October 2012

BioSupply Trends

Special Focus: INNOVATION

Quarterly

Crossing the Finish Line

Bringing New Medical Innovations to Market

Personalized Medicine:
The Future of Diagnosis & Treatment

Alternative Meets Mainstream:
A Novel Treatment Approach

- **Myths & Facts: Asthma**
- **Meningitis: A Serious Global Disease**
- **Autoimmune Disease: Exploring Treatment Options**

Shocking! HES Product Found to Be Deadly — Page 56

wilate®

von Willebrand Factor/Coagulation Factor VIII Complex (Human)

The Power to Control VWD

www.wilateusa.com

I **will** use only high purity VWF/FVIII for my patients with VWD*

I **will** expect reliable dosing and monitoring from a balanced, 1:1 ratio of VWF and FVIII

I **will** demand proven clinical efficacy for acute bleeding in both adult and pediatric patients

I **will** choose the first double virus inactivated VWF/FVIII

***The resulting specific activity of wilate is ≥ 60 IU VWF: RCo and ≥ 60 IU FVIII activities per mg of total protein.**

The clinical relevance of this data has not been established

I **will** help my patients take control of VWD

wilate® is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD), as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.

For more information, please contact us:

Octapharma USA, Inc.

121 River Street
Suite 1201
Hoboken, NJ 07030
201-604-1130
www.octapharma.us

Customer Service:

uscustomerservice@octapharma.com
866-766-4860

Medical Affairs:

usmedicalaffairs@octapharma.com
888-429-4535

Reimbursement:

usreimbursement@octapharma.com
Tel: 800-554-4440
Fax: 800-554-6744

To report suspected adverse reactions,
Contact Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

Important safety information:
wilate® is contraindicated for individuals with a history of anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container. Thromboembolic events have been reported in VWD patients receiving coagulation factor replacement therapies. FVIII activity should be monitored to avoid sustained excessive FVIII levels. wilate® is made from human plasma. The risk of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease agent, cannot be completely eliminated. The most common adverse reactions to treatment with wilate® in patients with VWD have been urticaria and dizziness. The most serious adverse reactions to treatment with wilate® in patients with VWD have been hypersensitivity reactions. Patients with VWD, especially type 3 patients, may potentially develop neutralizing antibodies (inhibitors to VWF).

Please see Brief Summary of Prescribing Information, and additional information, on adjacent page.

Print Date 6/12. WIL-004-PAD

octapharma

For the safe and optimal use of human proteins

BRIEF SUMMARY OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Wilate safely and effectively. See full prescribing information for Wilate.

Wilate, von Willebrand Factor/Coagulation Factor VIII Complex (Human), Powder for Solution, for Intravenous Use Only. Initial U.S. Approval: 2009

INDICATIONS AND USAGE

- Wilate is a von Willebrand Factor/Coagulation Factor VIII Complex (Human) indicated for the treatment of spontaneous and trauma-induced bleeding episodes in patients with severe von Willebrand disease (VWD) as well as patients with mild or moderate VWD in whom the use of desmopressin is known or suspected to be ineffective or contraindicated.
- Wilate is not indicated for the prophylaxis of spontaneous bleeding episodes, or the prevention of excessive bleeding during and after surgery in VWD patients.
- Wilate is also not indicated for Hemophilia A

DOSAGE FORMS AND STRENGTHS

- Wilate is a sterile, lyophilized powder for reconstitution for intravenous injection, provided in the following nominal strengths per vial:
  - 500 IU VWF:RCo and 500 IU FVIII activities in 5 mL
  - 1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL

CONTRAINDICATIONS

- Hypersensitivity with known anaphylactic or severe systemic reaction to human plasma-derived products, any ingredient in the formulation, or components of the container.

WARNINGS AND PRECAUTIONS

- Hypersensitivity reaction
- Thromboembolic events associated with von Willebrand factor/Coagulation Factor FVIII (VWF/FVIII) products: plasma levels of FVIII activity should be monitored to avoid sustained excessive FVIII levels, which may increase the risk of thrombotic events
- Potential for inducing antibodies to Factor VIII (inhibitors) and antibodies to VWF, especially in VWD type 3 patients
- Theoretical risk of infectious agents transmission as the product is made from human plasma

ADVERSE REACTIONS

The most common adverse reactions in clinical studies on VWD were urticaria and dizziness (each 2.2%) (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma USA Inc. at phone # 866-766-4860 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

- Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.
- Each vial of Wilate contains the labeled amount in International Units (IU) of von Willebrand factor (VWF) activity as measured with the Ristocetin cofactor assay (VWF:RCo), and coagulation factor VIII (FVIII) activity measured with the chromogenic substrate assay.
- The number of units of VWF:RCo and FVIII activities administered is expressed in IU, which are related to the current WHO standards for VWF and FVIII products. VWF:RCo and FVIII activities in plasma are expressed either as a percentage (relative to normal human plasma) or in IU (relative to the International Standards for VWF:RCo and FVIII activities in plasma).

Dosage in von Willebrand Disease

The ratio between VWF:RCo and FVIII activities in Wilate is approximately 1:1.

The dosage should be adjusted according to the extent and location of the bleeding. In VWD type 3 patients, especially in those with gastro-intestinal (GI) bleedings, higher doses may be required.

Dosing Schedule

Physician supervision of the treatment regimen is required. A guide for dosing in the treatment of major and minor hemorrhages is provided in Table 1.

The careful control of replacement therapy is especially important in life-threatening hemorrhages. **When using a FVIII-containing VWF product, the treating physician should be aware that continued treatment may cause an excessive rise in FVIII activity.**

Table 1 Guide to Wilate Dosing for Treatment of Minor and Major Hemorrhages

Type of Hemorrhages	Loading Dosage (IU VWF:RCo/kg BW)	Maintenance Dosage (IU VWF:RCo/kg BW)	Therapeutic Goal
Minor Hemorrhages	20-40 IU/kg	20-30 IU/kg every 12 – 24 hours*	VWF:RCo and FVIII activity through levels of >30%
Major Hemorrhages	40-60 IU/kg	20-40 IU/kg every 12 – 24 hours*	VWF: RCo and FVIII activity through levels of >50%

Treatment guidelines apply to all VWD types

*This may need to be continued for up to 3 days for minor hemorrhages and 5-7 days for major hemorrhages

Repeat doses are administered for as long as needed based upon repeat monitoring of appropriate clinical and laboratory measures.

Although dose can be estimated by the guidelines above, it is highly recommended that whenever possible, appropriate laboratory tests should be performed on the patient's plasma at suitable intervals to assure that adequate VWF:RCo and FVIII activity levels have been reached and are maintained.

In the unlikely event that a patient who is actively bleeding should miss a dose, it may be appropriate to adopt a dosage depending on the level of coagulation factors measured, extent of the bleeding, and patient's clinical condition.

NDC Number	Size	Protein Amount
67467-182-01	500 IU VWF:RCo and 500 IU FVIII activities in 5 mL	≤ 7.5 mg
67467-182-02	1000 IU VWF:RCo and 1000 IU FVIII activities in 10 mL	≤ 15.0 mg

HOW SUPPLIED/STORAGE AND HANDLING

- Wilate is supplied in a package with a single-dose vial of powder and a vial of diluent (Water for Injection with 0.1% Polysorbate 80), together with a Mix2Vial™ transfer device, a 10-mL syringe, an infusion set and two alcohol swabs.
- Each vial of Wilate contains the labeled amount of IU of VWF:RCo activity as measured using a manual agglutination method, and IU of FVIII activity measured with a chromogenic substrate assay.
- Components used in the packaging of Wilate contain no latex.

Shelf life

- Store Wilate for up to 36 months at +2°C to +8°C (36°F to 46°F) protected from light from the date of manufacture. Within this period, Wilate may be stored for a period of up to 6 months at room temperature (maximum of +25°C or 77°F). The starting date of room temperature storage should be clearly recorded on the product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature, or the expiration date on the product vial, whichever is earliest. Do not freeze.
- Do not use after the expiration date.
- Store in the original container to protect from light.
- Reconstitute the Wilate powder only directly before injection. Use the solution immediately after reconstitution. Use the reconstituted solution on one occasion only, and discard any remaining solution.

PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If allergic symptoms occur, patients should discontinue the administration immediately and contact their physician.
- Inform patients that undergoing multiple treatments with Wilate may increase the risk of thrombotic events thereby requiring frequent monitoring of plasma VWF:RCo and FVIII activities.
- Inform patients that there is a potential of developing inhibitors to VWF, leading to an inadequate clinical response. Thus, if the expected VWF activity plasma levels are not attained, or if bleeding is not controlled with an adequate dose or repeated dosing, contact the treating physician.
- Inform patients that despite procedures for screening donors and plasma as well as those for inactivation or removal of infectious agents, the possibility of transmitting infective agents with plasma-derived products cannot be totally excluded.

Manufactured by:

Octapharma Pharmazeutika Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria
U.S. License No. 1646

Distributed by:

Octapharma USA Inc.
121 River Street, 12th floor
Hoboken, NJ 07030

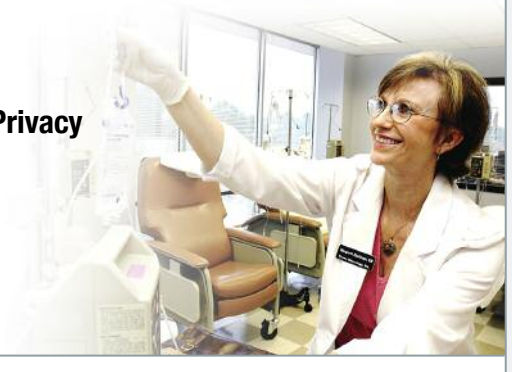
octapharma
For the safe and optimal use of human proteins

BioSupply Trends Quarterly

October 2012

Features

Special Focus: Innovation



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

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

Publisher: FFF Enterprises, Inc., 41093 County Center Drive, Temecula, CA 92591

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

BioSupply Trends Quarterly accepts manuscript submissions in MS Word between 600 and 2,500 words in length. Email manuscripts to or request submission guidelines at editor@BSTQuarterly.com. *BioSupply Trends Quarterly* retains the right to edit submissions. The contents of each submission and their accuracy are the responsibility of the author(s) and must be original work that has not been, nor will be, published elsewhere, without the written permission of *BioSupply Trends Quarterly*. A copyright agreement attesting to this and transferring copyright to FFF Enterprises will be required.

Advertising in BioSupply Trends Quarterly
BioSupply Trends Quarterly has a circulation of 50,000, with an approximate readership of more than 150,000 decision-makers who are comprised of general practice physicians, hospital and clinic chiefs of staff and buyers, pharmacy managers and buyers, specialist physicians and other healthcare professionals.

For information about advertising in *BioSupply Trends Quarterly*, you may request a media kit from Cheryl Brooks at (800) 843-7477 x1177, cbrooks@fffenterprises.com.

The Human and Economic Value of Healthcare Innovation

OUR INNOVATION ISSUE is one I always look forward to in anticipation of learning what novel technologies have the possibility of shaping the future of the healthcare landscape. While there is no shortage of promising medical initiatives in development at any given moment, the path from concept to commercialization can be filled with obstacles. Considering the far-reaching positive impact their availability would have on patients, providers and the economy, finding a path to market is a worthy undertaking.

In our feature Innovation Accelerators: From Concept to Commercialization, we take a close look at one venture group with a strategic methodology to hasten the development process through a streamlined model that includes a path to commercialization. We profile two of their companies: one that has developed a continuous smart glucose monitor for diabetics, and another that has developed a diagnostic for ductal carcinoma in situ for noninvasive breast cancer. These are examples of initiatives that have measurable human and economic value when they become readily available.

In this issue, we also take a look at companion diagnostics — the combination of diagnostic testing and treatment therapies that allows physicians to design a specific course of treatment based on a patient's genetic makeup. It is targeted therapy at its best, and although still relatively early in its journey, it is considered in many circles to be the future of personalized medicine.

Autoimmune disease is another area where the quest is on to develop new therapies. Only a decade ago, most autoimmune diseases were thought to be psychosomatic. With some 23 million Americans affected and more than 80 different types of autoimmune diseases identified, that's no longer the case. From vaccines to herbal remedies and cell-based research, treatment and reparation remain a strong focus. Though prevention continues to baffle researchers, some believe that beyond treatment, there may be hope for a cure. With research in diverse studies ranging from worm therapy to stem cells, scientists are hard at work to bring some answers to an area where mostly just questions exist.

The speed of innovation is certainly enhanced when thought leaders, academic labs, entrepreneurs and industry share information quickly and precisely. Technological breakthroughs almost always have an impact on medical science, and those on the front lines are quick to embrace innovations that help accelerate the quest to find the next prevention, treatment or cure.

As always, we hope you find this issue of *BioSupply Trends Quarterly* educational, insightful and innovative. Looking to the future, we hope to continue to bring you the information and resources that are helpful to you in your practice or business.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

BioSupply Trends Quarterly

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

Publisher
Patrick M. Schmidt

Editor
Ronale Tucker Rhodes, MS

Assistant Editor
Cheryl Brooks

Creative Director
Sheryl Perez

Artistic Director
Allan Bean

Graphic Artists
Allan Bean
Ben Drolet

Advertising Director
Sheryl Perez

Contributing Writers
Keith Berman, MPH, MBA
Kris McFalls
Trudie Mitschang
Amy Scanlin, MS
Carla Schick
Jim Trageser

Proofreader
Jackie Logue

Please direct editorial, advertising and marketing communications to
41093 County Center Drive
Temecula, CA 92591
Ph: (800) 843-7477
Email: editor@BSTQuarterly.com

Funds Committed to Expand Community Health Centers

In May, the Obama Administration committed $728 million to renovate and grow 398 community health centers. The funds, which were made available under the 2010 health law and the 2009 stimulus package, will help facilities in 48 states to expand their capacity to serve an additional 900,000 patients.

Since 2009, three million more patients have received care at community health centers. Currently, 8,500 locations around the U.S. provide care to 20 million people. With the new funding, an additional 1.3 million patients will be treated at these facilities in the next two years. And, it is predicted that demand will continue to grow when an expected 30 million Americans gain health coverage in 2014. ❖

New Law Aims to Accelerate Drug Approvals and Enhance Safety

On July 9, President Obama signed into law the Food and Drug Administration (FDA) Safety and Innovation Act, also known as S. 3187. The new regulation will help provide the FDA with the resources needed to continue to bring effective and safe drugs and devices to patients. The law also will maintain the nation's role as a forerunner in biomedical innovation and will protect the jobs maintained by drug and medical device development.

S. 3187 is expected to increase patient access to affordable medicines by driving the review of innovator drugs and devices, implementing the program proposed in the president's 2013 budget to accelerate approval of lower-cost generic drugs, and funding the new approval pathway for biosimilar biologics created by the Affordable Care Act. It also will require manufacturers of certain drugs to notify the FDA when they experience circumstances that could possibly lead to a national drug shortage.

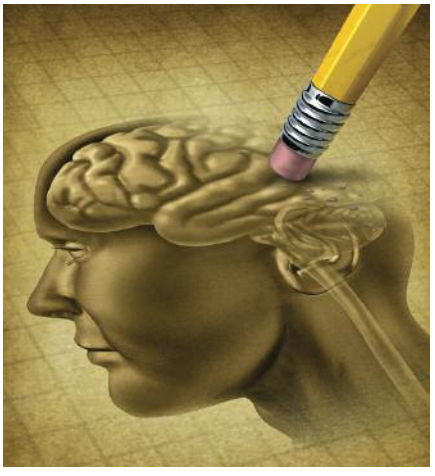
The new legislation will support the enhancement of drug supply chain safety in a market where counterfeiting is commonplace. Incentives have been put in place to increase the development of new antibiotics and innovative mechanisms to guarantee that children's medications are properly tested and labeled. In addition, the Act will expedite the development and review of drugs created for the treatment of serious and life-threatening illnesses. ❖

Revised CMS Rules to Decrease Healthcare Costs

The Centers for Medicare and Medicaid Services (CMS) issued new rules on May 10 to reduce redundant and outdated regulations on American hospitals and healthcare providers in order to decrease costs and allow for more emphasis on medical care. The revised Medicare Conditions of Participation for hospitals and critical access hospitals (CAHs) will result in an annual cost savings of $940 million. The revised Medicare Reform will eliminate overlapping and outdated regulatory requirements for healthcare providers and save $200 million in the first year. All totaled, the new rules will save the healthcare system approximately $1.1 billion in the first year and more than $5 billion over the next five years.

In addition to the cost savings, the new rules will let CAHs partner with other providers to ensure that efficient and safe delivery of care is arranged for their patients; eliminate outdated regulations, including obsolete infection control guidelines for ambulatory surgical centers, invalid Medicaid qualification standards for physical and occupational therapists, and unnecessary requirements for governing bodies of organ procurement organizations; increase flexibility for hospitals by permitting one governing body to superintend multiple hospitals in a single health system; and require that all qualified candidates be reviewed for possible appointment to the hospital medical staff where they will be given all rights, responsibilities and privileges of a selected staff member. ❖

Feds Take Additional Steps to Combat Alzheimer's Disease



Department of U.S. Health and Human Services (HHS) Secretary Kathleen Sebelius released an aggressive plan to combat Alzheimer's disease at the Alzheimer's Research Summit held May 15. The plan is part of the National Alzheimer's Project Act, which was signed into law by President Obama in January 2011, and this year Obama pledged to take immediate steps to implement parts of the plan by committing additional funds.

According to Sebelius, the plan includes three actions. The first will be the funding of two major clinical trials — an initial trial to test an insulin nasal spray for treating Alzheimer's disease and a prevention trial for people who are at high risk for developing Alzheimer's. The second focuses on the development of high-quality training and information for the nation's clinicians. The training material will teach providers how to recognize the signs and symptoms of the disease and how to best manage it. The third action will promote a new public education campaign and website that encourages caregivers to seek information at the new HHS website, www.alzheimers.gov, where they can find comprehensive resources to aid with the challenges of living with Alzheimer's disease.

The plan calls for a widespread, joint approach across federal, state, private and nonprofit organizations. ❖

HHS Creates Centers to Safeguard Public

On June 18, the U.S. Department of Health and Human Services (HHS) established three new centers to produce vaccines and other medications used to safeguard public health in the face of crises. Known as the Centers for Innovation in Advanced Development and Manufacturing, the centers will be the first major domestic infrastructure in the U.S. to develop and create medical countermeasures to defend Americans against bioterrorism, flu pandemics and other epidemics. They will be led by Novartis, The Texas A&M University System and Emergent Manufacturing Operations Baltimore LLC, each of which will be part of a public-private partnership model that will include small biotech firms and academic institutions.

HHS will invest $400 million in the initial phases of the centers, and the private partners will contribute 35 percent of the total cost for the preliminary building stage. Under the contracts, which can be renewed for up to 25 years, these groundbreaking facilities will be constructed or retrofitted to integrate flexible, advanced manufacturing services. They will use modern cell- and recombinant-based vaccine technologies that have the ability to manufacture vaccines swiftly and affordably in order to respond to a nationwide emergency. ❖

More Young Adults Now Have Health Insurance

A federal survey, known as the National Health Interview Survey, of 35,000 households shows that the share of young adults without health insurance fell by one-sixth in 2011 from the previous year. The share of people ages 19 to 25 who lacked health insurance fell to 27.9 percent, down from 33.9 percent in 2010, or about 1.6 million fewer uninsured people. This is the largest annual decline for any age group since the Centers for Disease Control and Prevention (CDC) began collecting the data in 1997.

The study's author, Matthew Broaddus, a research analyst at the liberal Center on Budget and Policy Priorities, said the increased coverage for young people was almost certainly due to a provision in the Affordable Care Act that allows children to stay on their parents' insurance policies until their 26th birthday. Joseph Antos, a healthcare policy expert at the conservative American Enterprise Institute, agreed that the provision of the new law was the only plausible explanation for the increase. Before the dependents' provision took effect, young adults were typically forced off their parents' plan at 18 or 21, after high school or college. The CDC data for 2011 captured the first full year that the provision allowed young people to stay on their parents' policies. The findings of the study are in line with a study released in June by the National Bureau of Economic Research, which found that young adults were a third more likely to be on their parents' employer policies since the provision on dependents went into effect.

The share of all Americans without health insurance stood at 15.1 pecent in 2011, or about 46 million people, which is down from 16 percent in 2010, but above the level in 2007 when 14.5 percent of Americans lacked health insurance. ❖

CARLA SCHICK *is a staff writer for* BioSupply Trends Quarterly.

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

Where can one find the current reimbursement rates for infliximab and other infusion medications used to treat Crohn's disease and ulcerative colitis?

Reimbursement rates vary by health plan and benefit level. The rates also are determined based on claims coding and individual medical necessity. Patients seeking reimbursement rates should contact the individual responsible for reimbursement at either their physician's office or their specialty pharmacy provider. Physicians can determine reimbursement rates by first locating the average wholesale price or average sales price and then calculating specific rates according to the contracts they accept. Medicare publishes its rates quarterly; they can be found at www.cms.gov/McrPartBDrugAvgSalesPrice.

More detailed information on coding and billing for infliximab can be found at http://www.janssenaccessone.com/pages/remicade/guide/reimbursement/reimbursement.jsp. ❖

How does reimbursement best work in an outpatient/nonhospital infusion center environment?

The answer to this question depends on who owns and operates the outpatient infusion center. If it is physician-owned, reimbursement is similar to that of an office visit. If the center is owned by a home infusion or specialty pharmacy provider, and their contract with a payer allows for patients to be seen in such a setting, it will work as if the patient were seen at home. Providers should be able to give specific coverage information to patients before services are provided.

In both instances, it is important for patients to know that it is their right to understand coverage *prior* to receiving services. There should never be any surprises concerning amounts owed. Most accredited providers also ask patients to sign a financial consent form, which outlines coverage and who is responsible for paying what, before they receive care. ❖

What can an individual do when he or she has been denied insurance coverage for immune globulin (IG) after his or her employer changes carriers?

Many commercial insurers have focused on decreasing payment for and restricting provision of IG for the last few years due to the high cost of the therapy. There are federal regulations regarding the right to appeal a coverage decision. Each state has additional regulations for appeals.

If denied coverage for IG, an individual should work with his or her physician and IG provider to appeal the denial. The appeal will need to build a case for coverage specifically based on the medical coverage criteria outlined by the carrier. The physician should have visit notes detailing the individual's progress and improvement on therapy. And, the IG provider should have nursing notes or other documents supporting improvement on therapy. Both the IG provider and/or the physician should be able to assist in writing a letter of appeal, which should outline the condition the individual has, the history and/or progression of disease, specific symptoms or issues experienced when not receiving IG, and objective improvement attained while on IG therapy. Additionally, if the physician has ever tried titrating dose or frequency of infusions, this should be noted in the appeal letter as well. ❖

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.

if you spot it, you can stop it

Name: Joseph Miller Age: 62 years

Model is used for illustrative purposes only.

Symptoms[1,2]:

- Arrives at the ER with spontaneous, severe gastrointestinal bleeding
- No prior history of bleeding

Labs[1,3]:

- Prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests and additional testing ordered by the attending physician

Treatments[1]:

- Did not respond to treatments, including platelets and fresh frozen plasma

Diagnosis: ACQUIRED HEMOPHILIA

Joe has acquired hemophilia (acquired inhibitors), which can be very difficult to diagnose and is **fatal in more than 20% of all cases**.[4]

You can help patients like Joe by being aware of the red flags of acquired hemophilia and bringing them up to the physician.

When you see an unusual order of factor VIII (FVIII), ask some simple questions:

- What is the reason for your recent unusual order of FVIII?
- Do you have a patient with congenital hemophilia?
- Is bleeding under control?
- What diagnostic tests, such as an aPTT or a mixing study, have been performed?
- Was the aPTT prolonged?
- Have you consulted a hematologist?
- Have you considered acquired hemophilia?

Find out more about acquired hemophilia and treatment at **CoagsUncomplicated.com/Joe**.

References: 1. Huth-Kühne A, Baudo F, Collins P, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. *Haematologica*. 2009;94(4):566-575. **2.** Collins PW, Hirsch S, Baglin TP, et al; for UK Haemophilia Centre Doctors' Organisation. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. 2007;109(5):1870-1877. **3.** Collins PW, Percy CL. Advances in the understanding of acquired haemophilia A: implications for clinical practice. *Br J Haematol*. 2010;148(2):183-194. **4.** Bitting RL, Bent S, Li Y, Kohlwes J. The prognosis and treatment of acquired hemophilia: a systematic review and meta-analysis. *Blood Coagul Fibrinolysis*. 2009;20(7):517-523.

Novo Nordisk Inc., 100 College Road West, Princeton, New Jersey 08540 U.S.A.

 Printed in the U.S.A. 0211-00001711-1 March 2011

novo nordisk®

Research

New Possible Cause for Unexplained Miscarriages

Researchers at St. Michael's Hospital in Toronto, Ont., Canada, have identified a potential new cause for unexplained miscarriages in mice. In addition, they have identified two possible treatments to prevent these miscarriages, which have broader implications for the development of new drugs to treat heart attacks and strokes.

The researchers found that the same kind of blood clotting in coronary arteries or blood vessels in the brain that causes heart attacks and strokes also happens in the placenta. The massive clotting can destroy the placenta, block blood flow to the fetus and cause miscarriages. This condition is known as fetal and neonatal immune thrombocytopenia (FNIT), a bleeding disorder that affects between one in 800 and one in 1,500 live births (most commonly among Caucasians) in which mothers generate antibodies that attack and destroy platelets in their fetuses and newborns. In severe cases, FNIT may

lead to bleeding in the brains of the fetuses and newborns and cause neurological impairment or even death.

