. The regimen was administered between six months and 12 months and was associated with a litany of significant side effects such as fatigue, anxiety, depression, anemia, low white blood cell and platelet counts, and provocation of autoimmune events such as lupus, rheumatoid arthritis, ulcerative colitis, psoriasis and thyroid disorders. So even though the cure rate was just over 50 percent with interferon and ribavirin, the true effectiveness was much more limited because very few patients actually went through the process of treatment. Potential contraindications, concerns about preexisting conditions, concerns about intolerability, or, for those who did start, actual intolerability, caused premature termination of the regimen. That led to very few patients being eligible or [even wanting to risk the side effects]."

"HCV belongs to a family of viruses called flaviviruses, which include the causative agents of yellow fever, dengue fever and West Nile encephalitis."

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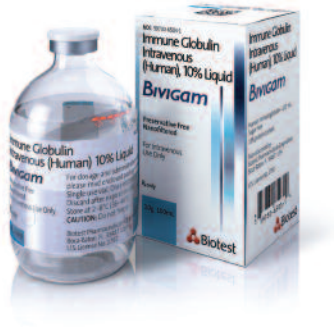

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Please see BIVIGAM Important Safety Information and Prescribing Information on next page, including black box safety warnings, contraindications, and dosing.

*IVIG is also known as IGIV, Immune Globulin Intravenous (Human).

References: 1. Wasserman RL. A new intravenous immunoglobulin (BIVIGAM®) for primary humoral immunodeficiency. *Expert Rev Clin Immunol.* 2014;10(3): 325–337.
2. BIVIGAM [package insert]. Boca Raton, FL: Biotest Pharmaceuticals Corporation; 2013.

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Indication and Usage: BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI).

Contraindications: BIVIGAM is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. BIVIGAM is contraindicated in IgA deficiency patients with antibodies to IgA and a history of hypersensitivity.

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Hypersensitivity:** Severe hypersensitivity reactions may occur with IGIV products, including BIVIGAM. In case of hypersensitivity, discontinue BIVIGAM infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions. BIVIGAM contains trace amounts of IgA (≤ 200 micrograms per milliliter). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. BIVIGAM is contraindicated in IgA deficient patients with antibodies against IgA and a history of hypersensitivity reaction. **Acute Renal Dysfunction and Acute Renal Failure**: Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering BIVIGAM. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of >65 years), administer BIVIGAM at the minimum infusion rate practicable. **Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia**: Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy, including BIVIGAM. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events. **Aseptic Meningitis Syndrome (AMS):** AMS may occur infrequently with IGIV treatments including BIVIGAM. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting . Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. **Hemolysis:** IGIV products, including BIVIGAM, may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration, [13] and acute hemolysis, consistent with intravascular hemolysis, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If these are present after BIVIGAM infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis. **Transfusion-Related Acute Lung Injury (TRALI):** Noncardiogenic pulmonary edema may occur in patients following IGIV treatment including BIVIGAM. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti- neutrophil antibodies in both the product and the patient's serum. TRALI may be managed using oxygen therapy with adequate ventilatory support. **Transmissible Infectious Agents**: Because BIVIGAM is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Biotest Pharmaceuticals Corporation at 1-800-458-4244. Before prescribing BIVIGAM, the physician should discuss the risks and benefits of its use with the patient . **Monitoring Laboratory Tests:** Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. Because of the potentially increased risk of thrombosis with IGIV treatment, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. If signs and/or symptoms of hemolysis are present after an infusion of BIVIGAM, perform appropriate laboratory testing for confirmation. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum. **Interference with Laboratory Tests** : After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

ADVERSE REACTIONS: Serious adverse reactions observed in clinical trial subjects receiving BIVIGAM were vomiting and dehydration in one subject. The most common adverse reactions to BIVIGAM (reported in ≥5% of clinical study subjects) were headache, fatigue, infusion site reaction, nausea, sinusitis, blood pressure increased, diarrhea, dizziness, and lethargy. **Clinical Trials Experience**: *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials cannot be directly compared to rates in the clinical trials of another product and may not reflect the rates observed in clinical practice.* In a multicenter, open-label, non-randomized clinical trial, 63 subjects with PI, on regular IGIV replacement therapy, received doses of BIVIGAM ranging from 254 to 1029 mg/kg (median dose 462.8 mg/kg) every 3 weeks or 4 weeks for up to 12 months (mean 317.3 days; range 66 – 386 days). The use of pre-medication was discouraged; however, if subjects required pre-medication (antipyretic, antihistamine, or antiemetic agent) for recurrent reactions to immune globulins, they were allowed to continue those medications for this trial. Of the 746 infusions administered, 41 (65%) subjects received premedication prior to 415 (56%) infusions. Fifty-nine subjects (94%) had an adverse reaction at some time during the study. The proportion of subjects who had at least one adverse reaction was the same for both the 3- and 4-week cycles. The most common adverse reactions observed in this clinical trial were headache (32 subjects, 51%), sinusitis (24 subjects, 38%), fatigue (18 subjects, 29%), upper respiratory tract infection (16 subjects, 25%), diarrhea (13 subjects, 21%), cough (14 subjects, 22%), bronchitis (12 subjects, 19%), pyrexia (12 subjects, 19%), and nausea (9 subjects, 14%). Adverse reactions (ARs) are those occurring during or within 72 hours after the end of an infusion . In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of BIVIGAM infusions with one or more temporally associated adverse reactions was 31%. The total number of adverse reactions was 431 (a rate of 0.58 ARs per infusion).

Seven subjects (11.1%) experienced 11 serious ARs. Two of these were related serious ARs (vomiting and dehydration) that occurred in one subject. One subject withdrew from the study due to ARs related to BIVIGAM (lethargy, headache, tachycardia and pruritus). All 63 subjects enrolled in this study had a negative direct antiglobulin (Coombs') test at baseline. During the study, no subjects showed clinical evid ence of hemolytic anemia. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. During the clinical trial no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV) , or hepatitis C virus (HCV). There was a single positive finding for parvovirus (B19 virus) during the study. This subject came in contact with acute B19 virus from working at a school greeting children where a child was reported to have symptomatic Fifth's disease. There was no cluster (no other cases in other subjects) of B19 virus transmission with the IGIV batch concerned.

Table: Adverse Reactions (ARs) (within 72 hours after the end of a BIVIGAM infusion) in ≥5% of Subjects

ARs	**No. Subjects Reporting ARs (% of Subjects) [n=63]**	**No. Infusions With ARs (% of Infusions) [n=746]**
Headache	27 (43%)	115 (15.4%)
Fatigue	15 (24%)	59 (7.9%)
Infusion Site Reaction	5 (8%)	5 (0.7%)
Nausea	5 (8%)	8 (1.1%)
Sinusitis	5 (8%)	5 (0.7%)
Blood Pressure Increased	4 (6%)	5 (0.7%)
Diarrhea	4 (6%)	4 (0.5%)
Dizziness	4 (6%)	4 (0.5%)
Lethargy	4 (6%)	4 (0.5%)
Back Pain	3 (5%)	3 (0.4%)
Blood Pressure Diastolic Decreased	3 (5%)	5 (0.7%)
Fibromyalgia[a]	3 (5%)	17 (2.3%)
Migraine	3 (5%)	8 (1.1%)
Myalgia	3 (5%)	4 (0.5%)
Pharyngolaryngeal Pain	3 (5%)	3 (0.4%)

[a]**Symptoms occurring under pre-existing fibromyalgia**

DRUG INTERACTIONS Live Virus Vaccines : Immunoglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibody may interfere with an active antibody response. The immunizing physician should be informed of recent therapy with BIVIGAM so that appropriate measures may be taken.

virus to replicate that, hopefully, eventually, and perhaps with some little subtle natural help from the immune system, you could eradicate this virus. That's exactly what we've learned."

Dr. Jacobson even goes so far as to call DAAs "miraculous." The first such drugs, Telaprevir (Incivek and Incivo) and Boceprevir (Victrelis), were considered cutting-edge in their time, but medicine has advanced so greatly and so quickly since then that the two drugs are no longer used. This, according to Dr. Jacobson, "is very fast in the grand sweep of things. It's kind of remarkable." Today, the focus is on more advanced DAAs such as Harvoni (ledipasvir and sofosbuvir) and the more recently approved Zepatier (elbasvir and grazoprevir).[7] Cure rates with the latest DAAs, including protease inhibitors, polymerase inhibitors and NS5A inhibitors, are as high as 97 percent.[8]

"Diagnosis almost always is a shock to patients."

