April 2013

BioSupply Trends

Special Focus: SAFETY

Quarterly

Drug Dangers

Minimizing Pharmaceutical Risks

The Growing Scourge of Counterfeit Medicines

Medication Interactions and Adverse Drug Events

Does Inflammation Cause Disease?

Vaccinating Healthcare Workers Against the Flu

Myths & Facts: Chronic Fatigue Syndrome — Page 46

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.**

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.

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.
- 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

April 2013

Features

Special Focus: Safety

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.

Up Front

BioTrends Watch

BioFocus

BioSources

Creating a Safe Environment in Healthcare

PATIENT SAFETY continues to be an ongoing topic of discussion in the healthcare industry. With good reason, as each year between 380,000 and 450,000 adverse drug events (ADEs) occur, costing hospitals billions of dollars and causing patients discomfort, injury or death. In response, in this safety-themed edition of *BioSupply Trends Quarterly*, we address this issue and how it can be improved.

In our article "Reducing the Risks of Medication Errors," we discuss technology solutions that can help reduce ADEs by as much at 81 percent when physicians use e-scripts, and when hospitals participate in barcode verification, ADEs can be reduced by as much as 50 percent. We also examine how patient education plays a critical role in improving healthcare.

Counterfeit drugs are a rising safety concern plaguing the U.S. and Western nations. As healthcare continues to become a more global industry, supply and demand play a pivotal role in the black market activity coming from China, India and South America. In our article "The Growing Scourge of Counterfeit Pharmaceuticals," we review the national laws that regulate the issue, as well as the lack of international consensus to crack down on counterfeit pharmaceuticals.

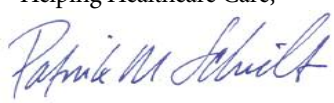
As we wind down from one of the earliest and most wide-spread flu outbreaks in U.S. history, we are reminded that influenza can be deadly, especially to those who are immunocompromised. Plus, the risks of acute ischemic heart disease and cerebrovascular disease resulting from the flu often include death. Yet, while a simple shot could avert mortality and complications, only 40 percent of the population receives a flu vaccine. This simple protection against the highly contagious flu reduces the spread of infection, worker absenteeism and saves lives, which is why the flu vaccine is especially critical for healthcare workers who come in contact with the most vulnerable and weak. As we report in our feature "Healthcare Workers and the Flu Vaccine: The Backlash," the Centers for Medicare and Medicaid Services' new regulations require hospitals to report employee flu vaccination numbers as a means to boost compliance. The goal is to hit 90 percent participation, and to gravitate toward this number, some states — Arkansas, Maine and Rhode Island — are imposing penalties for healthcare workers who refuse vaccination.

Also in this issue, we look at two conditions that are often perplexing to the medical community. First, chronic fatigue syndrome (CFS) has been around for nearly 200 years, but it has only been a legitimate medical condition for the past quarter century. In the past, it was thought to be a middle-aged, affluent Caucasian woman's disease caused by hysteria. That myth has been dispelled, but much about this mysterious disease is still unknown today. Continuing research shows a correlation between CFS and underlying biological abnormalities, and more is being discovered each year.

Second, the role of inflammation and how it interacts with chronic diseases such as diabetes, Alzheimer's and cancer has been the focus of a growing body of research. In our article "Chronic Inflammation: The Cause of Disease?" we probe the links connecting inflammation with illness. As increasing numbers of patients are diagnosed with inflammation-linked diseases, physicians are pondering the causation of inflammation. The jury is still out on the lingering question: Is inflammation the cause or a symptom of chronic illnesses?

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly* and find the content educational and insightful, and we welcome your comments.

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

Artistic Director
Allan Bean

Graphic Artists
Allan Bean
Ben Drolet

Advertising Director
Cheryl Brooks

Contributing Writers
Keith Berman, MPH, MBA
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

Fiscal Cliff Legislation Helps Recover Medicare Funds

As part of the fiscal cliff legislation enacted prior to the end of 2012, $10.5 billion in Medicare overpayments to hospitals will be recovered over the next few years. The money will go toward postponing $30 billion in scheduled payment cuts to physicians who treat Medicare patients.

In 2007, the Centers for Medicare & Medicaid Services (CMS) altered how hospitals submit bills for Medicare patients by creating 749 categories that permit hospitals to more accurately define the illness level of their patients. The system's intent was to make sure that, for instance, a hospital treating a person who has pneumonia and other illnesses, such as diabetes, would be paid more than a hospital treating an otherwise robust patient with pneumonia. With the extra coding in place, Medicare wanted to decrease its payments to counterbalance the change in billing, but hospitals discouraged the government from cutting rates. However, after inspecting the billing patterns, the Medicare Payment Advisory Commission (MedPAC), a congressional advisory committee, reported in 2010 that the improved coding increased payments by $6.9 billion between 2008 and 2009. In 2009, Congress gave Medicare permission to recover $6 billion in overpayments. But in the spring of 2012, MedPAC estimated that hospitals had received $11 billion in overpayments between 2010 and 2012, which Medicare was not able to recover.

In addition to the $10.5 billion in hospital payment cuts, the Affordable Care Act also includes another $155 billion in reductions to hospitals, which will take place over the next 10 years. The fiscal cliff legislation also extended the health law's reductions in payments for hospitals that treat large numbers of uninsured and low-income patients until 2022. The extended cuts will save $4.2 billion. ❖

Tax and Age-Rating Restrictions May Lead to Higher Insurance Premiums

Under the Affordable Care Act (ACA), the health insurance sales tax and age-rating restrictions will increase premiums for many, according to a report by Oliver Wyman, a management consulting firm.

The study shows the new sales tax included in the ACA will increase the cost of healthcare coverage for consumers and employers in all 50 states. It also will affect Medicare Advantage beneficiaries and Medicaid managed care programs. The tax will start at $8 billion in 2014, rise to $14.3 billion by 2018 and is projected to surpass $100 billion over the next 10 years.

In addition, the age-rating restrictions will affect the affordability of healthcare coverage for younger individuals. The ACA implements a 42 percent increase in premiums for people between the ages of 21 and 29 and a 31 percent increase for those between the ages of 30 and 39. According to the study's authors, if younger, healthier adults choose not to purchase insurance, the individual consumer market will be destabilized, premiums will increase across the board, and overall enrollment will decline. ❖

HHS Grants $1.5 Billion to Fund State-Based Marketplaces

The U.S. Department of Health and Human Services (HHS) has approved $1.5 billion in new Exchange Establishment Grants (EEG) to ensure states have the required resources to build marketplaces that meet the needs of residents. Currently, level one EEG one-year awards have been given to Delaware, Iowa, Michigan, Minnesota, North Carolina and Vermont. And level two grants, which are multi-year awards, have been given to California, Kentucky, Massachusetts, New York and Oregon.

Through the Affordable Care Act, consumers and small businesses will have access to health insurance marketplaces beginning in 2014. The marketplaces are expected to be a single location where plan buyers can find quality, affordable private health insurance options from qualified health plans. Consumers who purchase health insurance through the exchanges also may be eligible for tax credits to help pay for their health coverage.

States can apply for grants from now until the end of 2014 and may use funds through their start-up year. ❖

Healthcare Law Requires Pediatric Dental Coverage

Under the Affordable Care Act's "10 essential health benefits," individual and small group health plans sold under state-based health insurance exchanges and outside them on the private market will be required to cover pediatric dental services beginning in 2014. This requirement applies specifically to children who obtain coverage through private plans. However, large companies and plans that have grandfathered status under the law are not required to offer this coverage. Dental services already are included in the benefit package for children under Medicaid.

Specific coverage requirements will be determined by each state within guidelines set by the Department of Health and Human Services (HHS). The latest requirements by HHS suggest that medically necessary dental work may be required on top of preventive and restorative care. Under a private dental plan, preventive care is generally covered at 100 percent, but other services such as fillings, root canals and crowns require patients to pay up to half the cost, with coverage maxing out at about $1,500 per year. Under the ACA, pediatric dental coverage sold on the exchanges cannot have annual or lifetime limits on coverage. However, families who purchase dental health coverage on an exchange may be subject to an annual out-of-pocket cost-sharing charge. HHS recommends there be a reasonable annual limit. The National Association of Dental Plans suggests a limit of up to $1,000. The final rule, when issued, will clarify the amount. ❖

HHS Relaunches Website to Help Uninsured

The U.S. Department of Health and Human Services (HHS) has relaunched its website to attract the 43 million uninsured Americans needed to make the healthcare law work when open enrollment in state and federal healthcare exchanges begins in October. Enroll America, a group designed to promote the exchanges, aims to ensure that those who can be helped by health coverage understand what exchanges are, how much insurance will cost and the benefits it will provide. The new HHS website (healthcare.gov) helps to provide consumers with this information by allowing them to easily compare benefits and costs of health insurance plans. Along with the revised website is a new, consumer-friendly name for the federal exchange: the "Health Insurance Marketplace."

For the health law to function, the uninsured will be required to purchase a bronze, silver, gold or platinum plan from private insurers. Beginning in 2014, insurers will be required to offer health benefits to all Americans regardless of their health status, and the plans must be based on upfront costs vs. out-of-pocket costs. Tax credits also will be offered to help families within 400 percent of the poverty level to afford insurance. And failure to buy insurance will result in fines up to $95 for adults in 2014, $325 in 2015 and $695 in 2016. ❖

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

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

What vaccine codes have changed under the revised 2013 Current Procedural Terminology (CPT) code set?

Since the CPT's universal adoption in 1983, the American Medical Association makes changes on an annual basis to the CPT code sets under contract with the Centers for Medicare and Medicaid Services (CMS). Code changes affect all provider types that provide CPT professional services in all states.

The newest changes were effective Jan. 1, 2013, and are mandatory, as noncompliance is a HIPAA violation. The switch to the new codes is based on the date of service, not the date the claim was submitted. For dates of service prior to January 1, providers can bill with the old codes. CMS does not allow for a transition period; providers must bill with new CPT codes on January 1 for dates of service on or after January 1. This includes electronic claims.

Several additions and changes have been made to flu vaccine and other vaccine codes for 2013. One new code, 90653, was added for influenza vaccine, inactivated, subunit, adjuvanted, for intramuscular use. Code 90653 appears in the CPT codebook with the U.S. Food and Drug Administration (FDA) approval pending symbol. The administration of the vaccine is separately reported using Immunization Administration Vaccines/Toxoids codes 90460-90474.

Four influenza virus vaccine product codes have been revised to specify "trivalent" to prepare for the new quadrivalent influenza vaccines, which are expected to be available in 2013. These include:

- 90655: influenza virus vaccine, trivalent, split virus, preservative free, when administered to children ages 6 months to 35 months, for intramuscular use;
- 90656: influenza virus vaccine, trivalent, split virus, preservative free, when administered to individuals 3 years and older, for intramuscular use;
- 90657: influenza virus vaccine, trivalent, split virus, when administered to children 6 months to 35 months of age, for intramuscular use; and
- 90658: influenza virus vaccine, trivalent split virus, when administered to individuals 3 years of age and older, for intramuscular use.

Only one quadrivalent flu vaccine code, 90672, was added in the 2013 CPT for a quadrivalent live influenza virus vaccine, which received FDA approval in February 2012. However, the AMA has suggested four more quadrivalent codes, 90685 through 90688, for 2014.

Other new vaccine codes include 90739 — hepatitis B vaccine, adult dosage (2-dose schedule, pending FDA approval), for intramuscular use, and 90746 — hepatitis B vaccine, adult dosage (3-dose schedule), for intramuscular use.

The Hib-MenCY vaccine code, 90644, was changed to FDA-approved status. And deletions to the CPT code set include code 90665 for reporting Lyme disease vaccine, as it is no longer available; code 90701 for reporting the whole cell pertussis vaccine composed of whole cells killed Bordetella pertussis bacilli, combined with diphtheria and tetanus toxoids, as it is no longer used in the U.S.; and code 90718 to report preservative-containing tetanus and diphtheria (Td) toxoid vaccine, because no Td product currently on the market is considered "preservative-containing." ❖

Ask Our Experts

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

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

VERIFIED

INVENTORY PROGRAM™

COMING SOON!

FFF Enterprises' new VERIFIED INVENTORY PROGRAM™ will provide yet another reliable and accurate verification of our secure channel, augmenting our current systems, Verified Electronic Pedigree™ and Lot-Track.™

Look for more information in the next issue of BioSupply Trends Quarterly.

(800) 843-7477
www.FFFenterprises.com

FFF enterprises
Helping Healthcare Care®

Medicines

FDA Approves VARIZIG for Treatment of Varicella Zoster Virus in High-Risk Patients

VARIZIG, a hyperimmune globulin indicated for post-exposure prophylaxis of varicella zoster virus (VZV) in high-risk patients, has been approved by the U.S. Food and Drug Administration (FDA). Manufactured by Cangene Corp. in Winnipeg, Manitoba, Canada, VARIZIG is the only FDA-approved hyperimmune globulin for VZV after exposure available in the United States. An earlier FDA-licensed VZIG was removed from the U.S. market by the manufacturer in 2006, and VARIZIG has been available only under an investigational expanded access protocol during the licensing process. It was designated as an orphan drug by the FDA and received a priority review.[1]

VZV causes chickenpox in children and shingles in adults. VARIZIG is an antibody preparation manufactured from plasma of healthy donors with high anti-VZV antibody levels. It is administered in two or more injections,[3] depending on the weight of the recipient, and it is approved for immunocompromised children and adults, newborns, pregnant women, premature infants, children younger than 1 year, and adults with no immunity to VZV.[1,3]

According to the Centers for Disease Control and Prevention, immune-compromised individuals who contract chickenpox are at risk of developing severe complications that can sometimes be fatal. Pregnant women who contract the virus are at increased risk for developing pneumonia, and becoming infected early in pregnancy can put their newborns at risk for low birth weight and birth defects, including limb abnormalities.[3] When an expectant mother develops chickenpox in the week before birth, the virus can result in a life-threatening infection in a newborn.[2] According to the drug's manufacturer, VARIZIG is indicated for use in any of these instances.

"This approval fills an unmet need by providing a treatment to lower the risk of severe, potentially fatal varicella infections in vulnerable patients," Karen Midthun, MD, director of the FDA's Center for Biologics Evaluation and Research, said in a press release regarding the drug's approval.[1]

In studies, VARIZIG was shown to be comparable to VZIG and was as effective as VZIG in preventing severe infection during pregnancy. Data on VARIZIG collected from individuals treated under the expanded access protocol showed a low rate of severe VZV infection in susceptible individuals compared with the rate in untreated individuals. The studies also showed that VARIZIG is safe for its intended use, with the most common side effects being pain at the injection site and headache.[1]

Varicella vaccination is not recommended for children with congenital or acquired T-lymphocyte immunodeficiency, including children receiving long-term immunosuppressive therapy, because of risk for complications from live vaccine virus infection. These patients are at high risk for severe or fatal varicella and depend on indirect protection through high levels of varicella immunity among the general population, and especially among their close household contacts. In these patients, if exposure to VZV occurs, post-exposure prophylaxis with VARIZIG is recommended. VARIZIG should be administered as soon as possible after exposure, ideally within 96 hours for greatest effectiveness.[2,3]

VARIZIG is now exclusively distributed by FFF Enterprises (www.fffenterprises.com), a distributor of biopharmaceuticals, critical-care plasma products and vaccines. FFF also partnered with Cangene as sole distributor of VARIZIG during its investigational new drug expanded access protocol and clinical trial phases.

"We are very proud to continue as the exclusive distributor for this unique product," said Patrick M. Schmidt, chief executive officer, FFF Enterprises. "VARIZIG offers a specific protection to those most vulnerable to the varicella zoster virus. Having it readily available in our product portfolio supports our mission of 'Helping Healthcare Care.'" ❖

Sources

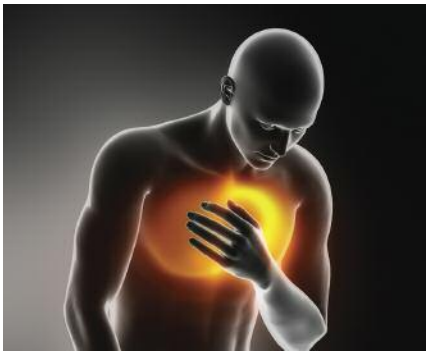
1. U.S. Food and Drug Administration. FDA Approves VARIZIG for Reducing Chickenpox Symptoms. News release, Dec. 21, 2012. Accessed at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333233.htm.
2. Centers for Disease Control and Prevention. Notes from the Field: Severe Varicella in an Immunocompromised Child Exposed to an Unvaccinated Sibling with Varicella — Minnesota, 2011. Morbidity and Mortality Weekly Report, Jul. 20, 2012. Accessed at www.cdc.gov/mmwr/preview/mmwrhtml/mm6128a6.htm.
3. Cangene Corp. VARIZIG Package Insert. Accessed at www.fda.gov/downloads/BiologicsBloodVaccines/.../UCM333220.pdf.

Research

Flu Shot Also May Prevent Heart Attacks

According to two recent studies, the flu vaccine may cut the risk of a heart attack or stroke by up to 50 percent. Scientists from the TIMU Study Group and Network for Innovation in Clinical Research analyzed published clinical trials involving 3,227 patients, half of whom had been diagnosed with heart disease. Participants, whose average age was 60, were randomly assigned to either receive the flu vaccine or a placebo shot, after which their health was tracked for 12 months. Those who received the flu shot were 50 percent less likely to suffer major cardiac events (such as heart attacks or strokes) and 40 percent less likely to die of cardiac causes. Similar trends were found in patients with and without previous heart disease.

Several studies have shown a link between heart attacks and a prior respiratory infection. One study conducted in 2010 of 78,000 patients aged 40 and older found that those who had gotten a flu shot in the previous year were 20 percent less likely to suffer a first heart



attack, even when such cardiovascular risks as smoking, high cholesterol, hypertension and diabetes were taken into account. Because up to 91,000 Americans die from heart attacks and strokes triggered by the flu each year, the American Heart Association and the American College of Cardiology issued guidelines recommending vaccination for patients with cardiovascular disease. Unfortunately, fewer than half of Americans with high-risk conditions such as heart disease get a flu shot. (See also The Heart of the Matter: A Flu Shot Could Save Your Life on p.54) ❖

Vaccines

CDC Recommends Expanded Use of Prevnar 13 Vaccine

The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP) is recommending the expanded use of Pfizer's Prevnar 13 vaccine for adults aged 19 and up with HIV, cancer, advanced kidney disease and other conditions that compromise the immune system. The vaccine, which prevents pneumococcal pneumonia or invasive disease, is not approved for the age 6 to 49 demographic, and while the U.S. Food and Drug Administration approved the vaccine for adults age 50 and older back in December, ACIP has yet to recommend it for older adults. According to an article in the June 20, 2012, edition of the *Chicago Tribune*, observers believe ACIP is waiting for results from a trial of more than 84,000 individuals aged 65 and older to be released in 2013 before making a recommendation. ❖

Research

Autoimmune Mechanism May Cause Drug-Induced Adverse Reactions

U.S. Food and Drug Administration (FDA) researchers have discovered a new mechanism for identifying and understanding drug-related autoimmune reactions. Specifically, they found that in certain at-risk patients, the anti-HIV drug Ziagen (abacavir) causes the immune system to "see" a patient's own healthy tissues and proteins as a foreign invader. The effect is similar to what happens when the immune system recognizes a viral or bacterial protein during an infection. Abacavir is known to cause allergic reactions, which can range from mild skin reactions to severe allergic shock and even death, in certain at-risk patients.

Abacavir interacts with molecules in the immune system called human leukocyte antigens (HLAs), specifically HLA-B*5701, which help the body to distinguish "self" versus "foreign" proteins. The drug can cause HLA-B*5701 to present for the first time certain "self" proteins that the body has not seen before and mistakenly treats them as foreign, resulting in the body trying to destroy its own tissues. HLA-B*5701 is known to be a risk factor for serious reactions to abacavir.

This discovery will provide the FDA with new tools to analyze the safety of drugs that have the potential to cause severe allergic reactions. And, it will advance the FDA's ability to approve therapies that are personalized for safety. The results also may give biopharmaceutical companies and other research organizations new methods to identify early in the development process drugs with the potential to cause severe adverse drug reactions. This may also serve as a model for future research to predict drug reactions in different populations of at-risk patients. ❖

Medicines

FDA Approves Octaplas

Octapharma USA's Octaplas, a solvent/detergent-treated pooled human plasma, has been approved by the U.S. Food and Drug Administration to manage preoperative or bleeding patients who require replacement of multiple plasma coagulation factors and patients with coagulation deficiencies due to hepatic disease or who are undergoing cardiac surgery or liver transplantation, as well as for transfusion or plasma exchange in patients with congenital or acquired thrombotic thrombocytopenic purpura.

Solvent/detergent treatment is a well-recognized method for reducing highly infectious enveloped viruses. Octaplas is designed to improve viral safety, avoid transfusion-related acute lung injury and nonhemolytic allergic reactions, and provide standardized levels of coagulation factors equivalent to single donor fresh frozen plasma.

"Plasma pooling, cell filtration and solvent/detergent treatment may neutralize antibodies against white blood cell antigens and reduce bioactive lipids known to mediate the development of transfusion-related acute lung injury, a severe yet underreported cause of transfusion-associated morbidity and mortality," said Anitha Vijayan, MD, director of the acute dialysis unit and associate professor of medicine at the Washington University School of Medicine in St. Louis. ❖

Research

Autoantibodies May Play Role in Alzheimer's

New research demonstrates how dying or damaged brain cells release debris into the bloodstream and give rise to specific autoantibodies that appear to be reliable biomarkers for early diagnosis of Alzheimer's and other neurodegenerative diseases. The research also identifies a key mechanism in the development of Alzheimer's that mirrors a process that is common in such autoimmune disorders as rheumatoid arthritis.

Conducted at the University of Medicine and Dentistry of New Jersey-School of Osteopathic Medicine (UMDNJ-SOM), the research focused on the role of enzymes, called PADs, in citrullination, a process that converts one type of amino acid into another (amino acids are the building blocks of proteins). After examining postmortem human brain tissue from individuals with Alzheimer's disease and healthy controls, the researchers found that neurons located in the area of the brain first affected by Alzheimer's disease accumulate both citrullinated proteins and a PAD enzyme. In addition, they demonstrated that a specific type of protein, PTCD2, which has been shown to be a potent biomarker for Alzheimer's, was present in citrullinated form in the neuron cells of the Alzheimer's disease brain samples.