Seventy-five percent to 95 percent of FNIT cases are caused by maternal antibodies to one specific platelet antigen, HPA-1. However, these researchers discovered that another antigen, HPA-2, causes a type of FNIT never described before that can lead to miscarriages in more than 83 percent of mice. They also discovered that the HPA-2 antibodies sometimes not only destroy platelets, but activate them and cause massive clotting in the placentas. Because only six to eight reported live human births in the world with FNIT caused by HPA-2 have been reported, this research suggests that the reason these cases are so rare is that most of the affected fetuses died through miscarriages before doctors examined them.

In mice, these miscarriages can be prevented using at least two therapies. One is the transfusion of immune globulin (IVIG). The other is the transfusion of an antibody known as anti-FcRn, which blocks the attacking maternal antibodies from crossing the placenta.

The research was reported in the November issue of the *Journal of Clinical Investigation*. It is hoped that the findings will be important in the development of safer antithrombotic drugs, which are under development by several companies. ❖

Award

HHS Recognizes Facilities for Preventing HAIs

The U.S. Department of Health and Human Services (HHS) recognized 37 hospital and healthcare facilities for their efforts to prevent, and eventually eliminate, healthcare-associated infections (HAIs), a leading cause of death in the U.S. The facilities are the first to be honored as part of a new national awards program to highlight successful and sustained efforts to prevent HAIs, specifically infections in critical care settings. Awards were given on two levels according to specific criteria tied to national standards. The Outstanding Leadership Award went to teams and organizations that sustained success in reaching their targets for 25 months or more. The Sustained Improvement Award recognized teams that demonstrated consistent and sustained progress over an 18- to 24-month period.

HHS recently launched the Partnership for Patients, a new national partnership with hospitals, medical groups, consumer groups and employers that will help save lives by preventing millions of injuries and complications in patient care over the next three years. HHS has set a goal of decreasing preventable hospital-acquired conditions by 40 percent (compared with 2010 rates) by the end of 2013. Achieving that goal should result in approximately 1.8 million fewer injuries and illnesses to patients, with more than 60,000 lives saved over the next three years. The partnership has the potential to save up to $35 billion across the healthcare system, including up to $10 billion in Medicare savings over the next three years. ❖

Did You Know?

"In 2010, four in 10 Americans struggled to pay their medical bills due to a recession-driven spike in unemployment levels, rising treatment costs and unaffordable insurance coverage."

— Commonwealth Fund

Research

Gene Therapy May Reverse Hemophilia

In a recent study, researchers altered the DNA of a common virus so that it would instruct the bodies of hemophiliacs to make the Factor IX (FIX) protein, which helps blood clot. They then injected six men with hemophilia B, the less-common form, with the altered virus. After a single treatment, four of the six men were successfully making the FIX protein and were able to stop weekly factor infusions. The two others have been able to stretch the time between their infusions from days to up to two weeks. To date, the procedure works to make the FIX protein in only hemophilia B patients. But, researchers say this approach could work for people who have the more common form, hemophilia A. They just need to find the right virus to deliver the genes that would help that disease. The study was published in *The New England Journal of Medicine*. ❖

Research

Malaria Vaccine Close to Reality

Preliminary results from a Phase III clinical trial in Africa showed that a malaria vaccine, known as RTS,S, cut the number of malaria cases by 50 percent in a 12-month period following vaccination. Fifteen thousand children between the ages of 5 and 17 in seven African countries are participating in the trial. The vaccine is designed specifically for children because their immune systems are still developing, making them the easiest prey for the parasitic disease. Children under the age of 5 account for the vast majority of the 800,000 people who die of the condition each year.

The developers, GlaxoSmithKline and the PATH Malaria Vaccine Initiative, say preliminary results suggest that the incidence of adverse effects of the vaccine are comparable to those found in children receiving other vaccines in this blind trial. The side effects will be monitored over the next three years to develop a safety profile. If approved for widespread use, RTS,S would be given in tandem with other childhood vaccines, enabling overstretched health systems to introduce it with little difficulty. A 30-month analysis of the vaccine's effectiveness will be complete by the end of 2014. ❖

Research

BRI and Novo Nordisk Collaborate on Autoimmune Disease Research

Novo Nordisk and Benaroya Research Institute at Virginia Mason (BRI), Seattle, Wash., have entered into a three-year collaborative agreement to potentially speed up translational research of the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel disease and lupus. The agreement establishes how Novo Nordisk and BRI research scientists and clinicians will collaboratively develop studies to better understand changes in the immune systems of patients living with these autoimmune diseases. The intent is to develop better therapies and improve how these treatments are used.

"Translational research" describes a research approach that seeks to move discoveries made in laboratory, clinical or population studies more quickly into clinical care. In this specific agreement, BRI scientists and Novo Nordisk researchers at the company's Seattle research center will work together to study samples and data registered in BRI's biobank of patients with these diseases, as well as people with no history of autoimmune disorders. The personal information of these patients will not be disclosed.

"Improving patient care through innovation is at the heart of our company culture, and this agreement represents one way that we can work together with the larger healthcare research community to achieve this objective," said Per Falk, senior vice president, Biopharmaceuticals Research Unit, Novo Nordisk. "We're pleased to be working closely with the Seattle scientific community, which is sharing its best and brightest with us in an effort to bring new medicines for patients."

In the United States alone, as many as 1.5 million people suffer from rheumatoid arthritis or inflammatory bowel disease, and more than half a million people suffer from lupus. ❖

Research

Personalized Immune Mouse to Study Autoimmune Disease

Columbia University Medical Center scientists have developed a new "personalized immune mouse," a new tool that allows them to re-create an individual's immune system to study autoimmune diseases. The mouse model also could have clinical applications, such as predicting how a particular patient might respond to existing drugs or immunotherapies. And, it could prove useful for developing individualized immunotherapies for fighting infection or cancer or for lessening a patient's rejection of transplanted tissue.

The mouse model is made by transplanting human bone marrow stem cells (also known as CD34+ cells), along

with a small amount of HLA-matched immature thymus tissue, into an immunodeficient mouse. The thymus tissue is implanted into the mouse's kidney capsule, a thin membrane that envelops the kidney and serves as an incubator. Within six to eight weeks, the transplanted thymus tissue is seeded by circulating human CD34+ cells (which are infused into the mouse's bloodstream), and begins generating human immune cells from the CD34+ cells.

While the researchers intend to use the personalized immune mouse to study type 1 diabetes, Dr. Megan Sykes, director for the Columbia Center for Translational Immunology, says that they "hope to find out what is fundamentally different about patients' immune systems, compared with those of healthy individuals, before any disease develops." ❖

People and Places in the News

FDA APPROVALS / DESIGNATIONS / SUBMISSIONS

Octapharma USA has submitted its biological license application for **octaplasLG** to the U.S. Food and Drug Administration (FDA) for the evaluation of octaplasLG an indication of managing preoperative or bleeding patients who require replacement of multiple plasma coagulation factors. The application also seeks to gain marketing approval for the substitution of intentionally removed plasma, such as plasma exchange, in patients with thrombotic thrombocytopenic purpura, a blood disorder that causes clot formation in small blood vessels.

Achillion Pharmaceuticals Inc. has received a Fast Track designation from the FDA for ACH-3102 as part of an interferon-free regimen for the treatment of **chronic hepatitis C (HCV)**. ACH-3102 is a pan-genotypic second-generation NS5A inhibitor against HCV that was discovered by Achillion and is currently being evaluated in a Phase 1 clinical trial.

The FDA has approved **Sanofi**'s Zaltrap in combination with a FOLFIRI chemotherapy regimen to treat adults with colorectal cancer. Zaltrap (aflibercept), an angiogenesis inhibitor, is intended for patients with **metastatic cancer** whose tumors are resistant to or progressed after an oxaliplatin-containing chemotherapy regimen.

APPOINTMENTS

Karin Hehenberger, MD, PhD, has been hired by **Coronado Biosciences Inc.** as senior vice president of scientific affairs to focus on broadening the scope of proof of concept trials in various autoimmune diseases with Coronado's lead product CNDO-201. Hehenberger was previously senior vice president for strategic alliances at the Juvenile Diabetes Research Foundation.

Lycera Corp., a biopharmaceutical company pioneering innovative approaches to developing novel oral medicines to treat autoimmune diseases, has appointed **Steven Gillis**, PhD, managing director of ARCH Venture Partners, and **Michael Steinmetz**, PhD, managing director of Clarus Ventures, to its board of directors.

Dr. **Jordan Orange**, an internationally recognized leader in studying and treating primary immunodeficiency disorders in children, will lead the new **Center for Human Immunobiology** at Texas Children's Hospital. His research, which will be funded by the National Institute of Allergy and Infectious Diseases, as well as the United States Immunodeficiency Network, will focus on the biology of natural killer cells and the innate immune system, with a clinical focus on primary immunodeficiency disease.

Research

Fundraising Effort in Progress for Treating Critical Care Patients

BioAegis Therapeutics is raising $6 million to advance the development of a natural human protein with anti-inflammatory benefits for critical care patients. As of May, the company has raised $500,000 to develop the recombinant human plasma gelsolin, which can restore plasma gelsolin levels in patients where it is depleted.

Plasma gelsolin, the fourth most prevalent protein in the body, plays a critical role in containing inflammation and preventing it from spreading. Recent findings have shown that it is a key part of the body's immunity that modulates and localizes inflammation while boosting immune function. Although the protein keeps inflammation local, a fall in the level of the protein can lead to organ failure.

BioAegis is the latest to option the technology after previous efforts by Biogen and Critical Biologics were dropped. Steven Cordovano, a spokesman for BioAegis, estimates that about $30 million has been invested in the protein's development, and previous attempts to develop the drug have produced a great deal of data. In addition to developing plasma gelsolin for applications in intensive care unit settings, BioAegis sees scope for other applications for recombinant human plasma gelsolin in orphan and chronic diseases such as trauma, sepsis burns and renal diseases. It also wants to develop it in biomarker partnerships. ❖

NexDx Inc., a science-driven molecular diagnostics company providing next-generation products and services for personalized medicine in rheumatoid arthritis and other autoimmune diseases, announced the appointment of internationally renowned physician and scientist **Mary K. Crow**, MD, to its scientific advisory board.

ACQUISITIONS

The Kedrion Group has acquired the **RhoGAM** line of products from Ortho-Clinical Diagnostics Inc. The acquisition includes the transfer of the Rho(D) Immune Globulin (Human) RhoGAM Ultra-Filtered PLUS and Rho(D) Immune Globulin (Human) MICRhoGAM Ultra-Filtered PLUS products, as well as Somerset Laboratories Inc., a wholly owned subsidiary of Ortho Clinical Diagnostics, a U.S. FDA-licensed donation center located in Williamsville, N.Y., which has collected blood plasma from the donor population used in the manufacturing process of the RhoGAM brand for more than 30 years.

AWARDS

Duane Wesemann, MD, PhD, of Brigham and Women's Hospital is the **2010 Young Investigator Award** recipient. The award, which is funded by an unrestricted grant from CSL Behring and administered by the American Academy of Allergy, Asthma and Immunology, supports the development of academic and/or clinical immunology research careers of junior faculty who have demonstrated a commitment to the study and care of patients with primary immune deficiency disease. Dr. Wesemann was selected for his research investigating why certain immune deficiencies are associated with high IgE levels.

Vaccines

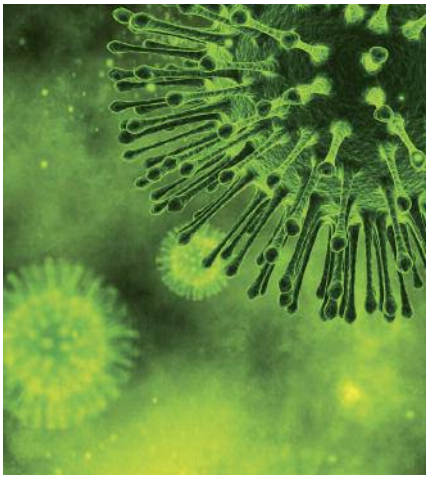
Flu Vaccine Coverage Well Below Healthy People 2020 Objectives

Researchers with the Centers for Disease Control and Prevention (CDC) have found that influenza vaccination coverage is well below the Healthy People 2020 objectives. The researchers analyzed data from 12,000 adults aged 18 to 64 during the 2008-2009 influenza season, taken from the 2009 National Health Interview Survey. Overall influenza vaccination coverage during the study period for adults aged 18 to 64 years was 28.2 percent, but it was significantly higher among adults aged 50 to 64 years than among those aged 18 to 49 years. Coverage among adults with high-risk conditions was 41.4 percent. Healthcare personnel had significantly higher influenza vaccination coverage (53 percent) compared with those who were not healthcare personnel (25.8 percent). And adults who had insurance were more likely to get the seasonal vaccine.

CDC researchers said their findings show insurance alone may not be enough to achieve the objectives set for influenza vaccination levels. They suggested that vaccine access and coverage could be improved by other provisions of the Affordable Care Act, such as increased payments for primary care services and coverage without cost sharing for recommended vaccines. ❖

Research

Osteoporosis Drug May Help Kill Flu Viruses



Pamidronate, an old osteoporosis drug, may be effective in killing a range of influenza viruses, including ones that are very dangerous to people, according to scientists in Hong Kong. Unlike antiviral drugs that target and mute flu viruses, pamidronate boosts a certain class of human immune cells, known as gamma-delta T cells, and sets them off on a killing spree to exterminate host cells that are infected with flu viruses.

In the study, the scientists used specially bred mice that had their own immune systems removed and substituted with a complete set of the human immune system. The mice were separated into three groups and infected separately with the pandemic H1N1 swine flu virus, H5N1 and H9N2 bird flu viruses. Within each of the groups, mice that were treated with the drug recovered very quickly, while those that were not given any treatment died within a few days. The drug did not work on the mice that did not have gamma-delta T cells to begin with, which means that the drug only boosts the numbers of these T cells, but does not create them. The study was reported on in the *Journal of Experimental Medicine*. ❖

Research

Study Confirms Breast Cancer and Autoimmune Arthritis Link

New research reveals that patients suffering from both breast cancer and arthritis have a more aggressive cancer, a finding that could suggest a possible treatment. Experiments by researchers at the University of North Carolina at Charlotte have shown an intimate relationship between mast cells — immune system cells that are located in various tissues and that can cause inflammation — and metastatic tumors.

Researchers worked with two strains of mice. The first group had spontaneous arthritis and the second group had spontaneous breast cancer. They found that the population of mast cells within the bone and lung microenvironment was significantly higher in those mice with arthritis and breast cancer versus those without arthritis and breast cancer. The differentiation of mast cells from bone marrow-derived stem cells also was significantly higher in the arthritic versus the nonarthritic tumor-bearing mice.

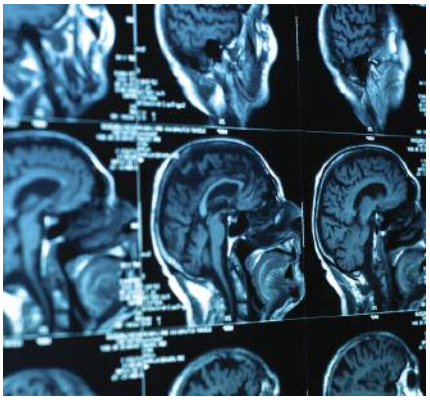
Their findings point to a relationship between the c-kit receptor found on mast cells and on the transmembrane stem cell factor (SCF) ligand found on metastatic breast cancer cells. The interaction between SCF and c-kit appears to play a critical role in facilitating metastasis. Because of the suspected relationship, the researchers tested the effect of blocking the receptor by treating the mice with an anti-c-kit receptor antibody and celecoxib, an anti-inflammatory medication, which resulted in a greatly reduced incidence of breast cancer metastasis to the bone and lung. ❖

Research

Brain Tumor Vaccine Shows Promise in Trials

A vaccine that jump-starts the immune system is showing promise in keeping patients diagnosed with glioblastoma, or malignant glioma, alive longer. Glioblastoma is the most common type of cancerous brain tumor, and those diagnosed die approximately 12 to 14 months after diagnosis.

In a Phase I clinical trial, researchers created individual vaccines for 34 patients using brain tumor tissue and each patient's own dendritic cells, which are part of the immune system. Ninety-one percent of patients who received the vaccine were alive after one year, 55 percent were alive after two years, and 44 percent survived three years or longer. Three patients are still alive after five years. According to the researchers, combining tumor tissue with the dendritic cells trains the immune system to recognize cancer cells and mount an attack.



The Phase I clinical results were reported in April at the American Association of Neurological Surgeons meeting in Denver. A Phase II clinical trial is currently being finished, and a Phase III multicenter trial is currently enrolling patients. ❖

FAMILIES FIGHTING FLU (FFF) is a nonprofit, 501(c)(3) volunteer-based advocacy organization dedicated to protecting the lives of children by helping to increase annual influenza vaccination rates among families. Our members include families whose children have suffered serious medical complications or died from influenza, as well as health care practitioners and advocates committed to flu prevention.

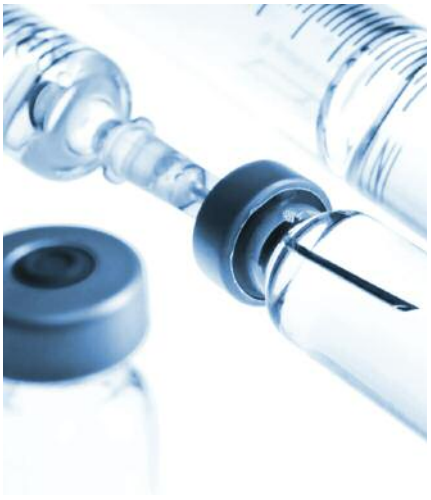
Share in our mission to protect all children against influenza and save lives.

Visit **www.FamiliesFightingFlu.org** Call **(888) 2ENDFLU** (888-236-3358)

FAMILIES FIGHTING FLU, INC.

Vaccines

Vaccine May Halt Autoimmune Disease



A synthetic vaccine based on nanotechnology may halt autoimmune diseases such as Crohn's and rheumatoid arthritis. The vaccine works by tricking the immune system into producing antibodies that target an enzyme that causes autoimmune diseases.

With autoimmune diseases, some members of the enzyme family, especially the enzyme matrix metalloproteinases (MMP), get out of control. MMPs are normally held in check naturally by inhibitor molecules called TIMPs, and previous attempts to mimic TIMPs with artificial drugs have produced serious side effects. Rather than target the MMPs directly, researchers at the Weizmann Institute in Rehovot, Israel, created tiny metallic vaccine molecules that fool the immune system into manufacturing its own MMP-suppressing antibodies. When tested on mice with a rodent version of Crohn's, the vaccine significantly reduced their symptoms. Untreated mice suffered severe damage to their colons, while those injected with the vaccine experienced only "limited" inflammation.

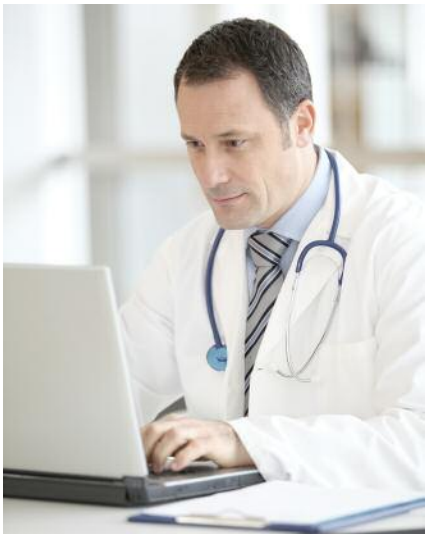
More research is needed before experts can be sure the therapy is safe for humans. The research was published in the journal *Nature Medicine*. ❖

Disease Guidelines

New Guidelines Issued for Severe Lupus

The American College of Rheumatology has issued new guidelines for the screening and management of lupus nephritis (kidney inflammation). According to the guidelines, patients who have not received treatment for lupus nephritis who show signs of kidney involvement should get a kidney biopsy. If there is kidney involvement, patients should be given the drug hydroxychloroquine. And, if there is any sign of protein in the urine, patients should be prescribed blood pressure-lowering medications called ACE inhibitors or angiotensin-receptor blockers.

When diagnosed with lupus, one in three patients already has kidney inflammation, and during the first 10 years with the disease, as many as 60 percent of patients will have some kidney problems. "Without treatment, lupus nephritis can lead to end-stage renal disease, which requires dialysis or a kidney transplant. But, not all types are this serious. It depends on the pattern of damage to the kidneys," says



Dr. Bevra Hahn, lead author of the new guidelines and a professor of medicine and chief of rheumatology at the David Geffen School of Medicine at the University of California, Los Angeles.

The guidelines were released online May 3 and were published in the June 2012 issue of *Arthritis Care & Research*. ❖

Research

New Criteria Proposed for Treating VWD

Octapharma researchers are proposing new objective criteria for evaluating the treatment of von Willebrand disease (VWD) based on clinical trials of wilate, which was approved by the U.S. Food and Drug Administration for the treatment of spontaneous or trauma-induced bleeding episodes in patients with severe VWD, as well as in patients with mild or moderate forms of the illness in whom the use of desmopressin is known or suspected to be ineffective or contraindicated. Products previously used to treat VWD were evaluated on a subjective four-point Likert scale with efficacy ranging from "none" to "excellent." The new more stringent evaluation was used in combination with the Likert scale during clinical trials. Results of the new objective criteria for evaluating the treatment of VWD were presented at the National Hemophilia Foundation annual meeting. ❖

Insurance

Point-of-Service Insurance Enrollment Is Recommended

Four healthcare leaders who analyzed the Foundation for Health Coverage Education's (FHCE) Eligibility Survey and found that a majority of uninsured individuals are unaware they are eligible for government coverage are suggesting point-of-service insurance enrollment. The FHCE Eligibility Survey was broken into two parts.

The Point-of-Service ER Survey was given to 13,069 uninsured patients who sought and received care in four high-volume emergency rooms in San Diego over an 11-month period. Findings revealed that 79.7 percent of uninsured patients could have had some form of government insurance but did not. As a result, the four hospitals did not receive government payments for a significant portion of the emergency medical care provided, estimated to total millions of dollars. In addition, 16.9 percent were eligible for private coverage (including group coverage of two or more

employees, individual coverage with medical underwriting, COBRA and Cal-COBRA), and 3.3 percent were eligible for high-risk pool coverage (including California's state-run high-risk pool, Major Risk Medical Insurance Program, and the newly implemented Pre-Existing Condition Insurance Plan).

A national Online Survey was given to 180,250 CoverageForAll.org visitors from all 50 states and Washington, D.C., who were seeking information on their health coverage options. This survey found that 61.7 percent were unaware they were eligible for state or federal health coverage programs. Most of these programs require individuals to have income of $44,700 or below for a family of four to qualify. In addition, the survey found 21.1 percent were eligible for private coverage (including individual, group or COBRA and MiniCOBRA). And, 15.4 percent were eligible for high-risk pool coverage (including state-run high-risk pools, as well as the newly implemented Pre-Existing Condition Insurance Plan).

Point-of-service enrollment would allow trained staff members in any qualified healthcare setting to go to an online address, input basic patient data, check for available options and enroll the patient in the relevant government health coverage program. It would include automated checkpoints for eligibility and it would contain fraud controls. ❖

Vaccine Update

Scientists at Mexico's **National Institute of Psychiatry** are working on a vaccine that could reduce addiction to **heroin**. The vaccine, which has been patented in the U.S., has been successfully tested on mice, and is being prepared for testing on humans. It makes the body resistant to the effects of heroin, so users would no longer get a rush of pleasure when they smoked or injected it.

Emergent BioSolutions has received a multiyear grant from the National Institute of Allergy and Infectious Diseases to advance the development of MVA85A, a candidate vaccine against **tuberculosis**. MVA85A is now completing a Phase IIb clinical trial to evaluate the safety and efficacy of the vaccine in over 2,700 infants in South Africa.

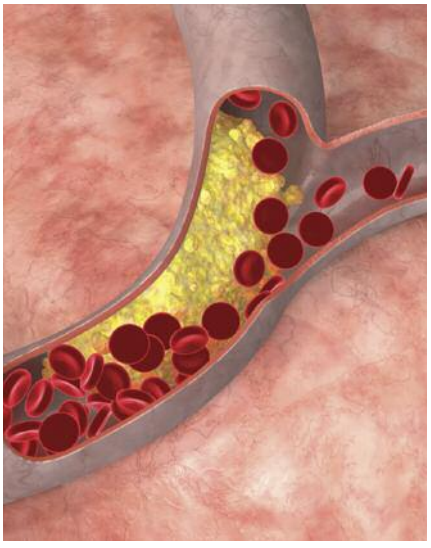
Scientists at the **Mayo Clinic** have created a vaccine that has successfully eradicated **skin cancer** in some mice. Results from early studies have shown that 60 percent of mice with melanoma were cured in fewer than three months with minimal side effects. The vaccine is made up of a combination of human DNA from melanoma cells and a cousin of the rabies virus called vesicular stomatitis virus (VSV). Known as cancer immunotherapy, the treatment used the genetically engineered version of VSV, which is symptomless in humans, to help target the cancer genes in the body.

Vaccines targeting the buildup of fatty deposits in arteries (plaque) could be available within five years to prevent **heart attacks**. Researchers at Cedars-Sinai Heart Institute in Los Angeles were able to formulate a vaccine that reduced plaque buildup by 60 percent to 70 percent in mice. The resulting CVX-210 vaccine, being developed as an injection by **CardioVax**, is awaiting regulatory clearance to start clinical trials.