Dr. Jacobson adds that some patient populations have been more difficult to treat, yet because of improved DAAs, they are increasingly responsive: "We leapfrogged from an era in which we still had to prove this, to an era in which an astonishingly high percentage of patients could be cured. Many had anticipated that this would occur in incremental steps. I like to say we thought it would be like the iPhone that keeps coming back in new versions year after year. That one year you could cure 20 percent, then 50 percent, then maybe 70 or 80. But instead, we've leapfrogged from nothing to extraordinary rates of cure, as high as 99 percent in some clinical trials."

Investigational Treatments

In light of the unprecedented cure rates with already existing drugs, Dr. de Jong wonders whether more research into investigational drugs is needed. "So the question is really, ongoing, what are investigational drugs?" he asks. "Do we need to go to three drugs or make one pill or two pills with three active components? Where, for example, instead of treating for 12 weeks or eight weeks, can we now go to six weeks or four weeks? That's one investigational direction the pharmaceutical companies are going. It would be ideal if a doctor could see a patient just once, give him a one-month prescription that insurance would cover, and then cure 99 percent of people with two or three drugs."

"Now we're focusing a lot of our attention on the relatively few patients who have treatment failure because we've gotten spoiled [by success]," says Dr. Jacobson. "We're not going to leave anybody behind. And so people are developing what are called salvage or rescue regimens for the patients who do fail these regimens."

"There are still investigational things coming down the pipeline," adds de Jong, "but the big debate in the field is whether we still need them. Because with the drugs we already have, we are able to cure perhaps 99 percent of patients in clinical trials. The trials are always a little bit better than real life, so say that is probably going to be 97 or 95 percent. What is the pharmaceutical market going to do? And if we go to three drugs, which everyone expects us to do, with all three classes of direct-acting antivirals in one tablet, we will probably cure 90 percent of the people who didn't respond previously. So, we'll end up with a very small pool of patients who cannot be treated. And that is the big debate right now. Do we still need investigational drugs to cure those very few people who cannot be cured with the current medications? We don't really know this yet."

Final Thoughts

Regardless of the unanswered questions, one thing is certain: Cure rates are unprecedented, and being diagnosed with hepatitis C is no longer the grave event it once was. "At this juncture, knowledge is power," concludes Dr. Chung. "Knowledge is responsibility to follow through to prove your own health. I would be very emphatic about the fact there's no excuse for not diagnosing every last person with this infection in view of the fact we will have treatment for every one of them."

More and more hepatitis C patients are discovering that hope. Just ask Sue Simon. ❖

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

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Narrative Medicine: How Stories of Illness Affect Caregiving

A physician diagnoses the condition and either treats it or refers the patient to someone else for treatment. End of story. Or is that just the beginning of the story? Narrative medicine challenges the medical model by bringing a new tool to the table: the story of the patient.

By Dana Martin

Theme. Setting. Characters. Point of view. These are some of the central elements of story development, ones you might remember from literature and composition classes. But they are also important to patient care, perhaps as important as gathering information through exams and testing. Narrative medicine is an emerging clinical discipline that focuses on medicine practiced with the narrative skills of recognizing, absorbing, interpreting and being moved by patients' stories of illness.[1,2] It marries the objectivity physicians have been trained to bring to their work with the empathy needed to understand and care for each patient as an individual with a unique story. As Bradley Lewis, author of *Narrative Psychiatry: How Stories Can Shape Clinical Practice*, writes, "The doctor's interest and concern ought to be as much about the objective facts about cancer of the colon, for example, as about how the unique individual in front of him or her subjectively experiences their situation and what this means for this particular individual's life."[3]

Though steeped in such disciplines as medical

humanities and bioethics, narrative medicine as a distinct concept is a relatively new approach to medical care.[4] In 2000, Rita Charon, MD, PhD, founded the Program in Narrative Medicine at the Columbia University College of Physicians and Surgeons. While pursuing her PhD in English at Columbia, she realized stories have clinical significance[5] in that sickness unfolds in stories.[6] As an internist, much of her job consisted of listening to people's stories, deciphering them and taking action. This aspect of medicine, she concluded, was all around her students, but it was never discussed.[6] "Before I started doing this, I knew my students had those experiences, but there was no way to capture it. There was no way to open it. There was no way to honor it."[7] The Program in Narrative Medicine not only brings the story element of medical care into the light, it also ensures students have the necessary training to gather, interpret, understand and act on their patients' stories.[5] This insight allows for better care, she says.[8] The program's goals include building trust, developing empathy and fostering a sense of shared responsibility in a patient's health.[5]

Developing Narrative Competence

Students in Columbia University's Program in Narrative Medicine primarily approach the art of narrative medicine by working with two types of charts. The first is the scientific charting they are familiar with. The second is a record, in essay form, of their encounters with and their emotional reactions to patients.[7] At first, it may seem counterintuitive to chart one's own response to patients. The objective is, after all, getting at the patient's story, not the story of how the caregiver responds to the patient. But Charon and others in the area of narrative medicine believe such introspection is necessary in terms of story excavation. One of the things students do as part of their parallel charting is talk about their own responses as part of their medical training. Charon says, "By doing it this way in training, it says, 'This is what it takes to be a doctor.'" Thus, the approach gives caregivers more access to knowledge about themselves as well as their patients. "What we know about going through this, however much it hurts, is that it makes us better. It makes you deeper, and you feel the defeats,"

Charon says. "You agonize over the mistakes, or even what you think could have been one. Your patients visit you in your dreams. And, paradoxically, there is a tremendous, joyous reward."[7]

Lewis Mehl-Madrona, MD, PhD, MPhil, has been studying indigenous doctoring with traditional North American healers for more than three decades, with an emphasis on narrative approaches. "Narrative medicine is the encompassing of our awareness of health and disease into a storied structure," he states. "We embed the illness into the life story of the person in such a way that we discover meaning and purpose in both the illness and the experience of recovery. And we come to a new respect for the illness, in the context of the life that it appears in." For him, a person's story includes friends, ancestors, interests and spiritual orientation. Ceremony is a central part of his work as it is part of the story of community and healing.[9]

The Need for Narrative Medicine

Charon writes: "Sick people need physicians who can understand their diseases, treat their medical problems, and accompany them through their illnesses."[10] Mehl-Madrona says the person is "as important to the outcome as the histology of a biopsy in the laboratory, maybe more important."[11] Narrative medicine allows for the understanding Charon speaks of, as well as the person-centered care for which Mehl-Madrona advocates. Four advantages of narrative medicine are outlined below.

First, narrative medicine can overcome the ways in which specialization and technical jargon can limit the work caregivers do with their patients.[7] Lewis asserts that the language of bioscience too often divides physicians from patients, themselves, colleagues and society, and that the goal of narrative medicine is to bridge those gaps.[4] "These gaps make it too hard [for] physicians to communicate and make it too easy for important variables of healthcare to escape," he explains.[4] In fact, there is preliminary evidence that narrative medicine creates caregivers with a deeper understanding of their patients' needs,[6] perhaps because it overcomes the barriers that language can present.

Second, narrative medicine can make caregivers more empathetic. One example is that of an experiment in which 891 diabetic patients were followed for three years to determine whether their health outcomes were correlated with their physicians' empathy levels, measured in part by an understanding of the patient's experiences, concerns and perspectives — the skills taught in narrative medicine. The results showed that the likelihood of good control was significantly higher in the patients whose doctors had high empathy scores than it was for patients whose doctors had low empathy scores.[12]

In another example, staff members at a mental health center employed a narrative approach to caregiving as part of a course in which they created narrative descriptions of patients presented by medical staff as hopeless.[13] Mehl-Madrona and Michael Valenti, PsyD, published one caregiver's narrative of a patient that reveals the power of the narrative process to positively affect how caregivers see patients. "Narratives give physicians the skills, methods and texts to learn how to imbue the facts and objects of health and illness with their consequences and meanings for individual patients and physicians," Valenti and Mehl-Madrona write. The narrative approach created the picture of a competent human being as opposed to the clinical narrative of incompetence that was usually presented. It also allowed the caregiver to see the patient in a more complex way, which leads to greater empathy on the part of the caregiver.[13]

Third, stories can contain information that's essential for treating the patient — information that would otherwise go ungathered. "By teaching clinicians how stories work, what happens to their tellers and listeners, and where stories hide their news — in form, in metaphor, in mood, in time and space — we enable them to enter the narrative worlds described by their patients," Charon says. "So clinicians can receive what their patients reveal about their lives and health, leading to accurate clinical diagnoses and personal recognition. They hear in depth what their colleagues report about their patients. They even come to be more forcefully aware of their own interior voices in self-awareness."[5]