These results suggest that when the brain cells die, they release their contents into the fluid that surrounds the brain. The cellular remains then enter the bloodstream and their presence generates the production of specific autoantibodies that target this neuronal debris. This same protein citrullination process has been linked to the development of autoantibodies in rheumatoid arthritis, one of the most common forms of autoimmune disease. The study appears online in the *Journal of Autoimmunity*. ❖

Vaccines

FDA Approves Meningitis Vaccine for Children

A new children's vaccine from GlaxoSmithKline that targets two common causes of bacterial meningitis, which can be fatal, has been approved by the U.S. Food and Drug Administration (FDA). The vaccine, Menhibrix, is meant for children ages 6 weeks to 18 months and combines vaccines for meningococcal disease and Hib disease, both of which are common causes of the infection. The safety of Menhibrix was tested in 7,500 children in the United States, Mexico and Australia. It is given in four doses, and common side effects include pain, redness and swelling at the injection site, irritability and fever.

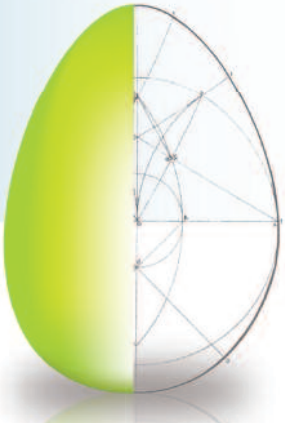
The FDA had rejected Menhibrix twice before in 2010 and 2011, but spokespeople for GlaxoSmithKline say the company has resolved regulators' questions about the vaccine's potency and efficacy. ❖

Vaccine Update

Initial results from a Phase 1 trial of the world's first HIV vaccine has shown no adverse effects while significantly boosting immunity. The vaccine, which is called SAV001-H and is being developed by a team of scientists at Western's Schulich School of Medicine & Dentistry in Canada, is based on a gentically modified, dead virus. If all continues to go well, the vaccine could be commercially available in five years. ❖

Switch to Privigen

Choose the IVIg therapy that is:



Simple.

- Ready-to-use 10% liquid IVIg
- 36-month room temperature storage

Sophisticated.

- First and only IVIg stabilized with proline
- Sucrose-free
- IgA ≤25 mcg/mL

Safe.

- 3-step virus inactivation/removal process, including nanofiltration to approximately 20 nanometers, reduces the risk of pathogen transmission. The risk of virus transmission cannot be completely eliminated

Guarantee your IVIg supply

the privigen® promise™

- Guarantee your IVIg supply for up to 5 years
- Minimize your hospital's supply risk
- Ensure your patients' needs are met

For more information, call **1-888-310-2525** or visit **www.Privigen.com**

privigen®
Immune Globulin Intravenous (Human), 10% Liquid
IVIg therapy made simple

Important Safety Information

Privigen is indicated as replacement therapy for patients with primary immunodeficiency (PI) associated with defects in humoral immunity, including but not limited to common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott- Aldrich syndrome, and severe combined immunodeficiencies. Privigen is also indicated to raise platelet counts in patients with chronic immune thrombocytopenic purpura (ITP).

WARNING: Use of Immune Globulin Intravenous (IVIg) products, particularly those containing sucrose, have been associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death. Privigen does not contain sucrose. Administer Privigen at minimum rate practicable in patients at risk of renal dysfunction or acute renal failure. At-risk patients include those with preexisting renal insufficiency, diabetes mellitus, volume depletion, sepsis, or paraproteinemia; over 65 years of age; or receiving known nephrotoxic drugs. See full prescribing information for complete boxed warning.

Privigen is contraindicated in patients with history of anaphylactic or severe systemic reaction to human immune globulin, in patients with hyperprolinemia, and in IgA-deficient patients with antibodies to IgA and history of hypersensitivity.

Monitor patient vital signs throughout infusion of Privigen. In cases of severe hypersensitivity or anaphylactic reactions, discontinue administration and institute appropriate medical treatment. In patients at risk for developing renal failure, monitor urine output and renal function, including blood urea nitrogen and serum creatinine. Thrombotic events have occurred in patients with risk factors; consider baseline assessment of blood viscosity for those at risk of hyperviscosity. Patients could experience increased serum viscosity, hyperproteinemia or hyponatremia; infrequently, aseptic meningitis syndrome (AMS) may occur (most often with high doses and/or rapid IVIg infusion).

Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to treatment with Privigen. Closely monitor patients for hemolysis and hemolytic anemia. Risk factors for hemolysis include non-O blood group, underlying inflammation, and high doses. Carefully consider relative risks and benefits before prescribing high-dose regimen for chronic ITP in patients at increased risk of thrombosis, hemolysis, acute kidney injury or volume overload.

Monitor patients for pulmonary adverse reactions and signs of transfusion-related acute lung injury (TRALI).

Privigen is derived from human plasma. The risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

In clinical studies of patients being treated with Privigen for PI, the most serious adverse reaction was hypersensitivity (one subject). Adverse reactions observed in >5% of subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

In clinical studies of patients being treated with Privigen for chronic ITP, the most serious adverse reactions were AMS (one subject) and hemolysis (eight subjects). Adverse reactions seen in >5% of subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, increases in conjugated and unconjugated bilirubin, hyperbilirubinemia, and increased blood lactate dehydrogenase.

Treatment with Privigen might interfere with a patient's response to live virus vaccines and could lead to misinterpretation of serologic testing.

Please see brief summary of full prescribing information on following pages.

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring-us.com www.Privigen.com PVG10-11-0014a 6/2012

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Privigen®, Immune Globulin Intravenous (Human), 10% Liquid

Before prescribing, please consult full prescribing information, a brief summary of which follows. Some text and references refer to full prescribing information.

WARNING: ACUTE RENAL DYSFUNCTION/FAILURE

- **Use of Immune Globulin Intravenous (IGIV) products, particularly those containing sucrose, have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephropathy, and death.[1] Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (above 65 years of age), volume depletion, sepsis, paraproteinemia, or receiving known nephrotoxic drugs (*see* *Warnings and Precautions [5.2]*). Privigen does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Privigen at the minimum infusion rate practicable (*see* *Dosage and Administration [2.3]*, *Warnings and Precautions [5.2]*).**

4 CONTRAINDICATIONS

- Privigen is contraindicated in patients who have a history of anaphylactic or severe systemic reaction to the administration of human immune globulin.
- Privigen is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).
- Privigen is contraindicated in IgA-deficient patients with antibodies to IgA and a history of hypersensitivity (*see Warnings and Precautions [5.1]*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur (*see Contraindications [4]*). In case of hypersensitivity, discontinue the Privigen infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Privigen contains trace amounts of IgA (≤25 mcg/mL) (*see Description [11]*). Individuals with IgA deficiency can develop anti-IgA antibodies and anaphylactic reactions (including anaphylaxis and shock) after administration of blood components containing IgA. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions with administration of Privigen. Privigen is contraindicated in patients with antibodies against IgA and a history of hypersensitivity.

5.2 Renal Dysfunction/Failure

Acute renal dysfunction/failure, osmotic nephropathy, and death may occur with the use of IGIV products, including Privigen. Ensure that patients are not volume depleted and assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Privigen and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Privigen. For patients judged to be at risk of developing renal dysfunction because of pre-existing renal insufficiency, or predisposition to acute renal failure (such as those with diabetes mellitus or hypovolemia, those who are overweight, those who use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Privigen at the minimum rate of infusion practicable (*see Boxed Warning*, *Dosage and Administration [2.3]*).

5.3 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.[2-4] Patients at risk 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/ suspected hyperviscosity.

Because of the potentially increased risk of thrombosis, consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/ markedly high triacylglycerols or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Privigen at the minimum rate of infusion practicable *(see Dosage and Administration [2.3]).*

5.4 Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur following treatment with IGIV products, including Privigen. The hyponatremia is likely to be a pseudohyponatremia, as demonstrated by a decreased calculated serum osmolality or elevated osmolar gap. It is critical to distinguish true hyponatremia from pseudohyponatremia, as treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thromboembolic events.[5]

5.5 Aseptic Meningitis Syndrome (AMS)

AMS may occur infrequently following treatment with Privigen (*see Adverse Reactions [6]*) and other human immune globulin products. Discontinuation of treatment has resulted in remission of AMS within several days without sequelae.[6] AMS usually begins within several hours to 2 days following IGIV treatment.

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.

AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

5.6 Hemolysis

Privigen may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin test (DAT) (Coombs' test) result and hemolysis.[7-9] Delayed hemolytic anemia can develop subsequent to Privigen therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[10] Cases of severe hemolysis-related renal dysfunction/failure or disseminated intravascular coagulation have occurred following infusion of Privigen.

The following can be associated with risk of hemolysis: high doses (eg, ≥ 2 g/kg), whether given either as a single administration or divided over several days; non-0 blood group; and underlying inflammatory state.[11,12] Hemolysis has been reported following administration of IGIV for indications including ITP AND PI.

Monitor patients for clinical signs and symptoms of hemolysis. If these are present after a Privigen infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis with clinically compromising anemia after receiving IGIV, perform adequate cross-matching to avoid exacerbating on-going hemolysis.

5.7 Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur following treatment with IGIV products, including Privigen.[11] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment.

Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-human leukocyte antigen (HLA) antibodies in both the product and the patient's serum.

TRALI may be managed using oxygen therapy with adequate ventilatory support.

5.8 Volume Overload

Carefully consider the relative risks and benefits before prescribing the high dose regimen (for chronic ITP) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

5.9 Transmissible Infectious Agents

Because Privigen is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Privigen.

Report any infection thought to be possibly transmitted by Privigen to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.10 Interference with Laboratory Tests

Various passively transferred antibodies in immunoglobulin preparations may lead to misinterpretation of the results of serological testing.

6 ADVERSE REACTIONS

The most serious adverse reactions observed in clinical study subjects receiving Privigen for PI was hypersensitivity in one subject. The most common adverse reactions observed in >5% of clinical study subjects with PI were headache, pain, nausea, fatigue, chills, vomiting, joint swelling/effusion, pyrexia, and urticaria.

The most serious adverse reactions observed in clinical study subjects receiving Privigen for chronic ITP were aseptic meningitis syndrome in one subject and hemolysis in two subjects. Six other subjects in the ITP study experienced hemolysis as documented from clinical laboratory data. The most common adverse reactions observed in >5% of clinical study subjects with chronic ITP were headache, pyrexia/hyperthermia, positive DAT, anemia, vomiting, nausea, hyperthermia, bilirubin conjugated increased, bilirubin unconjugated increased, hyperbilirubinemia, and blood lactate dehydrogenase increased.

6.1 Clinical Trials Experience

Because different 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 the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Treatment of Primary Humoral Immunodeficiency

In a prospective, open-label, single-arm, multicenter clinical study (pivotal study), 80 subjects with PI (with a diagnosis of XLA or CVID) received Privigen every 3 or 4 weeks for up to 12 months (*see Clinical Studies [14.1]*). All subjects had been on regular IGIV replacement therapy for at least 6 months prior to participating in the study. Subjects ranged in age from 3 to 69; 46 (57.5%) were male and 34 (42.5%) were female.

The safety analysis included all 80 subjects, 16 (20%) on the 3-week schedule and 64 (80%) on the 4-week schedule. The median dose of Privigen administered was 428.3 mg/kg (3-week schedule) or 440.6 mg/kg (4-week schedule) and ranged from 200 to 888 mg/kg. A total of 1038 infusions of Privigen were administered, 272 in the 3-week schedule and 766 in the 4-week schedule

Routine premedication was not allowed. However, subjects who experienced two consecutive infusion-related adverse events (AEs) that were likely to be prevented by premedication were permitted to receive antipyretics, antihistamines, NSAIDs, or antiemetic agents. During the study, 8 (10%) subjects received premedication prior to 51 (4.9%) of the 1038 infusions administered.

Temporally associated AEs are those occurring during an infusion or within 72 hours after the end of an infusion, *irrespective of causality*. In this study, the upper bound of the 1-sided 97.5% confidence interval for the proportion of Privigen infusions temporally associated with one or more AEs was 23.8% (actual proportion: 20.8%). The total number of temporally associated AEs was 397 (a rate of 0.38 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Table 2: PI Pivotal Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 Hours After the End of an Infusion, *Irrespective of Causality*

Adverse Event (Excluding Infections)	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Event [n=1038]
Headache	35 (43.8)	82 (0.079)
Pain	20 (25.0)	44 (0.042)
Fatigue	13 (16.3)	27 (0.026)
Nausea	10 (12.5)	19 (0.018)
Chills	9 (11.3)	15 (0.014)
Vomiting	7 (8.8)	13 (0.013)
Pyrexia	6 (7.5)	10 (0.010)
Cough	5 (6.3)	5 (0.005)
Diarrhea	5 (6.3)	5 (0.005)
Stomach discomfort	5 (6.3)	5 (0.005)

Of the 397 temporally associated AEs reported for the 80 subjects with PI, the investigators judged 192 to be at least possibly related to the infusion of Privigen (including 5 serious, severe AEs described below). Of these, 91 were mild, 81 were moderate, 19 were severe, and 1 was of unknown severity.

Table 3: PI Pivotal Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=80]	Number (Rate) of Infusions with Adverse Reaction [n=1038]
Headache	24 (30.0)	62 (0.060)
Pain, all types*	12 (15.0)†	26 (0.025)
Nausea	10 (12.5)	18 (0.017)
Fatigue	9 (11.3)	16 (0.015)
Chills	9 (11.3)	15 (0.014)
Vomiting	6 (7.5)	11 (0.011)

* Includes abdominal pain lower, abdominal tenderness, arthralgia, back pain, chest pain, infusion-site pain, injection-site pain, neck pain, pain, pain in extremity, and pharyngolaryngeal pain.

† Some subjects experienced more than one type of pain.

Sixteen (20%) subjects experienced 41 serious AEs. Five of these AEs (hypersensitivity, chills, fatigue, dizziness, and increased body temperature, all severe) were related to Privigen, occurred in one subject, and resulted in the subject's withdrawal from the study. Two other subjects withdrew from the study due to AEs related to Privigen treatment (chills and headache in one subject; vomiting in the other).

Seventy-seven of the 80 subjects enrolled in this study had a negative DAT at baseline. Of these 77 subjects, 36 (46.8%) developed a positive DAT at some time during the study. However, no subjects showed evidence of hemolytic anemia.

During this study, no subjects tested positive for infection due to human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or B19 virus (B19V).

An extension of the pivotal study was conducted in 55 adult and pediatric subjects with PI to collect additional efficacy, safety, and tolerability data. This study included 45 subjects from the pivotal study who were receiving Privigen and 10 new subjects who were receiving another IGIV product prior to enrolling in the extension study. Subjects ranged in age from 4 to 81 years; 26 (47.3%) were male and 29 (52.7%) were female.

Subjects were treated with Privigen at median doses ranging from 286 to 832 mg/kg per infusion over a treatment period ranging from 1 to 27 months. Twelve (21.8%) subjects were on a 3-week treatment schedule with the number of infusions per subject ranging from 4 to 38 (median: 8 infusions); 43 (78.2%) subjects were on a 4-week schedule with the number of infusions ranging from 1 to 31 (median: 15 infusions). A total of 771 infusions were administered in this study.

In this study, subjects who continued from the pivotal study were permitted to receive infusions of Privigen at a rate up to 12 mg/kg/min (as opposed to the maximum of 8 mg/kg/min allowed in the pivotal study) at the discretion of the investigator based on individual tolerability. Twenty-three (51%) of the 45 subjects from the pivotal study (41.8% of the 55 subjects in the extension study) received 265 (38.4%) infusions at a maximum rate greater than the recommended rate of 8 mg/kg/min (*see Dosing and Administration [2.3]*). The median of the maximum infusion rate in this subset was 12 mg/kg/min. However, because the study was not designed to compare infusion rates, no definitive conclusions regarding tolerability could be drawn for infusion rates higher than the recommended rate of 8 mg/kg/min.

In this study, the proportion of infusions temporally associated with one or more AEs occurring during a Privigen infusion or within 72 hours after the end of an infusion was 15%. The total number of temporally associated AEs, *irrespective of causality*, was 206 (a rate of 0.27 AEs per infusion), reflecting that some subjects experienced more than one AE during the observation period.

Of the 206 temporally associated AEs reported for the 55 subjects with PI, the investigators judged 125 to be at least possibly related to the infusion of Privigen. Of these, 76 were mild, 40 were moderate, and 9 were severe.

Eleven (20%) subjects experienced 17 serious AEs, none of which were considered to be related to Privigen. Three subjects experienced AEs that were considered to be at least possibly related to Privigen: dyspnea and pancytopenia in one subject, a transient ischemic attack 16 days after the infusion in one subject, and mild urticaria in one subject, resulting in the subject's withdrawal from the study.

Treatment of Chronic Immune Thrombocytopenic Purpura

In a prospective, open-label, single-arm, multicenter clinical study, 57 subjects with chronic ITP and a platelet count of 20 x 10^9/L or less received a total of 2 g/kg dose of Privigen administered as 1 g/kg infusions daily for 2 consecutive days (*see Clinical Studies [14.2]*). Subjects ranged in age from 15 to 69; 23 (40.4%) were male and 34 (59.6%) were female.

Concomitant medications affecting platelets or other treatments for chronic ITP were not allowed. Thirty-two (56.1%) subjects received premedication with acetaminophen and/or an antihistamine.

Table 6: Chronic ITP Study – Adverse Events Occurring in >5% of Subjects During a Privigen Infusion or Within 72 hours After the End of a Treatment Cycle, *Irrespective of Causality (Two consecutive daily infusions)*

Adverse Event	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Event [n=114]
Headache	37 (64.9)	41 (0.360)
Pyrexia/hyperthermia	21 (36.8)	22 (0.193)
Nausea	6 (10.5)	6 (0.053)
Epistaxis	6 (10.5)	6 (0.053)
Vomiting	6 (10.5)	6 (0.053)
Blood unconjugated bilirubin increased	6 (10.5)	6 (0.053)
Blood conjugated bilirubin increased	5 (8.8)	5 (0.044)
Blood total bilirubin increased	4 (7.0)	4 (0.035)
Hematocrit decreased	3 (5.3)	3 (0.026)

Table 7: Chronic ITP Study – Adverse Reactions Occurring in >5% of Subjects, *Irrespective of Time of Occurrence*

Adverse Reaction	Number (%) of Subjects [n=57]	Number (Rate) of Infusions With Adverse Reaction [n=114]
Headache	37 (64.9)	52 (0.456)
Pyrexia/hyperthermia	19 (33.3)	21 (0.184)
Positive DAT	6 (10.5)	7 (0.061)
Anemia	6 (10.5)	6 (0.053)
Vomiting	5 (8.8)	6 (0.053)
Nausea	5 (8.8)	7 (0.061)
Bilirubin conjugated, increased	5 (8.8)	5 (0.044)
Bilirubin unconjugated, increased	5 (8.8)	5 (0.044)
Hyperbilirubinemia	3 (5.3)	3 (0.026)
Blood lactate dehydrogenase increased	3 (5.3)	3 (0.026)
Hematocrit decreased	3 (5.3)	3 (0.026)

Of the 149 non-serious AEs related to Privigen, 103 were mild, 37 were moderate, and 9 were severe.

Three subjects experienced three serious AEs, one of which (aseptic meningitis) was related to the infusion of Privigen.

One subject withdrew from the study due to gingival bleeding that was not related to Privigen.

Eight subjects, all of whom had a positive DAT, experienced transient drug-related hemolytic reactions, which were associated with elevated bilirubin, elevated lactate dehydrogenase, and a decrease in hemoglobin level within two days after the infusion of Privigen. Two of the eight subjects were clinically anemic but did not require clinical intervention; these cases resolved uneventfully.

Four other subjects with active bleeding were reported to have developed anemia without evidence of hemolysis.

In this study, there was a decrease in hemoglobin after the first Privigen infusion (median decrease of 1.2 g/dL by Day 8) followed by a return to near baseline by Day 29.

Fifty-six of the 57 subjects in this study had a negative DAT at baseline. Of these 56 subjects, 12 (21.4%) developed a positive DAT during the 29-day study period.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The following adverse reactions have been identified and reported during the post-approval use of IGIV products.[12]

- **Infusion Reactions:** Hypersensitivity (e.g., anaphylaxis), headache, diarrhea, tachycardia, fever, fatigue, dizziness, malaise, chills, flushing, urticaria or other skin reactions, wheezing or other chest discomfort, nausea, vomiting, rigors, back pain, myalgia, arthralgia, and changes in blood pressure
- *Renal*: Acute renal dysfunction/failure, osmotic nephropathy
- *Respiratory*: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- *Cardiovascular:* Cardiac arrest, thromboembolism, vascular collapse, hypotension
- *Neurological:* Coma, loss of consciousness, seizures, tremor, aseptic meningitis syndrome
- *Integumentary:* Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- *Hematologic:* Pancytopenia, leukopenia, hemolysis, positive DAT (Coombs' test)
- *Musculoskeletal:* Back pain
- *Gastrointestinal:* Hepatic dysfunction, abdominal pain
- *General/Body as a Whole:* Pyrexia, rigors

Manufactured by:
CSL Behring AG
Bern, Switzerland
US License No. 1766

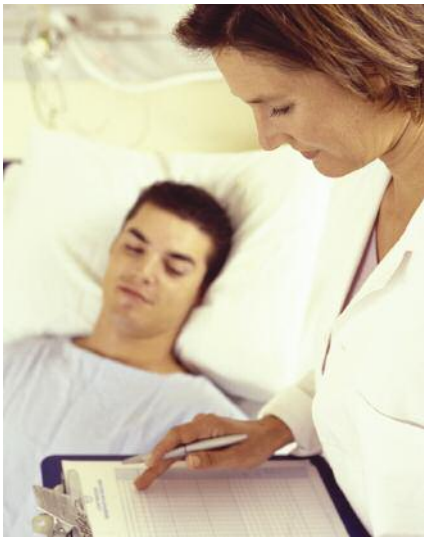
Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA
Based on May 2012 revision

Research

New Study Shows Possible Improvement for CIDP Patients

New study results suggest that treatment with Privigen (Immune Globulin Intravenous [Human], 10% Liquid), an intravenous immunoglobulin (IVIG), may lead to improvement in function in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

The Privigen Impact on Mobility and Autonomy (PRIMA) trial at the Peripheral Nerve Society Inflammatory Neuropathy Consortium Meeting in Rotterdam, Netherlands, a prospective, multicenter, open-label, single-arm study, investigated the efficacy and safety of Privigen in previously IVIG-treated and untreated patients with CIDP. The study achieved its primary efficacy endpoint, which was the percentage of patients responding — as measured by the Inflammatory Neuropathy Cause and Treatment (INCAT) scale — at study completion compared with baseline. The overall response rate was 60.7 percent. The 25-week treatment period



permitted the observation that a response to IVIG can occur late (i.e., after more than six weeks of therapy).