Sanofi SA's experimental vaccine against **dengue fever** proved effective and safe in a study of 4,000 children in Thailand, raising prospects for the first-ever inoculation against the mosquito-borne disease after decades of research. ❖

Research

Plasmapheresis May Reduce LDL and Increase HDL Cholesterol



A recent study conducted by Grifols suggests that the plasmapheresis process may reduce levels of low-density lipoprotein (LDL), or "bad" cholesterol, as well as total cholesterol in individuals who have high baseline levels. The study also suggests that plasmapheresis could increase levels of high-density lipoprotein (HDL), or "good" cholesterol, among individuals with low baseline levels. Plasmapheresis is a technique used to separate plasma from the remaining blood components, which are then immediately injected back into the donor at the time of the donation. Plasma obtained during plasmapheresis is used to produce lifesaving medicines for patients who have rare, genetic and life-threatening diseases.

The multicenter longitudinal study was conducted in nine plasma donor centers in the U.S., with blood analyses performed prior to plasma donations to measure initial levels of total cholesterol, HDL and LDL. Plasma was collected from first-time donors or from donors who had not donated plasma for at least six months. The researchers estimated from the study results that plasmapheresis could reduce the levels of LDL by more than 30 mg/dl among individuals with high levels (greater than 160 mg/dl) or higher than desirable levels (greater than 130 mg/dl) when plasmapheresis procedures are performed two to four days apart. This effect was more significant in women, in whom cholesterol could be reduced by up to 35 mg/dl. A similar reduction pattern is estimated to occur in individuals with high total cholesterol levels (greater than 240 mg/dl) or higher than desirable levels (greater than 200 mg/dl), with the reductions in these cases potentially reaching 45 mg/dl and 32 mg/dl, respectively.

However, the cholesterol-lowering effects of plasmapheresis appeared to last only as long as the procedure continued at regular intervals, with cholesterol levels gradually returning to baseline following long periods without plasmapheresis. The same pattern of reductions was seen, although to a lesser degree, when subsequent plasmapheresis procedures were performed more than 10 days apart. Among individuals with normal baseline cholesterol levels, the study results suggested that plasmapheresis would not cause significant changes. ❖

Medicines

FDA Approves Afinitor to Treat Pancreatic Cancer

The U.S. Food and Drug Administration (FDA) has approved Afinitor (everolimus) to treat patients with progressive neuroendocrine tumors located in the pancreas that cannot be removed by surgery or that have spread to other parts of the body. The FDA says the drug was deemed safe for use after a clinical trial involving 410 patients who either had progressive neuroendocrine tumors spread to other parts of the body or had a tumor that could not be removed with surgery. During the trial, some patients received Afinitor and others received a placebo. For those treated with Afinitor, the average length of time the patients lived without the cancer spreading or worsening was 11 months, compared with 4.6 months for those who received the placebo. Afinitor also has been approved to treat patients with kidney cancer and patients with a type of brain cancer called subependymal giant cell astrocytoma. ❖

Medicines

New Drug to Treat C. Diff Is Approved

The U.S. Food and Drug Administration (FDA) has approved the use of an antibacterial drug called Dificid to treat adult patients with Clostridium difficile (also known as C. diff), an infectious type of diarrhea that has become a significant problem in hospitals and long-term care facilities. Dificid comes in tablet form and is taken orally two times a day for 10 days, with or without food, according to the FDA. C. diff sickens about half a million people a year in the U.S. Dificid is the first antibiotic in nearly 30 years to be approved to fight the sometimes deadly C. diff-caused disease. ❖

Research

Breast Milk Is a Source for Stem Cells

Dr. Foteini Hassiotou, a member of the University of Western Australia Hartmann Human Lactation Research Group, has discovered that human breastmilk contains stem cells that are able to turn into not only breast cells, but also cells of the bone, cartilage, fat, brain, liver and pancreas, depending on the medium in which they are grown. "The benefit of obtaining stem cells from breastmilk is that they can be accessed non-invasively, unlike getting them from the bone marrow, umbilical cord blood or peripheral blood," said Dr. Hassiotou. "If we can understand the properties of these cells and their role in the breast and in the breast-fed baby, we can use them as models for breast cancer research and in innovative stem cell therapies." She is currently examining the in vivo transplantation potential of milk stem cells into animals. ❖

Disease Guidelines

AAN Releases IVIG Guideline for Neurology

The American Academy of Neurology (AAN) has released a new evidence-based guideline on the efficacy of intravenous immunoglobulin (IVIG) — used to treat a range of immune-mediated neurological diseases — for neuromuscular disorders, based on a comprehensive review of the literature by the AAN Therapeutics and Technology Assessment Subcommittee in the 43-year period between 1966 and 2009. The guidelines answer the following questions: What are the significant findings for treatment of neuromuscular disorders with IVIG? How would neurologists use these guidelines in practice? What are some of the side effects of the treatment? What are some of the alternate treatments, and how do they measure up? Why is the benefit from IVIG often short-lived? Where should further research be done? The review was published in the March 27 print issue of *Neurology*. ❖

Vaccines

Flu Shots During Pregnancy Could Benefit Babies

A new study suggests that women who get flu shots while pregnant could also be protecting the health of their babies before and after birth. The study compared women in the Canadian province of Ontario who did and did not receive an H1N1 vaccine during the 2009-10 swine flu pandemic. The results suggest that second- or third-trimester H1N1 vaccination was associated with improved fetal and neonatal outcomes during the recent pandemic.

In another study, a group of Canadian researchers discovered that the swine flu vaccine triggered a series of antibodies that protect against many other types of flu, including the highly lethal H5N1 bird flu strain.

The findings were published in May in the *American Journal of Public Health*. ❖

Diseases

CDC Urges Tdap Vaccine for Pregnant Women

With the rising number of pertussis cases in the U.S., the Centers for Disease Control and Prevention (CDC) is urging pregnant women to be vaccinated with the Tdap vaccine. To date, nine babies have died due to the whooping cough outbreak, which is most dangerous for infants. "Above all, I want to urge vaccination for pregnant women and anyone who will have contact with babies," said Anne Schuchat, director for the National Center for Immunization and Respiratory Diseases at CDC. "As of today, nationwide, nearly 18,000 cases have been reported to CDC. That's more than twice as many as we had at the same time last year. In fact, it's more than we had in each of the past five years. … We may need to go back to 1959 to find a year with as many cases reported by this time so far."

The CDC also is tracking higher pertussis rates in children between the ages of 13 and 14. The agency surmised that protection provided through early-childhood vaccines may be waning and recommends children get a booster of the pertussis vaccine at 11 to 12 years of age. According to Schuchat, the booster shot Tdap has been administered to about 69 percent of children between the ages of 13 and 17. Approximately 84 percent of toddlers between 19 months and 35 months have received four doses of the Tdap series; 95 percent have received three doses. ❖

Did You Know?

The number of drugs approved by the U.S. Food and Drug Administration (FDA) could gradually increase. As of May, 12 drugs had been approved this year, and the agency speculates it will approve more this year than the 21 it approved in 2010.

— Janet Woodcock, director for the FDA Center for Drug Evaluation and Research

From Concept to Commercialization

A look at one Southern California accelerator and two innovative medical breakthroughs poised to improve accuracy in continuous glucose monitoring and pinpoint risk factors following DCIS diagnosis.

By Sheryl Perez and Trudie Mitschang

According to Wikipedia, innovation is the creation of better or more effective products, processes, services, technologies or ideas that are readily available to markets, governments and society. It is often the latter part of this definition that is overlooked, as novel products and technologies are not always linked to a strategic path that can bring them to market. Capital is, of course, one of the necessary ingredients to help innovation on the path to commercialization, but it often isn't enough. There are strategic venture groups that not only invest in medical breakthrough technologies, but also function as accelerators to provide the many resources and strategic relationships necessary to bring these early-stage companies to market.

Roy Cosan, managing director, Fjord Ventures, says to create real value in today's marketplace, it is important to first maximize efficiencies. According to Cosan, Fjord does this by operating capital-efficient companies that can allocate a larger portion of their operating budget to development costs. This is enabled in part by sharing infrastructure expenses across multiple companies. "As an investment group and accelerator of medical technology, we always make sure to identify our strategic partners and the go-to-market approach before investing in the development of novel technologies that include pharmaceuticals, devices and diagnostics," Cosan says.

The Fjord model, founded by managing partner Olav Bergheim, focuses on novel, disruptive medical concepts that have been created through participation of leading academic labs, medical industry thought leaders, entrepreneurs, multinational corporations and experienced management.

Improved Monitoring Device for Diabetics

One of Fjord Ventures' portfolio companies, Metronom Health, has pioneered a smart sensing platform to continuously monitor glucose in diabetics. Metronom founder and CSO Troy Bremer explains his motivation for developing the device: "I was frustrated by the technology gap between what I was working with in the defense industry and the tools available to help my wife manage her disease — she is a type 1 diabetic, and there were no CGMs [continuous glucose monitors] on the market then." Though CGMs are now readily available, Dr. Bremer experiences firsthand the inadequacies inherent in such systems. "I continue to watch my wife struggle with devices that are helpful but still have limited utility," he states. "The monitors she uses have a false positive rate in the range of 30 to 40 percent. This uncertainty needs to be eliminated to allow patients to easily and effectively manage their disease."

Working as an aerospace engineer, Bremer was used to dealing

with complex challenges and left his career to pursue a PhD under the guidance of the world's leading expert in glucose biosensing at the University of California, San Diego. After graduating, Bremer and his colleague, professor Elliot Botvinick threw themselves into furthering the development of what they now refer to as a real-time smart glucose sensor.

Understanding Diabetes

Diabetes is the most rapidly growing chronic disease of our time. The downstream consequences of not properly monitoring and treating diabetes are staggering. As the leading cause of new blindness and kidney disease, it also contributes to the nation's No. 1 killer, cardiovascular disease. In addition, the cost of treating diabetes is staggering.[1] According to the American Diabetes Association, the annual cost of diabetes in medical expenses and lost productivity was $174 billion in 2007.[2]

Metronom's CGM has the potential to significantly impact the ability for patients and their caregivers to make meaningful real-time treatment decisions by having a smart device that provides accurate data. The lifestyle/human factor of the device that must be worn by a diabetic has also been improved with a form factor that is easier to insert and more pliant and comfortable to wear. Further, information can be relayed to a patient's smart phone, computer or other device for easier reading. The economic impact for a patient who is able to accurately monitor their glucose and treat surges and declines quickly is also significant when you consider the costs of treating the far more pervasive diseases that diabetes can lead to.

Looking ahead, the growth path of Metronom's technology holds tremendous promise as well. "While there is significant value in this CGM as a stand-alone product, what is especially exciting is the integration of this continuous glucose monitor with an insulin pump to eventually create an artificial pancreas with the capability of automatically pumping the correct amount of insulin based on each patient's variables such as height, weight and glucose level, without the patient or provider's intervention," says Cosan, chief executive officer, Metronom. The idea of an artificial pancreas is not new, but no current CGM in the market has shown the level of accuracy required to gain FDA approval. Metronom Health's CGM may be the missing link.

Breast Cancer Breakthrough

Another innovative company in the Fjord portfolio is Prelude Corp., which is currently pioneering the PreludePx DCIS test for patients diagnosed with ductal carcinoma in situ (DCIS), the most common type of noninvasive breast cancer.

According to The American Cancer Society, the majority of patients diagnosed with DCIS today undergo lumpectomy followed by radiation treatment. Radiation is typically given as a precautionary step to minimize the odds of the cancer recurring. Unfortunately, a significant number of patients who receive radiation and all of its health-compromising side effects may have been able to avoid treatment if there were a more accurate way to assess individual risk factors. The Prelude test promises predictive power beyond the traditional clinicopathologic features to more accurately stratify patient risk of recurrence following DCIS diagnosis. The test will build on previously validated molecular markers — assayed by immunohistochemistry (IHC) in the tumor tissue and establish clinicopathologic risk factors.

"We believe this prognostic will help physicians better balance treatment risk with patient benefit to prevent unnecessary overtreatment in low-risk patients and identify high-risk patients otherwise missed by traditional assessment," says Cosan, who also acts as chief executive officer, Prelude Corp.

Currently, despite the frequent use of adjuvant radiotherapy to treat DCIS, it only prevents recurrence in an estimated 5 percent to 10 percent of lumpectomy patients, and its ability to reduce breast cancer-associated mortality is likely less than 1 percent. "Tens of thousands of patients per year receive unnecessary radiation treatments contributing to morbidity and increased healthcare costs," says Cosan.

Cosan explains that accurately identifying patients by risk profile will enable treatment standardization and achieve higher-quality/lower-cost care. While the economic savings are significant, when it comes to deferring radiation treatment, the ability to minimize the human cost is even more significant. With the Prelude test, patients with a low-risk diagnosis may opt to decline radiation treatment entirely; their physician would then manage the ongoing standards of care through annual follow-up exams, mammograms and MRIs.

The PreludePx DCIS test is approximately two years away from market launch and is currently moving into the clinical trial phase.

Closing the Gap

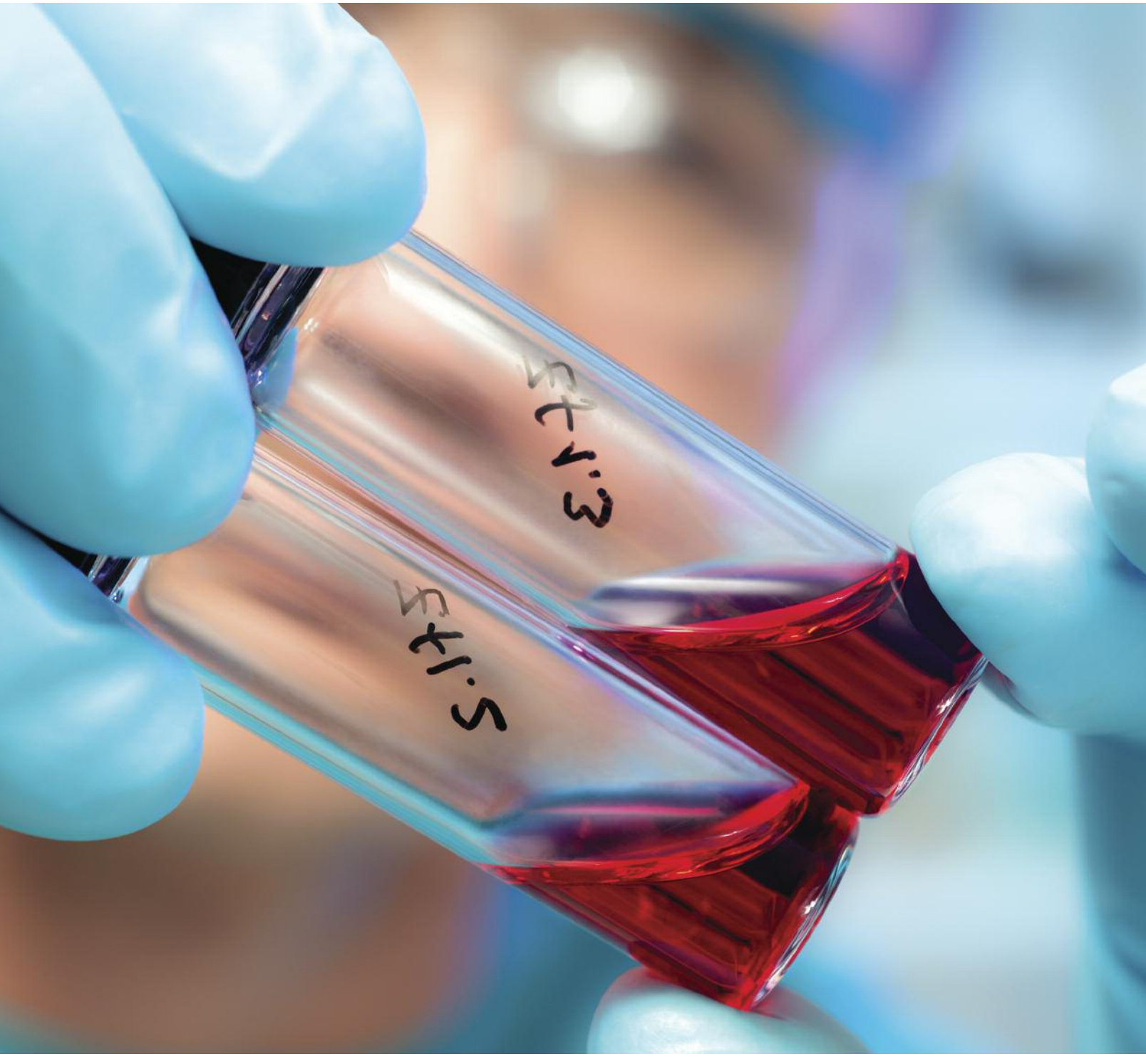
With so much to gain in human and economic value, it is not always clear why some of the most promising technologies remain dormant or are allowed to fall through the cracks. Many just run out of money. The secret may lie in the comprehensive understanding and strategic engineering that medical technology accelerators such as Fjord Ventures provide. ❖

SHERYL PEREZ *is vice president, marketing and communications at FFF Enterprises Inc., and* **TRUDIE MITSCHANG** *is a staff writer for* BioSupply Trends Quarterly *magazine.*

References

1. New York State Department of Health. Diabetes. Accessed at www.health.ny.gov/diseases/conditions/diabetes.
2. American Diabetes Association. Diabetes Statistics. Accessed at www.diabetes.org/diabetes-basics/diabetes-statistics/?loc=DropDownDB-stats.

COMPANION DIAGNOSTICS:
THE FUTURE OF PERSONALIZED MEDICINE



By pairing genetic testing with treatment therapies, physicians can better care for patients by knowing which therapies will be the most effective at specific doses.

By Amy Scanlin, MS

The future of healthcare lies in the development of personalized medicine, in which the combination of diagnostic testing and treatment therapies allows physicians to design a specific course of treatment based on a patient's genetic makeup.

These diagnostic tests, called companion diagnostics (CDx), are still early in their inception, but they are becoming more widely developed and utilized to offer healthcare providers the opportunity to identify the exact treatments that may have the greatest impact on a patient's condition, including specific drug dosages. In fact, worldwide acceptance of the ability to identify predictive biomarkers and subsequent CDx testing in the development of patient therapy has grown to be recognized as the next step forward in patient care.[1] With CDx testing, a patient's therapeutic interventions can be decided upon earlier because other therapies can be ruled out. In addition, treatment can provide maximum benefit, and side effects can be minimized.

CDx testing was first introduced in 1998 with the HercepTest, a diagnostic tool developed by DakoCytomation that identified patients for whom the cancer drug Herceptin (trastuzumab) would be effective. Since then, CDx tools are proving to be effective for a more patient-tailored approach to care.[2] The Personalized Medicine Coalition reports a sharp rise in the number of personalized medicine drugs, treatments and diagnostic products available to consumers just in the last year.[3] Not only are new drugs becoming available, but more and more research by both pharma companies and drug companies are identifying the populations they may best serve.

Right now and in the near future, oncology is the one area science is focusing on in the development of CDx testing.

"We are becoming more and more successful at identifying biomarkers," says Amy Miller, vice president of public policy at the Personalized Medicine Coalition, specifically in the area of cancer research. This is significant because, as Marc Boutin, executive vice president of the National Health Council, explains, it is not uncommon for medicines to work only 60 percent to 65 percent of the time, and in the area of oncology, that percentage drops to about 10 percent. Right now and in the near future, oncology is the one area science is focusing on in the development of CDx testing.

There were two significant U.S. Food and Drug Administration (FDA) CDx approvals in 2012. One was Pfizer's Xalkori (crizotinib), which was approved to treat patients with late-stage lung cancer who have an abnormal anaplastic lymphoma kinase (ALK) gene due to a gene rearrangement, and which comes with a CDx test to screen potential patients for the ALK mutation. Another is Daiichi Sankyo's and Roche's Zelboraf (vemurafenib), which was approved for the BRAF V600E-mutation positive melanoma drug in combination with a CDx test to screen patients for the mutation.[3]

Some argue that the addition of CDx testing will limit the production of certain drugs because the subset for whom they will be effective is limited. However, others see the promise of drugs that did not initially receive FDA approval realizing a new life because of a new group of people for whom they may be effective. Therefore, research and development dollars spent on those drugs may see a return after all, even though the market to whom drug makers can sell may be limited.

CDx: Easing the Way Toward Effective Treatments

There is no question that the era of personalized medicine has arrived. In 2006, only 13 tests were available to determine a patient's susceptibility to a particular disease or responsiveness to a particular treatment. Today, according to the Personalized Medicine Coalition, there are more than 72 FDA-approved therapies — a fivefold increase.[4] "Not all of these drugs came out new," explains Miller, "but drug companies ask for label changes based on research, or sometimes the FDA will change labels based on research." Though past success in the personalized medicine field has been debatable, industry observers say the science, regulation and business models are coming together in favor of CDx's promise.[5]

There is no question that the era of personalized medicine has arrived.

Today, patient therapy is largely based on demographics and both the doctor's and patient's hope that the therapy will work. But, because a given medicine often works in only a small percentage of the population, CDx can make an enormous difference in "getting the right treatment to the right patient at the right time." The challenge is to change physicians' behavior so that they test, when a test is available, for biomarkers prior to determining a treatment plan.

These biomarkers are the enzymes responsible for drug metabolism and the proteins that determine the cellular response to drugs, which can vary in expression depending on a patient's genetic makeup. Genetic tests can determine whether a patient carries these variations, which will allow physicians to individualize drug therapy. So, rather than basing dosing on height and weight, genetic testing will tell physicians how much, how well and how long it will take for a body to process medicine. This is known as pharmacogenomics, which gets the right dose of the right drug to the right patient at the right time, and it can save lives.[6]

Take, for example, rilotumumab (AMG 102), which in early studies did not fare well and, in turn, did not warrant further study for drugmaker Amgen. When the biomarker data came out for rilotumumab, the scales were tipped, and the drug is now a shining example of how genetic testing can impact the understanding of how the drugs work and for whom they'll work best.

Rilotumumab when used with chemotherapy nearly doubles the survival rate for those with high levels of the protein c-Met, which can bind with hepatocyte growth factor and create cancer cells. Rilotumumab blocks c-Met and hepatocyte from binding and increases the survival rate for those with gastric cancers to 11.1 months, compared with 5.7 months for patients taking a placebo. The American Cancer Society estimates there will be more than 21,000 new cases of gastric cancers this year and, thanks to advancements in personalized medicine, rilotumumab may play a large role in patients' survival.[4]

Ten percent of marketed drugs suggest genetic testing for optimal treatment.[7] Among the most common of the several genes responsible for drug metabolism are cytochrome P450 (CYP450) genes, more than 50 encoding enzymes that control

the metabolism of more than 70 percent of prescription drugs. Those who carry this gene often do not metabolize drugs at the same rate as most, leading to poor response or adverse reactions.

For example, the conversion of the drug codeine to morphine is mediated by the CYP450 enzyme CYP2D6. In some, metabolism is too slow and ineffective. In others, it is too rapid with subsequent risks of opioid toxicity. The FDA Public Health Advisory warns that the only way to assess the metabolism response prior to the administration of codeine is with a genetic test.[6]

Another example of how genetic variations affect drug metabolism in those patients whose genes encode drug-metabolizing proteins (or targets of the drugs themselves in such a way that certain drugs become ineffective) is clopidogrel (Plavix), a platelet inhibitor in patients with cardiovascular disease. It is estimated that 2 percent to 20 percent of patients carry mutations to the CYP450 enzyme CYP2C19, which makes them poor metabolizers with a reduced capacity to convert clopidogrel into its active metabolite. This results in not only a reduced anti-platelet effect, but it also makes patients more likely to have an ischemic event following therapy.[6]

Warfarin (Coumadin), an anticoagulant, is metabolized by the CYP2C9 enzyme, and its anticoagulant effect is mediated by the enzyme VKORC1. A combination of slow warfarin metabolism caused by CYP2C9 gene variations and reduced coagulation caused by VKORC1 gene variations increases the risk of bleeding during warfarin therapy. Warfarin product labeling states: "The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose."[6] It is estimated that 17,000 strokes could be prevented each year if a genetic test were given prior to the administration of warfarin to determine proper dosage.[7]

Now, CDx tests are being created alongside drugs, with partnerships forming between drugmakers and those in diagnostics so the drugs and tests can be approved by regulators at the same time. It's harder to get drugs approved through the FDA if there isn't a clear population they target, so this relationship means drugs could potentially be approved more quickly. According to the Personalized Medicine Coalition, 30 percent of treatments in late-stage clinical development and 50 percent of treatments in early-stage clinical development rely on biomarker data.[7] Matching the right diagnostic and drug partner can make for a smoother transition from research to marketplace, and these relationships are thought by many in the industry to be the key to advancing product development.[8]

"This is an area of a lot of activity at the moment," says Hakan Sakul, PhD, executive director and head of diagnostics, Worldwide R&D, for Pfizer Inc. "New applications are pairing drugs and diagnostics, but not everyone is used to seeing diagnostic testing on a drug label. The pharmaceutical industry is learning more about CDx, and how sharp that learning curve is depends on whether a pharma company has previous CDx experience."

Common CDx Tests

Collaboration is under way as drug developers partner with diagnostic testing manufacturers to address the issue of matching a drug with the appropriate patient. Drug developers want assurances that their product is going to reach a certain audience and be successful in its treatment. Likewise, diagnostic testing manufacturers can provide the means to that assurance and potentially help the drug to reach FDA approval more quickly by proving effectiveness. The relationship can be symbiotic for all parties involved, from researchers to patients. "There is constant interaction between diagnostic companies and pharma," says Dr. Sakul. "They [the diagnostic developers] come to us [the pharma industry] because they want to share new advances, new technology and new products. When the time comes to partner, we usually have a good idea of which companies to contact for potential CDx applications. This was the case for us with Xalkori. When we knew a diagnostic test would be required for FDA approval, we knew where to turn."