Resources

Books

- *Integrating Narrative Medicine and Evidence-Based Medicine: The Everyday Social Practice of Healing*, by James Meza and Daniel Passerman
- *Narrative Medicine: Honoring the Stories of Illness*, by Rita Charon
- *Narrative Medicine: The Use of History and Story in the Healing Process*, by Lewis Mehl-Madrona
- *Narrative Psychiatry: How Stories Can Shape Clinical Practice*, by Bradley Lewis

Programs

- Master of Science in Narrative Medicine at Columbia University: sps.columbia.edu/narrative-medicine
- Narrative Medicine Workshops at Columbia University: www.narrativemedicine.org/workshops.html

Videos

- Program in Narrative Medicine at Columbia University YouTube channel: www.youtube.com/channel/UCvpbfEqk0gbJ0s0Lx9jUuUQ
- "Bodies, Stories, and Selves: How Narrative Saves Lives" by Rita Charon: www.youtube.com/watch?v=OhSNzp4cGCE

Lastly, beliefs about illness can make a difference in patients' outcomes.[11] The flip side of objective data collection and monitoring is the subjective experience about illness, which is a story in and of itself — one that has tremendous power in terms of healing. Mehl-Madrona expands on this connection between one's personal narrative and health outcome. "Whatever you do to get well, it has to fit into the story you have about how people get sick and get well," he observes. These stories vary from one patient to the next, and none of them can be factored in or even influenced if they aren't identified and acknowledged. "Through metaphor, [patients'] stories help create a context of hope and a path to wellness — features that often are lacking from the 'story' patients get from mainstream medicine based on statistics and life-expectancy tables," Mehl-Madrona adds.[11]

The Limitations of Narrative in Medicine

Narrative medicine isn't beyond scrutiny. One criticism is that, in its current form, the approach largely ignores the limits of narrative. Nurse practitioner Josephine Ensign teaches narrative medicine but also asks questions about its limitations. She says there are human experiences beyond narrative, particularly those that fall within the contexts of trauma, suffering and oppression. Ensign argues that caregivers need more than listening skills. They need to learn to listen in socially just ways, which includes developing the skills necessary to listen to stories that challenge them, not just those that are comfortable.[14]

Other challenges of medicine based in narrative include the steep learning curve involved, which includes significant technical and attitudinal changes, and the fact that some patients don't want to share their stories.[15]

Learning the Art of Narrative Medicine

According to Charon, narrative medicine, simply put, is medicine practiced by someone who knows what to do with stories.[16] For those who can do so, training at the Program in Narrative Medicine is the ideal way to learn this skill. In 2009, Columbia University inaugurated a Master of Science in Narrative Medicine to fulfill the demand for training.[5] Columbia also offers basic and advanced workshops on the subject that each last three to four days. Other schools, such as the University of Virginia, are also incorporating narrative medicine into their programs.

For those who can't formally train in narrative medicine, there are things they can do to pay better attention to the stories their patients are telling. These include keeping a journal of their interactions with patients, paying better attention to their own reactions to patients, paying attention to nonverbal communication such as body language and facial expressions, and using ordinary language when speaking with those in their care.

Joan Didion writes: "We tell ourselves stories in order to live."[17] We also carry those stories into our roles as patient and caregiver alike. Listening to patients and understanding their stories, then allowing those stories to help guide care, is a skill just like any other acquired in medicine. It needs to be learned and practiced — honed over time, as opposed to picked up overnight. But the rewards of this work can be tremendous for everyone involved. ❖

Narrative medicine can make caregivers more empathetic.

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Myths and Facts: Venomous Snakebites

Although venomous snakebites are rare in the U.S. compared to other countries, they are still medical emergencies that need to be treated with today's safe and effective methods.

By Ronale Tucker Rhodes, MS

Globally, at least 421,000 venomous snakebites, known as envenomings, occur each year.[1] In the U.S., that number is considerably lower — between 7,000 and 8,000, which equates to fewer than one in 37,500 people[2] — due to fewer venomous snakes inhabiting this country. In fact, out of more than 3,000 species of snakes in the world, approximately 600 are venomous and only slightly more than 200 are considered to be medically important.[3] Of the latter, only two types are indigenous to the U.S.: pit vipers (rattlesnakes, copperheads, cottonmouths/water moccasins), which are also known as crotalids, and coral snakes, which are also known as elapids.[4] Nonetheless, when these uncommon bites occur, they are medical emergencies. Consequently, it's extremely important to dispel the many misconceptions about snakebites and how they should be treated.[1]

Separating Myth from Fact

Myth: Venomous snakebites aren't that dangerous.

Fact: Most venomous snakebites can cause significant pain and disability. And, this is especially true for children who are at higher risk of serious complications because of their small body size.[5] When an individual is injected with venom from a snake, it can cause paralysis, blindness and death.[6]

Myth: All venomous snakebites are the same.

Fact: According to Spencer Greene, MD, MS, FACEP, FACMT, director of the medical toxicology consultation services at Ben Taub General Hospital and Texas Children's Hospital, and a consulting toxicologist for the Southeast Texas Poison Center, "There are dozens of components in snake venom. Pit vipers have enzymes, metals and other antigens that can cause a variety of toxicity, from tissue damage to abnormal blood clotting (i.e., too little or too much), airway swelling and

other signs and symptoms. Some pit vipers also have neurotoxins that can decrease muscle strength and lead to paralysis, including respiratory paralysis. Coral snakes, the other group of venomous snakes found in the U.S., are not vipers. They're elapids, and their toxicity is primarily neurotoxic. There is some local swelling but you don't see the tissue destruction common in pit viper bites."

Myth: The symptoms of venomous snakebites occur immediately.

Fact: This is true for some venomous snakebites, but not for all. So, regardless of symptoms presenting immediately, medical treatment should be sought.

Symptoms depend on the type of toxin(s) secreted into the bite and on how much toxin is present in the tissue. Types of symptoms are attributed to four toxin categories: cardiotoxins (affecting the heart tissue), neurotoxins (affecting the nervous system tissue), cytotoxins (affecting the site of the bite or the tissue that absorbs the toxin) and hemotoxins (affecting the blood coagulation system).[6] As a result, symptoms can include bleeding, breathing difficulty, blurred vision, convulsions, eyelid droop, low blood pressure, nausea and vomiting, numbness, pain at the site of the bite, paralysis, rapid pulse, shock, skin color changes, stomach and abdominal pain, swelling, tingling, tissue damage, thirst, tiredness, weakness and weak pulse.[5] Other complications include vision damage, compartment syndrome, infection, limb loss, gangrene, sepsis, internal bleeding, cardiac damage and respiratory compromise.[6]

While pit viper bites are typically painful and result in symptoms that occur right away, symptoms from coral snakebites often don't develop for hours.[5] And, if left untreated, a concentrated snakebite will leave an individual paralyzed, blind[7] and, potentially, dead from cardiac and renal failure.[8]

Myth: Venomous snakes always deliver venom when they bite.

Fact: Snakes voluntarily deliver venom, so not all bites are venomous. Nonvenomous bites are known as dry bites. According to estimates, 20 percent to 25 percent of pit viper bites and 50 percent of coral snakebites are dry bites.[2] In addition, some snakes only deliver a specific amount of venom.[9]

Symptoms depend on the type of toxin(s) secreted into the bite and on how much toxin is present in the tissue.

Accretion of venom in snakes occurs in the mandibular gland that contains large alveoli (sacks made out of various types of tissues), which can contract or expand. The full venom solution sits inside the alveoli until it is used. When attacking, a snake will pull out its fangs to bite the victim, during which time it can contract the gland to release venom into a duct that carries the venom from the gland to its fangs, which release it into the victim's bloodstream.[7] However, snakes aren't known to attack prey larger than themselves unless they strike in self-defense. And, a defensive bite is more likely to be a dry bite. However, if a snake has already been injured, has been harassed or is in pain, it is more likely to deliver a fully envenomating bite.[10]

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Important Safety Information

The most common adverse events reported in clinical studies were mild or moderate reactions involving the skin and appendages (primarily urticaria, rash, or pruritus), which occurred in 14 out of 42 patients. Three patients experienced a serious adverse event. Two patients had a severe allergic reaction (severe hives and a severe rash and pruritus) following treatment. One patient had a recurrent coagulopathy due to envenomation, which required rehospitalization and additional antivenin administration. In clinical trials, recurrent coagulopathy (the return of a coagulation abnormality after it has been successfully treated with antivenin), characterized by decreased fibrinogen, decreased platelets, and elevated prothrombin time, occurred in approximately half of the patients studied. Recurrent coagulopathy may persist for 1 to 2 weeks or more. One patient discontinued CroFab® therapy due to an allergic reaction. Patients with allergies to papain, chymopapain, other papaya extracts, or the pineapple enzyme bromelain may also be at risk for an allergic reaction to CroFab®.