The INCAT scale is used to measure a patient's ability to perform tasks (i.e., walking, motor hand tasks, etc.). On this scale, patient scores rise with increasing weakness and disability, whereas improvement in basic motor functions is indicated by a reduction in the score. Results from this study showed that the mean overall INCAT score significantly improved from 3.7 at baseline to 2.3 at completion of treatment. Half of the responders achieved the clinically meaningful threshold by week four. This finding may encourage some treating physicians to continue IVIG therapy longer in their CIDP patients before assessing whether or not the therapy is working.

"CIDP is a rare, progressive disease that may cause permanent nerve damage, and studies show that current treatment options may not work for all patients," said Jean-Marc Leger, MD, Hospital de la Salpetriere. "Finding new treatment options to slow the advancement of the disease is extremely important. The results from this study are promising as they suggest that Privigen may help decrease weakness and loss of motor function in people with CIDP." ❖

People and Places in the News

AWARDS

CSL Behring has received a **2012 EURORDIS** (European Organization for Rare Diseases) Award for its pioneering work in developing and manufacturing therapies used to treat rare and serious medical conditions. In 2011, the company received the National Organization for Rare Disorders Corporate Award for new treatments for rare diseases brought to market in the U.S.

GRANTS/DONATIONS

Thomas Kodadek, a professor in the department of chemistry on the Scripps Florida campus, has been awarded $4.2 million from the National Institutes of Health in a program to advance what the agency calls "bold and creative research" into type 1 diabetes.

The Mount Sinai Medical Center, Hoboken, N.J., is the second grant recipient of Octapharma's 25th Anniversary Grants Program, which supports clinical or preclinical research focused on human protein therapies in hematology, immune therapy, intensive care and emergency medicine.

CSL Behring has awarded six patient advocacy organizations in the U.S. with Local Empowerment for Advocacy Development (LEAD) grants totaling nearly $70,000. LEAD grants are awarded semiannually and are intended to help local patient organizations achieve their advocacy objectives by further developing an existing initiative or developing a new one. The grants were awarded to the **Carolinas Healthcare Foundation**, **Neuropathy Action Foundation**, **Bleeding Disorder Foundation of Washington**, **Western Pennsylvania Chapter of NHF**, the **Bleeding Disorders Alliance of Illinois** and the **Bleeding Disorders Advocacy Network**.

Research

Previous Exposure to Flu Viruses May Protect the Elderly

A new global study of flu pandemics shows that, often, a large number of elderly individuals are immune to influenza because their bodies had been infected with a similar virus in the past. The research is a follow-up to Dr. Thomas Reichert's (of the Entropy Research Institute in Lincoln, Mass.) study with the National Institutes of Health published in the *Archives of Internal Medicine* in 2005 that showed flu shots don't work well in the elderly. In fact, the study showed that as more and more elderly got flu shots, death rates didn't go down, they went up. The study's authors said they "could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group."

The new study, published in the Dec. 12, 2012, edition of *BMC Medicine*, looked at all five influenza pandemics of the past 100 years. Findings showed that during the 2009 influenza pandemic, most people over age 62 were immune because the flu virus closely resembled viruses they'd been exposed to before 1947. In 1969, people over age 78 had immunity, and in 1918, it was those over age 45 to 55 who were best protected.

According to Dr. Reichert, the "immunity of past experience" has important implications. In pandemic seasons, flu shots and other resources could be diverted to younger people who aren't naturally protected, and businesses could consider cultivating a cadre of retired elderly to bring into the workforce in the event of a severe flu pandemic. ❖

Vaccines

Pancreatic Cancer Vaccine Is Promising

A Phase II clinical trial that is testing the success of a pancreatic cancer vaccine is giving researchers hope that the treatment might be ready for wide distribution within the next couple of years. In the trial, 62 percent of patients who used the vaccine in combination with traditional treatments were cancer-free for at least a year. The year-long survival rate was 86 percent.

Unlike preventive vaccines, the pancreatic cancer vaccine is given to patients after they have already been diagnosed with the disease. It is made up of two types of human pancreatic cancer cells, which the patient's body recognizes as foreign cells. "Theoretically, this primes a patient's immune system into trying to fight his or her own pancreatic cancer," says Jeffrey Hardacre, a doctor at the University Hospitals Case Medical Center in Cleveland, Ohio, and lead author of the study.

Researchers have been working on the vaccine for several years, and Phase III clinical trials have started. They are looking into using similar vaccines to treat melanoma and lung cancer. ❖

Vaccines

Vaccine May Block the Effect of Nicotine

Researchers at the Scripps Research Institute in La Jolla, Calif., have developed a vaccine that may one day protect people against the addictive effects of nicotine.

In the study, mice were injected with a viral shell that contained instructions for making the nicotine antibody. The viral shell also contained instructions to harmlessly infect the liver cells of the mice, thus essentially using the liver as a factory to continuously churn out antibodies that attach to nicotine once it hits the bloodstream. Weeks later, they found antibodies against nicotine in the blood of the treated mice. They then injected the mice with nicotine — about the amount in two cigarettes — and found the antibodies in their blood would bind to the nicotine and prevent it from getting to the brain.

The mice treated with the experimental vaccine had more nicotine in their blood than mice treated with a placebo vaccine, and nearly all of it (83 percent) had been captured by an antibody. The mice injected with the active vaccine also had far less nicotine in their brains compared to the placebo-treated mice. Finally, researchers found

that vaccinated mice didn't appear to experience any of the physical effects of nicotine.

Michael Fingerhood, MD, medical director of the comprehensive care practice at Johns Hopkins Bayview Medical Center in Baltimore, Md., who specializes in the treatment of addiction, called the vaccine a promising approach that warranted more research.

The study was published in the journal *Science Translational Medicine*. ❖

Medicines

Octapharma Initiative Expands Availability of Octagam 5%

Octapharma USA has started an initiative to make octagam (immune globulin intravenous [human] 5%), a therapy for primary immune deficiency, widely available to covered entities in the 340B Drug Pricing Program, which is managed by the Health Resources and Services Administration (HRSA) Office of Pharmacy Affairs (OPA). The 340B Drug Pricing Program is available to certain hospitals, clinics and outpatient treatment facilities that qualify as "covered entities" under Public Law 102-585, the Veterans Health Care Act of 1992, which is codified as Section 340B of the Public Health Service Act. More than 17,000 covered entity sites participate in the 340B Program, including six categories of hospitals that are generally considered safety net providers, and 11 categories of nonhospital covered entities, such as federally qualified health centers and specialized clinics and treatment centers.

"Octapharma is committed to providing therapies to treat life-threatening conditions to all patients, including those who are treated in facilities that have historically faced challenges accessing IGIV," said Octapharma USA President Flemming Nielsen. "We are pleased that the supply of octagam 5% is now sufficient to adequately serve 340B covered entities, that have in recent years experienced difficulties in accessing specialty drugs such as IGIV at 340B discount prices. Octapharma is committed to serving patient needs, regardless of where they receive treatment, and ensuring a steady supply of octagam 5% to all our hospital customers."

Octapharma USA intends to use FFF Enterprises of Temecula, Calif., and ASD Healthcare of Frisco, Texas, as the contact point for distribution. More distributors will be added later in the year. Octapharma USA, a subsidiary of Octapharma AG, one of the world's largest human protein product manufacturers, has been marketing octagam 5% since 2004. ❖

Vaccines

FDA Approves First Injectable Quadrivalent Flu Vaccine

The U.S. Food and Drug Administration (FDA) has approved Fluarix Quadrivalent, a new four-strain seasonal influenza vaccine made by GlaxoSmithKline (GSK), to immunize children ages 3 and older and adults against flu virus subtypes A and B contained in the vaccine. It is the first intramuscular vaccine to protect against four influenza strains.

Three-strain flu vaccines are currently administered to help protect against the two most common A virus strains and the B strain expected to be predominant in a given year. Since 2000, however, two B virus strains have circulated to varying degrees each season, meaning patients infected with the B virus not contained in the vaccine were not immunized. Fluarix Quadrivalent helps protect against the two A strains and adds coverage against a second B strain, the company said.

Three-strain vaccines "have helped protect millions of people against flu, but in six of the last 11 flu seasons, the predominant circulating influenza B strain was not the strain that public health authorities selected," said Dr. Leonard Friedland, head of clinical development and medical affairs for Glaxo's North American vaccines program. "Fluarix Quadrivalent will help protect individuals against both B strains and, from a public health standpoint, can help decrease the burden of disease."

GSK will make the vaccine available in time for the 2013-14 flu season and plans also to fulfill orders for its trivalent, or three-strain, vaccines. Fluarix Quadrivalent is not currently approved or licensed in any country outside of the United States. ❖

Vaccines

Use of Immunization Info Systems Is Increasing

A recent survey conducted by the U.S. Centers for Disease Control and Prevention (CDC) shows that the number of provider sites participating in immunization information systems (IIS), which are recommended as a way to increase vaccination rates, has increased to 48,048. In 2006, 34,639 public and private providers were using IIS. The survey also found that as of 2010, 82 percent of all U.S. children younger than 5 have immunization records that are in IIS, which is an increase from 78 percent in 2009. However, the latest number is still below the Healthy People 2020 target of 95 percent. Thirty-eight of 52 grantees who responded to the survey said they intended to use IIS to interface with the Vaccine Tracking System (VtrckS), the CDC's new national ordering and inventory system for publicly purchased vaccines. But challenges remain, according to the survey, including recruiting and training providers to participate in IIS. ❖

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

The Growing Scourge of Counterfeit Pharmaceuticals

Counterfeits pose a threat for healthcare professionals worldwide. And, while technological advancements are being made to protect the drug supply, international regulation and politics stand in the way of fixing the problem in the foreseeable future.

By Jim Trageser

One of the defining characteristics of modern medicine is the absolute trust both patients and providers place in the delivery system. From ambulance to admission, diagnosis to treatment, Western medicine has developed into such a forthright and upstanding infrastructure that we simply accept at face value the entire medical care chain — allowing physicians to focus their energy and time on dealing with whatever medical issues brought patients into their care in the first place.

However, the growing problem of counterfeit pharmaceuticals threatens this trust. Worse, it puts at risk the well-being, health and very lives of those exposed to these fraudulent products. It also potentially exposes physicians to liability — even though they may have accurately diagnosed the patient, prescribed the appropriate remedy and acted in good faith throughout.

Currently, counterfeit pharmaceuticals are a major problem mostly in developing areas of the world.[1] But with many physicians from developed nations volunteering their time and skills to serve people in the developing world through groups like Doctors Without Borders and many churches, the issue of counterfeit drugs is one that affects all doctors. And the threat of counterfeit prescriptions in Western nations is growing; the U.S. Food and Drug Administration (FDA) reported in February that a counterfeit batch of a cancer drug was discovered in the United States.[2]

Counterfeiting is a threat in all delivery routes. While a recent study from St. Thomas' Hospital in London indicated that the traditional supply route is less vulnerable to counterfeit infiltration than online purchases made directly by patients,[3] even that is not immune to being compromised.[4]

What Are Counterfeit Drugs?

Counterfeits are imitations of legitimate drugs, manufactured and packaged to look like the real thing and passed off to consumers as legitimate. Counterfeits generally are not chemically identical to the legitimate drug; they may contain harmful ingredients, or they may pose no health risk of their own but lack the active ingredients to combat whatever disease or condition the physician is treating. Other times, they contain the wrong dosages of the active ingredient or ingredients. As with other counterfeit goods, counterfeit drugs will be manufactured to look as close to the legitimate product as possible.[5] Indeed, the packaging and product may appear identical.[6]

It is important to note that counterfeit drugs are not generics. Generic drugs — low-cost versions of brand-name patented prescriptions — are subject to the same testing and regulation as the brand-name versions. In addition, counterfeit pharmaceuticals are not manufactured to compete with brand-name drugs the way generics are. They are a fraudulent criminal enterprise whose only purpose is to pass as a legitimate product. They undergo no testing, and those manufacturing them purposely avoid any regulation or oversight.

Who Makes Counterfeit Drugs?

Given the criminal nature of counterfeit drugs, it is impossible to say with any precision who is behind their manufacture and distribution. However, law enforcement officers from around the world believe that the same organized crime outfits that deal in other counterfeit goods are behind the growing counterfeit pharmaceuticals: the Mafia and other crime families, and even terrorist groups looking to finance their operations.[7] The pharmaceutical firm Pfizer reports that the profits from counterfeit prescriptions are often greater than those for street drugs like heroin or cocaine.[8]

Many counterfeit pharmaceuticals can be traced to China and India.[9] Other reports show that Latin America is a source of faked drugs.[10] As with any organized criminal enterprise, those spots around the world with a weak government and spotty law enforcement are most likely to host drug counterfeiters.

Infiltrating the Supply System

Of course, manufacturing a fake pill that looks almost exactly like a popular brand-name drug won't generate any money in and of itself. Money is made when there is a demand for scarce drugs or when there is a demand to pay less for more costly drugs.

Given the criminal nature of counterfeit drugs, it is impossible to say with any precision who is behind their manufacture and distribution.

In developing nations with little government oversight, inserting counterfeit pharmaceuticals into the supply chain is fairly simple. The World Health Organization estimates that some 64 percent of anti-malarial drugs in Nigeria are counterfeit.[11]

And those patients in the West who purchase prescription drugs online open themselves up to the risk of inadvertently purchasing counterfeits. A recent article in the *Chicago Tribune*

pointed out that when consumers buy from an unlicensed, overseas online pharmacy, they have no guarantee that the drugs they receive are what their packaging claims. That same article, though, also listed several recent breaches of the domestic U.S. pharmaceutical supply system — breaches in which respected national drugstore chains and some physicians in northern Illinois were victimized by prescription drug counterfeiters.[12]

Pfizer's brochure on counterfeiting warns that prescription drug wholesalers represent a weak link in the distribution chain, the point where counterfeit drugs can infiltrate the supply.[8] However, the physicians in northern Illinois had apparently dealt with an overseas provider. Either way, both examples are sobering reminders that the amount of money in legitimate pharmaceuticals — well into the hundreds of billions of dollars per year[13] — is attracting hardened and sophisticated criminal enterprises with little compunction about targeting doctors or the poor with their bogus products.

Photo credit: U.S. Food and Drug Administration

Counterfeit drugs often look like the real thing, which is why they should be purchased only from reputable distributors that do not deal in the so-called "gray market." Pictured: real Tamiflu (left); fake Tamiflu (right).

Fighting Back

The rising tide of faked prescription drugs is being addressed by both government agencies and legitimate pharmaceutical companies. With patient health and lives at risk, governments have an obvious interest in intervening. But with some $75 billion a year going to counterfeiters,[14] the pharmaceutical industry is realizing that it, too, needs to be proactive.

In developing nations with little government oversight, inserting counterfeit pharmaceuticals into the supply chain is fairly simple.

Governments are responding to the problem locally through stepped-up enforcement and new legislation, and globally with new treaty proposals and international agreements to stem the flow of counterfeit drugs across borders. And, while the pharmaceutical companies whose products are being counterfeited support many of the governmental approaches, they also are pushing for technological tools to better fight counterfeiting immediately. From lab tests that can detect counterfeits to controlled tracking of legitimate prescription drugs from manufacture to point of sale, new technology can at least make it more difficult and more expensive for counterfeiters to ply their illicit trade.

Updating the Law

The largest obstacle to cracking down on fake pharmaceuticals is the wide disagreement in national laws that regulate the issue, as well as the lack of international consensus — not only about how to tackle counterfeits, but also about the more central question of how to define counterfeits. When the problem of counterfeit pharmaceuticals was first discussed at a World Health Organization (WHO) conference in 1985,[15] existing trade and intellectual property laws and treaties were used to approach the problem. In the years since, those pre-existing laws and treaties have proved ineffective at stemming counterfeit pharmaceuticals.

Further complicating the legal landscape, ongoing disagreements about how to define (and ban) counterfeit drugs while allowing for the development of low-cost but legitimate generics often involve competing national interests among developing and developed countries — disputes that have prevented a unified front in the fight against purely criminal

counterfeits.[16] The governments of many developing nations portray efforts to crack down on counterfeits as nothing more than international bullying, accusing the U.S. and other Western nations of being more interested in protecting the profits of large pharmaceutical companies than in providing affordable care to poor people who can't afford patent-protected brand-name drugs.[17]

This ongoing disagreement over counterfeits versus generics has led to a situation in which there is no globally accepted standard of what constitutes a counterfeit, and so legal enforcement is a hodgepodge. Each nation has its own laws on trademark and copyright and its own web of treaties with other nations determining how complaints from abroad will be handled. The inability to craft agreement on just what constitutes an illegal counterfeit quite obviously makes it difficult to crack down on fake pharmaceuticals.

Promising Advances

If the law is years away from providing an internationally agreed-upon standard of what constitutes a counterfeit drug, technology is beginning to offer some tools for physicians, pharmacists and local governments to determine if a drug's contents match the labeling. And the promise of more such tools are on the horizon.

Thermo Scientific has developed handheld spectrometer scanners that can authenticate the legitimacy of pharmaceuticals at any point in the supply chain.[18] By comparing the spectrum signature of a pill or liquid against the known signature of legitimate pharmaceuticals, the scanner can detect counterfeits (or even bad batches of legitimate drugs that may not be effective due to poor quality control).

In Europe, a Swiss collaboration of academics and hospitals produced the Budget Capillary Electrophoresis, or ECB, which can quickly (in roughly 20 minutes) identify 80 percent of the 200 or so "core" medicines listed by the WHO by measuring how quickly they move through a capillary system and comparing that to known precise measurements for the legitimate drugs.[1]

Other pharmaceutical verification testing products are in the development stage, with technologies ranging from near-infrared spectroscopy to near-infrared chemical imaging. In each case, the test either scans with a light beam and measures the spectrum or uses a small sample for chemical analysis to compare the results against known values. If the measurement doesn't match the known value, the sample will be flagged.

Another technological approach is secure packaging in which each retail unit is embedded with a high-quality three-dimensional holographic image. DuPont's Izon technology[19] increases the difficulty counterfeiters have in making their bogus drugs look exactly like the legitimate products they are targeting, and also lowers the potential profit by significantly increasing the cost of package mimicry.

While these new technological innovations are widely available in the West, a new study from the Institute of Medicine of the National Academies in Washington, D.C., points out that few agencies, public or private, in the developing nations most in need of these new tools have the ability to pay for them.[20]

Technology Meets the Law

But none of these technologies can be effective in protecting the domestic prescription drug supply chain if there are not industrywide protocols in place to ensure that the supply is tested repeatedly and robustly to detect and remove counterfeited products. One such protocol is an e-pedigree. An e-pedigree is an electronic tag that tracks a specific product from manufacture to final retail sale. Unfortunately, at this time, the use of e-pedigrees is spotty and uneven globally, and even varies state to state in the U.S. While California and Florida have taken the lead in implementing e-pedigree standards for pharmaceuticals (with industry adoption mandated to begin as soon as 2015), political opposition from supply chain companies, among others, has kept Congress or the FDA from implementing a national standard.[21] The original proposed start date of 2015 has been pushed back significantly in most other states that have adopted an e-pedigree rule.

The largest obstacle to cracking down on fake pharmaceuticals is the wide disagreement in national laws that regulate the issue, as well as the lack of international consensus.

Protecting Yourself and Your Patients

The FDA's Counterfeit Medicine web page lists more than a dozen prominent counterfeit scams in the United States in just the past few years.[22] With that northern Illinois group of doctors facing FDA investigation for using counterfeit cancer drugs purchased from an overseas supplier, it's clear that physicians will have to be more aware of the source of their pharmaceuticals moving forward. As the FDA pointed out in a recent safety warning to healthcare professionals: "If a medication's price

sounds too good to be true, it can be a sign the drugs offered are substandard, unapproved, stolen or counterfeit. Purchasers should be wary of deep discounts on expensive drugs."[23]

When dispensing pharmaceuticals from a practice, it is imperative that physicians use the best practices they are already familiar with: Purchase only from reputable distributors that do not deal in the so-called "gray market" — overseas secondary wholesalers that buy and sell from one another, and may even repackage the products. This is the weak point in the distribution chain in Western countries.

Patients themselves remain perhaps the best indicator of the presence of counterfeit drugs in the supply chain.