Ten percent of marketed drugs suggest genetic testing for optimal treatment.

Xalkori, Pfizer's lung cancer drug, is effective only for a small percentage of patients whose non-small-cell lung cancer (NSCLC) has a rearrangement of the ALK gene on the 2p23 chromosome. About 85 percent of lung cancer patients have NSCLC, which corresponds to a very low survival rate. The drug can reduce tumor size in 57 percent of those patients and stop progression in 87 percent.[4] Partnered with Abbott's Vysis ALK Break Apart FISH Probe Kit, physicians can test for ALK gene-positive patients for whom Xalkori is appropriate.[9]

The biotechnology firm Qiagen has 15 signed agreements with drug developers for its molecular diagnostic testing business, including Pfizer, which is partnering with Qiagen to develop diagnostic testing for a potential lung cancer treatment.[4]

Abbott and Merck are collaborating on a CDx for an investigational cancer therapy using Abbott's proprietary FISH (fluorescence in situ hybridization) technology to design a test

for TP53 gene deletions in cancer patients.[9] Abbott also is working with GlaxoSmithKline (GSK) to develop polymerase chain reaction (PCR) tests to screen non-small-cell lung cancer and melanoma tumors for expression of the MAGE-A3 antigen and PRAME antigen in support of GSK's cancer immunotherapy research program.[9]

Already on the market are Roche Holding AG's Herceptin (trastuzumab) for the treatment of breast cancer (one of the first cancer medicines aimed at patients who have the genetic abnormality HER2) and a CDx called the PathVysion HER-2 DNA Probe Kit developed by Abbott that tests for the mutation.[9]

The Roche Group also has received expedited review and approval for the melanoma drug Zelboraf (vemurafenib), which targets patients with metastatic or unresectable melanoma whose tumors express a gene mutation called BRAF V600E. Its CDx, the cobas 4800 BRAF V600 Mutation Test, manufactured by Roche Molecular Systems, also was approved ahead of schedule. This BRAF mutation occurs in about half of late-stage melanomas, and Zelboraf can inhibit the function of the V600E-mutated BRAF protein. Zelboraf is marketed by south San Francisco-based Genentech, a member of the Roche Group.[10]

The FDA has created a personalized medicine program that is addressing policy and approval issues of therapeutics and diagnostics. Phases I and II have been completed, and the comment period for draft guidance on novel diagnostics ended in September 2011. Comments are now being analyzed to complete the final guidance regulations. "The FDA is quite serious about pairing drugs and diagnostics and wants them to be filed [for approval] together," explains Dr. Sakul. The FDA has made it very clear that it will require that "highest hurdle."

Various departments within the FDA, including staff trained in pharmacogenomics and biomarker expertise, will work in tandem to ensure regulatory oversight of therapeutics and diagnostics to better enable approved products to get to market safely and efficiently. An expedited approval process for "breakthrough therapies," which can shorten the regulatory approval process by 40 percent to 50 percent, also has been approved with the recent passage of FDA user fee authorization legislation.[11]

Payment for CDx

CDx can save insurance companies, physicians and patients hundreds of millions of dollars annually with the reduction or elimination of both ineffective treatments and incorrect dosages. However, financially speaking, the long-term cost savings of the tests may not always be immediately evident based on the costs of the tests themselves, which in some cases can be quite high.

For example, ineffective treatments costing thousands to tens of thousands of dollars may be avoided with a simple genetic test. However, if the genetic test itself also is expensive or there is another way to test for the necessity of treatment, insurance companies may be reluctant to pay those upfront costs without valid cost-benefit and cost-comparison information. Or, insurance companies may decide all patients should be tested if there is an available diagnostic to weed out a small few for whom a drug could be unsafe, as in the case of warfarin, or they may decide it is more cost effective to just remove patients from the drug should adverse effects be observed.

That being said, there is no standard method of payment for CDx testing, and reimbursement can range from just a few dollars to tens of thousands of dollars, with rates set in most cases by the Centers for Medicare and Medicaid Services (CMS) and Current Procedural Terminology (CPT) codes that provide a payment standardization for all payers.

At present, reimbursement is determined on a case-by-case basis based on whether the insurance companies deem the test appropriate for the course of treatment. One exception appears to be when a drug and its CDx come to market together. This inconsistency in reimbursement has led to confusion in coverage decisions and, it is feared, could hinder the development of the next generation of products, reducing access and impeding the progress of personalized medicine.

While the tests are of high value to the patient and high value to the system, as the National Health Council's Boutin explains, they are harder to value for payers. Not only are clinical trials conducted for FDA approval of the drug, but payers as well want to see a comparative advantage analysis to make sure the drug will be of value.

Collaboration is under way as drug developers partner with diagnostic testing manufacturers to address the issue of matching a drug with the appropriate patient.

It is important before a product goes to market that the developer provide a clear demonstration as to the cost-benefit of its tests through comparative effectiveness research. For instance, it is estimated that there would be a 34 percent reduction in chemotherapy use if women were given a genetic test prior to treatment for breast cancer[7] — a huge cost savings financially, emotionally and physically. Even with this evidence, insurance companies do not have a clear benchmark indicating which specific improvement would warrant what payment. There is clearly confusion in the marketplace, and this confusion will remain for the next few years.[12]

However, this confusion could be remedied with the passage of a bill called the MODDERN Cures Act, introduced by U.S. Rep. Leonard Lance of New Jersey and the National Health Council. The MODDERN Cures Act aims to reinvent the drug and diagnostic regulatory framework in part by extending a drug's pharmaceutical patent so that it doesn't expire before or soon after the drug is brought to market, providing patent protection from generic competition. The legislation also encourages the co-development of diagnostics and drug therapies. As of this writing, there are 35 House members on board, and it will be introduced into the Senate soon.

"This [the MODDERN Cures Act] could double or triple the investment in companion diagnostics and changes the business model," says Boutin. It will "change the insurance conversation with beneficiaries" as well. This is because as CDx are more predictive and more widely used, patients with the same disease will no longer be treated with the same medications, but ones tailored to their genetic makeup.

The Future of CDx with Regard to Personalized Care

While it appears the huge breakthrough in CDx is turning the tides of medicine, it is important to remember that science is still early in its journey and there is still much to be learned. New technologies will be developed to better understand disease and to better sort through the vast array of information we are gathering now and will gather in the future as science and technology progress. It is an exciting time for medicine and for patients and an exciting time to be on the ground floor.

"The future of diagnostic testing is in part being driven by prevailing science guiding where to focus efforts," explains Dr. Sakul. "Companion diagnostics can help to provide better opportunities for patients." Right now, the predominant focus is on cancer therapies. However, as science turns towards other diseases, drug and diagnostic companies will jump quickly to develop protocols. If a patient is diagnosed with cancer, learning which drug will be more likely to work will better benefit not only the patient but healthcare overall. ❖

AMY SCANLIN, *MS, is a freelance writer and editor specializing in medical and fitness topics.*

References

1. La Thangue, NB, Kerr, DJ. Predictive Biomarkers: A Paradigm Shift Towards Personalized Cancer Medicine. *Nature Reviews Clinical Oncology*, Aug 23 2011;8(10):587-96.
2. Zieba, A, Grannas, K, Söderberg, O, Gullberg, M, Nilsson, M, and Landegren, U. Molecular Tools for Companion Diagnostics. *Nature Biotechnology*, May 24, 2012.
3. Biotechnology Industry Organization. Drugs Need Friends Too, Jan. 19, 2012. Accessed at www.bio.org/articles/drugs-need-friends-too.
4. Flinn, R. Amgen Revives Defunct Drug as Old Therapies Seek New Cure. *Bloomberg News*, May 17, 2012. Accessed at www.businessweek.com/news/2012-05-16/amgen-revives-defunct-drug-as-old-therapies-seek-new-cure.
5. Overly, S. Qiagen Expands Manufacturing. *Washington Post*, Aug. 21, 2011. Accessed at www.washingtonpost.com/business/capitalbusiness/in-pursuit-of-personalized-medicine-companion-diagnostics-gain-traction/2011/08/18/gIQA7vifUJ_story.html.
6. American Medical Association. Pharmacogenomics: Increasing the Safety and Effectiveness of Drug Therapy. Accessed at www.ama-assn.org/resources/doc/genetics/pgx-brochure-2011.pdf.
7. Personalized Medicine Coalition. Factsheet: Personalized Medicine by the Numbers. Accessed at www.personalizedmedicinecoalition.org/sites/default/files/files/PM_by_the_Numbers.pdf.
8. Biotechnology Industry Organization. The Future of Healthcare: Personalized Medicine, May 21, 2009. Accessed at www.bio.org/articles/future-healthcare-personalized-medicine.
9. Abbott Molecular. Press Release: Abbott Receives FDA Approval for ALK Gene Test for Lung Cancer Therapy Selection, August 29, 2011. Accessed at www.abbottmolecular.com/us/aboutus/press-releases/abbott-receives-fda-approval-for-alk-gene-test-for-lung-cancer-therapy-selection.html.
10. U.S. Food and Drug Administration. Press Release: FDA Approves Zelboraf and Companion Diagnostic Test for Late-Stage Skin Cancer, Aug. 17, 2011. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268241.htm.
11. Miller, A. Congress Recognizes Value of Personalized Medicine Approaches in FDA User Fee Authorization Legislation. *The Age of Personalized Medicine*, Jun. 27, 2012. Accessed at ageofpersonalizedmedicine.wordpress.com.
12. Datin, JA. Life Sciences Trends for 2011: Companion Diagnostics, Reimbursement and Consumerization. *Momentum for Growth*, Jan. 19, 2011. Accessed at blog.safeguard.com/index.php/2011/01/19/life-sciences-trends-for-2011-companion-diagnostics-reimbursement-and-consumerization.

Kogenate® FS:

The brand you know with

Kogenate® FS with BIO-SET® offers:

- *Grab & Go* packaging contains materials necessary for safe and fast reconstitution

- BIO-SET® reconstitution system with user-friendly features
- Wide range of vial sizes for flexibility in preparing your dose
- Small diluent volumes make reconstitution fast and easy

250 IU	500 IU	1000 IU	2000 IU	3000 IU
2.5-mL Diluent			5.0-mL Diluent	

Ask your doctor if **Kogenate® FS** is right for you.

- **INDICATIONS**
  Kogenate® FS, antihemophilic factor (recombinant), is a recombinant factor VIII treatment indicated for the control and prevention of bleeding episodes and peri-operative management in adults and children (0-16 years) with hemophilia A. **Kogenate® FS** is also indicated for routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no preexisting joint damage.

Bayer HealthCare
Pharmaceuticals

the convenience you need

Kogenate® FS can be stored at room temperature (up to 77°F) **for up to 1 year***

*Store Kogenate® FS at 36°F to 46°F for up to 30 months from the date of manufacture. Within this period, Kogenate® FS may be stored for a period of up to 12 months at temperatures up to 77°F. The starting date of room temperature storage should be clearly recorded on the unopened product carton. Once stored at room temperature, the product must not be returned to the refrigerator. The shelf-life then expires after the storage at room temperature (up to 12 months) or the expiration date on the product vial, whichever is earlier.

For more information, visit **kogenatefs.com**.

IMPORTANT SAFETY INFORMATION

The most serious adverse reactions are systemic hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to AHF. The most common adverse reactions observed in clinical trials were inhibitor formation in previously untreated or minimally treated patients, skin-associated hypersensitivity reactions, infusion site reactions, and central venous access device (CVAD) line-associated infections.

Kogenate® FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

For important risk and use information, please see brief summary of Prescribing Information on the following page or visit **kogenatefs.com/prescribing-information.jsp**.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Kogenate® FS

antihemophilic factor (recombinant)

with BIO-SET®

needleless reconstitution system

Real Life...Real Protection

Kogenate FS (Antihemophilic Factor [Recombinant] Formulated with Sucrose) For Intravenous Use, Lyophilized Powder for Reconstitution with BIO-SET, a needle-less self-contained reconstitution system

Initial U.S. Approval: 1993

BRIEF SUMMARY - CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes

Kogenate® FS is an antihemophilic factor that is indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A.

1.2 Peri-operative Management

Kogenate FS is indicated for surgical prophylaxis in adults and children with hemophilia A.

1.3 Routine Prophylaxis in Children with Hemophilia A with No Pre-existing Joint Damage

Kogenate FS is indicated for routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no pre-existing joint damage.

Kogenate FS is not indicated for the treatment of von Willebrand's disease.

4 CONTRAINDICATIONS

Kogenate FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to Kogenate FS may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of Kogenate FS should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed. *[See Warnings and Precautions (5.4).]*

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic-type hypersensitivity reactions including anaphylaxis have been reported with Kogenate FS and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Discontinue Kogenate FS if symptoms occur and seek immediate emergency treatment.

Kogenate FS contains trace amounts of mouse immunoglobulin G (MuIgG) and hamster (BHK) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Neutralizing Antibodies

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests.[6] Inhibitors have been reported following administration of Kogenate FS predominantly in previously untreated patients. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed.*[See Warnings and Precautions (5.4).]*

5.4 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated. *[See Dosage and Administration (2).]*
- Monitor for development of factor VIII inhibitors. Perform assay to determine if factor VIII inhibitor is present. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of Kogenate FS. Use Bethesda Units (BU) to titer inhibitors.
  - If the inhibitor is less than 10 BU per mL, the administration of additional Kogenate FS concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.

Adequate hemostasis may not be achieved if Inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following Kogenate FS infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to AHF.

The most common adverse reactions observed in clinical trials (frequency ≥ 4% of patients) are inhibitor formation in previously untreated patients (PUPs) and minimally treated patients (MTPs), skin-related hypersensitivity reactions (e.g., rash, pruritus), infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections in patients requiring a CVAD for intravenous administration.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

During the clinical studies conducted in PTPs, 451 adverse events (irrespective of the relationship to the study drug) were reported in the course of 24,936 infusions (1.8%). Twenty-four of the 451 adverse events were assessed as related to Kogenate FS (0.1%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 3 below.

Table 3 Adverse Reactions (AR) in Previously Treated Patients (PTPs) with Frequency of ≥ 4%

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 73 No. of Patients with AR (%)	Total No. of Infusions: 24,936 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	6 (8.2%)	0.02
General Disorders and Administration Site Conditions	Infusion site reactions	3 (4.1%)	0.01

SOC = System Organ Class

Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs)

In clinical studies with pediatric PUPs and MTPs, 726 adverse events were reported in the course of 9,389 infusions (7.7%). Twenty-nine of the 726 adverse events were assessed as related to Kogenate FS (0.3%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 4 below.

Table 4 Adverse Reactions (AR) in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) with Frequency of ≥ 4% (Age Range 2-27 months)

MedDRA Primary SOC	Preferred Term	Total No. of patients: 61 No. of Patients with AR (%)	Total No. of Infusions: 9,389 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus, urticaria	10 (16.4)	0.01
Blood and Lymphatic System Disorders	Factor VIII inhibition	9 (15)[a]	N/A
General Disorders and Administration Site Conditions	Infusion site reactions	4 (6.6)	0.04

SOC = System Organ Class

a) *Denominator for *de-novo* inhibitors is N=60, since one patient had a pre-existing inhibitor.

Minimally Treated Patients (MTPs) in the Joint Outcome Study

In the Joint Outcome Study with pediatric MTPs treated with routine prophylaxis or episodic enhanced treatment for 5.5 years, 46 of the 65 randomized patients experienced adverse events over the study duration. Adverse events were not assessed for their relationship with Kogenate FS.

Table 5 Adverse Events (AE) in MTPs in the Joint Outcome Study (Age Range 0-6 years)

MedDRA Primary SOC	Preferred Term	Total No. of Prophylaxis Arm Patients: 32 No. of Patients with AE (%)	Total No. of Enhanced Episodic Arm Patients: 33 No. of Patients with AE (%)
Surgical and Medical Procedures	Central venous catheterization, Catheter removal	19 (59)	18[a] (55)
Infections and Infestations	Central line infection	6 (19)	6 (18)
General Disorders and Administration Site Conditions	Pyrexia	1 (3)	4 (12)

SOC = System Organ Class

a) Three patients from the enhanced episodic arm had catheter removal.

Immunogenicity

In clinical studies with 73 PTPs (defined as having more than 100 exposure days), one patient had a pre-existing inhibitor. In the other 72 patients, followed over 4 years, no de-novo inhibitors were observed.

In clinical studies with pediatric PUPs and MTPs, inhibitor development was observed in 9 out of 60 patients (15%), 6 were high titer[1] (>5BU) and 3 were low-titer inhibitors. Inhibitors were detected at a median number of 7 exposure days (range 2 to 16 exposure days).

In the Joint Outcome Study with Kogenate FS,[5] de-novo inhibitor development was observed in 8 of 64 patients with negative baseline values (12.5%), 2 patients

developed high titer[1] (>5 BU) and were withdrawn from the study. Six patients developed low-titer inhibitors. Inhibitors were detected at a median number of 44 exposure days (range 5 to 151 exposure days).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Kogenate FS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with Kogenate FS, cases of serious allergic/ hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who have previously reacted to other factor VIII concentrates.

The following table represents the post-marketing adverse reactions as MedDRA Preferred Terms.

Table 6 Post-Marketing Experience

MedDRA Primary SOC	Preferred Term
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders	Pruritus, urticaria, rash
General Disorders and Administration Site Conditions	Infusion site reaction Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity reactions

SOC = System Organ Class

7 DRUG INTERACTIONS

None known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

Animal reproduction studies have not been conducted with Kogenate FS. It is also not known whether Kogenate FS can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Kogenate FS should be used during pregnancy only if clinically needed.

8.2 Labor and Delivery

There is no information available on the effect of factor VIII replacement therapy on labor and delivery. Kogenate FS should be used only if clinically needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Kogenate FS is administered to nursing mothers. Kogenate FS should be given to nursing mothers only if clinically needed.

8.4 Pediatric Use

Safety and efficacy studies have been performed in previously untreated and minimally treated pediatric patients. Children in comparison to adults present higher factor VIII clearance values and thus lower recovery of factor VIII. This may be explained by differences in body composition[7] and should be taken into account when dosing or following factor VIII levels in such a population. *[See Clinical Pharmacology (12.3).]* Routine prophylactic treatment in children ages 0-2.5 years with no pre-existing joint damage has been shown to reduce spontaneous joint bleeding and the risk of joint damage. This data can be extrapolated to ages >2.5-16 years for children who have no existing joint damage. *[See Clinical Studies (14.3).]*

8.5 Geriatric Use

Clinical studies with Kogenate FS did not include patients aged 65 and over. Dose selection for an elderly patient should be individualized.

13 NONCLINICAL TOXICOLOGY

Preclinical studies evaluating Kogenate FS in hemophilia A with mice, rats, rabbits, and dogs demonstrated safe and effective restoration of hemostasis. Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any acute or subacute toxic effect for Kogenate FS in laboratory animals.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with Kogenate FS to assess its mutagenic or carcinogenic potential and impairment of fertility. Kogenate FS has been shown to be comparable to the predecessor product with respect to its biochemical and physiochemical properties, as well as its non-clinical in vivo pharmacology and toxicology. By inference, the predecessor product and Kogenate FS would be expected to have equivalent mutagenic and carcinogenic potential.

The predecessor product did not demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. In vivo evaluation with the predecessor product in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that the predecessor product did not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed due to the immune response to heterologous proteins in all non-human mammalian species.

17 PATIENT COUNSELING INFORMATION

See Patient Product Information and Instructions for Use

Advise patients to report any adverse reactions or problems following Kogenate FS administration to their physician or healthcare provider.

- Allergic-type hypersensitivity reactions have been reported with Kogenate FS. Warn patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.
- In clinical studies with Kogenate FS, a 15% incidence of inhibitor development was observed in PUPs/MTPs and zero de-novo inhibitors were observed with the PTPs. Inhibitor formation may occur at any time in the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center for further treatment and/or assessment, if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to consult with their healthcare provider prior to travel. While traveling advise patients to bring an adequate supply of Kogenate FS based on their current regimen of treatment.

Bayer HealthCare

Bayer HealthCare LLC Tarrytown, NY 10591 USA
U.S. License No. 8
(License Holder: Bayer Corporation)
http://www.kogenatefs.com/

83744929-473790006

Blending Alternative and Mainstream Therapies

From dietary supplements and acupuncture to yoga and meditation, many on-the-fringe interventions are becoming more accepted by patients and practitioners.

By Trudie Mitschang

When software engineer Tom Robinson found himself sidelined by a diagnosis of Crohn's disease, he quickly sought answers via online message boards. After reading dozens of posts from other patients, Robinson became familiar with the most common medications prescribed for this debilitating disease. As he would soon learn firsthand, many of the prescriptions that promised to ease his symptoms produced equally debilitating side effects. Frustrated, Robinson began seeking answers outside of mainstream medicine, eventually incorporating practices like detoxification and meditation into his treatment plan. Today, Robinson's Crohn's is in remission and he attributes his restored health to a treatment approach that embraced conventional medicine in tandem with alternative therapies. And he's not alone in his conviction.

The 2007 National Health Interview Survey (NHIS), which included a comprehensive look at complementary and alternative medicine (CAM) used by Americans, showed that approximately 38 percent of adults use CAM.[1] The study went on to note that several mind and body approaches ranked among the top 10 CAM practices reported by adults. For example, the survey found that 12.7 percent of adults had used deep-breathing exercises, 9.4 percent had practiced meditation, and 6.1 percent had practiced yoga. Progressive relaxation and guided imagery also were among the top-10 CAM therapies for adults, while acupuncture had been used by 1.4 percent of adults.

Understanding CAM

CAM is a field of healthcare that is rapidly evolving but difficult to define. The National Center for Complementary and Alternative Medicine defines CAM as a group of diverse medical and healthcare systems, practices and products that are not generally considered part of conventional medicine (also referred to as Western or allopathic medicine). While conventional medicine is practiced by medical doctors and other health professionals such as physical therapists, psychologists and registered nurses, CAM may be administered by an acupuncturist or naturopathic practitioner, or self-administered, as in the case of vitamin supplements, deep breathing exercises and personal meditation.

While people turn to alternative medicine for many reasons, studies show that the majority do so because they consider it to be more aligned with their values, beliefs and philosophies about health and life than a strictly conventional medical approach. And, as the modern healthcare system becomes more and more impersonal, many people are seeking healthcare solutions that address the whole person as opposed to simply treating symptoms. "People are seeking 'natural' options to manage their health because they want to feel empowered by seeking the underlying causes of illness," says Ann Louise Gittleman, PhD, CNS. "They are tired of simply putting a Band-Aid on symptoms and want to address the real issues of ill health from a body, mind and spirit perspective."

Mind Over Matter: How the Brain Deals with Pain

According to the American Pain Foundation, an estimated 50 million Americans suffer from persistent pain each year.[2] Chronic pain is typically managed with prescription pain medications that can be both physically and psychologically addictive. Non-pharmaceutical pain treatments are sometimes prescribed by doctors in an effort to get pain under control, while many people with chronic pain choose alternative and complementary therapies as a supplement to their main chronic pain treatment. "There's a strong mind/body component to managing chronic pain that some CAM treatments address — which drugs don't," says Russell Portenoy, MD, chair of the department of pain medicine and palliative care at Beth Israel Medical Center in New York City. "It's about learning how to use all of your resources to function better."[3]

In recent years, the medical community has begun to investigate and support the role of therapies such as biofeedback and meditation in pain control.

In recent years, the medical community has begun to investigate and support the role of therapies such as biofeedback and meditation in pain control. Research shows that pain is very complex, traveling along two pathways from its originating source back to the brain. One is the sensory pathway that transmits the physical sensation, and the other is the emotional pathway that goes from the injury to the amygdala and the anterior cingulate cortex — areas of the brain that process emotion. In an article published in *Health* magazine, Dr. Natalia Morone, assistant professor of general internal medicine at the University of Pittsburgh School of Medicine, says: "You may not be aware of it, but you're having a negative emotional reaction to chronic pain, as well as a physical reaction."

While still considered controversial, the mind-body connection to illness is becoming more accepted. In a 2005 study, researchers at Stanford University in Palo Alto, Calif., used functional magnetic resonance imaging (fMRI), which measures activity in different areas of the brain, to see whether subjects could learn to control a brain region involved in pain as a tool for altering pain perception. During the study, participants with pain-producing injuries were asked to do things that they knew increased their pain, while using positive and negative

imagery. One participant imagined her pain like a flame that would flare and increase as the pain escalated, and then minimize as the pain ebbed. After the test, the participant learned that she had been able to produce a 30 percent to 40 percent reduction in her overall pain.[4]

Biofeedback is another technique that uses the mind to control bodily functions. In a biofeedback session, sensors attached to the body are connected to a monitoring device that measures body functions such as breathing, perspiration, skin temperature, blood pressure and heartbeat. When patients relax and breathe deeply, heart rates dip in response. During the session, patients are able to observe the changing numbers on the monitors and make a connection between their conscious actions and unconscious reactions in the sympathetic nervous system. Because chronic pain or illness is stressful, it can create a vicious cycle of pain, stress and increased pain. Biofeedback can break that cycle and give patients a much-needed sense of control. Kenneth Holroyd, PhD, professor of health psychology at Ohio University, in Athens, Ohio, said this about the effects of biofeedback on migraines: "Through trial and error, you can learn to prevent migraines and to stop migraines when they begin to occur. You can change that physiological response through the action of your mind."[5]

Stress-Related Diseases on the Rise

Stress has become the great equalizer in modern society, affecting people from all economic, racial and social backgrounds and influencing the lifestyle and healthcare choices of people in almost every age group. According to the American Psychological Association, stress is a top health concern for U.S. teenagers, especially those in grades 9 through 12. Psychologists say that if teens don't learn healthy ways to manage stress, it could have serious long-term health implications for future generations.