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Because a snake's glands are "spongy," it is nearly impossible for it to expel all of its venom. After a bite, it takes between 15 days and 20 days for the secretory tissue to refill the glands. Nevertheless, venomous snakes may possess dangerous quantities of venom within a day or two of its expulsion.[9]

Snakes voluntarily deliver venom, so not all bites are venomous.

Myth: A baby venomous snake is more venomous than an adult venomous snake.

Fact: Actually, the opposite is true. An adult's venom is much more deadly than the venom in a baby snake. Not only do studies show that the "activity level of some venom enzymes tends to increase with the size and age of the snake," but an adult snake can deliver a lot larger venom dose than a smaller one. For example, a baby eastern diamondback rattlesnake can typically deliver less than 70 milligrams of venom, whereas an adult can deliver between 492 and 666 milligrams; 848 milligrams is the maximum dose that can be delivered in a single bite. A lethal dose in an adult human is about 100 milligrams.[11]

Myth: When bitten by a venomous snake, individuals should try to extract the venom.

Fact: After failing to obtain medical attention, tourniquets and electrotherapy, the next most dangerous myth pertaining to venomous snakebites is trying to extract the venom by sucking it out or slashing the wound. Extraction is one of many home remedies (including applying ice, immersing the wound in water and drinking alcohol or caffeine) that worsen the effects of the snakebite.

Without a doubt, attempting to extract the venom delays getting medical attention, and because the venom spreads very quickly into the blood system, time is critical. Attempting to suck the poison out of the wound can cause the poison to spread to the mouth and even into the lymphatics through any cuts in the lips or gums. Using suction cups contained in snakebite kits to remove venom from a bite is also inadequate because the venom progresses into the lymphatics much faster than it can be extracted. And, finally, cutting the wound will cause more tissue damage and more blood loss that will only weaken the body's immune system.[6]

Myth: All individuals bitten by a venomous snake are treated the same.

Fact: Treatment depends on the severity of the envenomation. Because the signs and symptoms can vary greatly, which can result in severe complications, a panel of experts developed a unified treatment algorithm in 2011 for the management of pit viper snakebites (the predominant form of snakebite) in the U.S. in hopes of reducing variation in care and possibly improving clinical outcomes.[12] The step-by-step algorithm consists of 15 actions that include assessing the patient, checking for signs of envenomation, checking for indications for antivenom, administering antivenom, determining if initial control of envenomation has been achieved, monitoring the patient, determining if the patient meets discharge criteria and post-discharge planning. In addition, there are steps to follow if envenomation is not present, if envenomation is minor, if initial control of envenomation is not achieved, as well as when to call a physician expert, when to administer maintenance antivenom therapy, post-discharge planning and treatments to avoid in pit viper snakebite.

Medscape also provides a list of "approach considerations" for pit viper snakebites that is divided into fields of care and hospital management. Fields of care consist of pulmonary, cardiovascular, local wound, gastrointestinal, hematological and central nervous system, each of which contains a scale of symptoms from none to moderate or severe that physicians can use to calculate a severity score to determine whether antivenom therapy is required.[13]

Myth: There is a shortage of antivenom to treat venomous snakebites.

Fact: Today, chances of dying from a venomous snakebite are very low because there is antivenom to reverse its effects. "In areas where snakebites are common, many, if not most, hospitals carry CroFab, which is used to treat pit viper bites. Pit vipers account for approximately 98 percent of bites from venomous snakes in the U.S., so it's important to have access to it," says Dr. Greene. "Coral snakes account for approximately 2 percent of venomous bites. There are three species of coral snakes in the U.S. Toxicity is unheard of from Arizona coral snakes. Significant toxicity is rare from Texas coral snakes. It's only Florida coral snakes that typically cause serious neurotoxicity, so it's important to have antivenom available in areas where these bites are common."

Snakebite antivenom is divided into two types: monovalent, which is useful against only one type of species, and polyvalent, which treats several types of venomous snakebites.[14]

In the U.S., there is only one polyvalent antivenom, which treats pit viper bites. CroFab (crotalidae polyvalent immune fab, ovine), manufactured by BTG International and approved by the U.S. Food and Drug Administration (FDA) in 2000, is produced by milking the venom from four species of snakes in Utah that is shipped to Wales for processing and then injected into sheep in Australia. Once the sheep create antibodies to the

venom, blood samples from the sheep are sent back to Wales to manufacture the antivenom. According to BTG, a typical dose involves four to six vials of CroFab given intravenously over an hour.[15]

Previously, Wyeth's USA Polyvalent was also available to treat pit viper bites. But, after CroFab was determined to be more specific against rattlesnake venom and less allergenic, manufacturing of the Wyeth product was discontinued.[16] Looking ahead, a competitor to CroFab will become available in 2018, which could help to lower the price of treatment. The new product is a result of a settlement of an infringement complaint filed by BTG against Instituto Bioclon of Mexico and Rare Disease Therapeutics of Nashville, Tenn., for the "unlawful and unauthorized importation and sale into the U.S. of certain crotalid antivenom pharmaceutical compositions that infringe one or more claims of BTG's U.S. Patent No. 8,048,414 (the '414 patent')." The agreement will allow Bioclon to sell its crotalid antivenom product relying on BTG's 414 patent beginning October 2018, with BTG receiving a royalty on sales until the patent's exclusivity period ends in 2028.[17]

There is also only one monovalent antivenom in the U.S., available since the 1960s, to treat coral snakebites (endemic to the southeastern U.S.). However, in 2003, Pfizer/Wyeth stopped producing the antivenom known as Micrurus fulvius, which is developed using horses as hosts to create antibodies to the venom. In response to the dwindling supply, FDA has extended the use-by dates on existing antivenom in frozen storage several times after testing samples for efficacy and safety. In addition, three Florida hospitals, which treat between 75 and 80 coral snakebites a year, are now participating in an end-phase clinical trial of experimental antivenom. Patients being treated for a coral snakebite are given the option of receiving the existing antivenom product or participating in the trial of the newer drug, which is funded by an FDA grant.[18]

If necessary, antivenom from other countries can be used. For instance, antivenoms are produced in Brazil and Costa Rica for non-North American coral snakes. And, Mexico produces antivenom that is likely effective for coral snakebites in the United States.[19]

Guidelines for stocking antidotes at hospitals that provide emergency care were established in 2009 by an expert panel and are expected to be updated in mid-2016. The guidelines were established because it was documented that important antidotes such as antivenom were not stocked at all or were stocked in an insufficient amount. The panel identified 24 antidotes for stocking, 12 of which they recommend be available for immediate administration on patient arrival; another nine, which included CroFab, that they recommend be available to administer within one hour of the patient's arrival, allowing the antidote to be stocked in the hospital pharmacy if the hospital has a mechanism for prompt delivery of antidotes; and three more that they recommend be stocked by the hospital but are not usually needed within the first hour of treatment.[20]

Florida has its own antivenom bank. Administered by the Miami-Dade Fire Rescue Department, the bank was started as a private project, and after years of development, it was able to dispatch the first antivenom in 1996. The bank sends the appropriate venom whenever it is notified by emergency departments, hospitals and poison centers that someone has been bitten by a venomous snake. Antivenom is available to facilities not only in Florida, but also to other states in the U.S. and areas outside the U.S. in North America, via an arrangement with American Airlines, which takes the antivenom on the first available flight to be met with a rescue official at its destination.[14]

Myth: Antivenom isn't always effective.

Fact: According to the World Health Organization, "Antivenoms can prevent or reverse most of the snakebite envenomings effects, and play a crucial role in minimizing mortality and morbidity."[21] Antivenom consists of antibodies that bind to the venom and chemically change it to something that cannot interact with the body, thus neutralizing its effects and halting further damage. "Think about your immune system," says Dr. Greene. "One of the ways a body fights a foreign substance is by making antibodies that specifically bind to those antigens and keep them from binding elsewhere and causing damage. Antivenom is essentially purified/modified antibodies made in an animal host that can bind to various snake venom antigens, keeping them from exerting toxicity until they are removed from the body."

Today, chances of dying from a venomous snakebite are very low because there is antivenom to reverse its effects.

Of course, the right type of antivenom must be given. And, it is recommended to be given early as it cannot reverse damage already done. Antivenom "is recommended to be used in the first six hours, but [patients] should see a benefit even afterward if there is still circulating venom for it to bind," says Dr. Greene. "That being said, there's a minimum amount of damage that is determined shortly after the bite that antivenom cannot reverse or prevent. Antivenom won't work if it's given incorrectly or given for the wrong species. For example, CroFab

won't work for coral snake envenomations because the antigens are completely different and toxicity manifests differently."