There is even more physicians and other healthcare professionals can do to protect their patients from counterfeit pharmaceuticals. When not providing a drug directly, but prescribing a controlled substance for patients, they can emphasize the importance of filling that prescription through a reputable local pharmacy. If patients are concerned about the costs, particularly of maintenance pharmaceuticals, physicians can work with them to identify low-cost generic alternatives. If no generic alternative exists, there may be a nonprofit organization to which physicians can refer them that is dedicated to the cause of affordable medication in the community.[24]

Patients themselves remain perhaps the best indicator of the presence of counterfeit drugs in the supply chain. The National Association of Boards of Pharmacy points out that patients are most likely to notice if a prescription tastes different than previously or if the texture or color has changed. They also will notice side effects or a lack of efficacy.[25] Physicians can and should counsel their patients on the dangers of counterfeit pharmaceuticals, and advise them to immediately report any concerns if they notice any of the above signs.[26]

A Continuing Problem

The problem of counterfeit pharmaceuticals is not going away any time soon, and for those of us in the West, it is likely to get worse before it gets better. As with all medical issues, it will be physicians who play a large role in how the problem is addressed — and how patients protect themselves in the here and now. ❖

JIM TRAGESER *is a long-time educator, editor and writer, including contributing to two reference books on the blues. He currently works as an executive in the nonprofit sector.*

References

1. Mombelli A. Swiss Technology Battles Fake Drugs. International Service of the Swiss Broadcasting Corp., Dec. 28, 2012. Accessed at www.swissinfo.ch/eng/science_technology/Swiss_technology_battles_fake_drugs.html?cid=34595272.
2. U.S. Food and Drug Administration. Health Care Provider Alert: Another Counterfeit Cancer Medicine Found in United States. Feb. 5, 2013. Accessed at www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/ucm338283.htm.
3. Jackson G, Patel S, Khan S. Assessing the problem of counterfeit medications in the United Kingdom. *Int J Clin Pract* 2012 Mar;66(3):241-50. doi: 10.1111/j.1742-1241.2011.02826.x. Epub 2011 Nov 9. Accessed at www.ncbi.nlm.nih.gov/pubmed/22070229.
4. Goralski MA, LeBlanc HP, Adams MG. Problems of Counterfeit International Pharmaceutical Products. *Business Research Yearbook*, 2011. Accessed at blue.utb.edu/lfalk/BRY2011v1.pdf#page=146.
5. Charatan, F. Fake prescription drugs are flooding the United States. *BMJ* 2001 June 16; 322(7300): 1446. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC1173338.
6. U.S. Food and Drug Administration. Counterfeit Drugs Flickr page. Accessed at www.flickr.com/photos/fdaphotos/sets/72157625426153869.
7. Finlay BD. *Counterfeit Drugs and National Security*. Stimson, February 2011. Accessed at www.stimson.org/images/uploads/research-pdfs/Full_-_Counterfeit_Drugs_and_National_Security.pdf.
8. *Counterfeit Pharmaceuticals: A Serious Threat to Patient Safety*. Pfizer Inc., 2007. Accessed at www.pfizer.com/files/products/CounterfeitBrochure.pdf.
9. McLaughlin KE. Counterfeit medicine from Asia threatens lives in Africa. *The Guardian*, Dec. 23, 2012. Accessed at www.guardian.co.uk/world/2012/dec/23/africa-counterfeit-medicines-trade.
10. What's in That Pill? *Bloomberg Business Week*, June 17, 2001. Accessed at www.businessweek.com/stories/2001-06-17/whats-in-that-pill.
11. Bad Medicine. *The Economist*, Oct. 13, 2012. Accessed at www.economist.com/node/21564546.
12. Shelton DL. Fake medicine poses growing threat to consumers. *Chicago Tribune*, Oct. 16, 2012. Accessed at articles.chicagotribune.com/2012-10-16/business/ct-met-online-pharmacy-fake-drugs-20121016_1_counterfeit-drugs-illegal-online-pharmacies-illegal-medicine.
13. Wikipedia.Pharmaceutical Industry. Accessed at en.wikipedia.org/wiki/Pharmaceutical_industry#Industry_revenues.
14. The Painful Costs of Counterfeit Prescription Drugs. CNBC.com, Oct. 4, 2011. Accessed at www.cnbc.com/id/44759614/The_Painful_Costs_of_Counterfeit_Prescription_Drugs.
15. World Health Organization. General Information on Counterfeit Medicines. Accessed at www.who/int/medicines/services/counterfeit/overview/en.
16. WHO: Approach to "Counterfeit" Drugs May Affect Access to Medicines. Third World Network. Accessed at twnside.org.sg/title2/wto.info/2009/twninfo20090101.htm.
17. Mara K. Counterfeit Medicines in WTO Dispute Process, Heating Up at WHO. Intellectual Property Watch, May 12, 2010. Accessed at www.ip-watch.org/2010/05/12/counterfeit-medicines-in-wto-dispute-process-heating-up-at-who.
18. Rapid Detection of Counterfeit Materials. Thermo Scientific. Accessed at www.ahura scientific.com/anti-counterfeiting/index.php.
19. DuPont Izon. DuPont. Accessed at www2.dupont.com/Authentication/en_US/products_services/ izon_3d_holographics.html.
20. Countering the Problem of Falsified and Substandard Drugs. Institute of Medicine of the National Academies, February 2013. Accessed at www.iom.edu/Reports/2013/Countering-the-Problem-of-Falsified-and-Substandard-Drugs.aspx.
21. Wikipedia. Epedigree. Accessed at en.wikipedia.org/wiki/Epedigree.
22. U.S. Food and Drug Administration. Counterfeit Medicine. Accessed at www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/default.htm.
23. New Counterfeit Avastin Found. The Partnership for Safe Medicines. Accessed at www.safemedicines.org/2013/02/new-counterfeit-avastin-found-medical-practitioners-advised-by-fda-to-be-wary-of-unfamiliar-wholesal-513.html.
24. RxAssist. Accessed at www.rxassist.org.
25. Counterfeit Drugs. National Association of Boards of Pharmacy. Accessed at www.nabp.net/programs/consumer-protection/buying-medicine-online/counterfeit-drugs.
26. U.S. Food and Drug Administration. Reporting of Counterfeit Drug Products. Accessed at www.fda.gov/Drugs/DrugSafety/ucm170314.htm.

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

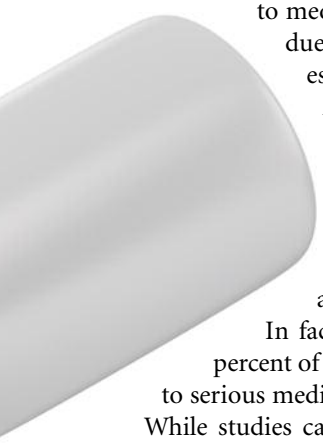
Reducing the Risks of Medication Errors

The federal government, physicians and consumers all have active roles to play in reducing medication errors that so often result in adverse drug events and a high cost burden.

By Amy Scanlin, MS

Medication errors are an enormous problem in the U.S., resulting in adverse drug events (ADEs) and, in many cases, death, as well as a monetary burden on hospitals, physicians, insurance companies and consumers. The more powerful a drug is, the more likely it is to have harmful side effects.[1]

The Institute of Medicine (IOM) of the National Academies estimates in its report *To Err Is Human* that there are between 44,000 and 98,000 hospital deaths annually attributed to medical errors,[2] more than 7,000 of which are due to medication errors.[3] And, the IOM's estimates of between 380,000 and 450,000 ADEs annually in hospital settings are believed to be grossly underestimated. Taking into account ADEs in long-term care and outpatient facilities, errors of omission and ADEs that go unreported, experts estimate that there could be as many as 1.5 million ADEs in the U.S. annually.[1] In fact, it is believed that about 5 percent to 10 percent of patients admitted to hospitals are subjected to serious medication errors.[2]



While studies calculating the cost of these events are not prevalent, it is estimated that each preventable ADE in a hospital setting costs upward of $8,700, including the cost of the hospital stay. Assuming a conservative estimate of 400,000 ADEs annually, the costs of preventable ADEs in a hospital setting alone are $3.5 billion![1]

The good news for physicians is that U.S. quality experts agree that the majority of the predicament is due to problems in the medical system itself, not the doctors and pharmacists functioning within it.[2] Yet while national organizations have expressed urgency in dealing with the issue, that sense of urgency is lacking among physicians and patients who don't view medical errors as the most important problem in healthcare.[4] Clearly, something must be done to improve the system.

The Role of the FDA

The U.S. Food and Drug Administration (FDA) works in conjunction with federal partners to track medication errors, which are defined as "any preventable event that may cause or lead to inappropriate medication use or harm to a patient." These partners include the U.S. Pharmacopeia and the Institute for Safe Medication Practices, which collect reports via the Voluntary Medication Error Reporting Program and automatically send them to the FDA's MedWatch program. Since 2000, the FDA has received more than 95,000 voluntary reports of medication errors via MedWatch."[5]

The FDA also reviews medication error reports for over-the-counter (OTC), prescription and generic drugs via the Division of Medication Error Prevention and Analysis within the Center for Drug Evaluation and Research. The National Coordinating Council for Medication Error Reporting and Prevention's definition of a medical error is "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."[6]

Medical professionals review these error reports and evaluate them for causality, after which the FDA provides recommendations to assist in the prevention of future medical errors. Some of these recommendations include:

- Reviewing and approving drug names to prevent similar-sounding drugs from entering the marketplace (the agency reviews about 400 submitted drug names annually from pharmaceutical companies and rejects one-third)
- Requiring OTCs to have a standardized drug facts label
- Requiring bar-code labeling for certain drugs and biologics, facilitating comparison via quick review of computerized patient information systems to ensure the right drug is given to the right patient at the right time
- Eliminating potentially confusing abbreviations such as IU, which can be mistaken for IV and the use of leading zeros before decimals instead of trailing afterward (for example, 0.5 mg, which has little chance of misinterpretation versus 5.0 mg, which can be confused for 50)

The more powerful a drug is, the more likely it is to have harmful side effects.

It is estimated that 45 percent of hospital admissions and 19 percent of treat-and-release emergency room visits are due to five drug categories, known as high-risk medications: corticosteroids, anticoagulants, antineoplastics and immunosuppressants, antibiotics and opiates.[7] Amy Ehlers, BS, PharmD, BCPS, director of pharmacy at NuFACTOR Specialty Pharmacy, says, "These medications have been identified to have a higher-than-expected risk to cause harm when used as intended or have a higher risk of causing significant harm when used in error." In addition, she says, "high-alert medications often require monitoring to ensure optimal therapeutic outcomes. The classification of high-alert medications may be due to the

type of drug itself (antineoplastics) or have a limited therapeutic window (anticoagulants), which makes dose titration more challenging. And, the side effects that they cause may be severe in the event something does go wrong (narcotics, for example, can cause decreased respiration rates in higher doses). Also, the patient population these drugs are prescribed for may cause a predisposition to adverse events. For instance, an older adult who is hospitalized for pneumonia may receive antibiotics, corticosteroids and opiates to treat the pneumonia, but it would not be unheard of for this same patient to be taking other high-risk medication as well."

The Role of the Physician

Hospital settings are a common place for medication errors to occur. From prescription, administration, monitoring and even procurement of the correct drug, there are many steps in the process during which a mistake can be made. Michael R. Cohen, author of the book *Medication Errors,* says the "five rights" of prescriptions (right patient, right drug, right time, right dose and right route of administration) place too much emphasis on individual performance and overlook the systemic problems that underlie the human errors. He emphasizes that "finding out who was involved is less important than learning what went wrong, how and why."[8]

The U.S. Food and Drug Administration (FDA) works in conjunction with federal partners to track medication errors.

Most commonly, mistakes occur during prescribing and administering a drug. One solution is computerized physician ordering systems such as e-scripts and bar-code verification technology. E-scripts provide an extra layer of protection by automatically comparing a patient's records against allergies, other medications and any contraindications of any new prescriptions, as well as confirmation of dosage amounts. Studies show that e-scripts can reduce errors by as much as 81 percent,[9] bar-code verification technology can reduce them by more than 50 percent, and transcription errors can be completely eliminated.[10]

However, a real challenge to these systems is proper usage by physicians, as well as notification types and methods of the system themselves. A recent study of nearly 3,000 physicians

and other prescribers showed that 90 percent of the time, warnings by electronic health records (EHRs) were not heeded, and the prescription was written as planned. Apparently, in many cases, physicians feel that the large number of alerts, often irrelevant to a patient's circumstances, appear to be overrunning the system. So, in systems that allow, adjustments are made so that only the highest level of alerts get through; in others, the clinical decision alerts appear to be turned off altogether due to the overwhelming alert numbers.[11]

In 2011, the American Academy of Family Physicians, the American College of Physicians, the American Medical Association, the Center for Improving Medication Management, the e-Health Initiative and the Medical Group Management Association teamed up to develop the 56-page *2011 Clinician's Guide to e-Prescribing*. The guide includes information on meeting the federal criteria for meaningful use of EHR systems — a necessary precursor to receiving federal health IT subsidies — as well as details on new Medicare e-prescribing requirements and frequently asked questions about adopting health information technology.[12]

Another common medication error is overprescribing. Some cite a lack of instruction on how to prescribe medications in medical school as partly to blame for the trend of overprescribing. Learning early on to start patients on one drug at a time, as well as continually being educated about possible adverse events and potential drug interactions, can be helpful for physicians.[13]

An additional way physicians can help reduce the risk of medication errors is to help patients fully understand their diagnoses, including the risks and possible side effects of all medications taken, and what to do if they notice anything unusual after taking medications.

The Role of the Consumer

Patients also have a responsibility to prevent unintended side effects of medicines. They should be encouraged to take an active role in their medical care to better understand their diagnoses and treatment options and to monitor their progress of care. "Patients [should] come to appointments prepared with a list of updates in regard to changes in their current health and medications, including prescription, over-the-counter and herbal medications," says Ehlers. In addition, she says, they should make a list of questions and make sure those questions and any other concerns are addressed. However, patients need to be realistic in their expectations. Many medications cause side effects in addition to the benefits they provide, and while some side effects may be manageable, others may not. The risks versus benefits should always be considered.

Monitoring for unusual side effects is especially important in this era of polypharmacy.

"Patients also should try to avoid using multiple pharmacies whenever possible," suggests Ehlers. "In the event that patients do, they need to ensure all pharmacists are kept up-to-date on medication or allergy information. And, when receiving a new medication, they shouldn't walk away or hang up the phone until they have a clear understanding of how to use it. Finally, if something doesn't seem right, they need to ask. Medication errors are an unfortunate part of healthcare, and in so many cases, someone noticed or felt that something wasn't right, but for various reasons did not say anything."

Monitoring for unusual side effects is especially important in this era of polypharmacy (the use of multiple medications by a patient); hospitalizations for medication side effects jumped by more than half between 2004 and 2008. Most major drugs are effective in only 25 percent to 60 percent of patients because of the variability in drug response due to reasons such as the environment, genetics and metabolism, to name a few.[14]

According to a report released by the Agency for Healthcare Research and Quality, less than 25 percent of drug-related emergency visits were due to physician or pharmacist error; the rest were due to unintended side effects when patients took prescriptions as they were instructed. With patients often seeing more than one doctor for various health concerns, it is inevitable that drug overlaps will occur since doctors are not always informed or even misinformed about how those patients are being treated by another doctor.[10]

Improved access to standardized patient medical records should help with drug overlaps, as well as an Obama administration proposal to track patients' medications and opioids via a prescription monitoring program.[10]

Reducing the Risks

While medication errors will likely never be fully eliminated, much is being done in the healthcare industry to reduce the risks. More sensitive EHRs that help to flag appropriate risks, more comprehensive training to ensure physicians understand the complete picture of the drugs they prescribe, and increased patient education about the importance of the active role they play in their medical care all will help to improve outcomes. ❖

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

References

1. Institutes of Medicine. Preventing Medication Errors. Report Brief, July 2006. Accessed at www.iom.edu/~/media/Files/Report%20Files/2006/Preventing-Medication-Errors-Quality-Chasm-Series/medicationerrorsnew.pdf.
2. Kaiser Permanente. Reducing Medical Errors. Accessed at www.kaiseredu.org/Issue-Modules/Reducing-Medical-Errors/Background-Brief.aspx.
3. U.S. Food and Drug Administration. FDA and ISMP Launch Campaign to Reduce Medication Mistakes Caused by Unclear Medical Abbreviations. Press release, June 14, 2006. Accessed at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108671.htm.
4. Blendon, RJ, DesRoches, CM, Brodie, M. Views of Practicing Physicians and the Public on Medical Errors. *N Engl J Med* 2002; 347:1933-1940. Accessed at www.nejm.org/doi/full/10.1056/NEJMsa022151.
5. U.S. Food and Drug Administration. FDA 101: Medication Errors. Accessed at www.fda.gov/ForConsumers/ConsumerUpdates/ucm048644.htm.
6. U.S. Food and Drug Administration. Medication Errors. Accessed at www.fda.gov/Drugs/DrugSafety/MedicationErrors/default.htm.
7. O'Reilly, K. Rx Side Effects Causing More Hospitalizations. American Medical Association *Med News*, May 2, 2011. Accessed at www.ama-assn.org/amednews/2011/05/02/prl20502.htm.
8. Committee on Identifying and Preventing Medication Errors and the Board on Health Care Services. Preventing Medication Errors. *N Engl J Med* 2007; 357:624-625. Accessed at www.nejm.org/doi/full/10.1056/NEJMbkrev58255.
9. Koppel, R, Metlay, JP, Cohen, A, et al. Role of Computerized Physician Order Entry Systems in Facilitating Medication Errors. *JAMA* 2005;293(10):1197-1203. Accessed at jama.jamanetwork.com/article.aspx?articleid=200498.
10. Poon, ED, Keohane, CA, Yoon, CS, et al. Effect of Bar-Code Technology on the Safety of Medication Administration. *N Engl J Med* 2010; 362:1698-1707. Accessed at www.nejm.org/doi/full/10.1056/NEJMsa0907115.
11. O'Reilly, K. Doctors Override Most Rx Safety Alerts. American Medical Association *Med News*, Mar 9, 2009. Accessed at www.ama-assn.org/amednews/2009/03/09/prsa0309.htm.
12. Medical Group Management Association-American College of Medical Practice Executives. *2011 Clinician's Guide to e-Prescribing*. Accessed at www.mgma.com/WorkArea/DownloadAsset.aspx?id/1248619.
13. Krupa, C. Physicians Advised to Adopt Conservative Prescribing Habits. American Medical Association *Med News*, June 27, 2011. Accessed at www.ama-assn.org/amednews/2011/06/27/hlsa0627.htm.
14. Wilkinson, G. Drug Metabolism and Variability among Patients in Drug Response. *N Engl J Med* 2005; 352:2211-2221. Accessed at www.nejm.org/doi/full/10.1056/NEJMra032424.

Healthcare Workers and the Flu Vaccine: The Backlash

Despite evidence that vaccinating healthcare workers against influenza helps to protect patients, many still refuse — even during the worst flu season in nearly a decade.

By Ronale Tucker Rhodes, MS

The 2012-2013 flu season is officially over, but the consequences due to the refusal by many healthcare workers to get vaccinated against the influenza virus are all too real. Unfortunately, the full impact of the spread of the flu from unvaccinated healthcare workers to the public will never be known, but this issue is especially troublesome during seasons with high levels of flu activity. And this past season was one of the worst in recent years because it started significantly earlier than normal. "This is the earliest flu season we've had in nearly a decade, since the 2003-2004 flu season,"

said Centers for Disease Control and Prevention (CDC) spokesman Thomas Frieden. In fact, this season is in stark contrast to last season, which set a record for the lowest and shortest peak for influenza-like illness. By mid-January, flu was widespread in most states, and at least 20 children had died. Five states were particularly hard hit: Tennessee, Mississippi, Alabama, Louisiana and Texas.

Curbing the spread of flu is difficult in the best of circumstances, but it is especially compounded when healthcare workers refuse to be vaccinated. Every day on the job, these workers have a high rate of contact with those who are most vulnerable such as the very young, the very old and the immunocompromised — populations that are most susceptible to suffering severe consequences from the flu, including death. In fact, this year's strain of the influenza virus is killing seniors at the highest rate (116 deaths per 100,000 cases) since age-related tracking began in 2005.[1]

The Irrefutable Risk of Contagion

A recent study indicates that the flu is much more contagious than once thought. Researchers at the Wake Forest School of Medicine in North Carolina sampled the air for flu-like symptoms in rooms of patients who visited the hospital during the 2010-2011 flu season. Using devices that were placed 1, 3 and 6 feet away from the patients while they lay in bed, they found potentially infectious flu virus particles at each of the sample locations. It was previously thought that the flu spreads mainly through large particles, or droplets, in the air that travel short distances, from 3 to 6 feet. But this study showed that most flu viruses are found in very small particles, which can travel farther than larger ones, in the air. And because the study didn't look at distances beyond 6 feet, the researchers can't say whether the flu virus can travel farther.[2]

Because healthcare ranks among the nation's largest industries, providing more than 14 million jobs, healthcare workers represent a significant source of potential spread of the flu. And when they're infected by the flu virus, patient avoidance isn't always an option. Indeed, a little known fact is that a person who has acquired the influenza virus is contagious for nearly a week, starting a day before any symptoms appear. Thus, it is possible to spread the flu over the course of an entire working day before workers even know they are sick.

During the 1991-1992 flu season, 65 nursing home residents in New York contracted the flu, and two died; only 10 percent of the home's healthcare workers had been vaccinated before the outbreak. In 2000, 19 babies in a neonatal intensive care unit in Ontario, Canada, were infected with the flu and one died; only 15 percent of healthcare workers were immunized. In 2008, nearly 100 patients caught the flu at Royal Liverpool University Hospital in England, including those on high-dependency wards treating blood diseases and kidney problems. And, several years ago, two pediatric patients at Children's Hospital in Philadelphia couldn't get the flu shot because they were receiving cancer treatment; both died from getting the flu at the hospital.[3]

Curbing the spread of flu is difficult in the best of circumstances, but it is especially compounded when healthcare workers refuse to be vaccinated.

The Stats

The CDC's goal is for 90 percent of healthcare workers to receive influenza vaccinations by 2020. According to Dr. Arthur Caplan, a bioethicist at New York University's Langone Medical Center, 90 percent is the level of immunity that will provide sufficient protection to the sick. "You don't get the 'herd immunity' until you hit 90 percent," said Caplan, a proponent of mandatory vaccinations.

Yet while the percentage of healthcare workers receiving the flu vaccine is growing, the CDC's goal remains elusive. According to a CDC survey of 2,006 healthcare personnel, the overall rate of flu vaccination for healthcare personnel across all settings is only 62.9 percent. So far this year, pharmacists have led the way with 88.7 percent receiving a flu vaccination, followed by 83.8 percent of physicians, 81.5 percent of nurses, 73.3 percent of nurse practitioners and physician assistants, and 76.7 percent of other clinical professionals (allied health professionals, dentists, technicians and technologists). When looking at the healthcare setting, 83.4 percent of workers at hospitals have been vaccinated this year, compared with 77.8 percent in 2011; 65.4 percent of staff at physician offices or ambulatory care settings have been vaccinated, compared with 64.4 percent in 2011; and 56.6 percent of workers at other facilities such as dental offices, pharmacies, home-medical sites and medical schools have been vaccinated, compared

with 57 percent in 2011. What's particularly disturbing in this survey, though, is that only 48.7 percent of healthcare workers at long-term-care facilities have been vaccinated.[4]

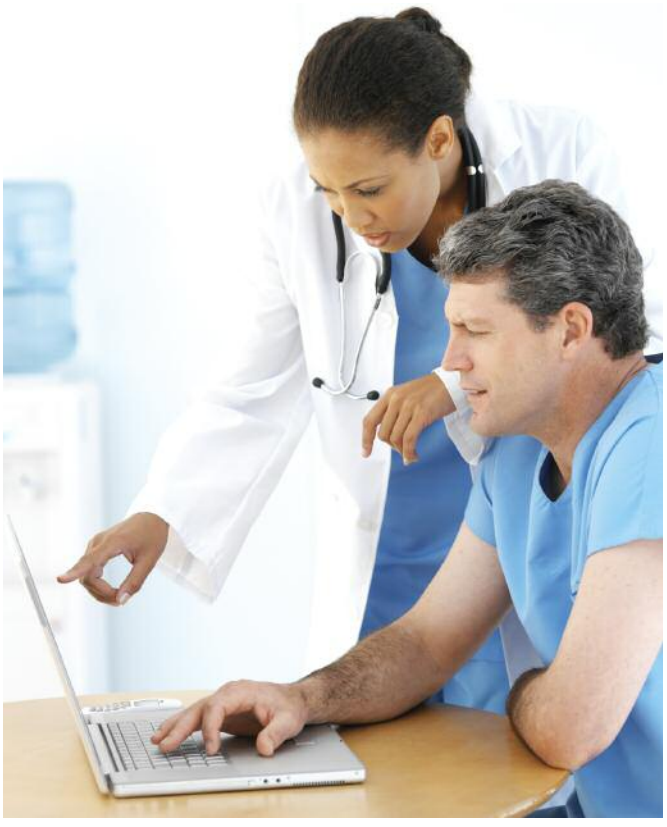
Why would people committed to protect sick patients refuse a flu shot? The reasons vary, from religious objections to skepticism about whether the vaccine works and whether vaccinating healthcare workers will prevent flu in patients, to allergies or complications arising from the vaccine. But serious reactions to the flu shot are extremely rare: Fewer than five in a million.[5] And, according to Dr. Carolyn Bridges, associate director for adult immunization at the CDC, the strongest evidence that vaccinating healthcare workers prevents flu in patients is from studies in nursing homes that link flu vaccination among healthcare workers with fewer patient deaths from all causes.[6]

Government and Private Organizations Step In

To combat healthcare workers' resistance to getting vaccinated against the flu, both government and private organizations are stepping in. The Centers for Medicare & Medicaid Services (CMS) issued new regulations requiring hospitals to report employees' flu vaccination rates as a means to boost the rates. The goal is to post the information on the agency's "Hospital Compare" website.[6] Even more significantly, the CMS will cut hospital reimbursements by 2 percent beginning in 2015 if they fail to report patient quality measures, including healthcare worker vaccination rates starting in February.[7]

Because healthcare ranks among the nation's largest industries, providing more than 14 million jobs, healthcare workers are a significant source of potential spread of the flu.