Common alternative therapies for stress management include yoga, acupuncture, meditation and mindful breathing exercises.

Stress can come from external sources such as work and employment issues, relationship problems and financial pressures, and internal sources such as psychological tendencies and a person's individual coping skills. As the world we live in becomes increasingly stressful, stress-related illnesses are

increasing as well, and the problem is not limited to the U.S. In Britain, stress has overtaken other reasons for long-term workplace absence, outranking repetitive strain injury and medical conditions such as cancer.[6]

Stress-related illnesses can span the spectrum from mild to life-threatening. On the mild side, maladies like head and back pain, insomnia and digestive problems can be bothersome. On the more serious end, heart disease, diabetes, asthma and even Alzheimer's disease have been linked to stress. While the number of health problems related to stress can appear alarming, stress-management techniques, including many CAM therapies, often offer significant benefits. One study from Duke University Medical Center found that a stress-management program cut the chances that a heart patient would suffer a heart attack or need surgery by 74 percent.[7]

Common alternative therapies for stress management include yoga, acupuncture, meditation and mindful breathing exercises. There's also some evidence that stress management can strengthen the immune system, and that various relaxation techniques may be an effective part of an overall treatment plan for many common disorders, including high blood pressure, asthma, irritable bowel syndrome, insomnia and fibromyalgia.

Chronic Conditions and Alternative Care

Chronic conditions present a unique challenge for patients and healthcare providers. With no known cure, conditions such as lupus, fibromyalgia and diabetes must be managed rather than actually treated. Even once-fatal diseases like HIV/AIDS and cancer are increasingly becoming chronic conditions with symptoms that require management. For a patient facing the prospect of living with long-term, life-altering illness, "think-outside-of-the-box" healthcare options can become very appealing.

While various CAM therapies have proved useful in the

treatment of chronic illness, one particularly promising field of study involves the use of music therapy. Music therapy may incorporate creating music, listening to music or simply talking about music, with the goal being to relieve stress and anxiety, and improve mood and quality of life. But studies show the benefits extend beyond simply making patients feel better.

According to a review published in 2008, music therapy may help patients battle depression.[8] Researchers compared data from five previously published studies and found that participants receiving music therapy were more likely to see a decrease in depression symptoms (compared with those who did not receive music therapy). According to the review's authors, patients appeared to experience the greatest benefits when therapists used theory-based therapeutic techniques such as painting to music and improvised singing.

In yet another study, researchers found that music therapy was beneficial to those with coronary heart disease, positively impacting blood pressure, heart rate, respiratory rate and pain.[9] Music therapy also is being used to improve communication skills in children with autism.[10] "Almost all children respond to music. Music is an open sesame, and if you can use it carefully and appropriately, you can reach into that child's potential for development," says Dr. Clive Robbins of the Nordoff-Robbins Music Therapy Clinic, which uses music therapy to help handicapped children learn and to relate and communicate with others.

Neurological disorders also have responded to the therapeutic use of music-based therapies. Some reports have shown that patients with neurological disorders who cannot talk or move are often able to sing, and sometimes even dance, to music. Music therapy also can help ease the trauma of grieving, lessen depression and provide an outlet for people who are otherwise withdrawn. "I regard music therapy as a tool of great power in many neurological disorders — Parkinson's and Alzheimer's — because of its unique capacity to organize or reorganize cerebral function when it has been damaged," says Oliver Sacks, MD, professor of neurology at Albert Einstein College of Medicine, New York, and author of *Musicophilia: Tales of Music and the Brain*.

CAM and Insurance Coverage

The reality for most patients seeking CAM therapies is that few treatments are covered by health insurance plans. According to the 2007 National Health Interview Survey (NHIS), one-third of uninsured respondents younger than age 65 paid "out of pocket" for CAM. The same survey found that adults in the U.S. spend an estimated $33.9 billion out of pocket on CAM treatments annually. Of the $33.9 billion, adults spent an estimated $22 billion on self-care costs such as products, classes and materials, while the remaining $11.9 billion was spent on office visits to CAM practitioners.[11]

Private health insurance plans may offer coverage of certain CAM therapies such as chiropractic, acupuncture and massage, since these practices have become more accepted by mainstream medicine. Still, overall coverage of CAM therapies is relatively limited compared with conventional therapies. One factor is a lack of scientific evidence regarding the cost-effectiveness of CAM therapies, but as consumer interest in CAM grows, more insurance companies and managed care organizations may consider offering coverage of CAM therapies in the future. And patients who have healthcare reimbursement accounts through their employers may find that many CAM therapies are covered by these plans. ❖

The reality for most patients seeking CAM therapies is that few treatments are covered by health insurance plans.

TRUDY MITSCHANG *is a staff writer for* BioSupply Trends Quarterly *magazine.*

References

1. National Center for Complementary and Alternative Medicine. 2007 Statistics on CAM Use in the United States. Accessed at nccam.nih.gov/news/camstats/2007.
2. Beyond Chronic Pain. Current Statistics on Chronic Pain. Accessed at www.beyondchronicpain.com/site/media/currentStatisticsOnChronicPain.php.
3. Woman's Day. 6 Alternative Treatments for Chronic Pain. Accessed at www.womansday.com/health-fitness/conditions-diseases/6-alternative-treatments-for-chronic-pain-115886.
4. Health. How the Mind Controls Pain. Accessed at www.health.com/health/condition-article/0,,20189613,00.html.
5. Health. 3 Ways Biofeedback Helps Patients Control Chronic Pain. Accessed at www.health.com/health/condition-article/0,,20189539_2,00.html.
6. The Guardian. Stress Now Commonest Cause of Long-Term Sick Leave — Report. Accessed at www.guardian.co.uk/business/2011/oct/05/stress-commonest-cause-long-term-sick-leave.
7. Next Avenue. Stress and Its Adverse Effect on the Human Heart. Accessed at www.nextavenue.org/article/2012-05/stress-and-its-adverse-effect-human-heart.
8. Marratos, AS, Gold, C, Wang, X, and Crawford, MJ. Music Therapy for Depression. *Cochrane Database of Systematic Reviews*, 2008 23;(1):CD004517. Accessed at altmedicine.about.com/od/musicsoundtherapy/a/benefits_music_therapy.htm.
9. Bradt, J, Dileo, C. Music for Stress and Anxiety Reduction in Coronary Heart Disease Patients. *Cochrane Database of Systematic Reviews*, 2009 15;(2):CD006577. Accessed at altmedicine.about.com/od/musicsoundtherapy/a/benefits_music_therapy.htm.
10. Gold, C, Wigram, T, Elefant C. Music Therapy for Autistic Spectrum Disorder. *Cochrane Database of Systematic Reviews*, 2006 19;(2):CD004381. Accessed at altmedicine.about.com/od/musicsoundtherapy/a/benefits_music_therapy.htm.
11. National Center for Complementary and Alternative Medicine. Paying for CAM Treatment. Accessed at nccam.nih.gov/health/financial.

Grifols Albumin

Broad selection and reliable supply

Albutein® 5%/25%
Albumin (Human) U.S.P.

Plasbumin®-5/25
Albumin (Human) USP

5% Albumin Products

Product Name	Size	NDC Number
Plasbumin® - 5	50 mL (2.5 grams)	13533-685-20
Plasbumin® - 5	250 mL (12.5 grams)	13533-685-25
Albutein® 5%	250 mL (12.5 grams)	68516-5214-1
Albutein® 5%	500 mL (25.0 grams)	68516-5214-2

25% Albumin Products

Product Name	Size	NDC Number
Plasbumin® - 25	20 mL (5.0 grams)	13533-684-16
Plasbumin® - 25	50 mL (12.5 grams)	13533-684-20
Albutein® 25%	50 mL (12.5 grams)	68516-5216-1
Albutein® 25%	100 mL (25.0 grams)	68516-5216-2
Plasbumin® - 25	100 mL (25.0 grams)	13533-684-71

Available from FFF Enterprises

Grifols' albumin is available through FFF Enterprises at **1.800.843.7477** or by contacting Grifols Customer Service at **1.800.243.4153** or **customer.service@grifols.com**.

Grifols Biologicals, Inc.
5555 Valley Boulevard, Los Angeles, California 90032 USA
www.grifols.com

Grifols: A Reliable Supplier of Plasma Protein Therapies

Vertical integration with geographic diversity helps ensure uninterrupted production of albumin

- The largest network of source plasma donor centers in the industry [1] enables Grifols to collect 100% of the plasma needed to produce our albumin and other plasma protein therapies
- Two Grifols-owned state-of-the-art plasma testing facilities
- The largest plasma protein fractionation capacity in the world [1]
- Four global plasma protein manufacturing facilities

State-of-the-art production processes

Sterile Albumin Filling Facility, Los Angeles, CA, FDA approved in December 2009

Grifols Fractionation Facility, Los Angeles, CA

Grifols Fractionation Facility, Clayton, NC

1. Marketing Research Bureau data, July 2011

GRIFOLS

Autoimmune Disease: Exploring Treatment Options

With the rising rates of autoimmune disease, the quest is on to research and develop new medicines to treat patients who often present with multiple disorders.

By Ronale Tucker Rhodes, MS

A decade ago, no one talked much about autoimmune disease; it simply wasn't well-known, and many believed that some of the autoimmune diseases recognized today were "all in one's head." That's no longer the case. Autoimmune disease is now discussed in all circles of life because it afflicts some 23 million Americans. Even so, fewer than 13 percent of people can actually name an autoimmune disease.[1] It's an evolving area of medicine that has scientists puzzled — not just about what causes it but how to prevent it,

because once it starts, autoimmune activity can be especially difficult to stop. The good news is that scientists are persevering, and many new discoveries are being made, resulting in some promising new treatments.

The Autoimmune Disease Puzzle

An autoimmune disease is a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissues. This occurs when the body can no longer tell the difference between healthy body tissues and antigens.[2] Recently, doctors have begun to differentiate between autoimmune diseases and autoinflammatory disorders. Both of them attack the body itself and cause inflammation, but autoimmune diseases target antigens in specific cells and tissues (such as the joints in arthritis) while autoinflammatory disorders launch a less-specific attack against the body (such as in familial Mediterranean fever and type 2 diabetes).[1] For the purposes of this article, the term autoimmune disease is used to refer to both types.

Autoimmune diseases can be broken down into two groups: organ-specific and non-organ-specific. Examples of organ-specific disorders are Addison's disease, celiac disease, Crohn's disease (see the Patient Profile on page 58), multiple sclerosis and type 1 diabetes. Examples of non-organ-specific disorders are juvenile dermatomyositis, lupus and scleroderma.[1]

More than 80 different types of autoimmune diseases have been identified, yet their cause is unknown. It is theorized that they are caused by either genetics, triggers, hormonal factors or a combination of the three. It's possible that susceptibility to the disease, rather than the disease itself, is inherited. And in those who are susceptible, a trigger may cause the disease to develop. Triggers can include a substance in the body that is normally confined to a specific area that is released into the bloodstream (such as a blow to the eye that releases fluid from the eyeball into the bloodstream); a normal body substance that is altered by a virus, drug, sunlight or radiation; a foreign substance that resembles a natural body substance that enters the body; or cells that control antibody production such as B lymphocytes. And, because autoimmune diseases occur more often in women, it is suspected that hormones may be a factor.[3]

More than 80 different types of autoimmune diseases have been identified, yet their cause is unknown.

Some of the more common autoimmune diseases and what they attack include autoimmune hemolytic anemia (red blood cells), bullous pemphigoid (skin), Goodpasture's syndrome (lungs and kidneys), Graves' disease (thyroid gland), Hashimoto's thyroiditis (thyroid gland), multiple sclerosis (brain and spinal cord), myasthenia gravis (neuromuscular junction), pemphigus (skin), pernicious anemia (cells in the stomach lining), rheumatoid arthritis (joints or other tissues), systemic lupus erythematosus (joints, kidneys, skin, lungs, heart, brain and blood cells), type 1 diabetes mellitus (beta cells of the pancreas) and vasculitis (blood vessels).[3]

Who is at greatest risk of developing an autoimmune disease depends upon which disease it is. However, researchers have found that females are almost three times as likely as males to have an autoimmune disease, with adolescent girls and young women being at greatest risk. Most autoimmune diseases affect younger and middle-aged people, and a family history of

autoimmune disease puts an individual at higher risk. Some reports show that people of different races are more prone to having certain autoimmune diseases. For example, African-Americans are more likely than Caucasians to develop lupus and scleroderma, but the opposite is true for type 1 diabetes and multiple sclerosis (MS). In addition, it is common for individuals who have one autoimmune disease to develop others.[1]

Treatment Options

Because there is yet no proven cure for autoimmune disease, the only hope is treatment. Treatment options have one of three goals: to relieve symptoms, preserve organ function or target disease mechanisms. Relieving symptoms may involve medication or surgery. When organs are threatened, drugs can be used to prevent damage such as drugs to control an inflamed kidney in people with lupus or insulin injections to regulate blood sugar in people with diabetes.[4]

Drugs can target how the disease works, thereby suppressing the immune systems, which reduces inflammation. WebMD.com lists 46 common drugs to treat autoimmune disease. Steroids have been the cornerstone of drug treatment. However, steroids act nonselectively, resulting in increased susceptibility to infections and decreased cancer immunosurveillance. There also are side effects such as hypertension, dyslipidemia, hyperglycemia, peptic ulcers, lipodystrophy, moon face, and liver and kidney injury. And, they can interact with other medicines and affect their metabolism and action.[5]

Because there is yet no proven cure for autoimmune diseases, the only hope is treatment.

Intravenous immune globulin (IVIG) has been found to be useful in treating several autoimmune diseases, especially autoimmune neuropathies such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and IgM paraproteinemic neuropathy. IVIG is currently approved by the U.S. Food and Drug Administration (FDA) to treat CIDP and MMN. Its anti-inflammatory effect is believed to modulate production of pro-inflammatory cytokines that attract and stimulate cytotoxic T cells, macrophages and other toxic inflammatory mediators, while upregulating anti-inflammatory cytokines. In addition, by interfering with inappropriate complement activation and scavenging active complement components, IVIG acts to prevent formation of the membrane attack complex (MAC) that directly causes tissue damage.[6]

In 2011, the FDA approved the first new treatment for lupus in five decades. Benlysta (belimumab) is used to treat patients with active, autoantibody-positive lupus (systemic lupus erythematosus) who are receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives and nonsteroidal anti-inflammatory drugs. It is delivered directly into a vein (intravenous infusion) in a physician's office or hospital setting, and it is the first inhibitor designed to target the B-lymphocyte stimulator (BLyS) protein, which may reduce the number of abnormal B cells thought to be a problem in lupus. However, clinical trials show that the drug does not appear to work in African-Americans.[7]

Research for Treatment

Scientists from across the globe are working hard to find new ways to better treat autoimmune diseases. In Australia, researchers have discovered that an injection can help regulate the body's natural immune response. This is unlike how current treatments work. Rather than focusing on preventing "bad" cells, this injection increases good regulating cells in the body. The researchers injected cloned interleukin-5 (II-5 cytokine) into rats with Guillain-Barré syndrome and found that the rodents recovered considerably faster; the rats also did not become ill if treated with the injection as a precaution.[8]

Another vaccine, developed by Israeli scientists from the Weizmann Institute of Science, tricks the immune system into attacking one of the players in the autoimmune process, an enzyme known as MMP9. When working properly, this enzyme plays an important role in mobilizing cells and healing wounds; when it dysfunctions, it can aid and abet autoimmune disease, as well as cancer metastasis. The vaccine uses a smart synthetic molecule, which artificially mimics the functional metal zinc-histidine complex at the heart of the MMP enzyme, and tricks the immune system into creating antibodies, named metallobodies, that block the enzyme at the active site. When mice were treated with metallobodies, various symptoms associated with autoimmune disease, including diarrhea, weight loss and tissue destruction, were significantly prevented. And, it was effective in both preventive and therapeutic mode of application. "Our antibodies will mimic the natural protective process in vivo," says Professor Irit Sagi at the Weizmann Institute. "In this respect, the new drug may be more efficient than other therapeutics such as steroids."[9]

Researchers at the La Jolla Institute for Allergy & Immunology say their findings may bolster the possibility of developing a vaccine that blocks the inflammatory response that causes heart disease, which they believe is an autoimmune

disease. They found a specific cell that is responsible for the attack on the artery wall using the deadly combination of inflammation and plaque. These CD4 T cells attack the wall when they sense a buildup of plaque. This discovery, say the researchers, brings them steps closer to developing a vaccine that could stop that reaction by making antigen-presenting cells unrecognizable, which would then stop the inflammation response that might lead to a heart attack.[10]

A 2,000-year-old Chinese herbal remedy known as chang shan, a root extract of a specific type of Himalayan hydrangea plant known as hortensia, also may be effective in treating autoimmune diseases, according to results of a new investigation by researchers from Massachusetts General Hospital, the Harvard School of Dental Medicine and elsewhere. The researchers evaluated the active components of chang shan and found that one component, halofuginone (HF), blocks the development of T helper 17 (Th17) cells, highly inflammatory cells that appear to play a primary role in the development of autoimmune diseases such as multiple sclerosis, psoriasis, juvenile diabetes, rheumatoid arthritis and Crohn's disease. Building upon previous research that identified how HF activates the body's amino acid response (AAR) pathway, the researchers identified that HF specifically targets and blocks the tRNA synthetase EPRS enzyme, which is responsible for incorporating proline, an amino acid, into cells. The blockage tells the AAR not to activate the inflammatory immune responses associated with autoimmune diseases.[11]

There are many other promising new treatments for autoimmune disorders. One is the development of a new compound called Bz-423, which interferes with the ability of diseased white blood cells known as T cells to feed themselves. Developed by Lycera, Bz-423 slows down the cell's ability to manufacture adenosine triphosphate, the molecule responsible for transporting energy between cells, by binding itself to the enzyme underlying the molecule. Lycera is setting its sights on creating orally delivered drugs based on Bz-423. Another is a small-molecule oral pill that interacts with novel protein targets called chemokines and chemokine receptors. Developed by ChemoCentryx, the pill limits the activity of the chemokine system to disrupt a vital process that leads to autoimmunity, without shutting down essential immune defense functions.[12]

Understanding the role of cells in autoimmune disease is where research is focused. At the National Institutes of Health (NIH), researchers have found evidence that a unique type of immune cell contributes to MS, which helps to define the effects of one of the newest drugs under investigation for treating MS — daclizumab — and could lead to a new class of drugs for treating MS and other autoimmune diseases. Their study shows that one effect of daclizumab is to thin the ranks for lymphoid tissue inducer (LTi) cells. In the study of MS patients participating in clinical trials of daclizumab, the number of LTi cells was elevated in patients not receiving daclizumab compared with those on the drug. Patients receiving daclizumab also had reduced signs of inflammation in the cerebrospinal fluid that surrounds the brain. In addition, daclizumab appears to steer the body away from producing LTi cells in favor of another type of cell that counteracts autoimmunity.[13]

Understanding the role of cells in autoimmune diseases is where research is focused.

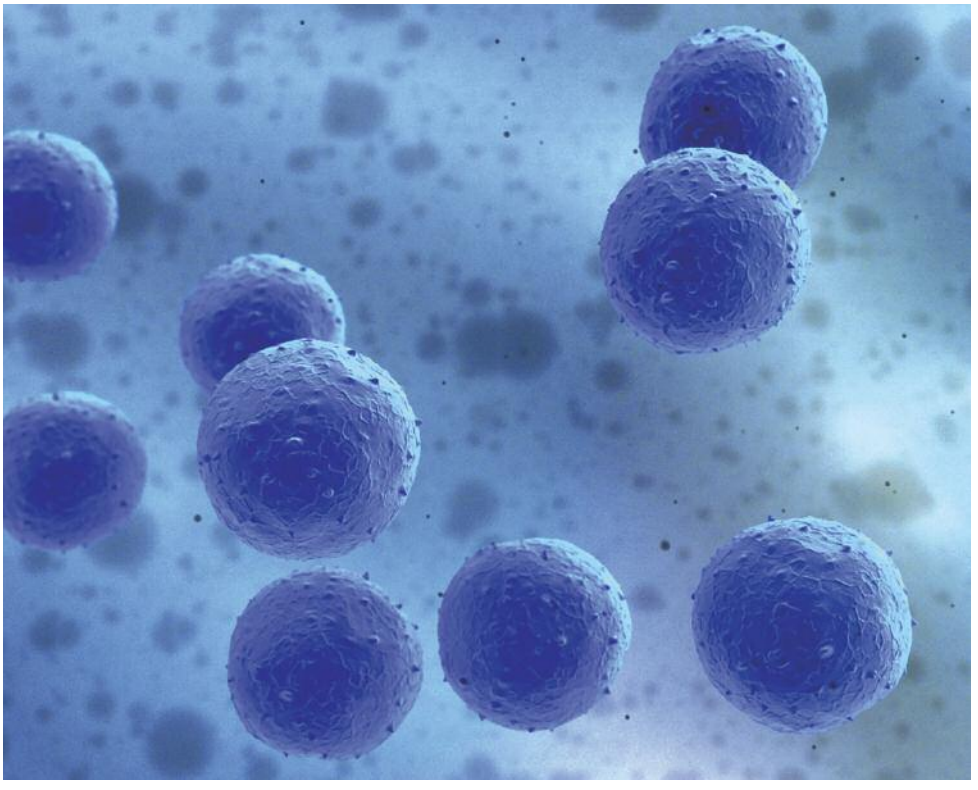
Another cell discovery has been made by researchers at the Department of Pathology and Molecular Medicine at McMaster University in Ontario, Canada. They found a molecule normally used by the body to prevent unnecessary immune reactions could be the key to create an entirely new set of treatments for autoimmune disease. The molecule, alphavbeta6, normally keeps the immune system from overreacting when food passes through the body. The researchers noticed that mice's intestines secreted alphavbeta6 when absorbing food, which induced their bodies to produce immune-tolerant cells to ensure that the food did not cause an excessive immune reaction. The researchers then generated alphavbeta6 using cultured intestinal cells and found that both could be used to generate the immune-tolerant cells needed to reduce or eliminate out-of-control immune reactions. "Our findings have the potential to repair the compromised immune-tolerant system so as to lead the body's immune system to 'correct' the ongoing pathological conditions by itself," said Ping-Chang Yang, a researcher involved in the study.[14]

One emerging field of study that is focusing on autoimmune disease is bioenergetics, the science of manipulating the way cells create, store and consume energy. The University of Colorado at Colorado Springs recently established an Institute of Bioenergetics and Immunology.[12]

Research for a Cure

Could there be hope for a cure rather than just treatment? Some studies suggest a cure may be possible.

While there is a lot of debate, as well as risk, surrounding worm therapy, there are anecdotal reports of it successfully curing autoimmune diseases, as well as one study that showed short-term success. Worm therapy, or helminthic therapy, involves being infected with microscopic hookworm larvae.



The therapy is consistent with the hygiene hypothesis, the theory that the organisms we consider harmful today were protecting our immune systems before modern medicine. In fact, prior to the 20th century, autoimmune diseases like Crohn's, MS and lupus, as well as asthma and allergies, were virtually nonexistent.

Jasper Lawrence, owner of Autoimmune Therapies and moderator of the Yahoo group of helminthic therapy, infected himself with Necator Americanus hookworms after suffering for years with allergies and asthma. Lawrence claims the therapy cured him. Others have had similar success in being cured of other diseases, including Crohn's disease. While the therapy is controversial, Dr. Joel Weinstock, professor and director of gastroenterology at Tufts Medical Center in Boston, has found that parasitic worms have a calming effect on their hosts' immune systems. Applying what he learned to the hygiene hypothesis, he and his colleagues began testing helminths in mice with asthma, type 1 diabetes, MS and inflammatory bowel disease, and they got better. Thereafter, they began a round of human trials in which they used Trichuris suis, or pig parasite, which can stay alive only for a few weeks. The results were published, and 23 out of 29 patients with Crohn's went into remission. Weinstock believes that a worm-based pill may one day be available. Indeed, similar studies are being conducted all over the world.[15]

One such study, being prepared by Coronado Biosciences, is a trial of 220 people with Crohn's disease that will test the drug trichuris suis ova (TSO), which is a pill that consists of the parasite eggs from the excrement of pigs suspended in a tablespoon of saline solution. Participants will receive a dose of 7,500 eggs or a placebo every two weeks for 12 weeks. While the pill does come with a few side effects such as gastrointestinal discomfort, researchers say that the side effects normally go away after the first two doses. The company's European partner, Dr. Falk Pharma GmbH, a German company, is currently in the midst of a mid-stage trial of TSO.

In a more conventional study of a handful of patients, researchers used a tuberculosis vaccine invented a century ago as an experimental cure for type 1 diabetes. While this was an early-stage trial, if the findings hold up, they would mean the generic bacillus Calmette-Guerin (BCG) vaccine in use since 1921 can regenerate insulin-secreting cells in the pancreas that, when lost, cause the disease. In type 1 diabetes, the body's immune system destroys insulin-producing "islet" cells in the pancreas. "We think we're seeing early evidence of effectiveness," says immunology researcher Denise Faustman of Massachusetts General Hospital, who led the trial. "We found that even low doses of the vaccine could transiently reverse type 1 diabetes, and this was in patients who have had the disease for 15 years." The effect, however, lasted for only approximately one week. And, other diabetes experts have expressed doubts about the effectiveness of the vaccine.[16]

Perhaps one of the more promising studies was conducted by researchers at Johns Hopkins University who have developed a technique that reboots the immune system by using a new approach to using stem cells. In the past, researchers focused on ways to destroy the disease-causing lymphocytes that cause autoimmunity and replace them with normal ones. To do this, stem cells were harvested before giving the patients high doses of cyclophosphamide, a chemotherapeutic drug, and then the stem cells were returned after chemotherapy. But, patients who go into remission after this procedure usually

relapse. "Stem cells contain an enzyme, called aldehyde dehydrogenase, which detoxifies cyclophosphamide," says Robert A. Brodsky, MD, assistant professor of oncology and medicine at Johns Hopkins University School of Medicine. "Like most blood cells, lymphocytes have very low levels of this enzyme, so cyclophosphamide destroys them but not the stem cells. That means it is not necessary to do a transplant to preserve the stem cells. Studies have shown that after chemotherapy — as the stem cells turn into the specialized blood cells that have been destroyed — those that become lymphocytes are normal and do not attack the body. The immune system has been repaired."