While CroFab is FDA indicated for the treatment of pit viper envenomations, there is currently a study being conducted to evaluate the recovery from copperhead snakebites in patients with mild or moderate venom effect who are treated with CroFab.[22] "Copperheads are pit vipers, but they were not included in the original research on CroFab, so there's no proof that it works on copperhead bites," says Dr. Greene. "And there are some people who minimize the potential significance of copperhead bites, so they don't want to use antivenom if it's not going to confer a benefit. I think people inappropriately minimize the significance of copperhead bites. People can have significant morbidity and, occasionally, mortality from these envenomations."

Guidelines for stocking antidotes at hospitals that provide emergency care were established in 2009 by an expert panel and are expected to be updated in mid-2016.

The study, which enrolled 76 patients and was conducted by emergency physicians, toxicologists and surgeons at hospitals in regions where copperhead bites are common, compared recovery with antivenom versus placebo as measured by the Patient Specific Functional Scale 14 days after treatment. "The study has just concluded, and the data are being analyzed, but in my experience, people tend to improve faster when they get antivenom than when they don't," adds Dr. Greene. "Hopefully, the study [for which he was principal investigator at two sites: Ben Taub General Hospital and Texas Children's Hospital] was powered sufficiently to show a difference. I would hate for people to not use antivenom because the study wasn't large enough to show the difference."

Dispelling the Myths Now

With so few cases of venomous snakebites, the myths about proper treatment continue to subsist, not just among the general public, but among medical professionals as well. Treatment shortcomings often arise when physicians who were trained years ago to treat venomous snakebites with outdated methods continue these dangerous practices today. "Most of the hospital interventions such as prophylactic antibiotics and surgery that were previously recommended are ineffective and detrimental," says Dr. Greene. Today, the only effective treatment is "antivenom combined with supportive care." Until doctors are educated about the current treatment processes, which include the recommended guidelines and published algorithms, Dr. Greene urges that patients be attended by physicians experienced in treating snakebites. ❖

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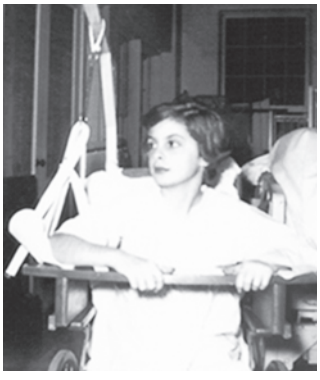
Polio: A Patient's Perspective

BY TRUDIE MITSCHANG

As a young girl, Karen Chase overcame the ravages of polio and later drew upon the experience to draft a riveting memoir.



Karen Chase was just a fifth-grader when she was diagnosed with polio. It took her four years to fully recover from the disease.

As an author and poet, Karen has written six books, including her memoir titled *Polio Boulevard*.

AN ACCLAIMED POET, essayist and author of five books (with a sixth on the way), Karen Chase is both an imaginative narrator and compelling heroine in her illuminating memoir *Polio Boulevard*. In it, Chase recounts the story of her childhood bout with polio, and charts her complicated and often painful road to recovery.

Chase's upbringing in Westchester County, N.Y., was as idyllic as it was ordinary. As an active and creative fifth-grader, she loved helping her older brother with his paper route, doting on her new baby sister and tooling around town on her beloved bike. It was on just such an ordinary day that mysterious leg pains signaled the presence of the insidious disease that would abort her carefree childhood. "I was walking home from school for lunch, kicking a stone down the road, and my legs began to hurt. After a peanut butter and jelly sandwich and glass of cold milk, I said, 'Mom, I can't go back to school today,'" recalls Chase. "My neck got stiff, my fever rose alarmingly, and what started as small pains turned into large ones. The doctor came, and soon I was rushed to the hospital in an ambulance and diagnosed with polio."

"Too Late for Us!"

The diagnosis landed Chase in the hospital for months to treat the resulting paralysis, followed by years of difficult surgery and encasement in a body cast to correct her curvature of the spine. It was with painful irony that Chase learned she was one of the last American victims of polio. In the spring of 1954, a few months into her hospitalization, news of a vaccine breakthrough was announced on the radio, and its timing was bittersweet. "I was playing Monopoly with my friends on the polio ward. The radio was on. A voice announced that a doctor named Jonas Salk had invented a vaccine to prevent polio," says Chase. "Some of us turned silent, some of us laughed, and one patient blurted out, 'Too late for us!' Here we were, a group of ill children on stretchers and in wheelchairs living through an historical moment when polio's peril was replaced by joy and relief."

Chase spent four years recovering from polio, transitioning from little girl to teen. During her stay in a second hospital for a spinal fusion, she remembers forging close friendships with other kids, earning a reputation as a practical joker. With optimism and resolve, Chase overcame years of braces and wheelchairs, eventually making a full recovery and returning to normal life as a plucky ninth-grader. "I was a polio survivor, although I never thought of myself in those terms," she explains. "For many decades, I never looked back. My polio became a distant memory."

Finding Her Voice

As an adult, Chase pursued her calling as a writer, even using her talent at one point to work with patients as a hospital poet. Her recovery from polio is not something she takes for granted, and she notes that many polio survivors of her generation suffered years of disability, while nearly half will develop post-polio syndrome later in life.

At one time, polio was one of the most feared diseases in industrialized countries, paralyzing hundreds of thousands of children each year. Today, its effect has been nearly forgotten by the post-vaccine generation, perhaps another reason why Chase's writing is so vitally important. "For those who have the opportunity to protect your children with the polio vaccine, think of those ill children on the polio ward," she says. "Do not hesitate for one moment. You and your families are beyond lucky to be able to avoid this paralyzing disease." ❖

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

Editor's note: Karen Chase's sixth book chronicles a nautical log written by former President Franklin D. Roosevelt as he seeks a cure for his polio-crippled legs. *FDR on His Houseboat: The Larooco Log, 1924-1926* will be released in the fall.

Polio: A Physician's Perspective

Dr. Frederick Maynard has dedicated 25 years to the unique problems of polio survivors.

DR. FREDERICK M. Maynard is a recently retired physiatrist (a specialist in physical medicine and rehabilitation) who has dedicated a significant portion of his academic and clinical practice over the last 25 years to the unique problems of polio survivors. He is also a board member of Post Polio Health International (PPHI), whose mission is to enhance the lives and independence of polio survivors through education, advocacy, research and networking.

BSTQ: What is post-polio syndrome (PPS)?

Dr. Maynard: PPS is a name given to a group of common new symptoms that are experienced in polio survivors, typically characterized by new pain, weakness and fatigue, but the definitive symptom is new weakness. The critical piece is that this new weakness is out of proportion of what you'd expect from growing older. It's important to note that PPS is not the same condition as post-polio sequelae (the late effects of polio). PPS is usually considered a specific new condition. Depending on which study you reference, between 25 percent and 40 percent of polio survivors experience PPS, while as many as 70 percent of polio survivors are said to have post-polio sequelae. It's been difficult for the medical profession as a whole to get their hands around this. Some want to put this label on every polio survivor, while there are others who say it does not exist.

BSTQ: How is PPHI working to educate the medical community about PPS?

Dr. Maynard: The effort to educate has been ongoing, and our focus now is on working with Internet sites. A lot of young physicians are not familiar with polio, and many use the Internet as a research tool. Unfortunately, there is a lot of misinformation out there, so as representatives of the greater polio community, we are trying to improve the accuracy of existing content.

BSTQ: Are there lessons to be learned from PPS that could apply to other diseases?

Dr. Maynard: Absolutely! Polio is an old, though not totally eradicated, viral problem that has shown it has the potential to mutate. If we can better understand the late ramifications of having had a severe viral infection like polio, we can better understand the long-term ramifications of modern viruses like Ebola. As we study PPS patients, we need to study the triggers that may cause non-contagious virus fragments in the nervous system to suddenly become pathogenic.

BSTQ: Are there any interesting studies underway?

Dr. Maynard: People with PPS frequently have difficulty finding ways to exercise without worsening symptoms or overexerting muscles. Whole body vibration (WBV) is a way to exercise that causes muscle contractions through stimulation of reflexes. A recent study looked at the feasibility of WBV as a means of weight-bearing exercise in people with PPS by assessing its effects on walking speed and endurance.