Last year, the American College of Physicians issued a new recommendation that all healthcare providers receive a variety of immunizations, including the seasonal influenza vaccine.[8] In addition, the Joint Commission, the top healthcare accreditation agency in the nation, enacted a plan to have



hospitals train and educate staffs about the benefits of flu vaccines. While the commission is not demanding mandatory vaccinations, it is requiring hospitals to show they are progressing toward 90 percent compliance by 2020.[7] On the other hand, the American Medical Association in November endorsed mandatory shots for those with direct patient contact in nursing homes. And, the American Nurses Association supports these mandates if they're adopted at the state level and affect all hospitals.[6] Even the National Workrights Institute, a spinoff of the American Civil Liberties Union, supports mandatory vaccinations. According to its president, Lewis Maltby, "You can't stick a needle in somebody's arm who doesn't want it stuck in their arm. [But], if the hospital wants to make it mandatory, [it] should be able to."[7]

Several states do have laws or regulations requiring flu vaccines for healthcare workers, and most provide exemptions for those with religious or medical reasons. But only three — Arkansas, Maine and Rhode Island — impose penalties for those who refuse. For instance, Rhode Island's regulation, which was enacted in December, requires unvaccinated workers in contact with patients to wear face masks during flu seasons, and those who refuse can be fined $100 and may face a complaint

or reprimand for unprofessional conduct that could result in losing their professional license.[6]

Setting an Example

A CDC analysis showed that factors associated with improved immunization rates against the flu among healthcare workers included employer requirements, promotion of influenza vaccination by an employer and having vaccines offered at no cost on multiple days at the workplace.[8] And, most hospitals have implemented these practices to persuade their workers to get vaccinated. A survey by CDC researchers found that in 2011, more than 400 U.S. hospitals required flu vaccinations for their employees.[9] Unfortunately, as the statistics show, many workers still fail to get an annual flu shot. Now, faced with losing Medicare dollars, the rule of simply encouraging workers to get vaccinated is over or about to end.

There is no official count of how many healthcare workers have been fired for refusing to get a flu shot or have resigned in protest. The CDC survey showed that in 2011, 29 hospitals fired unvaccinated employees.[9] With today's news reports, it's safe to say that the numbers are likely in the hundreds.

The Centers for Medicare & Medicaid Services (CMS) issued new regulations requiring hospitals to report employees' flu vaccination rates as a means to boost the rates.

Of course, many of these employees who have been fired have filed exemptions and others have filed lawsuits. In Rhode Island, more than 1,000 workers recently signed a petition opposing the state's mandate, according to a labor union that has filed suit to end the regulation.[6] But, in several instances, hospital officials are rejecting exemption applications using the guidelines provided by the CDC and the U.S. Equal Employment Opportunity Commission (EEOC). "The EEOC's guidelines specify that just because there are beliefs that are strongly held does not mean that they are protected by a religious blanket, so social, political and economic philosophies and personal preferences, those are not religious beliefs," said Melanie McDonald, a hospital spokeswoman for IU Health Goshen Hospital in northern Indiana that fired eight employees.[10]

Do No Harm

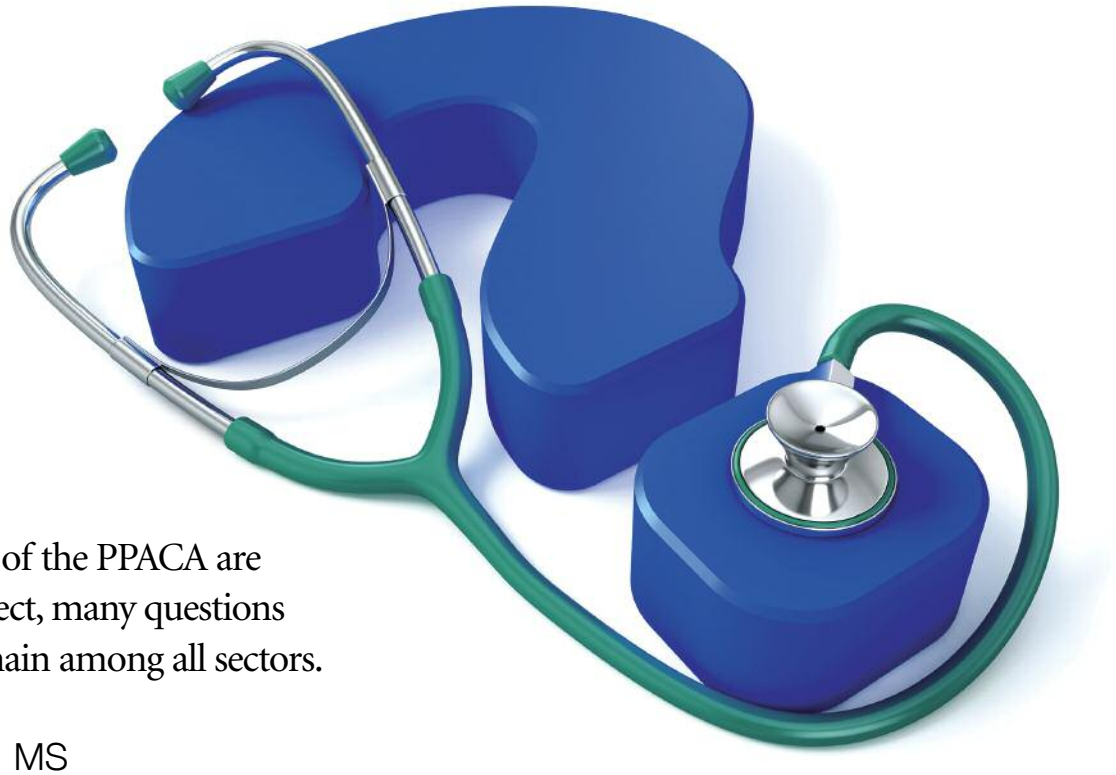
Considering CDC estimates that on average 200,000 hospitalizations and a range of 3,000 to 50,000 deaths occur annually due to influenza-related infection, getting a flu shot would seem to make sense, especially for those without religious or health exemptions. Vaccinating healthcare workers against the highly contagious flu reduces the spread of infection, reduces patient mortality and worker absenteeism, and in the long run, may save hospitals money. Most important, protecting the patient — already sick and susceptible to infection— is inherent to the healthcare profession. Paul Offitt, chief of infectious diseases at Children's Hospital in Philadelphia where two children died from contracting the flu, says this to healthcare workers: "It's not your inalienable right not to get a vaccine if you're helping care for vulnerable patients." ❖

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

References

1. Lloyd, J. Mandatory Flu Shots Opposed by Some Health Care Workers. *USA Today*, Jan. 16, 2013. Accessed at www.usatoday.com/story/news/nation/2013/01/16/mandatory-flu-shot-nurses/1832813.
2. Rettner, R. Stand Back: Flu Virus Travels Faster Than You Think. NBCNews.com, Jan. 31, 2013. Accessed at www.nbcnews.com/id/50652183/ns/health-cold_and_flu/#.URAwLXYnjdM.
3. Weise, E. Flu Attacking Elderly at Historically High Rates. *USA Today*, Feb. 4, 2013. Accessed at www.usatoday.com/story/news/health/2013/02/01/flu-cdc-warning-children-deaths/1882909.
4. Selvam, A. Flu Vaccination Rate Rises for Healthcare Workers, CDC Reports. ModernHealthcare.com, Dec. 3, 2012. Accessed at www.modernhealthcare.com/article/20121203/NEWS/312039950.
5. MedlinePlus. Influenza Vaccine, Inactivated. Accessed at www.nlm.nih.gov/medlineplus/druginfo/meds/a607017.html.
6. Hospitals Get Tough on Workers Refusing Flu Shots. Associated Press, Jan. 13, 2013. Accessed at www.modernhealthcare.com/article/20130113/INFO/301119984.
7. Darragh, T. Hospitals Requiring Staff to Get Flu Vaccines. *The Morning Call*, Dec. 1, 2012. Accessed at articles.mcall.com/2012-12-01/health/mc-pennsylvania-hospitals-require-flu-vaccinations-20121201_1_flu-vaccines-hospital-workers-flu-shots.
8. Neale, T. ACP Calls for Flu Shots for All Health Workers. MedPage Today, Jan. 15, 2013. Accessed at www.medpagetoday.com/InfectiousDisease/URItheFlu/36854.
9. Tanner, L. Hospital Workers Being Fired for Refusing Flu Shots. Associated Press, Jan. 12, 2013. Accessed at www.azcentral.com/news/free/20130112flu-shots-hospital-workers-fired.html.
10. Indiana Hospital Fires 8 Workers Who Refused Flu Shot. Associated Press, Jan. 1, 2013. Accessed at www.foxnews.com/health/2013/01/01/indiana-hospital-fires-8-workers-who-refused-flu-shot.

HEALTHCARE REFORM: THE EFFECTS OF THE ELECTION



As the provisions of the PPACA are being put into effect, many questions and concerns remain among all sectors.

By Amy Scanlin, MS

President Obama has been re-elected, and the Patient Protection and Affordable Care Act (PPACA) has been declared constitutional. As such, changes in healthcare coverage and implications for insurance companies, drug and medical device manufacturers, physicians and patients are moving forward, amid many questions as to what is to be expected. With the plans and policies of the PPACA still evolving, it will be many years before the full implications are seen. However, there are some key effects of the election outcome that will prepare us for what to expect in the near term.

First, some facts:

• Health insurance exchanges will be fully in place by January 2014.

• In 2011, drug companies were taxed higher to the tune of $27 billion, and in 2013, it is expected that new taxes on medical devices will total approximately $20 billion.[1]

• An estimated 16 million to 18 million people, or anyone with incomes lower than 133 percent of the federal poverty level, will be added to the Medicaid system.

• The influx of patients will strain access to providers who accept Medicaid. According to a survey of providers conducted by Sermo and Athena Health, 66 percent of physicians have considered dropping out of government-run health programs.[2]

• High-risk insurance pools have not had the level of anticipated success so far, so changes to enrollment are being made. In addition, a proposed long-term care provision called the Community Living Assistance Services and Support program (CLASS Act) has been suspended due to an inability by officials to find a way to make it financially feasible.[3]

Universal Coverage

While the government estimates the PPACA will reduce the number of uninsured by 32 million by 2019, further estimates say that 23 million will continue to remain uninsured. Medicaid will see an increase of between 16 million and 18 million people, and 24 million people will become eligible to be insured through state-based exchanges beginning in 2014.

Many predict that those seeking care through Medicaid will

have a tough time finding providers because low Medicaid reimbursement rates have reduced the number of physicians who accept it. Faced with a scarcity of providers, many Medicaid-eligible patients may seek healthcare through emergency room visits, by some estimates even more than the number of emergency room visits by the uninsured.[4]

However, it is not just Medicaid patients who may have trouble finding care. With millions of newly insured patients in the system, appointments will become harder to find for most everyone. "There is not much the country can do about the shortage of primary care physicians in the near term," says Marc Boutin, executive vice president and chief operating officer at the National Health Council. "However, federal and state legislators have been working on the idea of getting allied health professionals to take on more services under primary care, for example using physician assistants and moving responsibilities to other levels. There is certainly anxiety [about the vast numbers of new patients coming into the system], but we need to realign the delivery system in an appropriate way."

Starting in 2014, unless exempt for financial hardship or religious reasons, those who can afford it will be required to have health insurance or pay a fine of 1 percent of their income or $95 for an individual in 2014 and increasing to 2.5 percent of their income or $695 by 2016. For families, the penalty would be 2.5 percent of household income or $2,085, whichever is greater. Subsidies to purchase insurance will be provided for those who need it, or they may qualify for Medicaid.

Children presently cannot be denied coverage for a pre-existing condition, and this will extend to adults in 2014.

Employers may choose to keep the insurance plans they currently offer, but they are under no obligation to do so, and they may also change premiums, deductibles and co-pays. However, in 2014, small businesses that employ 50 or more people, have at least one employee using subsidized healthcare, and choose not to provide healthcare insurance will be fined $2,000 per full-time employee. Tax credits will be offered to small businesses to help encourage them to provide insurance coverage.[3]

The Supreme Court has ruled that states cannot be forced to require state-based exchanges or to provide Medicaid insurance to all those who fall 133 percent or more below the poverty level. As well, federal funding for Medicaid cannot be withheld from states that choose not to create their own state-based exchange. However, states must determine whether they will offer their own state-based exchange, default to a federally facilitated exchange or form a hybrid of the two. Those states that choose not to increase Medicaid coverage will continue to receive their Medicaid subsidies at their present rate. Those that choose to increase coverage will receive 100 percent coverage for all newly enrolled beneficiaries between 2014 and 2016, and 90 percent thereafter. In addition, states that choose to increase Medicaid coverage are also able to reduce that coverage after 2016 when the 100 percent coverage drops to 90 percent.[5]

A lot of decisions about how to implement the new rules are being left to the states as well. "Right now, there is no uniform anti-discrimination language [and] no uniform appeals process. What we expect within a plan may vary from state to state. States may leave these things up to the insurance companies to define." says Boutin. That becomes especially confusing for physicians who participate in multiple insurance plans, Medicare and Medicaid. "They will have a different definition within each plan. That lack of standardization within states has the potential for real challenge, and the physician's ability to appeal on behalf of the patient is a great concern right now. We really think standard definitions and applications around medical necessities and the appeals processes are important. It [the essential health benefits package] will have diminished impact without it."

With the plans and policies of the PPACA still evolving, it will be many years before the full impacts are seen.

The PPACA aims to improve healthcare in rural and underserved areas through a federally funded program (to the tune of $230 million over the next five years) called the Teaching Health Center Graduate Medical Education Program (THCGMEP). Medical residents may participate in training at community-based health centers that operate a primary care residency program, such as federally qualified health centers, community mental health centers and health centers run by the Indian Health Service. While medical residents have always had the option to train in underserved areas, this provides additional federal funding to encourage them to do so.

Eleven THCGMEP centers were federally funded in 2011, and in 2012, 22 resident programs received funding. The program is being expanded again this year in hopes that those in residency in primary care centers will stay in primary care, an area of medicine that currently has a shortage of physicians and projects a shortfall of 45,500 primary care providers by 2020, according to the American Colleges Center of Workforce Studies.[6]

High-risk patients also stand to benefit from the PPACA. Just recently, President Obama signed into law the Medicare IVIG Access Act (HR 1845) as part of the PPACA, which provides for a three-year demonstration project to address expanding access for Medicare patients with primary immunodeficiency diseases to intravenous immune globulin (IVIG) treatments administered at home. Prior to signing the bill, the cost of the IVIG drug was covered under Medicare Part B, but not the associated costs of administration, which effectively made the ability for at-home treatments ineffective. One note of caution, however, is that more clarification is needed on the specifics of the law, specifically with regard to pre-existing conditions, because some IVIG treatments are warranted for conditions not covered under Medicare.[7]

While the government estimates the PPACA will reduce the number of uninsured by 32 million by 2019, further estimates say that 23 million will continue to remain uninsured.

One provision for those with high-risk conditions that has been adjusted since the inception of the PPACA is that of high-risk insurance pools, or the pre-existing condition insurance plan. It was expected that between 200,000 and 400,000 would join these pools designed for those with pre-existing conditions who are unable to purchase insurance through private carriers. However, enrollment has been much lower than expected.[3] Therefore, the requirements to join the pools, as well as the premiums, have been adjusted to encourage enrollment, and advertising has been increased, particularly through the Social Security Administration insurance application receipts. These efforts are working, with enrollment increasing in recent months.[8]

Job Satisfaction

The future of the PPACA is a big question mark for many physicians, who are concerned about the industry. Based on results from surveys conducted in 2012, the Physicians Foundation has published its top-five concerns facing doctors in 2013:

- uncertainty about the specifics of how the PPACA will be fully implemented
- the consolidation of private practices into hospitals and medical groups and how this will affect quality of care and costs
- how 30 million newly insured patients will be cared for (In addition to the 45,500 projected shortage of primary care physicians by 2020, it is expected that there will be a shortage of more than 90,000 physicians in total, and a 130,000 shortage by 2025.)
- the decline in autonomy due in part to a decrease in payments and an increase in regulation
- an increase in administrative burdens due to increasing regulation on healthcare, which is causing a reduction of time spent with patients[9]

Reimbursement is also a concern. On average, Medicaid pays only 66 percent of Medicare rates. But, there is a PPACA provision that requires states to pay primary care doctors providing services to Medicaid-insured patients 100 percent of Medicare rates for the next two years. While this is only a short-term solution, it is a welcome one, especially for physicians in California, Florida, Michigan, New Jersey, New York and Rhode Island, all of which expect to see their payments increase significantly, on average 73 percent. Some argue, though, that this increase is merely due to the fact that their reimbursement rates were much too low to start with. For instance, physicians in Rhode Island, the state that is seeing the biggest increase in pay rates of 200 percent, were being paid only a third of what Medicare pays, which often didn't cover the cost of seeing the patient. Eleven other states will see smaller increases because they already are being paid closer to Medicare rates. However, there is some concern that this short-term pay increase will be eliminated due to budget cuts. As a consequence, many physicians are not yet making plans for their practices based on the increase until it is sure to remain.[10]

Enrolling new patients in the healthcare system remains an issue. The PPACA has mandated certain practices to help get the word out to new patients, including online tools that Boutin anticipates could look something like that of the Medicare Part D calculator. Navigators, who will help patients find the right tools for their needs, are being established at the state level, and, of course, there will be insurance brokers selling their products. With both nonprofit and for-profit people working on behalf of consumers, Boutin believes enrollment will go pretty well: "People are expecting this," he says of the fact that changes to insurance are right around the corner. "It's not dissimilar to the Medicare Part D uptake, which at the time was one of the largest expansions."

Funding the Law

The question of how to pay for those newly insured at both the federal and state level, without reducing physician payments and patient benefits to the point of severity, has many proposing options, all of which are controversial.

The Alliance on Healthcare Reform's report, titled *High and Rising Costs of Healthcare in the U.S. — The Challenge: Changing the Trajectory*,[11] points out that if healthcare's increasing costs are funded by tax increases, the marginal tax rate for high-income earners could be 70 percent by 2060, and these increased expenses coupled with increased taxes could cause the gross domestic product to decline by 11 percent. Five percent of patients represent about 50 percent of the costs of healthcare, and 20 percent of patients represent around 80 percent. Patients costing the most tend to have chronic diseases such as diabetes, arthritis and high blood pressure, and the obesity epidemic is a major culprit.

With higher Medicare taxes (2.35 percent) on high earners, higher taxes on medical devices (though a repeal has already passed in the House) and brand-name drugs on the table, a novel proposal has been submitted by the National Coalition on Healthcare, which includes members such as the American Heart Association and CVS pharmacy. The proposal includes, in part, a controversial plan that calls for taxing sweetened beverages a penny per ounce, higher taxes on tobacco and alcohol, as well as penalties for underperforming hospitals,[12] to earn revenue to help pay for the rising costs of healthcare.

The future of the PPACA is a big question mark for many physicians, who are concerned about the industry.

The proposal also spells out numerous possible spending cuts, as well as savings and restructuring of payments such as rewarding physicians for value rather than volume and utilizing market competition to lower costs, in part by expanding competitive bidding for medical devices for Medicare services, and enhancing quality and better coordinating care of high-cost patients (with the implementation of MedPAC's recommendations of expanding PACE [Program for Accelerated College Education] and supporting meaningful-use incentive payments for behavioral health providers).