The researchers first tried this procedure with aplastic anemia patients. Seven out of the first 10 patients treated have remained disease-free for 10 years, and in some cases, more than 20 years. The system was later tried with 27 other patients with autoimmune disease, the majority of whom were lupus patients. "Most are still in remission, and some are off medications two and three years later," says Dr. Brodsky. "All of the patients we've studied have, at the very worst, remained stable. Virtually all have had major reductions in their immunosuppression medications." However, Brodsky cautions that before this procedure can be called a cure for autoimmune diseases, the patients must remain disease-free for 10 or more years.[17]

Many institutes, including the NIH, are dedicated to supporting research and promoting progress toward conquering autoimmune diseases.

An Uncertain Future

Much more research is being conducted about autoimmune disease treatments and cures than what is discussed in this article. Many institutes, including the NIH, are dedicated to supporting research and promoting progress toward conquering autoimmune diseases. As former director of the NIH Elias A. Zerhouni, MD, states in the organization's 2005 report titled *Progress in Autoimmune Diseases Research*,[18] "without a cure, patients face a lifetime of illness and treatment." And, without effective treatment or a cure, "they often endure debilitating symptoms, loss of organ function, reduced productivity at work and high medical expenses." Clearly, he says, "more needs to be learned about the genetic and environmental factors contributing to these diseases to be able to develop effective prevention strategies that arrest the autoimmune process before it can irreversibly damage the body."

In August, U.S. Rep. Marie Buerkle of New York introduced legislation to increase awareness and education about autoimmune diseases. H.R. 6218, The Mary Colella Autoimmune Disease Awareness Act of 2012, will require an assessment of national progress on autoimmune disease research and an update of the national strategic plan and recommendations that can be used to develop a national curriculum on autoimmune diseases. ❖

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

References

1. Boston Children's Hospital. Autoimmune Diseases. Accessed at www.childrenshospital.org/az/Site614/mainpageS614P1.html.
2. American Accreditation Healthcare Commission. Autoimmune Disorders. *The New York Times* Health Guide. Accessed at health.nytimes.com/health/guides/disease/autoimmune-disorders/overview.html?WT.z_gsac=1.
3. Autoimmune Disorders. *The Merck Manual Home Health Handbook*. Accessed at www.merckmanuals.com/home/immune_disorders/autoimmune_disorders/autoimmune_disorders.html.
4. MedTV. Autoimmune Disease Treatment. Accessed at diseases.emedtv.com/autoimmune-diseases/autoimmune-disease-treatment.html.
5. Wikipedia. Immunosuppressant Drug. Accessed at en.wikipedia.org/wiki/Immunosuppressive_drug.
6. Berman, K. IVIG: At the Intersection of Immunology and Clinical Research. *BioSupply Trends Quarterly*, January 2010. Accessed at www.epaperflip.com/aglaia/viewer.aspx?docid=a77cc21c6d7448a2b6febcdbdb15363e.
7. U.S. Food and Drug Administration. FDA Approves Benlysta to Treat Lupus. Press release, Mar. 9, 2011. Accessed at www.fda.gov/newsevents/newsroom/pressAnnouncements/ucm246489.htm.
8. MedicalNewsToday. Autoimmune Disease Treatment with New Injection, Jun. 5, 2012. Accessed at www.medicalnewstoday.com/articles/246211.php.
9. Gerrard, N. New Vaccine Tested Against Autoimmune Diseases. NoCamels, Jan. 24, 2012. Accessed at nocamels.com/2012/01/new-vaccine-tested-against-autoimmune-diseases.
10. Besant, A. Heart Disease Vaccine May Be on the Horizon, Says New Study. *GlobalPost*, Aug. 14, 2012. Accessed at www.globalpost.com/dispatch/news/health/120814/heart-disease-vaccine-may-be-the-horizon-says-new-study.
11. Benson, J. 2,000-Year Old Chinese Herbal Remedy Could Be Used to Treat Autoimmune Disorders, Harvard Scientists Find. *Natural News*, Apr. 24, 2012. Accessed at www.naturalnews.com/035661_Chinese_medicine_autoimmune_disorders_herbs.html.
12. Lee, T. Lycera Plows Ahead with Drugs to Treat Autoimmune Disorders. xconomy, Feb. 24, 2011. Accessed at www.xconomy.com/detroit/2011/02/24/lycera-plows-ahead-with-drugs-to-treat-autoimmune-disorders/.
13. National Institutes of Health. NIH Researchers Implicate Unique Cell Type in Multiple Sclerosis. Press release, Aug. 1, 2012. Accessed at www.nih.gov/news/health/aug2012/ninds-01.htm.
14. Science Daily. 'Master Key' to Unlock New Treatments for Autoimmune Disorders Discovered, Oct. 1, 2011. Accessed at www.sciencedaily.com/releases/2011/09/110929122858.htm.
15. Doyle, JR. Parasitic Worms: A Retro Cure for Autoimmune Disease? FoxNews.com, Oct. 6, 2010. Accessed at www.foxnews.com/health/2010/10/04/parasitic-worms-cure-autoimmune-diseases.
16. Begley, S. Tuberculosis Vaccine Used in Controversial Type-1 Diabetes "Cure." *The Huffington Post*, Aug. 8, 2012. Accessed at www.huffingtonpost.com/2012/08/09/tuberculosis-vaccine-diabetes-type-1-tb_n_1757798.html.
17. American Autoimmune Related Diseases Association Inc. "Rebooting" — A Promise for Autoimmune Diseases? Accessed at www.aarda.org/infocus_article.php?ID=11.
18. National Institutes of Health The Autoimmune Diseases Coordinating Committee. Progress in Autoimmune Diseases Research. Report to Congress, 2005. Accessed at www.niaid.nih.gov/topics/autoimmune/documents/adccfinal.pdf.

An Update on Meningitis

By Jim Trageser

While the incidence of meningitis is relatively low in the U.S., this dangerous disease can be lethal. Fortunately, preventive vaccines are available.

In the United States and other developed nations, bacterial meningitis is increasingly being viewed as an "historical" disease — a disease consigned to the history books. This is due to the availability of vaccines combined with relatively low instances of infection.

But unlike polio or Hansen's disease (leprosy), nearly all new cases of which are brought to the United States from abroad, bacterial meningitis (primarily meningococcal meningitis) remains endemic to this country. And while the incidence rate is low (ranging from 900 to 3,000 cases of

meningococcal meningitis infections per year), bacterial meningitis remains a life-threatening disease, one that claims several hundred lives annually.[1]

Around the world, meningitis is an even more serious health problem. In Brazil, sub-Saharan Africa and parts of India, infection rates are five times greater than in the U.S. and Europe. And, while reliable statistics are not always available, rates of up to 800 per 100,000 population have been reported — compared to rates of five per 100,000 or fewer in the developed world.[2]

Not only is it a challenge to effectively diagnose and treat meningitis, but the various types are symptomatically indistinguishable from one another. And since the treatments vary widely depending on the cause of infection, an accurate diagnosis is critical. Only a culture of cerebrospinal fluid can confirm the cause of the meningitis infection.

While viral meningitis is typically less dangerous than bacterial, the quickly developing nature of a bacterial infection (often measured in hours) and its lethal potential indicate that all cases of meningitis should be approached at first as if caused by the meningococcus or other bacteria, since their treatment is the most time-sensitive.

What Is Meningitis?

Meningitis is the name given to any inflammation of the protective coverings of the brain and spinal column, which are known as the meninges.[3]

The Centers for Disease Control and Prevention (CDC) classifies meningitis into five categories, based on what causes the infection.[4] Viral are the most common, followed by bacterial. Fungal and parasitical infections (which can be as serious as a bacterial meningitis infection) are very rare, and even rarer are noninfectious causes, such as cancer, head injuries and some drugs.[5]

Any form of meningitis poses risks to the patient, as the swelling can cause injury to the brain and/or spinal column. Viral infections tend to run their course without treatment and without serious long-term impacts on the patient. But the more dangerous forms (most typically meningococcal meningitis) may lead to brain damage, hearing loss and even severe infection of limbs resulting in amputation.[6]

Symptoms of Meningitis

In its early stages, any form of meningitis can manifest similarly to flu; Fever, nausea and vomiting, and headache all are common symptoms. It is possible to distinguish between meningitis and flu if the patient presents with symptoms of confusion and stiff neck, or a sudden sensitivity to light.[6]

Treating Meningitis

When meningitis is suspected, the CDC recommends immediate testing of the cerebrospinal fluid to determine the cause. The severity, and even potential fatality, of the infection can be lowered through timely, effective treatment.

As mentioned, most cases of viral meningitis run their course in a few weeks without intervention. The typical treatment for viral meningitis is bed rest and fluids for seven to 10 days.

Depending on the specific virus (enteroviruses and herpes simplex are the two most common),[6] antivirals can be introduced in rare situations to help fight a severe infection. While less serious than other forms and rarely life-threatening, viral meningitis typically takes longer to recover from — with headaches, memory loss and fatigue often lasting months and sometimes even longer following a severe case.[7]

Bacterial meningitis remains a life-threatening disease, one that claims several hundred lives annually.

Although fungal and parasitical sources of meningitis can be as deadly as bacterial meningitis, they also are extremely rare. The CDC reports that effective treatments with antifungals are available;[8] however, amoeba-caused meningitis is not currently treatable and is nearly always fatal.[9]

For bacterial meningitis, the antibiotics treatment will depend on the specific bacteria causing the infection, as determined by the cerebrospinal fluid culture. According to the CDC, the type of bacteria causing meningitis is associated with the age of the patient (although exceptions are common). With newborns, the most common causes are Group B Streptococcus, Escherichia coli and Listeria monocytogenes. For infants and children, they are Streptococcus pneumoniae, Neisseria meningitidis (meningococcus) and Haemophilus influenzae type b. Adolescents and young adults are most susceptible to Neisseria meningitidis (meningococcus) and Streptococcus pneumoniae. The elderly are most prone to infection from Streptococcus pneumoniae, Neisseria meningitidis (meningococcus) and Listeria monocytogenes.

Preventing Meningitis

While effective treatments for bacterial meningitis are widely available, the CDC still recommends inoculation as the best approach.[10]

There are effective antibiotics to treat the various bacteria that can cause meningitis, but there also are three different vaccines available to help prevent most cases of bacterial meningitis. Neisseria meningitidis (meningococcus), Streptococcus pneumoniae (pneumococcus) and Haemophilus influenzae type b (Hib) all have vaccines available to prevent infection.[11]

There are three different vaccines available to help prevent most cases of bacterial meningitis.

The Hib vaccine is already part of the normal childhood regimen of inoculations.[11] But, the pneumococcal conjugate vaccine also is recommended by the CDC for all children, as well as for the elderly.[12]

For the meningococcal bacteria, there are currently two vaccines available in the United States: MCV4 and MPSV4. The CDC recommends that all children receive one of these vaccines between ages 11 and 12, as well as a booster at age 16.

Studies show that young people living in close proximity are at higher risk of contracting bacterial meningitis than the population at large. Therefore, many colleges and universities now require proof of a recent booster for admission. In addition, military recruits are advised to receive an immunization or booster, as barracks are not much different from dorm rooms when it comes to pooling bacteria among a population.

Those traveling to areas of the world where meningococcal meningitis is prevalent should also receive an inoculation or booster.

Certain high-risk infants also may be recommended for vaccination.[13] In addition, the chicken pox and measles, mumps and rubella (MMR) vaccines will help prevent infection by several of the viruses that can cause meningitis.[14]

To prevent viral meningitis, hygiene is a key factor. Washing one's hands with hot water and soap can kill many of the viruses that can cause meningitis. Particularly important is paying attention to hygiene when changing diapers, before and after meals, and when using the bathroom.

The Importance of Vaccination

The CDC, the American Medical Association[15] and private patient-support organizations such as the National Meningitis Association (United States) and the Meningitis Trust (United Kingdom) all advocate for the importance of vaccinations, and they point out that vaccinations are highly tested and have established records of safety.

With the recent push-back against vaccinations from some parents (often influenced by conspiracy-theory advocates), it can oftentimes be a challenge for pediatricians to convince parents to inoculate their children with all the recommended vaccines — particularly those to prevent a disease like meningitis with a low rate of occurrence in this country.

Therefore, it is important that parents realize how dangerous meningitis is (particularly bacterial meningitis), and how quickly it can strike. Even among the majority of patients who survive, many will suffer for years from brain damage and its effects, including learning disabilities, speech impediments and worse. When counseling parents and young adults, it is imperative that they have all the information relevant to the risks — both of the vaccine, and of not being vaccinated. ❖

JIM TRAGESER *is an editor for a daily newspaper in the San Diego, Calif., area, and is a contributor to two reference books.*

References

1. National Meningitis Association. About Meningitis. Accessed at www.nmaus.org/meningitis.
2. Wikipedia. Meningitis Epidemiology. Accessed at en.wikipedia.org/wiki/Meningitis#Epidemiology.
3. Wikipedia. Meningitis. Accessed at en.wikipedia.org/wiki/Meningitis.
4. Centers for Disease Control and Prevention. Meningitis. Accessed at www.cdc.gov/meningitis/index.html.
5. Wikipedia. Meningitis Causes. Accessed at en.wikipedia.org/wiki/Meningitis#Causes.
6. Meningitis Trust. After Meningitis. Accessed at www.meningitis-trust.org/meningitis-info/after-meningits.
7. Centers for Disease Control and Prevention. Fungal Meningitis. Accessed at www.cdc.gov/meningitis/fungal.html.
8. Centers for Disease Control and Prevention. Parasitic Meningitis. Accessed at www.cdc.gov/meningitis/parasitic.html.
9. Centers for Disease Control and Prevention. Bacterial Meningitis. Accessed at www.cdc.gov/meningitis/bacterial.html.
10. Centers for Disease Control and Prevention. Bacterial Meningitis Prevention. Accessed at www.cdc.gov/meningitis/bacterial.html#prevention.
11. Centers for Disease Control and Prevention. HiB — Fact Sheet for Parents. Accessed at www.cdc.gov/vaccines/vpd-vac/hib/fs-parents.html.
12. Centers for Disease Control and Prevention. Pneumococcal Vaccination. Accessed at www.cdc.gov/vaccines/vpd-vac/pneumo/default.htm.
13. Centers for Disease Control and Prevention. Meningococcal: Who Needs to Be Vaccinated? Accessed at www.cdc.gov/vaccines/vpd-vac/mening/who-vaccinate.htm.
14. Centers for Disease Control and Prevention. Viral Meningitis Prevention. Accessed at www.cdc.gov/meningitis/viral.html#prevention.
15. American Medical Association. Meningitis Vaccination Fact Sheet. Accessed at www.ama-assn.org/ama/pub/physician-resources/public-health/vaccination-resources/pediatric-vaccination/fact-sheet-new.page.

Alphanate®

Antihemophilic Factor/von Willebrand Factor Complex (Human)

FACTORS FOR HEALTH

The Power of FVIII/VWF Complex

Convenient Room Temperature Storage

First FVIII/VWF product in the US stable for 3 years, up to the expiration date printed, when stored at or below 77°F (25°C). Do not freeze.

Please see brief summary of Alphanate® Full Prescribing Information below.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Alphanate Antihemophilic Factor/von Willebrand Factor Complex (Human) safely and effectively. See Full Prescribing Information for Alphanate.

ALPHANATE (ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX [HUMAN])
Sterile, lyophilized powder for injection

For Intravenous Use Only

Initial U.S. Approval: 1978

INDICATIONS AND USAGE

Alphanate is an Antihemophilic Factor/von Willebrand Factor Complex (Human) indicated for:

- Control and prevention of bleeding in patients with hemophilia A.
- Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand Disease in whom desmopressin (DDAVP) is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

CONTRAINDICATIONS

- Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components.

WARNINGS AND PRECAUTIONS

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Alphanate should be discontinued, and emergency treatment should be sought.
- Development of activity-neutralizing antibodies has been detected in patients receiving FVIII containing products. Development of alloantibodies to VWF in Type 3 VWD patients have been occasionally reported in the literature.
- Thromboembolic events may be associated with AHF/VWF Complex (Human) in VWD patients, especially in the setting of known risk factors.
- Intravascular hemolysis may be associated with infusion of massive doses of AHF/VWF Complex (Human).
- Rapid administration of a FVIII concentrate may result in vasomotor reactions.
- Plasma products carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk.

ADVERSE REACTIONS

The most frequent adverse events reported with Alphanate in > 5% of patients are respiratory distress, pruritus, rash, urticaria, face edema, paresthesia, pain, fever, chills, joint pain and fatigue.

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Biologicals Inc. at 1-888-GRIFOLS (1-888-474-3657) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed.
- Labor and Delivery: No human or animal data. Use only if clearly needed.
- Nursing Mothers: No human or animal data. Use only if clearly needed.
- Pediatric Use: Clinical trials for safety and effectiveness in pediatric hemophilia A patients have not been conducted. The hemostatic efficacy of Alphanate has been studied in 20 pediatric subjects with VWD 18 years of age and under. Based on the data from a subset of these subjects, age had no effect on the pharmacokinetics of VWF:RCo.
- Geriatric Use: No human or animal data. Use only if clearly needed.

For more information: **Grifols Inc.**
Customer Service: 888 325 8579 Fax: 323 441 7968

A803-0911

Grifols Biologicals Inc.
5555 Valley Boulevard, Los Angeles, 90032 CA - USA Tel. 888-GRIFOLS (888 474 3657)
www.grifols.com

GRIFOLS
a new era begins

Infusion Environments: Comparing Costs, Safety and Privacy

By Kris McFalls and Ronale Tucker Rhodes, MS

When choosing a site of care for immune globulin therapy, each patient's unique situation needs to be considered.

Physicians who treat patients who require immunoglobulin (IG) therapy must choose the appropriate site of care. There currently are many different IG infusion environments, including the hospital, physician's office, infusion clinic and home. And, which site to choose is driven by a variety of reasons. But the chief considerations include cost, safety and privacy. In addition, patient age can be a factor; the choice made for a child or young adult may not be right for an older adult, and vice versa.

Costs

Costs related to the site of care include doctor visits, facility charges, administration fees, supplies, labs and nursing. In general, the costs of infusion in a hospital are highest, followed by slightly lower costs in a doctor's office and infusion clinic and even lower costs at home. In addition, whether the infusions are intravenous (IV) or subcutaneous (SC) influences cost. During IVIG infusions, medical supervision is required, whereas SCIG patients who self-infuse incur no infusion nursing costs. Yet, even for IVIG patients, the cost to infuse at home is less than at a healthcare site.

One of the cost considerations for IVIG patients who prefer home treatment (mostly because it reduces the expense and time of traveling to a clinical setting) is that Medicare Part B will pay only for IVIG preparation in the home for primary immune deficiency (PIDD) patients. Unless these patients are certified as homebound, nursing and supplies in the home are not covered. For indications other than PIDD, IVIG in the home can be covered under Medicare Part D, but again, supplies and nursing are not covered. Since Medicare Part D reimbursement is typically higher, some homecare companies will often bundle the cost of nursing with the cost of the IVIG product if the reimbursement rate is high enough. In addition, many HMOs don't allow for IVIG home therapy because they are not set up to accommodate it.

Overall, SCIG therapy in the home setting has a more favorable reimbursement rate than IVIG therapy. And, Medicare covers SCIG under the durable medical equipment (DME) benefit because, under the FDA approval, SCIG requires the use of a mechanical pump.

Safety

Protocol requires that patients receive at least their first infusion in a clinical setting, whether infusing subcutaneously or intravenously. However, because IVIG requires monitoring by either an infusion nurse or doctor, choices may be limited for some. Many IVIG patients can be infused safely at home, while others and their doctors may prefer the higher level of safety in a hospital or clinical setting — especially for patients at high risk of anaphylactic reaction or other issues such as myocardial infarction, brittle asthma, renal disease, etc., says Dr. Terry Harville, medical director at the Special Immunology Laboratory at the University of Arkansas for Medical Sciences.

For instance, IVIG patients have a higher risk of thrombosis because infusion is administered through the vein. This risk is further heightened by a health history of diabetes, renal dysfunction, age (65 and older), coronary artery disease, hypertension, cerebrovascular disease, hyperviscosity disorder (including multiple myeloma, macroglobulinemia and polycythemia), thrombotic events and peripheral vascular disease. In addition, any patient who has had a vascular or cardiac episode while receiving IVIG should be infused in a monitored setting.

For some patients, medical status will play a role in the site of care decision. For example, some patients have autoimmune conditions that require higher IVIG dosings that may be difficult to be delivered subcutaneously, thus necessitating IVIG in a clinical setting.

Many patients can be infused safely at home, while others and their doctors may prefer the higher level of safety in a hospital or clinical setting.

Other patients may be more likely to be noncompliant with therapy. In these instances, clinical infusions allow doctors and/or nurses to interact with patients on a frequent basis and provide a higher level of supervision for monitoring patients' overall health and response to treatment. This higher level of supervision can protect against desensitization, a lack of awareness many patients can develop when they are so adept at living with chronic disease that they become anesthetized to symptoms that may be precursors of an increased disease state or of oncoming infection. Desensitization causes patients to sometimes fail to be good historians of their disease process, which can lead to less-than-optimal treatment. However, experienced infusion nurses who have monthly contact with patients can quickly spot subtle changes in patients' health. In fact, these nurses become skilled at asking questions that help the patients become better historians of their health status.

Regardless of whether patients are being treated with IVIG or SCIG, the risk of contaminated products is the same. All IG products must meet certain criteria established by the FDA for purity and safety. Yet, because IG is derived from human plasma, risk of potentially infectious agents cannot be totally eliminated. In the U.S., however, there has never been a documented case of HIV transmitted in IG.

The final safety consideration centers on exposure to infection. Theoretically, there is a higher risk of contracting infection in a hospital or infusion clinic through exposure to other patients who may be sick.

provided at hospitals, physicians' offices and clinics.

Youth versus Adult

While home infusion offers many advantages to patients, there are reasons why it may not be the best treatment or the treatment of choice for children and young adults. Lack of compliance and insecurity about performing treatments are perhaps the biggest drawbacks when it comes to SCIG. Self-infusing can be scary and difficult, especially for young people. When short on confidence, they simply fail to infuse when needed — often without their parents' or medical providers' knowledge. Providing adequate supervision during the transition to self-treatment is key to keeping young patients confident and compliant with their therapy.

Privacy

Privacy is often an important concern for patients. In a hospital, physician's office or infusion clinic, visual privacy may be available, but rarely auditory privacy. Typically, infusion clinics consist of one large room, with multiple chairs for patients, screened by curtains. With no solid room dividers, complete privacy is not possible. In contrast, infusing in the privacy of a home offers convenience, autonomy and flexibility not found in the clinical setting.

In the end, the site of care is a decision that must be made by both physicians and their patients.

But privacy is not a concern for some. Many patients appreciate being with other patients going through the same treatment. In fact, they prefer the social opportunity

A Joint Decision

In the end, the site of care is a decision that must be made by both physicians and their patients. Physicians may feel that patients are best treated in a clinical setting due to their high risk of adverse events. On the other hand, physicians may feel that their patients are at no risk and that the home setting would offer them more convenience and privacy. Patients, on the other hand, may prefer a clinical setting because they would rather let someone else take care of them for a while and they appreciate the comfort and safety they experience in that setting. Indeed, home infusions offer many cost and privacy advantages, but there are those who prefer to keep their home a home — without the medical equipment as constant reminders of their disease.

Each patient's situation is unique, including medical history, response to treatment, compliance with therapy and lifestyle. Therefore, all factors should be weighed to make the decision that best suits the individual needs of the patient. ❖

KRIS MCFALLS *was previously the full-time patient advocate for* IG Living *magazine, written for patients who depend upon immune globulin products and their healthcare providers, and* **RONALE TUCKER RHODES**, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

Specialty solutions in Chronic Care.

Making a difference—one patient at a time.

Offering safe, convenient & reliable solutions for home infusion and critical-care products.

Immune Globulin Subcutaneous

Immune Globulin Intravenous

Coagulation Products

NuFACTOR has earned The Joint Commission's Gold Seal of Approval™

NuFACTOR®
Specialty Pharmacy

(800) 323-6832
www.NuFACTOR.com

Myths and Facts: Asthma

By Ronale Tucker Rhodes, MS

Despite the widespread belief that asthma is not serious, it's a potentially lethal illness that can be managed by understanding the facts about how to prevent and treat asthma attacks.

Chances are, everyone knows someone who has asthma. In fact, asthma is so common that most don't believe it's a serious illness. But it is. More than 25 million people in the U.S. have asthma, seven million of whom are children,[1] and an estimated 300 million people worldwide have asthma.[2] Every day, 30,000 Americans suffer an asthma attack, and each year, asthma accounts for 25 percent (two million) of all emergency room visits in the U.S. The annual national cost of asthma is estimated to be nearly $18 billion.[3] Unfortunately, asthma results in death for some — deaths that could be avoidable if the facts were understood about this potentially lethal illness.