Another highly discussed treatment for polio survivors is the use of intravenous immune globulin (IVIG). A multi-center, multi-country study is currently underway to assess the effectiveness of IVIG treatment for patients with PPS symptoms. Principal investigators believe the study holds promise because it's the first to examine the long-term effects of a drug like IVIG in post-polio patients. IVIG has been successfully used to modify the immune system when treating many different autoimmune neuromuscular diseases. Even though PPS is not an immune disease, a number of immune factors do seem to play a role.

PPS is usually considered a specific new condition.

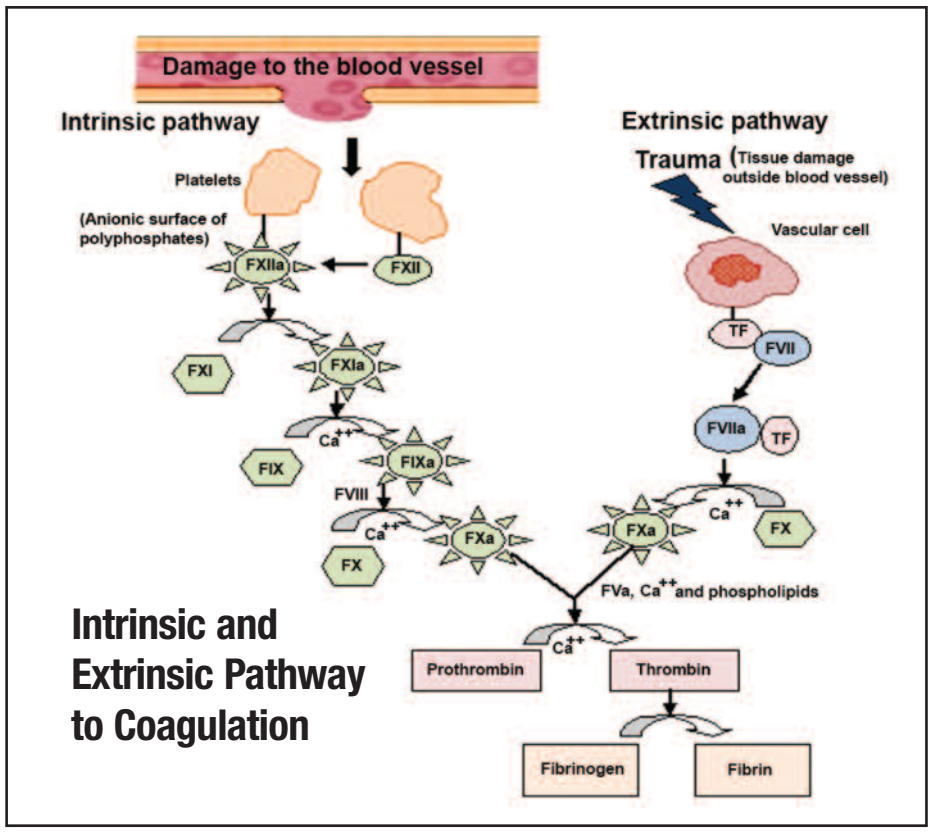
BSTQ: What is the current prognosis for patients with PPS?

Dr. Maynard: My own work has focused on rehabilitation. Our aging polio survivors are largely dealing with aging disorders such as pain and not being able to function like they used to. We've found there's a lot you can do about that. We use a holistic approach emphasizing sleep, nutrition and exercise at the right dosage to control symptoms and lead to improvement. We've done residential treatment retreats where we take a week to work on these issues with our patients, and results have been promising. ❖

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

The New Therapeutic Renaissance for Patients with Rare Bleeding Disorders

BY KEITH BERMAN, MPH, MBA



Intrinsic and Extrinsic Pathway to Coagulation

TODAY, THE ROUGHLY 15,000 persons with hemophilia A who require factor replacement are presented with a smörgåsbord of products from which they and their physicians can choose. Six conventional and two extended half-life recombinant factor VIII products are available, as well as four high-purity plasma-based factor VIII concentrates. Three additional extended half-life factor VIII products have completed clinical testing and may soon join the crowd. While persons with hemophilia B number only about one-quarter that of the hemophilia A population, they and their providers can select from three conventional recombinant factor IX products, one extended half-life product (with two others awaiting U.S. Food and Drug Administration [FDA] approval), and three high-purity plasma-based factor IX concentrates.

For decades, manufacturers focused their energies and resources on developing treatments for these two predominant hereditary bleeding disorders. But more recently, the industry at last turned its attention — and in particular its expertise in recombinant proteins process development — to design therapeutics targeting much rarer hereditary and acquired coagulation disorders. The result is five new factor replacement therapies approved and introduced over the last five years that are specifically indicated to treat congenital factor X deficiency, factor XIII deficiency, acquired hemophilia A and the subset of patients with von Willebrand disease who require factor replacement therapy.

COAGADEX for Congenital Factor X Deficiency

Originally named Stuart-Prower factor after the names of the first two adults diagnosed in the 1950s, clotting factor X is the initial enzyme in the common pathway of thrombus formation. Activation of factor X to factor Xa occurs both through the intrinsic and extrinsic clotting cascades. Once formed, factor Xa mediates conversion of prothrombin to thrombin, which in turn activates fibrinogen to form a fibrin clot.

In October, a novel high-purity human factor X concentrate produced by Bio Products Laboratory — COAGADEX — was approved for on-demand treatment and control of bleeding episodes in adults and children aged 12 years and older with hereditary factor X deficiency.

Inherited factor X deficiency is an autosomal recessive disorder; thus, heterozygous individuals with one defective gene encoding factor X are usually asymptomatic. As it requires inheritance of a defective gene from both parents, factor X deficiency is among the rarest of all congenital bleeding disorders, affecting an estimated one individual per 500,000 to 1 million.[1] Not unlike other hereditary bleeding disorders, factor X deficiency can vary from mild to severe. Hemorrhagic symptoms variously include easy bruising, soft-tissue bleeds, disabling hemarthroses, recurrent epistaxis and menorrhagia. Trauma-associated hemorrhage in more severely affected patients can lead to death.

Historically, clinicians have relied on fresh frozen plasma (FFP) or prothrombin complex concentrates to treat hemorrhages in patients with factor X deficiency. While FFP can be effective for bleeding control in persons with milder forms of the disease, its low factor X content limits its utility in more severely affected individuals. Further, factor X titers vary from one unit of FFP to the next and are not measured, forcing the clinician to dose empirically with a product that is not without potential adverse effects, including fluid volume overload and acute transfusion reactions. Use of prothrombin complex concentrates presents a significant risk of thromboembolic events.

In October, a novel high-purity human factor X concentrate produced by Bio Products Laboratory (BPL) — COAGADEX — was approved for on-demand treatment and control of bleeding episodes in adults and children aged 12 years and older with hereditary factor X deficiency. Available in 250 IU or 500 IU dosages, the product is also indicated for perioperative management of bleeding in patients with a mild form of the disease. In a multicenter, open-label clinical trial of 16 subjects with moderate to severe hereditary factor X deficiency, COAGADEX was rated excellent (91 percent) or good (7 percent) in 98 percent of bleeding episodes, more than 80 percent of which required only a single 25 IU/kg infusion.

COAGADEX also appears to be effective for the treatment of acquired factor X deficiency associated with systemic light-chain amyloidosis.[2] In these fragile patients, both unpredictable kinetics of infused factor X and a much more rapid decline in plasma levels require frequent monitoring of factor X levels and typically higher and/or more frequent dosing to reach target thresholds similar to patients with inherited factor X deficiency (10 to 15 IU/mL). The standardized content of factor X in COAGADEX makes it possible to monitor the hemostatic response and tailor treatment to the patient's individual needs.

Corifact and TRETTEN for Congenital Factor XIII Deficiency

When activated by thrombin at the site of vascular injury, circulating factor XIII performs an essential function at the very end of the coagulation cascade: It promotes cross-linking of fibrin and protects the clot against fibrinolysis; for this reason, it is also sometimes referred to as "fibrin stabilizing factor." Cross-linked fibrin provides tensile strength to the primary hemostatic platelet plug. Up to 30 percent of patients without prophylactic coverage sustain a spontaneous intracranial hemorrhage, the leading cause of mortality. Other symptoms may include nose and mouth bleeds, muscle bleeds and delayed bleeding after surgery. Inherited in an autosomal recessive fashion — defective genes must be inherited from both parents — it occurs once in every three to five million live births, making it the rarest of all factor deficiencies.

Factor XIII is present in FFP and cryoprecipitate, but their use is accompanied by a number of serious limitations that may include 1) potential for fluid overload due to the need to transfuse high volumes to supply enough factor XIII, 2) risk of allergic reactions and transfusion-related acute lung injury (TRALI),[3] a leading cause of transfusion-related mortality, and 3) risk of exposure to infectious agents.[4] In addition, the natural variability in factor XIII content from one unit of plasma to the next complicates the clinician's effort to adjust dosing to maintain plasma factor XIII in a therapeutic range.