More to Come

Much of the PPACA is taking shape: Preventive services are more accessible, health insurance can't be cut if you become sick and the doughnut hole in Medicare Part D coverage has begun to close, saving seniors $4.8 billion on prescription drugs so far.[3]

However, much remains to be done, including solidifying expectations of doctors, states, manufacturers, patients and taxpayers. For instance, questions persist about what will be required of the medical industry in order to meet the growing demand of the newly insured and how we will collectively pay for it all. This is shaping up to be an interesting year, and as more of the PPACA plan rolls out, more will be revealed. ❖

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

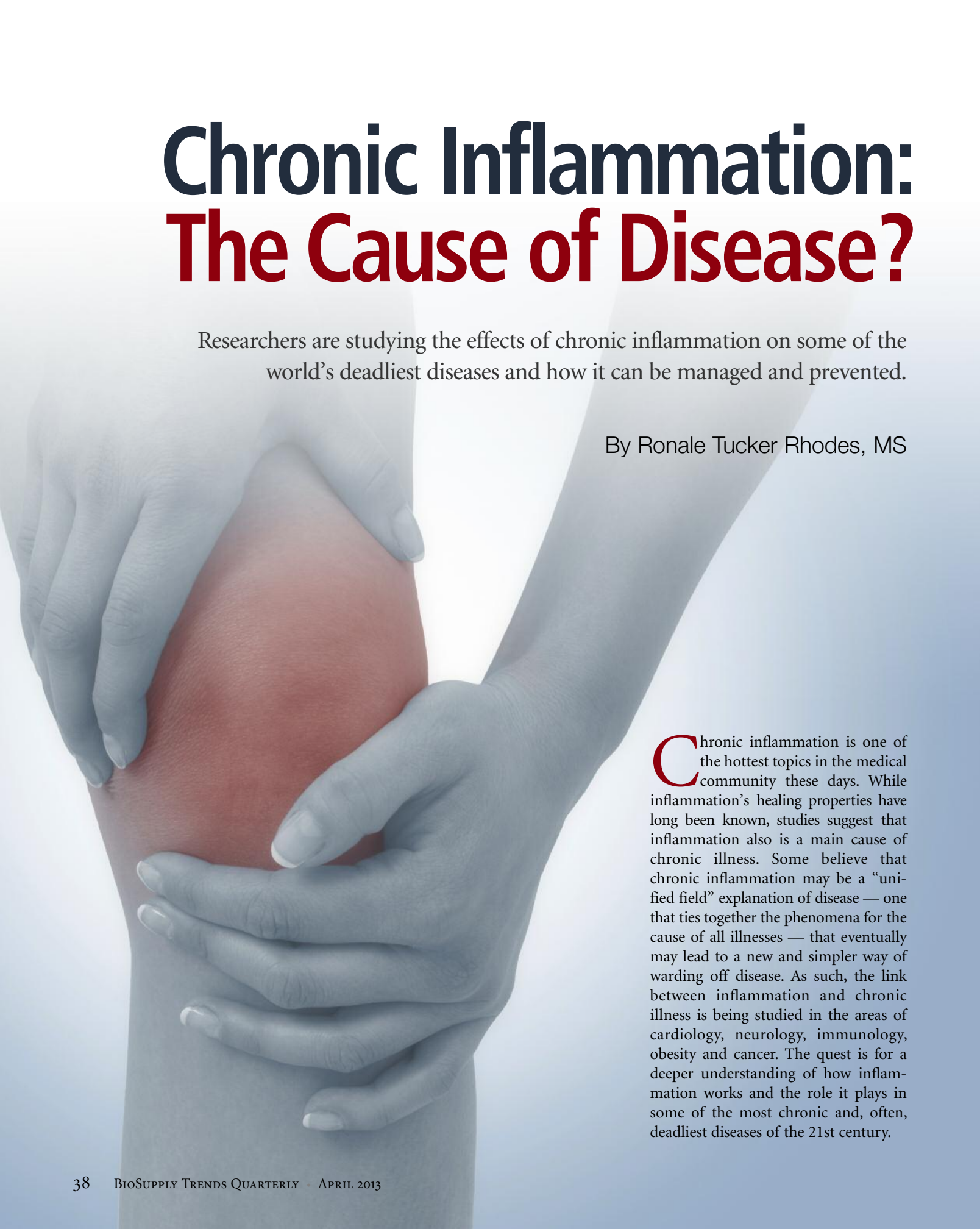
References

1. The Heritage Foundation: The Impact of Obamacare on Seniors. Accessed at www.heritage.org/research/projects/impact-of-obamacare.
2. Moffit, RE. Obamacare: Impact on Doctors. The Heritage Foundation, May 11, 2010. Accessed at www.heritage.org/research/reports/2010/05/obamacare-impact-on-doctors.
3. Carey, MA, and Gold, J. After the Election: A Consumers' Guide to the Health Law. *Kaiser Health News*, Nov. 8, 2012. Accessed at www.kaiserhealthnews.org/Stories/2012/March/22/consumer-guide-health-law.aspx.
4. Nix, K. Obamacare: Impact on the Uninsured. The Heritage Foundation, Apr. 20, 2010. Accessed at www.heritage.org/research/reports/2010/04/obamacare-impact-on-the-uninsured.
5. What's Next for ACA Implementation: Post-Election Health Care Reform and the Road Ahead for Physicians and Patients. American Medical Association. Accessed at ama-assn.org/resources/doc/washington/affordable-care-act-the-road-ahead.pdf.
6. Krupa, C. New GME Model Strives to Keep Doctors in Underserved Areas. *American Medical Association News*, Jan. 21, 2013. Accessed at www.ama-assn.org/amednews/2013/01/21/prsb0121.htm.
7. Watkins, N. Newly Passed Medicare IVIG Access Act Eases Burden of PIDD Patients. *National Association of Specialty Pharmacy*, Jan. 11, 2013. Accessed at www.nasprx.org/news/113628/Newly-Passed-Medicare-IVIG-Access-Act-Eases-Burden-of-PIDD-Patients.htm.
8. Popper, R. Covering More Uninsured Americans Who Have Preexisting Conditions. Healthcare.gov blog, Feb. 10, 2011. Accessed at www.healthcare.gov/blog/2011/02/pcip-enrollment.html.
9. Ter Maat, S. ACA Tops List of 5 Biggest Physician Concerns for 2013. *American Medical Association News*, Dec. 31, 2012. Accessed at www.ama-assn.org/amednews/2012/12/31/bisb1231.htm.
10. Lubbell, J. Medicaid Primary Care Pay to More Than Double in 6 States. *American Medical Association News*, Dec. 31, 2012. Accessed at www.ama-assn.org/amednews/2012/12/31/gvsa1231.htm.
11. Alliance for Health Reform. *High and Rising Costs of Health Care in the U.S. — The Challenge: Changing the Trajectory*. Accessed at www.allhealth.org/publications/Alliance_for_Health_Reform_121.pdf.
12. National Coalition on Health Care. *Curbing Costs and Improving Care: The Plan to an Affordable Health Care Future*. Accessed at http://nchc.org/sites/default/files/NCHC%20Plan%20for%20Health%20and%20Fiscal%20Policy.pdf.

Chronic Inflammation: The Cause of Disease?

Researchers are studying the effects of chronic inflammation on some of the world's deadliest diseases and how it can be managed and prevented.

By Ronale Tucker Rhodes, MS



Chronic inflammation is one of the hottest topics in the medical community these days. While inflammation's healing properties have long been known, studies suggest that inflammation also is a main cause of chronic illness. Some believe that chronic inflammation may be a "unified field" explanation of disease — one that ties together the phenomena for the cause of all illnesses — that eventually may lead to a new and simpler way of warding off disease. As such, the link between inflammation and chronic illness is being studied in the areas of cardiology, neurology, immunology, obesity and cancer. The quest is for a deeper understanding of how inflammation works and the role it plays in some of the most chronic and, often, deadliest diseases of the 21st century.

The Role of Inflammation

Inflammation, also known as an inflammatory response, is one of the ways the immune system responds to antigens that cause disease. The immune system produces disease-fighting chemicals (histamine, macrophages and cytokines) to fight off antigens, which results in redness, swelling and pain. This type of inflammation, known as acute inflammation, typically ends when the antigens are destroyed. But, it is now known that in some cases, the body continues to produce disease-fighting chemicals in the absence of antigens, resulting in chronic inflammation.[1]

Chronic inflammation, also known as low-grade or systemic inflammation, plays a puzzling and long-lasting role in the body. In essence, the body attacks its own healthy tissues and organs; it becomes a victim of its own success. "We evolved as a species because of our ability to fight off microbial invaders," explains Dr. Peter Libby, chief of cardiovascular medicine at Brigham and Women's Hospital at Harvard Medical School in Boston. "The strategies our bodies used for survival were important in a time when we didn't have processing plants to purify our water, when we didn't have sewers to protect us." But this evolutionary perspective is changing now that people are living longer and our lifestyles have so dramatically changed.[2]

Measuring Inflammation in the Body

While there are many signs of an inflammatory response, clinically the most common tests to diagnose inflammation include measuring erythrocyte sedimentation rate, white blood count and albumin levels, all of which are high markers of inflammation. However, all of these tests could show an abnormal result that may be a cause of a condition unrelated to inflammation.

Various cytokines and adhesion molecules also can be measures of inflammation. They are not often used in clinical settings because they don't identify the source of the inflammation within the body. But, they often are used in basic scientific studies to investigate the cellular and molecular processes involved in the pathogenesis of inflammation-related disease.

The prototypic clinical biomarker of cardiac-related inflammation and a general marker of inflammation is C-reactive protein (CRP), an acute-phase reactant protein synthesized in the liver. Because cardiovascular disease is now thought to be caused by inflammation, those individuals who have already had a heart attack can be given a highly sensitive CRP, or hs-CRP, test.[3] Even so, a CRP test is not routine as there is no certainty about what an individual's CRP level should be.[4]

Chronic Inflammation as a Cause of Chronic Diseases

One question is whether inflammation actually causes chronic diseases or merely accompanies them. And while the jury is out yet, the connection between the two can't be overlooked.

Poor lifestyle habits such as obesity, high blood pressure, unhealthy cholesterol levels, smoking, etc., are believed to have a great effect on how the body's immune system can spiral out of control.[5] Other likely causes of chronic inflammation include those from agents that persist for a long period of time, including microbial infections, environmental antigens, autoimmune reactions or persistent activation of inflammatory molecules.[3]

While the effects of chronic inflammation vary widely depending on where the inflammation occurs, more and more research suggests that chronic inflammation could be at the root of a host of diseases. And, the link between chronic inflammation and disease is changing the way many scientists conduct research. Several years ago, researchers went about their own fields of study; today, cardiologists, rheumatologists, oncologists, allergists and neurologists across the world are all talking to one another because they are realizing that they are all studying the same thing: inflammation. Below are some of the diseases currently under study.

Chronic inflammation, also known as low-grade or systemic inflammation, plays a puzzling and long-lasting role in the body.

Heart disease. Dr. Paul Ridker, a cardiologist at Brigham and Women's Hospital, was the first to study the link between inflammation and bursting plaques that result in heart attacks. In the 1990s, using an hs-CRP test, Dr. Ridker looked at low levels of CRP (less than 10 mg/L) that are found in otherwise healthy people and that indicated only a slightly elevated inflammation level. By 1997, Dr. Ridker and his colleagues had shown that healthy middle-aged men with the highest CRP levels were three times as likely to suffer a heart attack in the next six years as were those with the lowest CRP levels.

Inflammation experts eventually determined that having a CRP reading of 3.0 mg/L or higher triples the risk of heart disease, and the danger is even greater in women. By contrast, those with extremely low levels of CRP, less than 0.5 mg/L, rarely have heart attacks. The theory is that as the level of LDL cholesterol increases in the blood, some of it seeps into the lining of the coronary arteries and gets stuck there. When the macrophages come in to try to clean out the cholesterol, for some reason, the cytokine signals increase the inflammatory process instead of decreasing it, and the plaque becomes unstable. "This is not about replacing cholesterol as a risk factor," says Dr. Ridker.

"Cholesterol deposits, high blood pressure, smoking — all contribute to the development of underlying plaques. What inflammation seems to contribute is the propensity of those plaques to rupture and cause a heart attack. If there is only inflammation but no underlying heart disease, then there is no problem."

While cardiologists still don't recommend that the general population be screened for inflammation levels, there is a general consensus that CRP should be measured in those with a moderately elevated risk of developing cardiovascular disease.[2]

More recently, an international consortium of more than 170 researchers conducted a massive meta-analysis that pooled genetic data from more than 190,000 research participants to provide insights into the molecular pathways causing the plaque buildup seen in coronary artery disease. They identified 15 new genetic regions that may be linked to heart disease, bringing the number of genetic links to heart disease found through genome-wide association studies to 46. Twenty-five percent of those genetic regions were strongly linked to cholesterol, especially high levels of low-density lipoprotein (bad cholesterol), and 10 percent were linked to high blood pressure. But, according to Themistocles Assimes, an assistant professor of medicine at Stanford University, "Perhaps the most interesting results of this study show that some people may be born with a predisposition to the development of coronary atherosclerosis because they have inherited mutations in some key genes related to inflammation. There has been much debate as to whether inflammation seen in plaque buildup in heart vessels is a cause or a consequence of the plaques themselves. Our network analysis of the top approximately 240 genetic signals in this study seems to provide evidence that genetic defects in some pathways related to inflammation are a cause."[6]

One question is whether inflammation actually causes chronic diseases or merely accompanies them.

Arthritis. Chronic inflammation is the hallmark of autoimmune disorders such as arthritis, multiple sclerosis and lupus. But what causes this inflammation remains a puzzle. A team of researchers from Brigham and Women's Hospital and Merck Frosst Centre for Therapeutic Research in Quebec studied the role of leukotriene B4 (LTB4) in leukocyte recruitment and inflammation in inflamed arthritic joints. They found, among other things, that levels of LTB4 were significantly elevated in the joint tissues of mice with chronic arthritis, whereas there were no leukotrienes detected in the joint tissues of mice without arthritis. In addition, they found that increasing concentrations of LTB4 correlated strongly with increasing arthritis severity while the disease was becoming established.[7]

Diabetes. Diabetes was first treated with high doses of salicylates, a group of aspirin-like compounds, which worked to reduce sugar levels but also caused side effects such as a constant ringing in the ears, headaches and dizziness. Fortunately, insulin was isolated in the 1920s as a treatment for diabetes. But in the past few years, researchers are once again looking at the salicylate approach, and they have found that diabetes is a complex interplay between inflammation, insulin and fat (either in the diet or in large folds under the skin). In a study conducted at the Joslin Diabetes Center in Boston, a strain of mice bred with fat cells that were "supercharged inflammation factories" became less efficient at using insulin and went on to develop diabetes. "We can reproduce the whole syndrome just by inciting inflammation," says Steve Shoelson, a senior investigator. The results suggest that a well-timed intervention in the inflammatory process might reverse some of the effects of diabetes.[2]

There also is research to suggest that high CRP levels may indicate a greater risk of diabetes. Epidemiologic studies have demonstrated a positive association between CRP level and diabetes mellitus in U.S. race ethnicities. One specific study, however, examined the association between high-sensitivity CRP level and diabetes mellitus in a representative sample of U.S. non-Hispanic blacks. Among the 1,479 participants ages 20 years and older, higher CRP levels were positively associated with diabetes mellitus, independent of smoking, waist circumference, hypertension and other confounders. In addition, the association persisted in separate analyses among men and women, and the results were consistent in subgroup analyses by categories of age, smoking, body mass index and hypertension status. According to the researchers, inflammatory processes previously shown to be related to diabetes mellitus in other race ethnicities may be involved in non-Hispanic blacks also.[8]

Alzheimer's. In 1997, neurologists presented research that showed people who had been regularly taking anti-inflammatory medicine like ibuprofen had much lower rates of Alzheimer's disease. Then, in 2001, a study showed an 80 percent reduction in risk of Alzheimer's among those taking anti-inflammatory medicines daily for two years. According to Linda Van Eldik, a neurobiologist at Northwestern University School of Medicine, whenever the brain is injured or irritated, glial cells pump out cytokines, chemical signals to begin the inflammatory process. But "in chronic neurogenerative diseases like Alzheimer's, these glial cells are activated too high or too long or both."[9]

In the January 2012 issue of this publication, we ran an advertisement for octagam® [Immune Globulin Intravenous (Human) 5%] that omitted required risk information. The advertisement for octagam® below contains all required risk information.

octagam®

Immune Globulin Intravenous (Human) 5% Liquid Preparation

RESEARCHED

Proven clinical efficacy in patients with primary humoral immunodeficiency (PI)[1,2]

REFINED

Enhanced fractionation process for thromboembolic safety [3]

REASSURED

Established pathogen safety profile

For more information, please contact us:

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

Medical Affairs:
usmedicalaffairs@octapharma.com
888-429-4535

Customer Service:
uscustomerservice@octapharma.com
866-766-4860

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

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age >65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. octagam® (Human) 5% liquid does not contain sucrose. (See Dosage and Administration and WARNINGS and PRECAUTIONS in enclosed Full Prescribing Information for important information intended to reduce the risk of acute renal failure.)

CONTRAINDICATIONS

octagam® 5% liquid is contraindicated in patients who have acute severe hypersensitivity reactions to human immunoglobulin. octagam® 5% liquid contains trace amounts of IgA (not more than 0.2 mg/ml in a 5% solution). It is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity. octagam® 5% liquid is contraindicated in patients with acute hypersensitivity reaction to corn. octagam® 5% liquid contains maltose, a disaccharide sugar which is derived from corn. Patients known to have corn allergies should avoid using octagam® 5% liquid.

WARNINGS AND PRECAUTIONS

IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions. Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure. Falsely elevated blood glucose readings may occur during and after the infusion of octagam® 5% liquid with some glucometer and test strip systems. Hyperproteinemia, increased serum viscosity and hyponatremia 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 has been reported with octagam® 5% liquid and other IGIV treatments, especially with high doses or rapid infusion. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration. IGIV recipients should be monitored for pulmonary adverse reactions (TRALI). The product is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

References
1. Octagam®, Immune Globulin Intravenous (Human) 5% Liquid Preparation, complete Prescribing Information. 2009.
2. Ochs HD, Pinciaro PJ. Octagam® 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. J Clin Immunol 2004;24:309-14.
3. Roemisch J, et al. Identification of activated FXI as the major biochemical root cause in IVIG batches associated with thromboembolic events. analytical and experimental approaches resulting in corrective and preventive measures implemented into the Octagam® manufacturing process. WebmedCentral Immunother 2011;2:WMC002002.

Please see Highlights of Prescribing Information on adjacent page.

Date of Preparation 8/12. GAM5-006-PAD

octapharma
For the safe and optimal use of human proteins

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Octagam, Immune Globulin Intravenous (Human), safely and effectively. See full prescribing information for Octagam.

Octagam® [Immune Globulin Intravenous (Human)]
5% Liquid Preparation
Initial US Approval: 2004

WARNING: ACUTE RENAL DYSFUNCTION and RENAL FAILURE
See full prescribing information for complete boxed warning.

- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may be associated with Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiveing IGIV products containing sucrose. Octagam 5% liquid does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions – Hyperproteinemia 8/2008

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

- Octagam is an immune globulin intravenous (human), 5% liquid, indicated for treatment of primary humoral immunodeficiency (PI).

----------DOSAGE AND ADMINISTRATION----------

Intravenous use only.

Indication	Dose	Initial Infusion rate	Maintenance infusion rate (if tolerated)
PI	300-600mg/kg	0.5mg/kg/min	3.33mg/kg/min Every 3-4 weeks

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Octagam 5% liquid if renal function deteriorates.
- For patients at risk of renal dysfunction or thrombotic events, administer Octagam 5% liquid at the minimum infusion rate practicable.

----------DOSAGE FORMS AND STRENGTHS----------

Octagam 5% liquid is supplied in 1.0g, 2.5g, 5g, 10g, or 25g single use bottles

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

- Anaphylactic or severe systemic reactions to human immunoglobulin.
- Immunoglobulin A (IgA) deficient patients with antibodies against IgA and a history of hypersensitivity.
- Patients with acute hypersensitivity reaction to corn.

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

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- Epinephrine should be available immediately to treat any acute severe hypersensitivity reactions.
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure.
- Falsely elevated blood glucose readings may occur during and after the infusion of Octagam 5% liquid with some glucometer and test strip systems.
- Hyperproteinemia, increased serum viscosity and hyponatremia 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 has been reported with Octagam 5% liquid and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infection agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease agent.

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

The most serious adverse reactions observed with Octagam® 5% liquid treatment have been immediate anaphylactic reactions, aseptic meningitis, and hemolytic anemia.

Most common adverse reactions with an incidence of >5% during a clinical trial were headache and nausea. **To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4860 or FDA at 1-800-FDA-1008 or** www.fda.gov/medwatch.

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

- The passive transfer of antibodies may confound the results of serological testing.
- The passive transfer of antibodies may interfere with the response to live viral vacancies.

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

- Pregnancy: no human or animal data. Use only if clearly needed.
- In patients over age 65 or in any person at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Octagam 5% liquid at the minimum infusion rate practicable.

----------HOW SUPPLIED----------

	1g	2.5g	5g	10g	25g
Size	20ml	50ml	100ml	200ml	500ml
NDC#	67467-843-01	67467-843-02	67467-843-03	67467-843-04	67467-843-05
NDC#	68209-843-01	68209-843-02	68209-843-03	68209-843-04	

MANUFACTURED BY:
OCTAPHARMA Pharmazeutika
Produktionsges.m.b.H.
Oberlaaer Strasse 235
A-1100 Vienna, Austria

DISTRIBUTED BY:
Octapharma USA, Inc.
121 River Street, Suite 1201
Hoboken, NJ 07030
Tel: 201-604-1130
Fax: 201-604-1131
www.octapharma.com/usa

Revised: September 2009

octapharma
For the safe and optimal use of human proteins

A study reported on in 2005 supported the conclusion that neuroinflammation is associated with Alzheimer's disease. In the study, both the microglia (the immune cell of the brain) and astrocytes (glial cells of the brain) were shown to generate beta-amyloid protein (Abeta), one of the main pathologic features of Alzheimer's. Abeta has been shown to act as a pro-inflammatory agent causing the activation of many of the inflammatory components.[10]

Cancer. For the past three decades, researchers at the Massachusetts Institute of Technology (MIT) have been studying chronic inflammation of the liver, stomach or colon as a risk factor for cancer of those organs. In their most recent study, the researchers looked at how a bacterium called Helicobacter hepaticus (H. hepaticus) alters genes and chemicals in the liver and colon. After examining mice with H. hepaticus, they found that after 10 weeks, the mice developed severe colitis and hepatitis, and at 20 weeks, some also had developed colon cancer. They also examined the tissue damage in the mice over the course of those 20 weeks to assess damage to DNA, RNA and proteins. They found that levels of one of the damaged products in DNA and RNA, chlorocytosine, correlated well with the severity of the inflammation, which they determined could serve as a marker to predict the risk of chronic inflammation in patients with infection in the colon, liver or stomach.

The researchers also noticed that the liver responded differently than the colon. When the DNA of healthy tissue comes under attack, it triggers a mechanism that attempts to repair the DNA, but that repair was more active in the liver than in the colon, even though both experienced DNA damage. What's more is that in the colon, but not the liver, neutrophils released hypochlorous acid (a constituent of household bleach). The acid causes significant damage to molecules like DNA, RNA and proteins by attaching a chlorine atom, which is an effective way to kill bacteria, but it can cause similar damage to the epithelial cells in the lining of the colon if the acid leads into surrounding tissue. "It's possible that we have kind of a double whammy [in the colon]," says Peter Dedon, a professor of biological engineering at MIT. "You have this bacterium that suppresses DNA repair, at the same time you have all this DNA damage happening in the tissue as a result of the immune response to the bacterium."[11]

Many studies are looking into the possibility that mutation and inflammation are mutually reinforcing processes that can transform normal cells into potentially deadly tumors. For instance, it is known that macrophages and other inflammatory cells produce oxygen-free radicals to destroy anything that crosses their path, particularly DNA. But if the oxygen-free radicals damage rather than destroy a cell, it could lead to a genetic mutation that keeps on growing and dividing. According to Lisa Coussens, a cancer biologist at the Comprehensive Cancer Center at the University of California, San Francisco, the abnormal growth may not be a tumor, but to the immune system, it looks like a wound that needs to be fixed. "When immune cells get called in, they bring growth factors and a whole slew of proteins that call other inflammatory cells," she explains. "Those things come and go 'heal, heal, heal.' But instead of healing, you're 'feeding, feeding, feeding.'"[2]

Treating Chronic Inflammation

Of course, the intent behind all this research is to determine how to stop the inflammatory process that can cause disease in the first place. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen help inflammatory conditions, and many people take it to prevent heart attack and stroke. But NSAIDs can have significant side effects like gastrointestinal bleeding and liver damage.