Separating Myth from Fact

Myth: Asthma mainly affects adults.

Fact: Asthma can affect people at any age. It is more common among adult women than adult men, but it is more common among male children than female children. Asthma is the most common serious chronic disease among children and the No. 1 reason children miss school, accounting for more than 14 million total missed days of school.[3]

Myth: Asthma is not a life-threatening illness.

Fact: According to the Asthma and Allergy Foundation of America, there are approximately 4,000 deaths due to asthma each year in the U.S.[4] And, African-American women are three times more likely to be both hospitalized and die from asthma.[3]

"Asthma mortality has been increasing in recent years," said Donald R. Elton, MD, FCCP, at Lexington Pulmonary and Critical Care, Lexington, S.C. "Various experts have debated why this is so, but several facts are apparent from the available data. First, most patients who die of asthma do not die in the hospital. Most do not die suddenly and have frequently been in the midst of an exacerbation for several days."[5]

Myth: Asthma is all in people's heads.

Fact: It was once believed that asthma was caused by an emotional problem. But while emotional triggers such as stress can cause flare-ups of asthma, asthma is not a psychological condition; it is a chronic (long-term) lung disease that inflames and narrows the airways. It causes recurring periods of wheezing (a whistling sound during breathing), chest tightness, shortness of breath, and coughing that often occurs at night or early in the morning.[2]

Myth: Asthma is the same in all people.

Fact: Advances in understanding asthma have led experts to define specific types of the disease, including exercise-induced asthma, cough-variant asthma, occupational asthma and nighttime (nocturnal) asthma. Exercise-induced asthma is triggered by exercise or physical exertion. With this type of asthma, airway narrowing peaks five to 20 minutes after exercise begins, making it difficult to catch one's breath. Symptoms can include wheezing and coughing, and an asthma inhaler (bronchodilator) before exercise may be needed. With cough-variant asthma, coughing is the predominant symptom, usually triggered by respiratory infections and exercise. This type of asthma is vastly underdiagnosed and undertreated. Occupational asthma results from workplace triggers. Some common jobs associated with this type of asthma include animal breeders, farmers, hairdressers, nurses, painters and woodworkers. Most people with occupational asthma suffer from a runny nose and congestion or eye irritation; they also may have a cough instead of the typical asthma wheezing. Nocturnal asthma results in symptoms that are more pronounced during sleep because asthma is powerfully influenced by the sleep-wake cycle (circadian rhythms). These symptoms of wheezing, coughing and troubled breathing can be dangerous; most deaths related to asthma occur at night.

Individuals also differ in the severity of their asthma. In those with mild intermittent asthma, symptoms occur less than twice a week, and there are rare exacerbation or asthma attacks and infrequent nighttime asthma symptoms. Those with mild persistent asthma have symptoms more than twice a week, but less than once a day. In these people, asthma attacks affect activity, and nighttime symptoms occur more than twice a month. Moderate persistent asthma results in symptoms that occur daily, nighttime symptoms that occur more than once a week and asthma attacks that affect activity and that may last several days, requiring quick-acting asthma medication to control symptoms. Last, people with severe persistent asthma have symptoms that occur day and night, have limited activity and frequent attacks.[6]

Understanding which type of asthma an individual has is key to getting the right treatment. It's also possible that an individual does not have asthma, but rather another illness that has the same symptoms as asthma. For instance, cardiac asthma is a form of heart failure in which the symptoms mimic some of the symptoms of regular asthma. Vocal cord dysfunction also mimics asthma symptoms.[7]

There are approximately 4,000 deaths due to asthma each year in the U.S.

Myth: Asthma is caused by one's environment.

Fact: It is unknown exactly what causes asthma, but researchers believe it is caused by both genetic and environmental factors, including an inherited tendency to develop allergies (atopy), parents who have asthma, certain respiratory infections during childhood, or contact with some airborne allergens or exposure to some viral infections in infancy or in early childhood when the immune system is developing.[8]

It's common for allergies and asthma to go hand in hand. Allergic rhinitis (hay fever), which causes inflammation of the inside lining of the nose, is the most common chronic allergic disease, causing a constant runny nose, ongoing sneezing, swollen nasal passages, excess mucus, weepy eyes, a scratchy throat and, sometimes, a cough due to the constant postnasal drip.[7]

An individual whose parents don't have asthma has a 6 percent chance of having asthma. If one parent has asthma, that person has a 30 percent chance of having asthma, and if both parents have asthma, that person has a 70 percent chance of having

asthma.[6] If atopy runs in the family, exposure to irritants such as tobacco smoke might make the airways more reactive to substances in the air.[8]

There also is the hygiene hypothesis. Researchers believe that the Western lifestyle that emphasizes hygiene and sanitation has resulted in younger children no longer being exposed to the same types of environments and infections as they were in the past. Therefore, the way in which young children's immune systems develop during early childhood may increase their risk for atopy and asthma, especially in children who have close family members with one or both of these conditions. However, this hypothesis has yet to be proved.[8]

Myth: Asthma doesn't need to be diagnosed with tests.

Fact: It's important to confirm that an individual does in fact have asthma and if there are other co-existing conditions such as allergies, gastroesophageal reflux disease (GERD) or sinusitis so that a doctor can prescribe the proper medications to help manage the asthma and to prevent attacks. Asthma can be diagnosed with lung function tests, tests for allergies, blood tests and tests that measure levels of immunoglobulin E, a key antibody that is released during an allergic reaction.

Understanding which type of asthma an individual has is key to getting the right treatment.

The two most common lung function tests are spirometry and methacholine challenge tests. Spirometry is a simple breathing tests that measures how much and how fast a person can blow air out of his or her lungs to determine the amount of airway obstruction. The methacholine challenge test is performed if symptoms or the spirometry test doesn't establish an asthma diagnosis.

A chest X-ray can show whether or not something other than asthma such as bronchitis or a broken bone is causing symptoms. Other specific tests can determine whether a person has GERD, which can worsen asthma symptoms, or sinusitis, which can make asthma harder to treat and control.[9]

Myth: People with asthma should avoid exercise.

Fact: Exercise can actually help people with asthma. The key is to begin an exercise program carefully and to discuss the program with the person's physician. Asthma symptoms often can be prevented by taking medications prior to exercising.[10] The best forms of exercise for people with asthma are swimming and sports with stop-and-go activity such as baseball, football and short-term track and field rather than sports that have a lot of ongoing activity such as soccer, basketball, field hockey or long-distance running. Walking, leisure biking and hiking are also good sporting activities. And, warm-ups and cool-downs may prevent or lessen symptoms.[2]

Children should especially be encouraged to exercise. They can play, take gym class and play sports, but they also may need to take medication before they play.[11]

Myth: Medicine should be taken for asthma only when there are symptoms.

Fact: The best way to control asthma is with carefully planned treatments. The goal is to put people in control of their asthma rather than letting the asthma control them. Asthma medication is divided into two categories. Quick-relief asthma medication treats acute asthma symptoms. Controller asthma medication attempts to prevent asthma symptoms. Controller asthma medication should not be stopped when individuals feel well. When individuals are feeling well and are not experiencing symptoms or breathing problems, it is because the medicine is working. On the other hand, quick-relief medication should not be used when individuals feel well; it should be used only as needed when there are symptoms, problems breathing or as pretreatment before exercise.[11]

Which medicines are prescribed depends upon a person's age, symptoms, asthma triggers and what works best to keep the asthma under control. There are five types of long-term control medications. Inhaled corticosteroids typically take several days to weeks before they reach their maximum benefit and have a relatively low risk of side effects. Leukotriene modifiers are oral medications that relieve asthma symptoms for up to 24 hours and, in rare instances, they have been linked to psychological reactions such as agitation, aggression, hallucinations, depression and suicidal thinking. Long-acting beta agonists are inhaled medications that are intended to be taken only in combination with an inhaled corticosteroid. Research shows they may increase the risk of a severe asthma attack, and they are not to be used for an acute asthma attack. Combination inhalers contain a long-acting beta agonist along with a corticosteroid, and they also may increase the risk of a severe asthma attack. Theophylline is a daily pill that relaxes the muscles around the airways to help keep the airways open. However, it is not prescribed as often as in the past.

There are three quick-relief medications. Short-acting beta agonists can be taken using a portable, handheld inhaler or a nebulizer to rapidly ease symptoms during an asthma attack. Ipratropium (Atrovent) acts quickly to relax the airways, making it easier to breathe. And, oral and intravenous corticosteroids, which include prednisone and methylprednisolone, relieve airway inflammation caused by severe asthma. However, because these corticosteroids can cause serious side effects when used long-term, they are used only on a short-term basis.[12]

Myth: Medicines for asthma can be addictive.

Fact: Because people with asthma are dependent upon their medications to stay well and to stop attacks, many fear they will become addicted to them. However, there is no evidence of the development of addiction to asthma medications. Patients with severe asthma may become "steroid dependent" for control of their disease, but that does not represent an addiction to medication. And, in the case of systemic corticosteroids, the management of reduction and withdrawal of these agents must be closely supervised due to possible adrenal insufficiency.[13]

Myth: Alternative and complementary approaches are better for treating asthma.

Fact: The verdict is still out on whether complementary or alternative approaches to treating asthma really work and are safe. Some studies suggest that symptoms may improve with acupuncture. While there's no clear evidence as of yet, it is a relatively low-risk alternative treatment. A number of studies also have shown that people's asthma symptoms have improved with breathing exercises. And, some clinics and researchers offer breathing technique instructions as part of asthma treatment. Two breathing techniques used are Buteyko and pranayama (yoga breathing).

Herbal remedies, which have been used for thousands of years to treat lung disorders, have shown promise in research. These include butterbur, dried ivy, ginkgo extract, tylophora indica, French maritime pine bark extract (Pycnogenol), Indian frankincense (Boswellia serrata) and choline. When using herbal remedies, certain combinations of herbs may be more effective than taking one alone, and certain concerns should be considered, including the quality and dose, side effects (which can range from minor to severe) and drug interactions.

There also are some vitamins and supplements that show promise. These include antioxidants such as vitamin C, vitamin A and magnesium to boost the immune system, omega-3 fatty acids to reduce inflammation, and vitamin D.

Other treatments that either show no evidence of relieving asthma symptoms or that experts discourage include homeopathy (using very small doses of substances that cause symptoms), inspiratory muscle training, massage and chiropractic treatment, and relaxation therapy.[14]

Myth: In some people, asthma will eventually go away.

Fact: People who have asthma have asthma; they cannot grow out of it. In 50 percent of children with asthma, the condition may become inactive in the teenage years. But the symptoms may recur at any time in adulthood.[6]

Myth: Asthma is curable.

Fact: There is no cure for asthma. Even moving to a new location won't cure asthma as some people believe. After relocating, people will become sensitized to the new environment and the asthma symptoms will return with the same or even greater intensity. However, asthma can be controlled with good medical care.[6]

The best way to control asthma is with carefully planned treatments.

Dispelling the Myths Now

With the number of asthma cases on the rise, there is continued investment in a search for a cure. While many experts agree that a cure is unlikely, some also predict that the disease will afflict only a small number of people in 10 to 20 years due to significant improvements in the currently used treatments.[15] For now, however, the best way for asthma sufferers to live free from the effects of the disease is to be armed with the knowledge of how to prevent and manage it. ❖

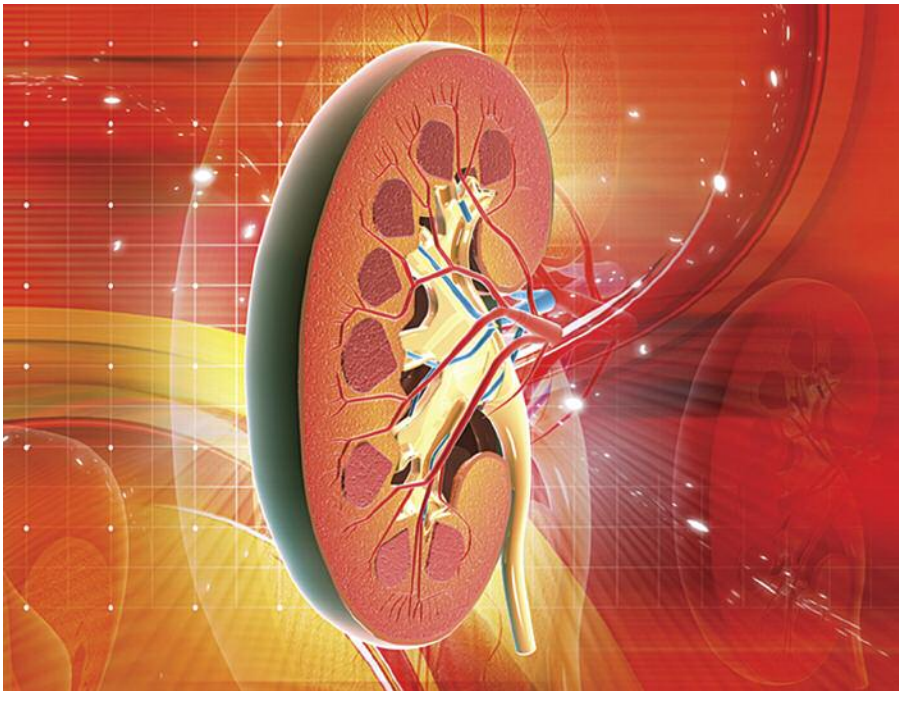
RONALE TUCKER RHODES, *MS, is the editor of* BioSupply Trends Quarterly *magazine.*

References

1. National Heart Lung and Blood Institute. What Is Asthma? Accessed at www.nhlbi.nih.gov/health/health-topics/topics/asthma.
2. American Academy of Allergy Asthma & Immunology. Asthma and Exercise: Tips to Remember. Accessed at www.aaaai.org/conditions-and-treatments/library/asthma-library/asthma-and-exercise.aspx.
3. DoSomething.org. 11 Facts About Asthma. Accessed at www.dosomething.org/tipsandtools/11-facts-about-asthma.
4. Moore, K. Why Is Asthma Life-Threatening? eHow. Accessed at www.ehow.com/facts_5712988_asthma-life-threatening_.html.
5. Elton, DR. Life Threatening Asthma. Accessed at www.lexingtonpulmonary.com/education/asthma/asthma.html.
6. MedicineNet.com. Asthma Myths. Accessed at www.medicinenet.com/script/main/art.asp?articlekey=20351.
7. WebMD. Types of Asthma. Accessed at www.webmd.com/asthma/guide/types-asthma.
8. National Heart Lung and Blood Institute. What Causes Asthma? Accessed at www.nhlbi.nih.gov/health/health-topics/topics/asthma/causes.html.
9. WebMD. Asthma Tests. Accessed at www.webmd.com/asthma/guide/diagnosing-asthma-tests.
10. American College of Allergy, Asthma & Immunology. Exercising with Allergies and Asthma. Accessed at www.acaai.org/allergist/asthma/asthma-treatment/management/Pages/exercising-with-allergies-asthma.aspx.
11. The Children's Hospital of Philadelphia. Common Myths About Asthma. Accessed at www.chop.edu/service/asthma-program/asthma-myths-and-facts.html.
12. Mayo Clinic. Asthma Treatment and Drugs. Accessed at www.mayoclinic.com/health/asthma/ds00021/dsection=treatments-and-drugs.
13. AsthmaMedicines. Are Asthma Medications Addictive? Accessed at www.asthmamedicines.org/articles/are-asthma-medications-addictive.html.
14. Mayo Clinic. Asthma Treatment: Do Complementary and Alternative Approaches Work? Accessed at www.mayoclinic.com/health/asthma-treatment/AS00032.
15. Brennan, C. Asthma — Vision of the Future. NetDoctor. Accessed at www.netdoctor.co.uk/asthmaandallergy/asthma/special_reports.htm.

Shocking: A "Newer" Hetastarch Product Is Nephrotoxic and Deadly in Severe Sepsis

By Keith Berman, MPH, MBA



OVER THE LAST four decades, 6% hydroxyethyl starch (hetastarch) products have been promoted as a less-expensive alternative to 5% human albumin for blood volume expansion. But as we are now learning from a stream of recent published evidence, for selected populations, hetastarch (HES) can come with its own price to pay — in safety.

The 450/0.7 class* of high-molecular-weight HES, which includes Hespan and Hextend, actually comprises polymers of varying sizes, mainly removed from the circulation by slow excretion through the kidneys. Special care is advised in the prescribing information for patients with impaired renal clearance[1] to minimize the risk of acute renal failure.

Because HES products also directly lower circulating factor VIII activity and von Willebrand antigen levels, their labeling recommends use "with caution" in open-heart surgeries for several decades before published retrospective case reviews[2,3,4] showed that administration of HES sharply increases the risk of excessive bleeding in relation to albumin use in typically cold, hemodiluted and anti-coagulated patients undergoing cardiopulmonary bypass surgeries. Finally in 2003, a specific warning was added to the U.S. labeling for all 6% HES products.

"Improved" Low-Molecular-Weight HES Products

It was against this backdrop that a new class of lower-molecular-weight (130/0.4*) HES products was introduced in Europe in the late 1990s, including Tetraspan 6% 130/0.4 in Ringer's acetate (B. Braun Medical) and Voluven 6% 130/0.4 in 0.9% sodium chloride injection (Fresenius Kabi). The U.S. Food and Drug Administration approved Voluven for sale in 2007, and it is currently distributed through Hospira. These "improved" HES products feature more rapid renal excretion than the older 450/0.7 products and lesser effect on coagulation function. Thus, there is reason to expect them to have a better overall adverse event risk profile compared with the older 450/0.7 HES products that still predominate in U.S. hospitals.

** "450" and "130" refer to the minimum molecular weight, and "0.4" and "0.7" refer to the degree of molar substitution of hydroxyethyl groups on the glucose units of the starch polymer.*

For years, there has been controversy over whether HES products could have deleterious effects on renal function in patients without a history of kidney disease. Similar to the instance in which excessive bleeding complications were eventually shown to be a problem specifically in cardiopulmonary bypass surgery, it turns out that the answer depends on which patient populations one looks at.

A large 2007 observational study examining a heterogeneous population of 3,147 patients across 198 European intensive care units determined that administration of HES had no influence on renal function or the subsequent need for renal replacement therapy (RRT).[5]

The long-standing "controversy" over renal toxicity actually reflects an issue of research focus.

This finding seemingly contrasted with a 2001 report by French researchers who documented an 83 percent higher risk of acute renal failure in severe sepsis or septic shock patients receiving a 200 kDa HES product than in those receiving a gelatin-based volume expander.[6]

In fact, the long-standing "controversy" over renal toxicity actually reflects an issue of research focus. The matter now appears to have been settled by two recent landmark studies, both published in *The New England Journal of Medicine*. In a 2008 study, a German team reported that 262 severe sepsis patients randomized to receive a high-molecular-weight (200/0.5) HES product had significantly higher rates of acute renal failure and renal replacement therapy than 275 others who received Ringer's lactate.[7]

Then this year, a Scandinavian team reported on a clinical trial in which they randomized 804 severe sepsis patients to 130/0.4 HES or Ringer's acetate, and documented a significantly increased risk of severe bleeding, RRT requirement and death for those receiving HES.[8] Not in critical care patients generally, but specifically in severe patients, a low-molecular-weight HES product chemically similar to Voluven has now been shown to be both nephrotoxic and coagulopathic.

Broader Implications of the New HES/Sepsis Findings

While HES is generally safe and effective for treatment of hypovolemia, the available evidence convincingly shows that administration of at least two popular types of hetastarch products is independently associated with increased risk of renal and other serious complications in patients with severe sepsis. Adding a new warning to the labeling of these HES products or perhaps specifying the presence of sepsis or septic shock as a contraindication may therefore be in order. But will this suffice to protect other patients from potential harm?

Possibly not. Consider the debilitated, very elderly and/or immunocompromised patient undergoing a major abdominal, urological or extensive trauma surgery who is perioperatively infused with large volumes of HES in lieu of human albumin. A small but meaningful percentage of these at-risk patients will have the misfortune of developing postoperative sepsis, in some cases progressing to severe sepsis or septic shock.

The elimination half-life of conventional 450/0.7 and 130/0.4 HES products is about 46 and 12 to 16 hours, respectively.[9] In certain surgical subpopulations at increased risk of postoperative sepsis, could there be a corresponding increased risk of nephrotoxicity, bleeding or death associated with residual non-excreted HES? It is a difficult question that might be answerable only with painstaking retrospective analysis of many thousands of discharge records. Such a study might never be done.

In the meantime, it may be worthwhile to consider the recent clinical literature before reflexively substituting "cheaper" HES for the colloid that nature has perfected in its own evolutionary laboratory: human serum albumin. ❖

References

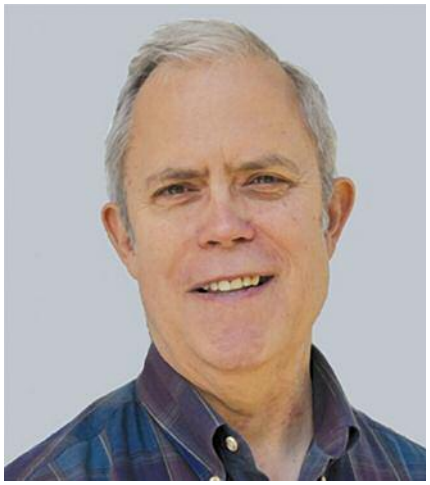
1. Full prescribing information for HEXTEND (Hospira Inc.), September 2008; and HESPAN (B. Braun Medical, Inc.), July 2011.
2. Cope JT, Banks D, Mauney MC, et al. Intraoperative Hetastarch Infusion Impairs Hemostasis After Cardiac Operations. *Ann Thorac Surg* 1997;63:78-83.
3. Herwaldt LA, Swartzendruber SK, Edmund MB, et al. The Epidemiology of Hemorrhage Related to Cardiothoracic Operations. *Infect Control Hosp Epidemiol* 1998;19:9-16.
4. Knutson JE, Deering JA, Hall FW, et al. Does Intraoperative Hetastarch Administration Increase Blood Loss and Transfusion Requirements After Cardiac Surgery? *Anesth Analg* 2000;90:801-7.
5. Sakr Y, Payen D, Reinhart K, et al. Effects of Hydroxyethyl Starch Administration on Renal Function in Critically Ill Patients. *Br J Anaesth* 2007;98(2):216-24.
6. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of Hydroxyethylstarch and Gelatin on Renal Function in Severe Sepsis: A Multicentre Randomised Study. *Lancet*, 2001 Mar 24;357(9260):911-6.
7. Brunkhorst FM, Engel C, Bloos F, et al. Intensive Insulin Therapy and Pentastarch in Resuscitation in Severe Sepsis. *N Engl J Med* 2008 Jan 10;358(2):125-39.
8. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl Starch 130/0.42 Versus Ringer's Acetate in Severe Sepsis. *N Engl J Med* 2012 Jul 12;367(2):124-34.
9. Cada D, Levien T and Baker DE. Hydroxyethyl Starch 130/0.4. *Hosp Pharm* 2008;43(5):396-408.

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.*

The Road to Remission

Tom Robinson refused to passively accept his diagnosis of debilitating Crohn's disease and instead embarked on a journey that not only restored his health but launched a new career.

by TRUDIE MITSCHANG



After being diagnosed with Crohn's disease, Tom Robinson took charge of his health by leading a targeted campaign to find the right physician for him, as well as changing his diet and lifestyle and, ultimately, his career.

FIFTEEN YEARS AGO, Tom Robinson received a diagnosis that would alter the course of his life. After enduring three years of troubling symptoms that included rashes, rectal bleeding and abdominal pain, Tom was finally diagnosed with Crohn's disease. In hindsight, Tom says his real challenge began when he started searching for a gastroenterologist. "Initially, I saw many doctors who were not very empathetic — I wanted a doctor who saw me as a human being and not just an illness to treat," he says. "I also wanted to try alternative, as well as standard, treatments; I wanted a doctor who was OK with that."

Tom's search for the right doctor led to a creative and targeted campaign; the software engineer wrote letters to every gastroenterologist within a 25-mile radius of his home, explaining his prognosis, his goals and the attributes he was (and was not) seeking in a physician. He got two responses; one became his doctor.

Treating Crohn's Disease

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract. Named after Dr. Burrill B. Crohn, who first described the disease in 1932 along with colleagues Dr. Leon Ginzburg and Dr. Gordon D. Oppenheimer, Crohn's disease belongs to a group of conditions known as inflammatory bowel disease (IBD).

"I wanted a doctor who saw me as a human being and not just an illness to treat."

Crohn's disease may affect as many as 700,000 Americans, and its cause is not well understood. Recent research suggests hereditary, genetics and/or environmental factors contribute to the development of Crohn's disease. Depending on the severity of the symptoms, it may be treated with a variety of medications, including aminosalicylates, antibiotics, corticosteroids and immunomodulator medicines.

"When I needed it, prednisone was effective in greatly reducing inflammation. But the side effects were very unpleasant, so I got off of it as soon as possible," Tom says. He was also prescribed sulfasalazine, a combination of salicylate and a sulfa antibiotic, resulting in fatigue, sleeplessness and hay-fever-like symptoms. Looking back, Tom says the most helpful treatment prescribed was Remicade (infliximab). Administered by IV, Remicade is often recommended for Crohn's when other medications have failed. "Most people need Remicade every six to eight weeks; I went into remission after the first treatment, had a second treatment two months later for good measure, and then went off all drugs for over four years," Tom says.