In December 2013, less than three years after the introduction of Corifact, FDA approved Novo Nordisk's TRETTEN, a recombinant version of the factor XIII A-subunit.

The solution developed by CSL Behring was to purify factor XIII from pooled plasma, using precipitation followed by adsorption and ion exchange chromatography steps. Corifact, approved by FDA in February 2011, is indicated both for routine prophylaxis and for perioperative management of surgical bleeding in patients with congenital factor XIII deficiency. Remarkably, thanks to an unusually prolonged mean circulating half-life (between six and seven days), Corifact can be dosed prophylactically every 28 days to maintain a protective trough level of 5 percent to 20 percent of normal factor XIII activity.

In December 2013, less than three years after the introduction of Corifact, FDA approved Novo Nordisk's TRETTEN, a recombinant version of the factor XIII A-subunit. Ninety-five percent of patients with factor XIII deficiency have the A-subunit deficiency, while just 5 percent have the B-subunit form. TRETTEN is specifically indicated for routine prophylaxis of bleeding in patients with A-subunit deficiency. Similar to Corifact, TRETTEN has about a seven-day half-life and can be dosed once monthly to achieve a target trough level of factor XIII at or above 10 percent. Thus for the 95 percent of patients with the A-subunit form of factor XIII deficiency, there are two very good prophylactic treatment options to prevent serious or life-threatening bleeds.

OBIZUR for Acquired Hemophilia A

For reasons that are not well-understood, typically older adults with no personal or family history of bleeding spontaneously develop IgG autoantibodies — "inhibitors" — that neutralize the procoagulant function of their own normal factor VIII. About half have a malignancy, autoimmune disorder, active infection or other possible underlying condition; the remaining half of cases are idiopathic. The result of this functional deficiency of factor VIII is a bleeding disorder that can range from mild superficial bruising to life-threatening hemorrhage. Based on a European patient registry,[5] hemophilia A is believed to occur in about 500 U.S. patients each year.

Prior to its withdrawal from the market in 2004 due to detection of parvovirus, a porcine factor VIII product purified from the plasma of pigs (Hyate:C) was available to treat acquired hemophilia A. Its efficacy lay in the fact that the inhibitor against human factor VIII tends not to cross-react with porcine factor VIII, allowing the porcine clotting protein to remain in the circulation and perform the same enzymatic functions as endogenous human factor VIII.

Animal studies of a novel recombinant analogue of porcine factor VIII developed by Baxalta — OBIZUR — demonstrated that it has similar pharmacokinetics as Hyate:C and is similarly well-tolerated.[6] In a prospective, open-label clinical trial, all 28 subjects with acquired hemophilia A who received OBIZUR had a positive response to treatment at 24 hours after a median of three doses to manage the initial bleeding episode.[7] While about one-quarter developed anti-porcine factor VIII antibodies, no safety concerns were identified in the trial.

Prior to approval of OBIZUR in 2014, hematologists relied on Novo Nordisk's recombinant activated human factor VIIa product (NovoSeven RT) as first-line therapy. NovoSeven RT acts as a bypassing agent, circumventing the inhibition of factor VIII by targeting a different part of the coagulation cascade. As no validated laboratory test is available to monitor the efficacy of bypassing agents, response to NovoSeven RT must be assessed by clinical observation.[8] Response to OBIZUR can be monitored by subjective clinical assessments in combination with achieved objective factor VIII levels.[9] Clearly, OBIZUR provides hematologists with a helpful new treatment option in managing bleeding episodes in adults with acquired hemophilia A.

VONVENDI for von Willebrand Disease

Named after the Norwegian physician who first characterized the familial bleeding disorder caused by its deficiency, von Willebrand factor (VWF) is a large glycoprotein stored as

ultra-large multimers released from platelets into the bloodstream, where it is cleaved by a proteolytic enzyme (ADAMTS13) to smaller multimers. Once circulating in the plasma, VWF acts to promote hemostasis by mediating platelet adhesion to damaged vascular sub-endothelial matrix and platelet aggregation, and serves as a carrier protein for factor VIII to protect it against rapid proteolysis.

Historically, plasma-derived factor VIII preparations rich in VWF have been used to treat spontaneous or trauma-induced bleeding events in patients with severe von Willebrand disease (VWD), or in patients with mild to moderate VWD that does not respond to desmopressin. Because factor VIII is being co-administered with the VWF, clinicians are instructed to carefully monitor trough factor VIII levels to avoid excessive accumulation of the clotting protein. Particularly with repeated dosing, the factor VIII that accompanies VWF in plasma-derived preparations could result in a supraphysiologic level of factor VIII and an associated increased risk of a thromboembolic event.

This same warning applies for Baxalta's newly approved VONVENDI (von Willebrand factor [recombinant]).[10] The binding capacity and affinity of VONVENDI to factor VIII is comparable to endogenous VWF, thus enabling VONVENDI to reduce the rate of factor VIII clearance. But VONVENDI may be advantageous in certain clinical circumstances: With the same administered dose of VWF measured in VWF:Ristocetin Cofactor (VWF:RCo) international units (IU) as a plasma-based product in patients with a baseline factor VIII level already sufficient to assure hemostasis, the absence of factor VIII in VONVENDI translates into a lesser likelihood of an excessive surge in the level of circulating factor VIII.

VONVENDI can be administered either with or without recombinant factor VIII as appropriate to achieve target plasma levels of greater than 0.6 IU/mL (60 percent) of VWF:RCo and greater than 0.4 IU/mL (40%) of factor VIII:C. In a pivotal clinical study, all bleeding episodes treated with VONVENDI alone or in combination with Baxalta's ADVATE recombinant factor VIII were controlled with an efficacy rating of excellent (96.9 percent) or good (3.1 percent).[10]

More Products on the Way

Other innovative new products are well along in the research and development pipeline. A recombinant form of ADAMTS13 is now being investigated for use as replacement therapy in patients with thrombotic thrombocytopenic purpura. Novel extended half-life versions of factor VIIa currently in development may enable clinicians to more effectively treat patients with congenital factor VII deficiency and prevent bleeding episodes in hemophilia A and B patients with inhibitors.

As it has since the first commercially produced factor VIII concentrate introduced in 1968 instantly transformed the lives of American hemophilia A patients, innovation continues to be the life-blood of this industry.

As it has since the first commercially produced factor VIII concentrate introduced in 1968 instantly transformed the lives of American hemophilia A patients, innovation continues to be the life-blood of this industry. ❖

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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BioResources

Recently released resources for the biopharmaceuticals marketplace.

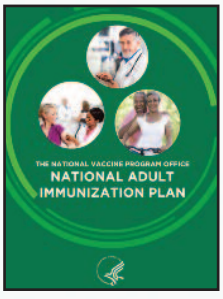
Healthcare Trends and Forecasts in 2016: Performance Expectations for the Healthcare Industry

Author: Health Intelligence Network (HIN)

HIN's 12th annual business forecast highlights the trends likely to impact the industry in the year to come and proposes tactics healthcare executives can employ to distinguish their operations in the marketplace. The 27-page resource begins with a set of metrics that document healthcare organizations' top concerns, challenges and successes in 2015 based on responses to HIN's November 2015 survey. Then, thought leaders Laura Jacobs, executive vice president of GE Healthcare Camden Group, and Paul Keckley, managing director of Navigant, outline strategies to build on 2015 accomplishments and avoid common mistakes in 2016. The report covers growth in the Medicare Advantage market and accountable care organizations; consolidation across market sectors; shared risk models; health information technology; retail health trends; risk management; and more.

hin.3dcartstores.com/Healthcare-Trends-Forecasts-in-2016-Performance-Expectations-for-the-Healthcare-Industry_p_5099.html.pdf

The National Adult Immunization Plan (NAIP)



Author: National Vaccine Program Office

The NAIP provides an overview of actions needed to be taken by federal and nonfederal partners to protect public health and achieve optimal prevention of infectious diseases and their consequences through vaccination of adults. The plan establishes four key goals, each of which is supported by objectives and strategies to guide implementation through 2020. The goals include 1) strengthen the adult immunization infrastructure, 2) improve access to adult vaccines, 3) increase community demand for adult immunizations and 4) foster innovation in adult vaccine development and vaccines-related technologies.