The majority of the research on chronic inflammation has focused on fighting it with drugs, and there are many studies that have identified common drugs already in use that may help to reduce chronic inflammation. There also are some promising new drugs in development, as well as some studies that have identified proteins in the body that may help scientists to develop other new medications.

Chronic inflammation is the hallmark of autoimmune disorders such as arthritis, multiple sclerosis and lupus.

In February, researchers from King's College London and clinicians from Guy's and St. Thomas' NHS Foundation Trust in London developed a protein agent modeled on the body's own natural defenses to combat the inflammation that can destroy joints. The agent, binding immunoglobulin protein (BiP), is found in insufficient quantities in the joints of people with rheumatoid arthritis to have a therapeutic effect. Previous research indicates that giving a single intravenous dose of BiP quickly boosts a patient's anti-inflammatory response by resetting their immune system. Now, the first human trial of BiP with up to 50 patients has started. "If BiP works as we expect," says Gabriel Panayi, professor emeritus of rheumatology at King's College London and honorary consultant rheumatologist at Guy's and St. Thomas', "then a single dose should be sufficient to put patients into remission for months."[12]

Last year, scientists at Monash University's Australian Regenerative Medicine Institute (ARMI) discovered an important

step in the body's process for healing wounds that may lead to a new way of treating inflammation. Building on previous research, they identified the enzyme, myeloperoxidase, that signals the leukocytes (that protect tissue from infection) to switch off once they are no longer needed for healing. "White blood cell activity is important for determining the balance between repair, scarring and healing. Understanding what regulates leukocyte activity during inflammation should ultimately allow us to manipulate this system and maximize healing and repair," said lead researcher Professor Graham Lieschke of ARMI. "Our research has identified a new pathway to target with anti-inflammatory drugs. There is a significant need for new treatment options as current drugs are not effective in all circumstances."[13]

Also this past year, researchers at University College London reported that, while studying the connection between inflammation and atherosclerosis, they found that the signaling protein in the blood called interleukin-6 receptor (IL6R) is responsible for an increased inflammatory response and that an existing anti-inflammatory drug is able to act on it. A companion study also found that a genetic variant in the IL6R gene reduces inflammation and subsequently lowers the risk of heart disease. Their results were similar to those found in trials of tocilizumab, an anti-inflammatory drug currently used to treat the inflammation of rheumatoid arthritis. The next step, according to the researchers, is to conduct clinical trials to prove that anti-inflammatory drugs prevent heart disease.[14]

In August 2012, the National Institutes of Health launched a multi-site trial to determine whether a common anti-inflammatory drug can reduce heart attacks, strokes and deaths due to cardiovascular disease in people at high risk for them. The Cardiovascular Inflammation Reduction Trial (CIRT) will determine whether treatment with methotrexate, a drug specifically targeting inflammation, reduces rates of cardiovascular events among adults who have had a heart attack within the past five years and who also have type 2 diabetes or metabolic syndrome. Methotrexate is an inexpensive generic drug commonly used at low doses to treat rheumatoid arthritis, and at higher doses to treat certain forms of cancers such as leukemias and lymphomas. Participants in the trial will be randomly assigned to receive methotrexate given at 10 mg to 20 mg weekly for three to four years or a placebo. In March, CIRT began to enroll 7,000 patients at 350 to 400 sites across the U.S. and Canada over the next two and a half years.[15]

Aside from medications, many physicians advocate adopting a more healthful lifestyle, which can have a profound impact on reducing chronic inflammation. Some foods and herbs have anti-inflammatory properties such as ginger, curcumin, rosemary, basil and cherries.[9] While there is no evidence that an anti-inflammatory diet prevents inflammation, some believe that the Mediterranean-style diet does. Components of this diet include consuming whole-grain foods, unsaturated fats such as plant oils, fruits, vegetables, nuts, fish, poultry, eggs and moderate amounts of dairy foods, as well as avoiding red meat, butter, sweets and white foods such as rice, potatoes and pasta as much as possible.

The benefits of dairy and omega-3 fats are being proven. Researchers at the University of Tennessee's Department of Nutrition conducted a study in which patients were given three-and-a-half servings of dairy daily over 12 weeks, which resulted in reductions in several markers of inflammation, as well as reduced blood pressure, compared with a group given just half a serving of dairy per day.[5] The American Heart Association encourages people with heart disease to consume 1 gram of omega-3s a day from fish or supplements, which are believed to reduce inflammation.[4] Researchers at Vanderbilt University are currently focusing on whether omega-3 fatty acids reduce the risk of colorectal cancers and diminish the production of inflammatory molecules.[5]

Then there is the uncharted area of nutrition: dietary supplements. Unlike prescription drugs, dietary supplements are not regulated by the U.S. Food and Drug Administration, and there are no requirements for them to undergo clinical trials for safety and effectiveness. However, some have shown to be effective. Cat's claw (Uncaria tomentosa) has had modest

benefits for easing rheumatoid arthritis joint pain and osteoarthritis knee pain during activity, according to limited studies. Devil's claw (Harpagophytum procumbens) has been shown in studies to be effective in short-term treatment of osteoarthritic pain and is used extensively in Europe as an anti-inflammatory agent. Mangosteen (Garcinia mangostana) is credited with anti-allergy, antibacterial, antifungal, antihistamine and anti-inflammatory qualities and even as a possible cancer treatment. And, milk thistle (Silybum marianum) appears to protect the liver and block or remove harmful substances from the organ. It also appears to improve organ function in people with cirrhosis and in treating hepatitis.[16] However, more study is needed to verify the effectiveness of all of these and other herbal supplements.

Aside from medications, many physicians advocate adopting a more healthful lifestyle, which can have a profound impact on reducing chronic inflammation.

Exercise to promote weight maintenance is perhaps the newest advice for preventing inflammation. A significant discovery is how obesity promotes inflammation. Fat cells, particularly those in the visceral fat that settles in the belly and around organs, were long thought to store excess weight, but instead, they have been found to produce molecules known as cytokines that set inflammation in motion, says Dr. Libby. "We've learned that abdominal fat tissue is a hotbed of inflammation that pours out all kinds of inflammatory molecules," he explains.[5] In a study conducted at Tufts University, scientist Andrew Greenberg found that as fat cells reach their maximum size, they break down and die, and then macrophages, which are responsible for most of the inflammatory chemicals released in fat tissue, rush in to clean up the debris. "When fat cells die, macrophages surround the dead lipids the same way white cells surround a wooden splinter in your skin," explains Greenberg. "The immune system is essentially surrounding and sequestering the dead fat cells and gorging on the leftover lipids and cellular debris," which explains why obesity complicates arthritis, insulin resistance, diabetes and heart disease.[9]

Last, getting enough sleep, not smoking and keeping a positive attitude all are credited with reducing inflammation. Psychiatrists at King's College London found that people who were physically or sexually abused as children are twice as likely to have significant levels of CRP, which explains why abused children show a higher incident of heart disease and diabetes as adults.[9]

Stay Tuned

Chronic inflammation is now recognized as a primary factor in the development of all kinds of chronic illness, including cardiovascular disease, obesity, autoimmune disorders, neurological disease and cancer. And researchers are working together in an effort to determine not only how this type of inflammation plays a role in these diseases, but also how to manage and prevent it. All that can be done now is to stay tuned as new discoveries become available to improve the health of millions of people across the world. ❖

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

References

1. Second Opinion. Inflammation (transcript). Accessed at secondopinion-tv.org/episode/inflammation.
2. Gorman, C, Park, A, Dell, K. Cellular Inflammation: The Secret Killer. Inflammation Research Foundation. Accessed at www.inflammationresearchfoundation.org/TimeMagazineArticle.aspx.
3. Drake, VJ. Two Faces of Inflammation. Oregon State University Linus Pauling Institute. Accessed at lpi.oregonstate.edu/ss07/inflammation.html.
4. Berkeley Wellness Alerts. Is Inflammation the Root of All Disease? Accessed at www.wellnessletter.com/ucberkeley/feature/inflammation
5. Landro, L. The New Science Behind America's Deadliest Diseases. *The Wall Street Journal*, Jul. 16, 2012. Accessed at online.wsj.com/article/SB10001424052702303612804577531092453590070.html.
6. Paddock, C. Large Gene Study Links Plaque in Heart Disease to Inflammation. Medical News Today, Dec. 3, 2012. Accessed at www.medicalnewstoday.com/articles/253507.php.
7. Chen, M, Lam, BK, Kanaoka, Y, et al. Neurophil-Derived Leukotriene B4 Is Required for Inflammatory Arthritis. *Journal of Experimental Medicine*, 2006; 203: 837-42.
8. Shankar, A, Li, J. Positive Association Between High-Sensitivity C-Reactive Protein Level and Diabetes Mellitus among U.S. Non-Hispanic Black Adults. *Experimental and Clinical Endocrinology & Diabetes*, 2008 Aug;116(8): 455-60. Accessed at www.ncbi.nlm.nih.gov/pubmed/18924263.
9. Chronic Inflammation & Chronic Disease. Allergy Consumer Report, February 2007. Accessed at www.achooallergy.com/chronic-inflammation-disease.asp.
10. Tuppo, EE, and Arias, HR. The Role of Inflammation in Alzheimer's Disease. *International Journal of Biochemistry & Cell Biology*, 2005 Feb;37(2): 289-305. Accessed at www.ncbi.nlm.nih.gov/pubmed/15474976.
11. Paddock, C. From Infection to Inflammation to Cancer: Scientists Offer New Clues. Medical News Today, Jun. 14, 2012. Accessed at www.medicalnewstoday.com/articles/246523.php.
12. Hope, J. 'Natural' Drug Could Offer Long-Lasting Arthritis Relief by 'Rebooting' Immune System. Mail Online, Feb. 7, 2013. Accessed at www.dailymail.co.uk/health/article-2275418/Natural-drug-offer-long-lasting-arthritis-relief-rebooting-immune-system.html.
13. Study Gives New Insight on Inflammation. ScienceDaily, Aug. 30, 2012. Accessed at www.sciencedaily.com/releases/2012/08/120830125958.htm.
14. Nusca, A. Anti-Inflammatory Drugs May Prevent Heart Disease. SmartPlanet, Mar. 14, 2012. Accessed at www.smartplanet.com/blog/smart-takes/anti-inflammatory-drugs-may-prevent-heart-disease/24217.
15. NIH Launches Trial to Evaluate Anti-Inflammatory Treatment for Preventing Heart Attacks, Strokes and Cardiovascular Deaths. National Institutes of Health News, Aug. 22, 2012. Accessed at www.nih.gov/news/health/aug2012/nhlbi-22.htm.
16. Bauer, B. Buzzed on Inflammation. *Mayo Clinic Health Letter*, Online Edition. Accessed at healthletter.mayoclinic.com/editorial/editorial.cfm/i/163/t/Buzzed%20on%20inflammation.

Myths and Facts: Chronic Fatigue Syndrome

CFS is a legitimate medical condition that needs to be better understood by the medical community to help patients manage their disease and scientists to develop effective treatments.

By Ronale Tucker Rhodes, MS

Some 25 years after chronic fatigue syndrome (CFS) was officially recognized as a legitimate medical condition, many in the healthcare field still doubt whether it truly exists. "This is a disease that is very difficult to diagnose and very difficult to understand and treat," said Julie Gerberding, MD, a past Centers for Disease Control and Prevention (CDC) director. "[It] has been shrouded in a lot of mystery and controversy." But the statistics generated from research conducted in 2004 by the CDC speak for themselves: At least one million Americans have been diagnosed with CFS, and it is predicted

that number represents less than 20 percent of Americans who actually have CFS. CFS is a costly disease, resulting in $9 billion in lost productivity in the U.S. annually, and $20,000 annually in lost wages and income per family.[1]

Also known as myalgic encephalomyelitis (ME), CFS can be as disabling as AIDS or multiple sclerosis, say researchers, and its prevalence is greater than that of ovarian cancer, lung cancer or lupus.[1] In severe cases, patients describe their experience as a "living death." Not only do their bodies feel like lead, but their symptoms include nausea, headaches, dizziness, cognitive problems, light sensitivity, vertigo and pain.[2] Now, with decades of research, there is a commanding need to put the misconceptions and speculation surrounding this disease to rest.

Separating Myth from Fact

Myth: CFS is a new disease.

Fact: Although research focusing on CFS is relatively recent, severe fatigue illnesses of unknown origin have been reported for more than 150 years in countries across the world,[3] and many conditions strikingly similar to CFS go back at least several hundred years. In the mid 1700s, a condition called febricula (little fever) was reported, and in the 1870s, a similar disorder was called Da Costa's syndrome (named for the American internist who described "utter fatigue with effort").[4] Since the turn of the last century, fatigue illnesses have been labeled epidemic neuromyasthenia, myalgic encephalomyelitis, atypical poliomyelitis, post-polio syndrome, chronic encephalomyelitis, Iceland disease, royal free disease, chronic brucellosis and hypoglycemia.[3,4]

CFS can be as disabling as AIDS or multiple sclerosis, say researchers, and its prevalence is greater than that of ovarian cancer, lung cancer or lupus.

In the 1980s, when two cluster outbreaks of chronic Epstein-Barr virus occurred, researchers in the U.S. took a renewed interest in fatigue illnesses, which eventually led to the involvement by the CDC, which named the illness CFS. In 1988, the CDC created a U.S. case definition for diagnosis of CFS, which was refined in 1994 by an international concensus group. It is that definition, commonly called Fukuda definition, that is the basis for most current research in the U.S. Unfortunately, other case definitions across the world, including the Ramsey definition developed in England in 1981, the London criteria of 1992, the 2004 Canadian consensus definition and the 2005 Australian case definition, have clouded the diagnostic, epidemiological and etiological picture worldwide, making research comparisons difficult.[3]

Myth: There are diagnostic and lab tests to diagnose CFS.

Fact: There are no diagnostic tests or biomarkers to diagnose CFS. Instead, a diagnosis requires a thorough physical exam

and health history to identify case-definition symptoms,[5] as well as a mental status screening and a minimum battery of lab tests, including a urinalysis, thyroid function and C-reactive protein test, among others.[1] And, because the main symptoms of CFS — fatigue, pain and headaches — are common to many other illnesses, it's necessary to exclude other possible treatable causes such as thyroid or neurological disorders, multiple sclerosis, lupus or malignancies.[1,5]

There are no diagnostic tests or biomarkers to diagnose CFS.

It's important to note that many routine tests that are used to rule out other causes of fatigue such as blood counts, kidney function, liver tests and thyroid tests are normal in those with CFS. This is one reason why some physicians question whether CFS is real. But, there are other tests in those with CFS that routinely are abnormal. For example, the hypothalamus and pituitary gland, key parts of the brain that control a number of hormones and many of the body's vital functions, frequently demonstrate abnormal activity in people with CFS. In addition, many people with CFS have abnormal blood pressure responses to changes in position, suggesting that brain signals to the nerves controlling blood pressure are not functioning. And, some researchers have found abnormal numbers of types of white blood cells, antibodies and tests of immune function.[4]

Myth: There is no set of diagnostic criteria for CFS.

Fact: In 1994, a group of international CFS experts, including the CDC, developed criteria to define the condition to help researchers select appropriate cases for study. Those criteria, which also are used by many clinicians to diagnose CFS, include medically unexplained fatigue of at least six months that is not the result of other disease or conditions; continued fatigue despite rest that leads to a significant reduction in social, personal, educational and job-related activities; and at least four of several characteristic symptoms that present concurrently.[1] Characteristic symptoms include sore throat, muscle pain, joint pain without evidence of swelling or warmth, headaches (either increasing in severity or of recent onset), sore lymph nodes in the neck or under the arms, poor memory or reduced concentration, the need for more sleep despite getting plenty of sleep, and feeling unwell for a day or more after physical activity.[4]

In 2003, a Canadian expert concensus panel developed the first clinical case definition for CFS. According to the panel: "This definition is clearly a vast improvement over the CDC's 1994 case definition for CFS, which led to misunderstanding in both research and treatment modalities by making 'fatigue' a compulsory symptom but by downplaying or making optional the disease's hallmark of post-exertional sickness and other cardinal ME/CFS symptoms. In sharp contrast to the CDC's 1994 definition, this new clinical case definition makes it compulsory that in order to be diagnosed with ME/CFS, a patient must become symptomatically ill after exercise and must also have neurological, neurocognitive, neuroendocrine, dysautonomic, circulatory and immune manifestations. In short, symptoms other than fatigue must be present for a patient to meet the criteria."[6]

Myth: CFS is a type of depression or mental illness.

Fact: Because CFS can't be diagnosed with tests and it is often treated with antidepressants, many people often believe it is a form of depression. (Antidepressants are a common treatment because they alter the function of certain neurotransmitters that also are involved in multiple nonpsychological functions, including sleep, memory, cognitive ability and some aspects of muscle function.) But, several studies have shown that depression is significantly different from CFS, and current diagnostic criteria can tell a difference.[7]

Myth: People with CFS are just tired a lot and need more rest.

Fact: Individuals with CFS don't just get tired a lot; they are tired all of the time — for at least six months or longer. And, their tiredness isn't relieved by rest, which means it doesn't matter how much they sleep because sleep is not refreshing.[5,7]

Because of this misbelief about being tired a lot, a few decades ago, CFS was labeled the "yuppie flu," also known as type-A personality burnout. This label was thought to be the result of type As being the only ones who pushed their doctors hard enough to get a diagnosis. But, research shows that all personality types can end up with CFS.[7]

Myth: It is primary middle-aged Caucasian women who get CFS.

Fact: While research indicates that the prevalence of CFS is highest in people aged 40 to 59 and it affects women at four times the rate of men, people of any age, gender, ethnicity and socioeconomic group have CFS.[5] The misconception about who CFS affects is due to the first generation of prevalence studies that were obtained by asking physicians and clinics to identify patients who had specific fatigue-related symptoms, the majority of whom identified Caucasian women who were well-educated and middle- or high-income earners. It is now believed that minorities and low-income individuals were underrepresented because these groups tend to have less access to the healthcare system. In fact, later studies show comparable or higher levels of CFS prevalence among minorities. And, several studies showed that people with annual household incomes below $40,000 and lower educational and occupational status had a higher prevalence of CFS-like illness.[3]

Myth: CFS is not associated with other diseases.

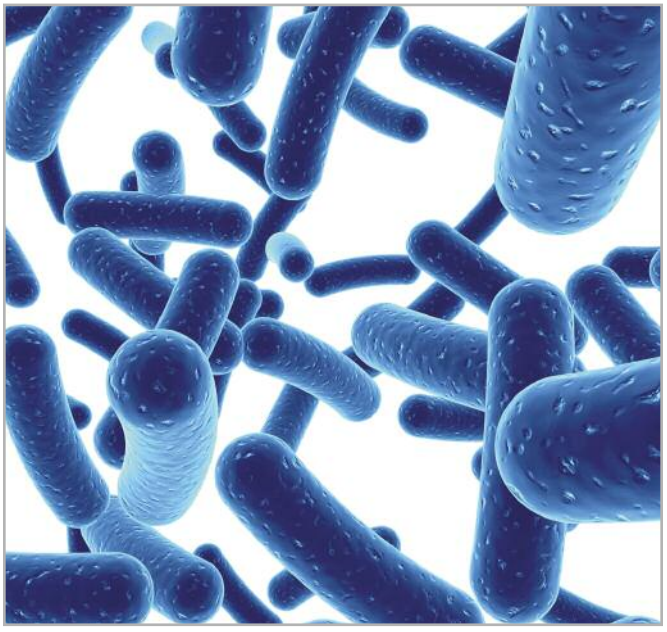
Fact: CFS patients often have comorbid conditions. While the most common one is fibromyalgia, others include depression, irritable bowel syndrome and interstitial cystitis. And, according to a 2005 study, those with Gulf War syndrome often meet criteria for CFS or go on to develop CFS. "In some cases, comorbidities arise because people wait several years to see a doctor for CFS and develop other problems in the meantime," said Suzanne Vernon, PhD, team leader of the CDC's molecular epidemiology program and a chronic fatigue expert.

But CFS also may be the result of comorbidities. According to Anthony L. Komaroff, FACP, a Harvard Medical School professor of medicine and CFS expert, more than 4,000 published studies show that patients with CFS have underlying biological abnormalities, many of which center on brain hormones and the autonomic nervous system. Komaroff identified three research areas as the most promising: 1) evidence that the immune system is chronically activated and that pro-inflammatory cytokine production is increased, 2) evidence that there is something wrong with energy metabolism and the oxidative electron transport chain in mitochondria and 3) evidence that CFS develops following several different kinds of infections, and people with genetic vulnerability are most likely to get CFS when infected with certain kinds of infectious agents.[1]

Individuals with CFS don't just get tired a lot; they are tired all of the time — for at least six months or longer.

Myth: CFS is not an infectious disease.

Fact: While infection has not been proved to cause CFS, it is a prime theory. CFS presents in two ways: sudden or gradual onset. Patients with sudden onset are more likely to experience symptoms of an infectious nature, including fever, sore throat, chills and tender lymph nodes, suggesting that sudden onset CFS may be indicative of a viral/infectious illness.[3] In fact, many infectious diseases can cause prominent fatigue for prolonged periods, including mononucleosis and hepatitis B and C.[4] In 2007, researchers in California found that CFS may be linked to the presence of enteroviruses (viral microorganisms that reside in the gut). Using endoscopies, the researchers analyzed stomach tissue biopsy samples from patients with CFS and found that more than 80 percent of them had high levels



of viruses in their digestive system (all had gastrointestinal complaints as part of their symptoms).[8]

A focus of recent research has been on the HHV-6 herpes virus, a common cause of rash and fever in infants and young children that can persist in the body for many years. It is thought that the virus is contained enough in the body to prevent damage to vital organs, but that its persistence might cause symptoms of low-grade fever, fatigue and other symptoms of CFS.[4]

Myth: CFS is not fatal.

Fact: A 2011 study reported that over 10 years, the mortality rate among patients with CFS was 12.5 percent, which is higher than the population at large. However, the cause of death may be related to comorbidities. In a 2006 study of 166 deceased CFS patients, there was an increased risk of premature death from cancer (47.8 patients versus 72 in the general population), heart failure (58.7 patients versus 83.1 in the general population) and suicide (39.3 patients versus 48 in the general population). Another study published in 2009 suggests the immune system abnormalities seen in CFS patients could explain the increased risk for cardiac failure. And, yet another study published in 2009 suggests that low Coenzyme Q10 may be a factor in cardiac failure.[2]

Myth: Most people with CFS recover within a year.