Exploring Alternative Therapies

For some patients, a combination of traditional and alternative treatments help alleviate symptoms of Crohn's disease. Seeking treatment options, Tom

Crohn's Disease: A Physician's Perspective

David T. Rubin MD, assistant professor of medicine at the University of Chicago Pritzker School of Medicine, is a leading authority on Crohn's disease and ulcerative colitis. In an article titled Leading Expert Has Answers on Crohn's Disease, he answers common questions regarding symptoms, diagnoses and treatment. To read the full article, go to http://www.ibsgroup.org/other/articles/Dr_Rubin_QA.htm.

Q: What causes Crohn's disease?

A: In people who are susceptible to Crohn's disease, it is believed that some element of the environment triggers an immune response that loses control. There are theories about Crohn's disease that suggest it is caused by infections or that there is a specific organism that is at the heart of most patients' disease. However, it is believed that while infections may trigger the onset of the disease in some people, it is likely more complicated than that.

Q: Is Crohn's disease hereditary?

A: About 10 percent to 15 percent of people with Crohn's disease have a family member with Crohn's disease or another inflammatory bowel condition.

Q: What is the goal with treatment?

A: The treatment of Crohn's disease is defined with specific goals, the first goal being remission — that the patient is feeling healthy and well. The second goal is known as maintenance, meaning the absence of flares of the disease. This should involve safe and effective therapies that people are willing to take and stay on.

Q: How does stress impact the disease?

A: Although there is no confirmatory evidence that stress drives Crohn's disease flares, I certainly appreciate that many of the people I treat believe that stress does aggravate their disease and, obviously, when people are stressed, they have poor sleep and eating habits, which may contribute to additional gastrointestinal symptoms.

read Jini Patel Thompson's book *Listen to Your Gut* and made several dietary adjustments, including eating an easily digestible protein powder instead of food, drinking aloe vera juice and taking several probiotic capsules daily. Over time, he saw improvements. He also incorporated meditation into his life and, believing toxic metal poisoning from old fillings was one of the factors contributing to his symptoms, Tom also embarked on a whole-body detoxification process. "I feel strongly, but can't prove, that the reason Remicade was so helpful was because I had all 13 of my mercury amalgam fillings removed, and then spent well over a year getting treatments to remove mercury from my organs prior to my infusions," he says.

Making a Fresh Start

As is often the case, Tom's first bout with Crohn's disease was not his last, although symptoms were milder the second time around. Today, Tom is once again in remission and has opened himself up to new possibilities — including a new career. "My job as a software engineer and manager had ceased to be satisfying, so I became a life coach for people with chronic illness; I've been doing that ever since. Being able to make a big difference in my clients' lives has been tremendously satisfying and fulfilling."

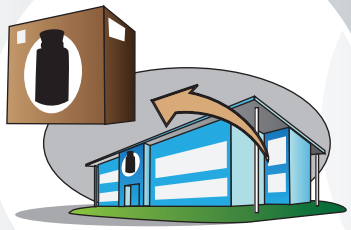
For some patients, a combination of traditional and alternative treatments help alleviate symptoms of Crohn's disease.

Tom says he has taken full responsibility for his health now, and while he benefited greatly from modern medicine, there were many times when prescribed treatments made him feel worse. "The many horrible symptoms I had during the three years my Crohn's disease was at its worst taught me that good health was not something I could take for granted. And I don't. I am very grateful for it." ❖

TRUDIE MITSCHANG *is a staff writer for* BioSupply Trends Quarterly.

Do you **know** where your products have been?

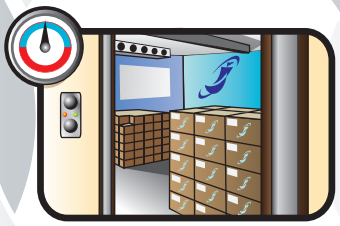
BRINGING TRUST TO



1

PURCHASING

Products are purchased only from the manufacturer – never from another distributor or source.



2

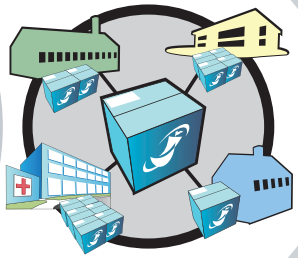
STORAGE

State-of-the-art warehouse. Checkpoints include: access, temperature and intertransit handling.

3

SPECIALTY PACKAGING

Analysis of the specific requirements of each product ensures protein integrity is maintained during storage and transit.



4

INTERACTIVE ALLOCATION

Assures responsible, demand-based distribution. Reduces potential for price gouging and gray-market purchasing to accommodate critical demand issues.

When they come from **FFF**, you can be **sure** you do.

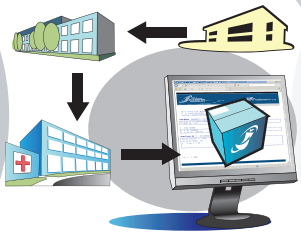
THE MARKETPLACE

5

DELIVERY
Products are delivered only to certified healthcare providers with a DEA license and only to the address on the license.

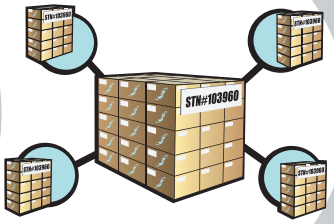
6

METHODS OF DELIVERY
Monitoring and adjusting for extreme weather conditions allow time-sensitive delivery to ensure product integrity.



7

VERIFICATION
Verified Electronic Pedigree™, FFF's proprietary system, verifies product pedigree from the manufacturer and receipt by the healthcare provider to validate our safe channel.



8

TRACKING
Lot-Track™, another FFF service, provides accurate product lot tracking and recall notification within four hours.

The 8 Critical Steps to Guaranteed Channel Integrity™

FFF Enterprises has made the uncompromising decision to purchase only from the manufacturer and sell only to licensed healthcare providers, shortening the supply chain to avoid secondary distribution channels that open the doorway to counterfeiters.

The 8 Critical Steps to Guaranteed Channel Integrity assure that patient safety, product efficacy and fair pricing are maintained throughout our safe channel. From purchasing to storage and delivery, these best practices maintain the strength of each link in the chain,
with patient welfare at the center of every decision.

(800) 843-7477 | www.FFFenterprises.com

FFF enterprises
Helping Healthcare Care®

BioResearch

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

2010-2011 Trivalent Influenza Vaccine with all Three Vaccine Strains Was Moderately Effective

U.S. investigators assessed vaccine effectiveness during the 2010-2011 season in an attempt to characterize the relationship between antigenic characteristics of circulating viruses and effectiveness of seasonal influenza vaccines. They employed a case-control study design, capturing vaccination histories both for subjects with acute respiratory illness confirmed by positive real-time reverse transcription polymerase chain reaction (PCR) for influenza, and influenza test-negative controls.

Subjects in communities in four states with acute respiratory illness of ≤7 days duration were enrolled. History of immunization with the 2010-2011 vaccine was ascertained from vaccine registries or medical records. Vaccine effectiveness was estimated using logistic regression models adjusted for study community, age, race, insurance status, enrollment site and presence of a high-risk medical condition.

A total of 373 cases of influenza A/H1N1, 334 cases of influenza A/H3N2 and 333 cases of influenza B were identified, and their vaccination histories were compared against 3,717 influenza-negative controls. Overall adjusted vaccine effectiveness was 60% (95% confidence interval [CI], 53% to 66%). Age-specific vaccine effectiveness estimates ranged from 69% (95% CI, 56% to 77%) in children aged 6 months to 8 years, to 38% (95% CI, -16% to 67%) in adults aged ≥65 years. It was judged that influenza vaccines were moderately effective in preventing medically attended influenza during this 2010-2011 season in which all three flu vaccine strains were antigenically similar to circulating viruses.

Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of Seasonal Influenza Vaccines in the United States During a Season with Circulation of All Three Vaccine Strains. Clin Infect Dis*, 2012 Jul 25 [Epub ahead of print].*

rIX-FP Protein Exhibits Prolonged Circulating Half-Life in Hemophilia B Patients

An investigational recombinant "fusion protein" linking coagulation factor IX and human albumin was developed by CSL Behring to facilitate extended intravascular half-life of the clotting protein and thereby enable less frequent factor IX (FIX) dosing by persons with hemophilia B. A multinational team evaluated the safety and pharmacokinetics of 25, 50 and 75 IU/kg single infusions of this investigational agent (rIX-FP) in 25 previously treated subjects with hemophilia B (≤2 IU/dL).

No allergic reactions or inhibitors were observed in any subject. Four mild, possibly treatment-related adverse events were reported. In the 50 IU/kg cohort comprising 13 subjects, the mean half-life of rIX-FP was 92 hours, more than five times longer than the subjects' previous FIX product. After 25 or 50 IU/kg rIX-FP administration, the baseline-corrected mean FIX activity remained elevated at day seven (7.4 IU/dL and 13.4 IU/dL, respectively) and day 14 (2.5 IU/dL and 5.5 IU/dL, respectively).

The investigators concluded that these and other reported results demonstrate both the safety and improved pharmacokinetics of rIX-FP, "indicating this new product with extended half-life as possibly able to control and prevent bleeding with less frequent injection."

Santagostino E, Negrier C, Klamroth R, et al. Safety and Pharmacokinetics of a Novel Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) in Hemophilia B Patients. Blood*, 2012 Aug 2 [Epub ahead of print].*

IVIG Discontinued Much Less Frequently than Methylprednisolone for CIDP

Intravenous immunoglobulin (IVIG) therapy was less frequently discontinued due to inefficacy, adverse events or intolerance than intravenous methylprednisolone for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), according to a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 45 patients conducted at Milan University.

A dose of 0.5 g/kg of IVIG or 0.5 g of methylprednisolone was administered daily for four consecutive days on a monthly basis for six months. The primary study outcome was the difference in the number of patients discontinuing either therapy owing to inefficacy or intolerance. Secondary endpoints included the difference in the proportion of patients experiencing adverse events or worsening after therapy discontinuation.

Eleven of 21 (52%) patients stopped methylprednisolone therapy during the study period, while only three of 24 (13%) patients treated with IVIG stopped therapy, translating into a relative risk of 0.54 (95% CI, 0.34 to 0.87; p=0.0085). The proportion of patients experiencing adverse events did not differ between the methylprednisolone and IVIG groups. Following discontinuation of therapy, however, more patients on IVIG therapy worsened and required further therapy (8 of 21; 38%) than did those on methylprednisolone (0 of 10; p=0.0317).

Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous Immunoglobulin Versus Intravenous Methylprednisolone for Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Randomized Controlled Trial. Lancet Neurol*, 2012 Jun;11(6):493-502.*

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.*

BioResources

Recently released resources for the biopharmaceuticals marketplace.

Guide to International Pharma Regulation, 2012 Edition

Author: U.S. Food and Drug Administration

This guide provides quick, accurate answers about emerging changes in inspection practices, changes to quality manufacturing requirements, developing biosimilars approvals pathways, new labeling and marketing regulations, changing product registration requirements, pricing and reimbursement debates, anti-counterfeiting measures, and dozens more key topics in drug regulation worldwide. This 2012 edition includes more than 150 reports highlighting changes from the past year concerning coverage of the EU, Asia, Latin America, the Middle East, North America and Australia/Pacific, essential international regulatory changes from all of 2010, comprehensive summaries and explanations of the changes, full-text printouts of key regulations and more.

www.fdanews.com/store/product/detail?display=0&productId=30131&hittrk=12503&utm_source=MagnetMail&utm_medium=email&utm_term=rrhodes@igliving.com&utm_content=BIPRM12 - 12503 - 5/3/12 - CTBR/CTBS/ CTN/DD/DR/MB/&utm_campaign=Announcing%3A All-New 2012 Guide to International Drug Regulation

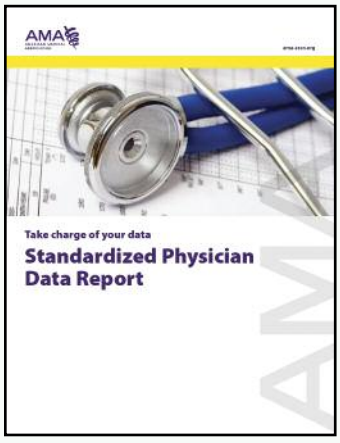
Clinical Trials Adverse Event Reporting Reference Guide, Second Edition

Author: U.S. Food and Drug Administration

This reference guide provides clinical trial operators with more than 200 pages of rules, regulations, interpretations and guidances including newly issued guidance from OHRP on IRB continuing review of research, new guidance on reporting incidents to OHRP, new FDA guidance, safety reporting requirements for INDs and BA/BE studies, plus numerous new enforcement cases involving adverse event reporting. It also provides answers to how to determine if an adverse event needs to be reported, when an expected adverse event becomes an unanticipated adverse event, how adverse events differ from unanticipated problems, how to assess if an event is unexpected, how to assess whether an event is related to research, what needs to be included in adverse event reports and more.

Also featured is an analysis of relevant warning letters that illustrate ways adverse event reporting requirements often are misconstrued or overlooked.

www.fdanews.com/store/product/detail?productId=28212&hittrk=12517NT&utm_source=MagnetMail&utm_medium=email&utm_term=rrhodes@igliving.com&utm_content=BCTAEG12 - 12517NT - 5/17/12 - CTBR/CTBS/ CTN/DR/MD&utm_campaign=What is an Adverse Event%3F Revised Guide Clarifies Murky Area



Physician Educational Tools

Author: American Medical Association

The American Medical Association's Private Sector Advocacy team has developed two educational tools to support physicians in the new, data-driven environment. *Take Charge of Your Data* is a new guide designed to help physicians understand and verify the accuracy of the complex profiling reports provided by public and private health insurers. Using practical information and step-by-step instructions, the guide simplifies the review of data reports and teaches physicians how to use both quality and cost-of-care data to identify practice improvement opportunities. Developed to be used in tandem with the guide is the *Standardized Physician Data Report*, which encourages payers to adopt a uniform format for physician profiling reports. Currently, each payer uses its own unique format to report physician performance data, making it challenging for physicians to decipher the reports from various insurers. The standardized report offers a uniform reporting format for payers' physician data reports and includes the patient-specific detail needed for the reports to be meaningful and actionable for physicians. When used together, the physician guide and the standardized report can help physicians identify common report features, interpret quality and cost-of-care performance results, and use the information to improve care and/or increase efficiency.

www.ama-assn.org/go/physiciandata

BioProducts

Predictive Modeling Tool

Medalogix has developed a predictive modeling tool that is designed to reduce rehospitalization rates and boost quality of care for patients. The company has partnered with post-acute healthcare provider Alternate Solutions to use its tool, which focuses on the two most significant factors in predicting geriatric patient rehospitalization: medication and geography. As of October 1, new provisions of the Affordable Care Act went into effect that penalize hospitals when a patient is readmitted under the same diagnosis within 30 days of his or her discharge; Medicare will not reimburse the hospital for care provided after the readmission. Studies have shown that up to 31 percent of elderly patient hospital admissions are associated with drug-related problems. Over the three-year period that the Medalogix predictive algorithms have been in development, they have demonstrated the ability to predict a patient's risk of hospitalization with an accuracy exceeding 74 percent.
Medalogix, (615) 200-8443, www.medalogix.com

R&D Management Solution

iGATE Research is an accelerator platform for Life Sciences, a streamlined program designed to reduce the cycle times and costs of bringing a new drug or medical device to market. The research accelerator empowers pharmaceutical developers and contract research organizations with fully integrated clinical information management technology and iGATE's business outcomes-based methodology, enabling them to make better, faster, more informed decisions throughout the drug development process. This end-to-end management solution for research and development data links the systems and data-related procedures through every phase of the clinical process — from data capture to clinical data management, product registrations, document and submission management, pharma co-vigilence risk management, reporting and analytics, and clinical operations research and development portfolio management.
iGate Corp., (412) 490 9620, www.iGate.com

ePrescribe Solution

Mitochon has launched a new free ePrescribe solution that is integrated into the company's Physicians EHR workflow. The solution complements Mitochon's existing EHR, HIE, PHR, mobile and soon-to-be-launched PM solutions. Features of the eRX include automatically checking for contraindications like drug-drug interactions or potential allergies, reducing script errors, incorporating automatic formulary checking, and providing immediate authorization or denial capabilities. It also includes free instructional information for patients and a "favorites" tool for listing commonly prescribed medications. The company provides free client support.
Mitochon Systems Inc., (877) 817-0902, www.mitochonsystems.com

Hizentra Dosing App

The Hizentra Dosing Calculator App by CSL Behring UK Ltd. is designed for use on iPhone and Android handsets. The app assists healthcare professionals with dosage calculation when administering Hizentra (human normal immunoglobulin, SCIG) by calculating the correct volume of Hizentra to be infused based upon entry of only two key pieces of information: a patient's weight and the weekly dosage required. The app can be downloaded and installed for free directly from the phone, by going online to the iTunes store at http://itunes.apple.com/gb/app/hizentra-dosing-calculator/id483147404, or by visiting Google Play at https://play.google.com/store/apps/details?id=com.nitrogen.hizentradose#?t=W251bGwsMSwxLDIxMiwiY29tLm5pdHJvZ2VuLmhpemVudHJhZG9zZSJd.
CSL Behring UK Ltd. (610) 878-4000, www.cslbehring.com

Assay Kits for Autoimmune Disease

The first assay kits — the Maverick ENA 4 and ENA 6 — for the Maverick Detection System are now available. The assays simultaneously screen for several of the most common autoantibodies found in autoimmune connective tissue disorders such as systemic lupus erythematosus (SLE). Their simplified one-step workflow delivers results in 15 minutes and can be run using small-volume samples from a variety of matrices, including serum and plasma. The Maverick ENA 4 assay includes four multiplexed tests per sample, while the ENA 6 assay covers six multiplexed tests per sample. They are available to participants in Genalyte's Early Access program.
Genalyte, (858) 956-1200, www.genalyte.com

BioDashboard

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective October 1, 2012 through December 31, 2012.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+4% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$63.21	$64.43
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$68.86*	$68.86
GAMMAGARD LIQUID	Baxter BioScience	J1569	$73.81	$75.23
GAMMAGARD S/D	Baxter BioScience	J1566	$63.21	$64.43
GAMMAKED	Kedrion	J1561	$75.11	$76.56
GAMMAPLEX	Bio Products Laboratory	J1557	$74.50*	$74.50
GAMUNEX-C	Grifols	J1561	$75.11	$76.56
OCTAGAM	Octapharma	J1568	$65.16	$66.41
PRIVIGEN	CSL Behring	J1459	$68.96	$70.28

*ASP + 6% (pass-through drug)

Calculate your reimbursement online at www.FFFenterprises.com.

IVIG/SCIG Reference Table

Product	Indication	Size	Manufacturer
CARIMUNE NF Lyophilized	IVIG: PIDD, ITP	3 g, 6 g, 12 g	CSL Behring
FLEBOGAMMA 5% & 10% DIF Liquid	IVIG: PIDD	0.5 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
GAMMAGARD LIQUID 10%	IVIG: PIDD, MMN SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g	Baxter BioScience
GAMMAGARD S/D Lyophilized, 5% or 10%	IVIG: PIDD, ITP, CLL, KD	2.5 g, 5 g, 10 g	Baxter BioScience
GAMMAKED Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Kedrion
GAMMAPLEX Liquid, 5%	IVIG: PIDD	5 g, 10 g	Bio Products Laboratory
GAMUNEX-C Liquid, 10%	IVIG: PIDD, ITP, CIDP SCIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 20 g	Grifols
HIZENTRA Liquid, 20%	SCIG: PIDD	5 mL, 10 mL, 20 mL	CSL Behring
OCTAGAM Liquid, 5%	IVIG: PIDD	1 g, 2.5 g, 5 g, 10 g, 25 g	Octapharma
PRIVIGEN Liquid, 10%	IVIG: PIDD, ITP	5 g, 10 g, 20 g	CSL Behring

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

2012-2013 Influenza Vaccine

Administration Codes: G0008 (Medicare plans) 90471 (non-Medicare plans)
Diagnosis Code: V04.81

Product	Size	When Administered to Indicated Age Group	Code
FLUZONE Intradermal	0.1 mL microinjection	Influenza virus vaccine, split virus, preservative free, for intradermal use	90654
FLUZONE Pediatric	0.25 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90655
AFLURIA	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
AGRIFLU	0.5 mL prefilled syringe		
FLUARIX	0.5 mL prefilled syringe		
FLUVIRIN	0.5 mL prefilled syringe		
FLUZONE	0.5 mL single-dose vial		
FLUZONE	0.5 mL prefilled syringe		
FLUZONE	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUMIST	0.2 mL nasal spray	Influenza virus vaccine, live, for intranasal use, when administered to individuals 2-49 years of age	90660
FLUZONE High-Dose	0.5 mL prefilled syringe	Influenza virus vaccine, split virus, preservative free, enhanced immunogenicity via increased antigen content, for intramuscular use	90662
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, split virus, when administered to individuals 3 years and older, for intramuscular use	Q2035
FLULAVAL			Q2036
FLUVIRIN			Q2037
FLUZONE			Q2038

GAMUNEX®-C

Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®-C safely and effectively. See full prescribing information for GAMUNEX-C.

GAMUNEX-C, [Immune Globulin Injection (Human) 10% Caprylate/Chromatography Purified]

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. GAMUNEX-C does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.**

----------INDICATIONS AND USAGE----------

GAMUNEX-C is an immune globulin injection (human) 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI)
- Idiopathic Thrombocytopenic Purpura (ITP)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

----------CONTRAINDICATIONS----------

- Anaphylactic or severe systemic reactions to human immunoglobulin
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity

----------WARNINGS AND PRECAUTIONS----------

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Have epinephrine available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of developing acute renal failure.
- GAMUNEX-C is not approved for subcutaneous use in ITP patients. Due to a potential risk of hematoma formation, do not administer GAMUNEX-C subcutaneously in patients with ITP.
- Hyperproteinemia, with resultant changes in serum viscosity and electrolyte imbalances may occur in patients receiving IGIV therapy.
- Thrombotic events have occurred in patients receiving IGIV therapy. Monitor patients with known risk factors for thrombotic events; consider baseline assessment of blood viscosity for those at risk of hyperviscosity.
- Aseptic Meningitis Syndrome (AMS) has been reported with GAMUNEX-C and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. Monitor patients for hemolysis and hemolytic anemia.
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI]).
- Volume overload
- GAMUNEX-C is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.
- Passive transfer of antibodies may confound serologic testing.

----------ADVERSE REACTIONS----------

- **PI** – The most common adverse reactions (≥5%) with intravenous use of GAMUNEX-C were headache, cough, injection site reaction, nausea, pharyngitis and urticaria. The most common adverse reactions (≥5%) with subcutaneous use of GAMUNEX-C were infusion site reactions, headache, fatigue, arthralgia and pyrexia.
- **ITP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- **CIDP** – The most common adverse reactions during clinical trials (reported in ≥5% of subjects) were headache, fever, chills, hypertension, rash, nausea and asthenia.

To report SUSPECTED ADVERSE REACTIONS, contact Talecris Biotherapeutics, Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- The passive transfer of antibodies may transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella. Passive transfer of antibodies may confound serologic testing.

----------USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric: In patients over 65 years of age do not exceed the recommended dose, and infuse GAMUNEX-C at the minimum infusion rate practicable.

Talecris BIOTHERAPEUTICS

Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1716

08939771/08939782-BS
Revised: October 2010

The PROOF is everywhere you look

GAMUNEX-C has proven efficacy and patient outcomes in CIDP, PI, and ITP*[1]

Important Safety Information for GAMUNEX-C

Gamunex-C, Immune Globulin Injection (Human), 10% Caprylate/Chromatography Purified, is indicated for the treatment of primary humoral immunodeficiency disease (PI), idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gamunex-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gamunex-C at the minimum concentration available and the minimum infusion rate practicable.

Gamunex-C is contraindicated in individuals with acute severe hypersensitivity reactions to Immune Globulin (Human). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

Gamunex-C is not approved for subcutaneous use in patients with ITP or CIDP. **Due to the potential risk of hematoma formation, Gamunex-C should not be administered subcutaneously in patients with ITP.**

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Thrombotic events have been reported in association with IGIV. Patients at risk for thrombotic events may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity.

There have been reports of noncardiogenic pulmonary edema [Transfusion-Related Lung Injury (TRALI)], hemolytic anemia, and aseptic meningitis in patients administered with IGIV.

The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Gamunex-C is made from human plasma. Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

After infusion of IgG, 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.

In clinical studies, the most common adverse reactions with Gamunex-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PI) and infusion site reactions, headache, fatigue, arthralgia and pyrexia with subcutaneous use (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in one subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in one subject (in PI), and myocarditis in one subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP).

*CIDP=Chronic inflammatory demyelinating polyneuropathy; PI=Primary immunodeficiency; ITP=Idiopathic thrombocytopenic purpura.

Reference: 1. Data on file, Grifols.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Please see adjacent page for brief summary of GAMUNEX-C full Prescribing Information.

gamunex®-C

immune globulin injection (human), 10% caprylate/chromatography purified

Evidence based. Patient proven.

To get GAMUNEX-C call 1-888-MY GAMUNEX (694-2686)
USA Customer Service: 1-800-243-4153
www.gamunex-c.com

GRIFOLS a new era begins

www.grifols.com

Now it's easy when

YOU CHOOSE

your delivery dates!

Visit MyFluVaccine.com to secure **YOUR** best delivery dates.

Choice
Select from a broad portfolio of products

Convenience
Choose your delivery dates

Safety
Count on a secure supply

YOU PICK THE QUANTITY • YOU PICK THE DATE • WE DELIVER

FFF MyFluVaccine™ | (800) 843-7477 | www.MyFluVaccine.com

Brought to you by FFF Enterprises, Inc., the nation's largest and most trusted distributor of flu vaccine and critical-care biopharmaceuticals.