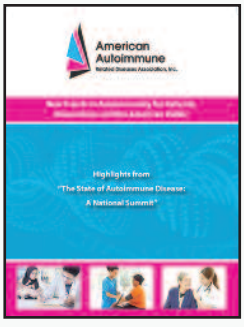
www.hhs.gov/nvpo/national-adult-immunization-plan/naip.pdf

Preventive Services Tracker

Author: Kaiser Family Foundation

The new Preventive Services Tracker presents up-to-date information on the adult preventive services nongrandfathered private plans must cover, by condition, including a summary of the recommendation, target population, effective date of coverage and related federal coverage clarifications. Also included is a link to an article explaining the Affordable Care Act requirements, the four broad categories of services, coverage rules and implementation challenges, and the impact of the rules.

kff.org/health-reform/report/preventive-services-tracker



New Trends in Autoimmunity for Patients, Research and the American Public

Author: American Autoimmune Related Diseases Association (AARDA)

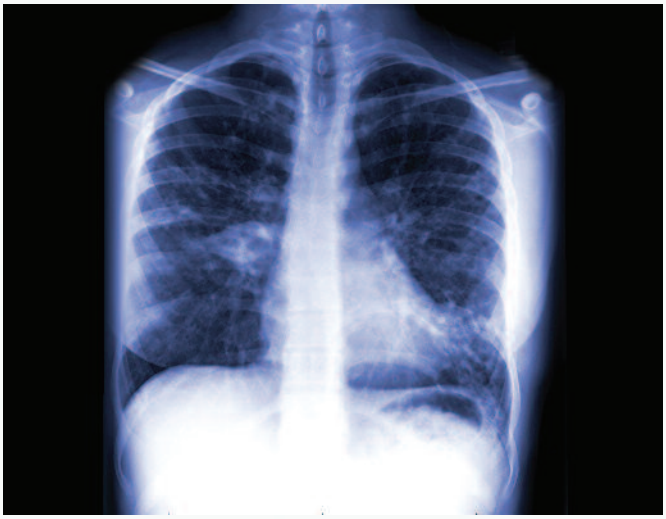
This report highlights the major themes, news and developments that emerged during the daylong event co-hosted by AARDA and the National Coalition of Autoimmune Patient Groups held in March 2015. Among the questions discussed were: What are the known environmental factors that trigger autoimmune disease and what are the latest technologies being developed to measure an individual's exposure to such risks? Why and how are researchers using rheumatic fever as a guidepost for one day curing other autoimmune diseases, and is the approach promising? Why is autoimmune-related fatigue different from normal tiredness, and why is it increasingly a focus of medical attention and research? The summit brought together roughly 20 leading experts to advance knowledge and understanding by sharing the most current thinking in autoimmune disease research, advocacy and patient issues.

www.aarda.org/wp-content/uploads/2015/12/HighlightsFromSummitMarch20151.pdf

BioResearch

Summaries of up-to-date clinical research published internationally.

Inhaled Alpha-1 Proteinase Inhibitor Safe, Well-Tolerated and Effective in Raising Sputum Levels in Patients with Cystic Fibrosis



Inhalation of aerosolized alpha-1 proteinase inhibitor (A1PI) permits delivery of drug to the site of active airway disease while limiting systemic exposure, and has been shown to reduce neutrophil elastase burden and inflammation in respiratory secretions of alpha-1 antitrypsin-deficient patients. Utilizing an electronically regulated nebulizer system to deliver the A1PI, Grifols researchers and collaborators at six U.S. academic centers conducted a randomized, double-blind, placebo-controlled Phase IIa study to evaluate the safety of 100 mg or 200 mg of an investigational Alpha-1 Hydrophobic Chromatography Process (Alpha-1 HC) inhaled once daily for three weeks in 30 adult subjects with cystic fibrosis (CF).

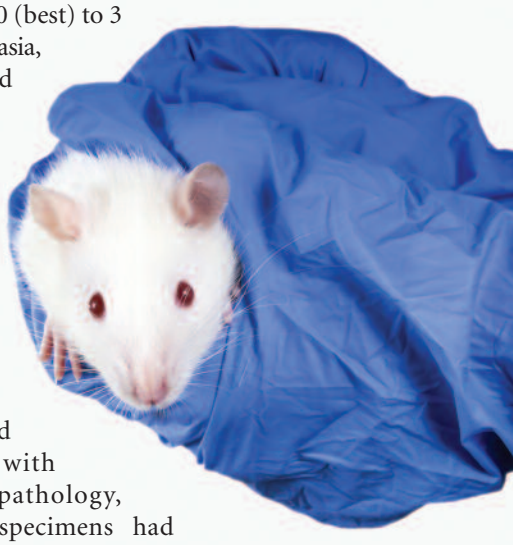
Subjects were randomized 2:1 to receive Alpha-1 HC or placebo. Drug delivery was confirmed by a dose-dependent increase in the sputum A1PI. Seven (20%) of 35 adverse events in the 100 mg dose group, three (13%) of 23 in the 200 mg dose group, and four (14.3%) of 28 in the placebo group were drug-related in these subjects. One serious adverse event occurred in one subject within each group. The investigators concluded that Alpha-1 HC was safe and well-tolerated, adding that further studies are needed to determine efficacy and potential use of Alpha-1 HC as chronic therapy in CF lung disease.

Gaggar A, Chen J, Chmiel JF, et al. Inhaled alpha1-proteinase inhibitor therapy in patients with cystic fibrosis. J Cyst Fibros *2015 Aug 25 [Epub ahead of print]*

Single IVIG Infusion Associated with Improved Recovery and Histopathological Profile in Rat Model of Ischemic Stroke

With the aim of determining whether there may be beneficial effects of intravenous immunoglobulin (IVIG) therapy following acute ischemic stroke, Turkish investigators conducted an exploratory study of IVIG usage in the experimentally induced middle cerebral artery occlusion (MCAo) rat stroke model.

Thirty adult male Sprague-Dawley rats were randomly divided into two equal groups: a control group (n = 15) and an IVIG group (n = 15). The intraluminal filament used to establish cerebral ischemia was withdrawn after two hours of MCAo to allow reperfusion. Physiological saline (0.5 mL/kg) was administered to the control group and 400 mg/kg IVIG was given intravenously to the IVIG group animals. On subsequent neurological examination, animals were rated from 0 (best) to 3 (worst). Following euthanasia, brain tissue was prepared for histopathological examination.



On neurological examination, the IVIG group showed significantly improved recovery in relation to the control group. While brain tissue specimens obtained from the IVIG group showed findings correlating with grade 1 and 2 histopathology, control group brain specimens had lesions in ischemic areas consistent with grade 3 histopathology. The investigators concluded that IVIG may be useful in the treatment of ischemic stroke patients.

Tunik S, Aluclu MU, Acar A, et al. The effects of intravenous immunoglobulin on cerebral ischemia in rats: An experimental study. Toxicol Ind Health *2016 Feb;32(2):229-34.*

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.*

Medicare IVIG/SCIG Reimbursement Rates

Rates are effective April 1, 2016, through June 30, 2016.

Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
BIVIGAM IVIG	Kedrion Biopharma	J1556	$78.46	$77.20
CARIMUNE IVIG	CSL Behring	J1566	$70.04	$68.91
FLEBOGAMMA IVIG	Grifols	J1572	$78.31	$77.05
GAMMAGARD SD IVIG	Baxalta	J1566	$70.04	$68.91
GAMMAPLEX IVIG	Bio Products Laboratory	J1557	$74.55	$77.36
OCTAGAM IVIG	Octapharma	J1568	$91.71	$90.24
PRIVIGEN IVIG	CSL Behring	J1459	$76.51	$75.28
HIZENTRA SCIG	CSL Behring	J1559	$84.69	$83.33
HYQVIA SCIG	Baxalta	J1575	$114.70	$112.86
GAMMAGARD LIQUID IVIG/SCIG	Baxalta	J1569	$77.64	$76.40
GAMMAKED IVIG/SCIG	Kedrion	J1561	$83.64	$82.30
GAMUNEX-C IVIG/SCIG	Grifols	J1561	$83.64	$82.30

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

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Manufacturer	Indication	Size
BIVIGAM Liquid, 10%	Kedrion Biopharma	**IVIG:** PI	5 g, 10 g
CARIMUNE NF Lyophilized	CSL Behring	**IVIG:** PI, ITP	6 g, 12 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%	Baxalta	**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)	Baxalta	**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%	Baxalta	**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

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 (IIV3)	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**	TBD
GSK	FLUARIX (IIV4)	0.5 ML prefilled syringe, 10-BX	3 YEARS AND OLDER	90686
GSK	FLULAVAL (IIV4)	5 ML multi-dose vial	3 YEARS 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
			6 MONTHS 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

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.

** Pending approval (age of 4 years and older and product licensing) expected early 2016, available for booking now.

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