Fact: Recovery rates for CFS are unclear, with some people sick with CFS for less than two years and others ill for decades.[5] In a 2005 review of published studies, improvement rates varied from 8 percent to 63 percent with a median of 40 percent of patients improving during follow-up.[3] But the follow-up period may be important. Because of the relapsing-remitting nature

of the illness, some patients may be in remission at follow-up, suggesting their illness duration is shorter than it actually is unless the follow-up period extends for a period of years and detects any relapses.[5]

Recovery also may be influenced by many factors. Older age at illness onset, greater symptom severity, gradual onset, longer duration of illness, depression, less education, being unemployed, higher use of sedating and antidepressant drugs, poor coping skills and a belief that the illness is due to psychological rather than physical causes have all been implicated as possible risks factors for a poorer outcome. And, full recovery from CFS is rare; it is estimated that only 5 percent to 10 percent actually sustain total remission.[5]

Myth: There are medications approved to treat CFS.

Fact: There are no FDA-approved medications to treat CFS. However, there are certain classes of drugs that are prescribed off-label to treat CFS. Because researchers say the bodies of CFS patients act as if they're fighting a viral infection, antimicrobial drugs, including antivirals, antibiotics, antifungals and antiprotozoals, often are prescribed. One example is the antiviral Valcyte (valganciclovir) that treats HHV-6, which has produced encouraging results in small studies, but researchers say larger and better-designed studies are needed for reliable conclusions.[7]

Another antiviral that shows great promise is Ampligen (poly I:poly C12U) that works by jump-starting the body's natural antiviral pathway and regulating levels of RNase L (a substance in the cells that attacks viruses), which can be high in people with CFS. However, this year, after Phase 3 clinical trials that resulted in significant improvements in patients with CFS who were prescribed Ampligen versus a placebo, the FDA declined to approve Hemispherx Biopharma's new drug application, and requested the company conduct at least one additional clinical trial, as well as complete various nonclinical studies and perform a number of data analyses.[9]

Antidepressants, most commonly selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) and tricyclic agents, also are prescribed to treat CFS. Serotonin helps process pain signals and is important to the sleep-wake cycle, while norepinephrine (a type of adrenaline) is involved in the stress response and bursts of energy. Examples of SSRIs and SNRIs are Cymbalta (duloxetine), Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Effexor (venlafaxine), Desyrel (trazodone) and Wellbutrin (bupropion). Tricyclic agents sometimes improve sleep and relieve mild, widespread pain in people with CFS. Examples of tricyclics include Adapin and Sinequan (doxepin); Elavil, Etrafon, Libitrol and Triavil (amitriptyline); Norpramin (desipramine); and Pamelor (nortriptyline).[7]

In some cases, anti-anxiety drugs are prescribed, and to relieve the pain and fever associated with CFS, nonsteroidal anti-inflammatory drugs such as ibuprofen, naproxen and piroxicam can be used.[7]

What's important to note is that a medicine that relieves one symptom may aggravate another. For instance, a stimulant prescribed for cognition difficulties can exacerbate restless sleep, and sleep medications may cause daytime sedation. Since so many patients are particularly sensitive to medication, the CDC advises starting at low doses and increasing slowly.[1]

While infection has not been proved to cause CFS, it is a prime theory.

Myth: Many supplements are effective in treating CFS.

Fact: There is no proof that supplements definitively improve symptoms of CFS. However, many patients and physicians do claim that some do help. Supplements shown to reduce the symptoms of CFS include magnesium (300 to 1,000 mg per day) to reduce fatigue; essential fatty acids such as those found in fish oil (1,000 mg three times per day) and primrose oil (3,000 to 6,000 mg per day) to help reduce

fatigue; NADH (5 to 20 mg per day), a naturally occurring chemical involved in energy production in the body; DHEA (50 to 200 mg per day), a hormone produced by the body that may improve energy levels; vitamin B12 (2,500 to 5,000 mcg by injection every two to three days for several weeks) to improve energy in people not getting enough B12; beta-carotene (50,000 IU per day) to strengthen immune function; L-carnitine (500 to 1,000 mg three times per day for eight weeks) to support energy production in the cells; and vitamin D (600 to 1,000 IU daily).

One of the most effective ways to manage CFS is with exercise.

Recent research suggests that Coenzyme Q10 (CoQ10) might have a very helpful antiviral effect. In a 2009 study, researchers found highly reduced levels of CoQ10 in CFS and that low CoQ10 levels were associated with increased symptoms. In another study conducted in 2011, researchers found highly reduced CoQ10 levels in people with depression and CFS and tied the lower CoQ10 levels to cardiovascular and inflammatory issues in depression and ME/CFS.[10]

While herbs can trigger side effects, they also have been shown to help with symptoms of CFS. These include ginseng (100 to 300 mg two times per day) to improve energy and echinacea (200 mg two times per day) to boost the immune system. Essential oils such as jasmine, peppermint and rosemary can help reduce stress when used as aromatherapy by placing several drops in a warm bath or on a cotton ball.[11]

Myth: Exercise and other lifestyle changes don't help to manage CFS.

Fact: One of the most effective ways to manage CFS is with exercise. While some people with CFS can't tolerate minimal amounts of exercise, supervised physical therapy can help. For many others, exercise often makes symptoms worse in the short run, but it is a mainstay of treatment if patients start slowly and gradually increase the amount of exercise over time.[4]

In fact, exercise and cognitive behavior therapy are the best documented treatments for CFS. Research shows that cognitive behavioral therapy can help people with CFS to improve by learning about their ability to control their health and then taking steps to do so. Therapists teach self-help strategies, such as performing gentle exercise, improving sleep habits, learning to pace daily activities, getting support from others, and performing daily meditation and relaxation exercises.[12]

Many other lifestyle changes also can help CFS patients manage their disease. These include trying not to do too much when feeling energetic and less tired; improving sleep habits by going to bed only when sleepy and getting up every day at the same time; avoiding alcohol, caffeine and tobacco before bed; taking naps if needed; and joining a support group.[13]

Dispelling the Myths Now

One of the most common and inaccurate stereotypes about CFS patients "is that this is a bunch of hysterical, upper-class professional white women who are seeing physicians and have mass hysteria," said Dr. William Reeves, the previous Centers for Disease Control and Prevention chief of the chronic viral disease branch.[1] But as research shows, this myth has been debunked. CFS is a disease that affects all kinds of people, and far more patients are afflicted with CFS than those who are diagnosed. While CFS can't be cured and there are no known effective treatments to date, understanding the facts about CFS will help dispel misinformation about the disease so that patients can receive attentive medical care to adjust to their illness, and scientists can get the support they need to develop effective treatments. ❖

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

References

1. Berthold, J. Putting Chronic Fatigue Syndrome's Myths to Bed. *American College of Physicians Observer*, May 2007. Accessed at www.acpinternist.org/archives/2007/05/fatigue.htm.
2. ME/CFS Worldwide Patient Alliance. Top Seven Myths. Accessed at mcwpa.org/what-is-mecfs/top-ten-myths.
3. Jason, LA, Torres-Harding, SR, and Njoku, MGC. The Face of CFS in the U.S. CFIDS Chronicle, 2005-2006. Accessed at www.cfids.org/special/epi.pdf.
4. Schmerling, RH. Chronic Fatigue Syndrome: Names and Claims. Intelihealth, Oct. 23, 2012. Accessed at www.intelihealth.com/IH/ihtPrint/WSIHW000/35320/35323/490819.html?d=dmtHMSContent&hide=t&k=basePrint.
5. CFIDS Association of America. CFS Fact Sheet: Basic CFS Overview. Accessed at www.cfids.org/resources/free-materials.asp.
6. Myalgic Encephalomyelitis Society of America. Canadian Expert Consensus Panel Clinical Case Definition for ME/CFS. Accessed at www.cfids-cab.org/MESA/ccpc.html.
7. Dellwo, A. Chronic Fatigue Syndrome Myths. About.com, Oct. 12, 2012. Accessed at chronicfatigue.about.com/od/whatischronicfatigue/a/Chronic-Fatigue-Syndrome-Myths.htm.
8. Burkholder, A. Living with Chronic Fatigue. CNN.com, Sept. 18, 2007. Accessed at www.cnn.com/HEALTH/blogs/paging.dr.gupta/2007/09/living-with-chronic-fatigue.html.
9. Hemispherx Biopharma Receives Complete Response Letter From FDA on Ampligen New Drug Application for Chronic Fatigue Syndrome. Drugs.com, Feb. 4, 2013. Accessed at www.drugs.com/nda/ampligen_130205.html.
10. Phoenix Rising. Coenzyme Q10. Accessed at phoenixrising.me/treating-cfs-chronic-fatigue-syndrome-me/energy-ii/alternative-treatments/treating-chronic-fatigue-syndrome-mecfs-coenzyme-q10.
11. University of Maryland Medical Center. Chronic Fatigue Syndrome. Accessed at www.umm.edu/altmed/articles/chronic-fatigue-000035.htm.
12. Chronic Fatigue Syndrome: Using Cognitive-Behavioral Therapy. WebMD. Accessed at www.webmd.com/chronic-fatigue-syndrome/cognitive-behavioral-therapy-for-chronic-fatigue-syndrome#.
13. Chronic Fatigue Syndrome: Home Treatment. WebMD. Accessed at webmd.com/chronic-fatigue-syndrome/chronic-fatigue-syndrome-home-treatment.

The industry

refers to us as a DISTRIBUTOR.

Our customers see us as MUCH MORE.

FROM AFFORDABILITY, SAFETY AND AVAILABILITY,
to our teams of professionals and portfolio of industry resources, FFF goes **BEYOND DISTRIBUTION** to help our customers provide the best care for their patients.

- Availability
- Guaranteed Channel Integrity™
- Experienced Field Service Team
- Wow! Customer Care™

Experience the FFF DIFFERENCE!

Helping Healthcare Care is the benchmark by which we measure all our actions. We consider this not just the FFF way, but the *only* way.

FFF enterprises
Helping Healthcare Care®

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

The Heart of the Matter: A Flu Shot Could Save Your Life

An ounce of prevention is worth a pound of cure.

— Benjamin Franklin

by KEITH BERMAN, MPH, MBA

HOW MANY times have you asked a patient, friend or acquaintance if he or she got the annual flu shot yet, only to get some version of this reply: "No. Do I really need it?"

Earlier this year, I had that conversation with a 67-year-old New York City cab driver on my way out of town. Somehow, we got to chatting about news reports that influenza was hitting the area much harder than usual. "I got really sick with the flu two years ago," he recalled. "I couldn't get out of bed for almost two weeks. But now I'm stronger against it, so I don't need a flu shot, right?"

While I tried my best to persuade this man to get his flu vaccine, I entirely forgot to pitch perhaps the most compelling reason of all: A flu shot could prevent a heart attack or even save his life. Thanks to a flurry of recent studies, it is now apparent that many thousands of people are walking around today because they took a few minutes to get a simple, inexpensive vaccination against seasonal influenza virus.

Flu, Cardiovascular Events and Death

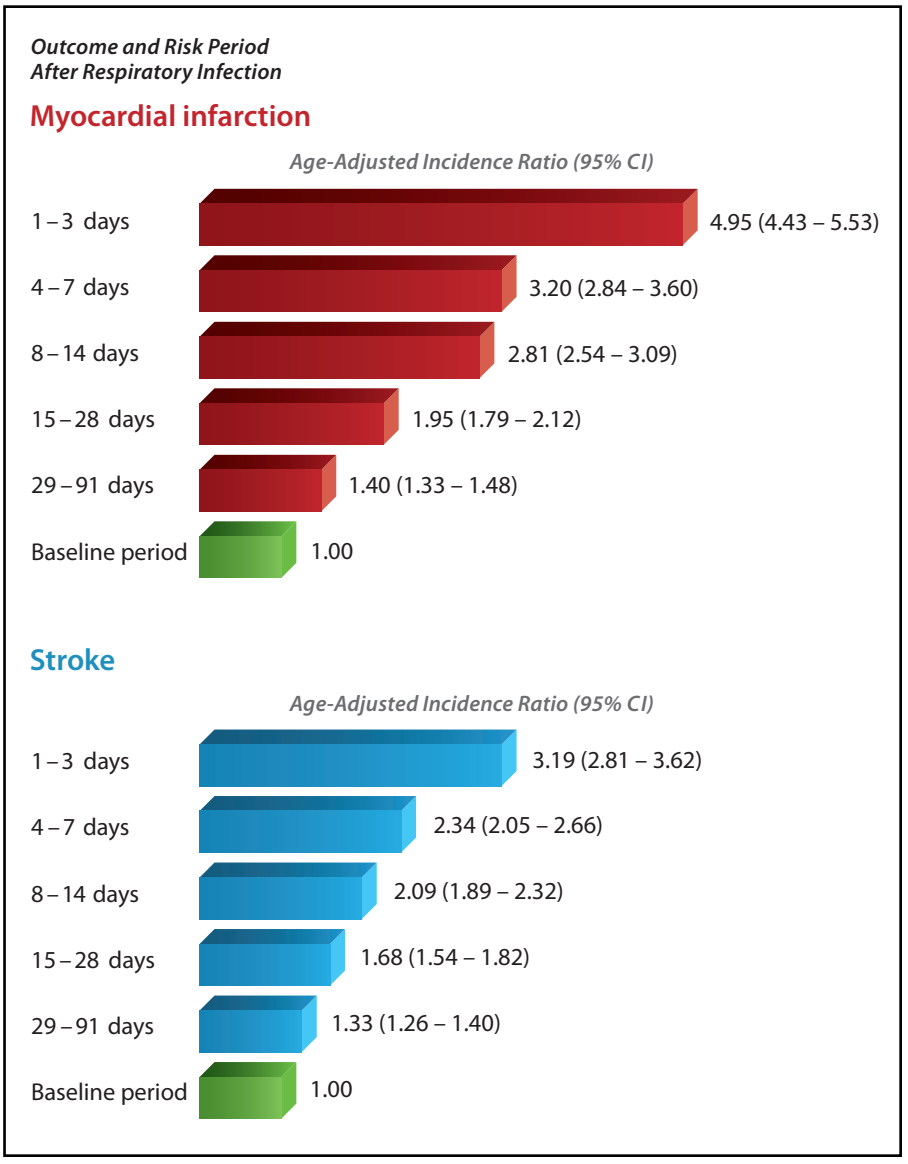
A causal relationship between flu epidemics and increased death rates from nonrespiratory causes was first proposed more than 80 years ago.[1] Decades later, a large 1994 population study estimated that roughly 20,000 excess deaths from cardiovascular disease occur each winter due to acute respiratory infections in England and Wales.[2] Separate analyses of U.S. mortality data over a 40-year period also strongly suggested that excess wintertime deaths from acute ischemic heart disease and cerebrovascular disease can be directly attributed to influenza.[3]

The underlying link between influenza and fatal or nonfatal acute cardiovascular events isn't entirely clear. The most widely proposed theory is that a spike in circulating levels of various inflammatory molecules that accompany flu infection can promote endothelial damage in the coronary and systemic vasculature, or destabilize atherosclerotic plaques, resulting in thrombosis. But other flu-related mechanisms may also play a role, including dehydration or the prothrombotic effects of bed rest during the illness.

Flu Vaccine as a "Heart Vaccine"

In 2004, a British research team examining the health records of 5.8 million adults reported sharply increased rates of both acute myocardial infarction (AMI) and stroke over the first 91 days following an acute respiratory tract infection (Figure 1).[4] At that time, there were also concerns about potential risk of vascular events associated with the pro-inflammatory effects of vaccination. But the investigators found instead that influenza vaccination was associated with a significantly *reduced* risk of both AMI and stroke over several weeks following administration. By contrast, neither tetanus nor pneumococcal vaccinations had any influence on these event rates at all.

Figure 1. Age-Adjusted Incidence Ratios for a First Myocardial Infarction or Stroke in Risk Periods Following Acute Respiratory Infection



Source: Adapted from Smeeth L et al. *New Engl J Med* 351;2611-18.

Subsequent studies have confirmed that a simple flu shot cuts the risk of AMI, particularly in older adults and those with known chronic cardiovascular disease. A 2010 study of the health records of nearly 79,000 unselected post-AMI patients aged 40 years and older found that influenza vaccination was associated with a 19 percent reduction in AMI risk. Further, patients vaccinated before mid-November had a lower risk of AMI than those vaccinated later in the flu season.[5]

A valid concern about retrospective studies like these is the potential for unintended bias. People who get a flu

Table 1. Influenza Vaccination Coverage in U.S. Adults, 2010-11 and 2011-12 Seasons

Age	2010 - 2011 flu season	2011 - 2012 flu season	Change
18 - 49 years	30.5%	31.8%	+1.3%
50 - 64 years	44.5%	42.7%	-1.7%
≥ 65 years	66.6%	64.9%	-1.7%

Source: U.S. Centers for Disease Control and Prevention (CDC)

shot, or who get their vaccine early in the season, could happen also to embrace lifestyle behaviors that place them at lower risk for AMI or other serious cardiovascular events. But a very recent meta-analysis of four randomized controlled trials, collectively enrolling 3,227 patients with and without a history of cardiovascular disease, appears to put these questions to rest.[6] In these generally older patients, whose average age was 60 years, influenza vaccine significantly reduced the one-year risk of major adverse cardiovascular events by nearly 50 percent (odds ratio [OR] 0.52; 95% confidence interval [CI] 0.37 to 0.74; p = 0.0002). In addition, there was a directionally consistent trend toward reduced cardiovascular death (OR 0.58; 95% CI 0.25 to 1.36; p = 0.21).

The Challenge: Connecting Patient and Vaccine

Whether due to lack of awareness, misconceptions about safety, needle-phobia or other factors, flu vaccination rates have plateaued (Table 1). Disappointingly, fewer than 40 percent of adults receive a flu vaccine, and only about two-thirds of adults are over age 65 years — whose high rates of coronary artery disease place them at highest risk for a cardiac event.[7,8]

Investigators found that influenza vaccination was associated with a significantly reduced risk of both AMI and stroke over several weeks following administration.

Mainly through the U.S. Centers for Disease Control and Prevention, the word is getting out to the medical community that annual vaccination against the flu can protect against cardiac-related events.[9,10] As always, it remains up to physicians and pharmacists to deliver this message and professional recommendation to their patients: Get your flu shot, get it as early as possible after it becomes available, and reduce your risk of heart attack and other potentially fatal acute vascular events. ❖

References

1. Collins S. Excess mortality from causes other than influenza and pneumonia during influenza epidemics. *Public Health Reports* 1932;47:2159-79.
2. Woodhouse PR, Khaw KT, Plummer M, et al. Seasonal variations of plasma fibrinogen and factor VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994 Feb 19;343(8895):435-9.
3. Reichert TA, Simonsen L, Sharma A, et al. Influenza and the winter increase in mortality in the United States. *Am J Epidemiol* 2004 Sep1;160(5):492-502.
4. Smeeth L, Thomas SL, Hall AJ, et al. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med* 2004;351:2611-8.
5. Siriwardena AN, Gwini SM, Coupland CA. Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case-control study. *CMAJ* 2010 Oct 19;182(15):1617-23.
6. Udell JA, Farkouh ME, Bhatt DL. Influenza vaccination and reduction of cardiovascular events — a systematic review and meta-analysis. *Can J Cardiol* 2012 Sep;28(5 Suppl): S161.
7. Flu vaccination coverage, United States, 2011-12 influenza season. U.S. Centers for Disease Control and Prevention (CDC). Accessed February 20, 2013, at http://www.cdc.gov/flu/professionals/vaccination/coverage_1112estimates.htm#age-group.
8. Final state-level influenza vaccination coverage estimates for the 2010-11 season, United States. Accessed at http://www.cdc.gov/flu/professionals/vaccination/coverage_1011estimates.htm.
9. Bresee J. Influenza: It's not too late to vaccinate! (CDC Expert Commentary). *Medscape News*. Accessed February 20, 2013, at http://www.medscape.com/viewarticle/757344.
10. Bridges C. Influenza and cardiac disease. *QuantiaMD*. Accessed February 20, 2013, at http://quantiamd.com/player/vcbrzszn?bc=1&partner=cdc&m=111128_102468_cdc.

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.*

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.

Frontrunner Solutions in Genetic Testing Diagnostics

"As personalized medicine becomes a clinical reality, our goal is to provide accurate and relevant information for physicians to understand the scope and trajectory of the genetic testing industry and how it may impact their practices now and in the years ahead."

— Mark Harris, PhD, CEO, NextGxDx

BY TRUDIE MITSCHANG

THE FIELD OF genetic testing has grown tremendously in the past three years. Fueled by a revolution in DNA sequencing and accelerated research in genetics and genomics, one to two new genetic testing products, it is estimated, are launched daily from molecular diagnostic laboratories across the industry. With information about specific tests scattered in many locations, inconsistent ordering processes and cumbersome results reporting, there is a rapidly growing need for tools that will help healthcare providers navigate this explosive field. Enter Mark Harris, PhD, founder and chief executive officer of NextGxDx.

NextGxDx is a healthcare information technology company that provides a web-based genetic diagnostics marketplace, allowing hospitals and physicians to quickly and efficiently identify appropriate genetic tests while cross-referencing multiple test providers. The company's online portal curates information on the more than 10,000 genetic testing products currently offered by clinical laboratory improvement amendments (CLIA)-certified labs in the U.S. As a first-to-market platform, NextGxDx's database is the most comprehensive catalogue of genetic testing products available to U.S. healthcare providers.

"Our research shows there are nearly 10 times more genetic tests available today than commonly thought, and yet there has not been a centralized, well-curated, user-friendly platform to help healthcare providers find and order the right test for a patient," says Harris.

Innovation in the Online Marketplace

Harris was first introduced to the issues surrounding genetic testing diagnostics in 2010, when he was invited to join the leadership development program at Athena Diagnostics. Harris was tasked with spearheading a technology initiative, and it wasn't long before he began to notice a significant lack of transparency in the industry surrounding genetic testing. Another issue he identified was the time-consuming test-ordering process, with the majority of tests ordered through a paper-based and extremely laborious process, requiring hours of research to identify the appropriate test and laboratory for the patient's particular disease state. Once identified, it could take many more hours to complete the ordering process and wait for results. For Harris, the challenge presented an opportunity, and he began researching online marketplace concepts known for streamlining the selection process of goods and services and simplifying the end-user experience. From there, it was a matter of adapting and applying these concepts to the field of genetic testing.

"The goal was to simplify the ordering process for physicians and hospitals and improve ordering accuracy," explains Harris. "From a lab's perspective, this platform offers the opportunity to showcase the newest tests and attract new customers — it's a win-win for all involved."

With a solid idea in place, Harris joined forces with molecular geneticist Jud Schneider, PhD, along with a respected team of physicians, researchers, web designers and software engineers, and set out to create a web experience that would provide a one-stop shop for genetic testing. After developing a prototype, Harris and his team demonstrated the concept to more than 1,000 physicians, and after

getting universally enthusiastic feedback, began presenting the idea to labs. Interest levels on both sides were high, and the NextGxDx platform was launched in October 2012.

"One of the features we developed to save physicians time was a program that links all the tests to specific disorders, and then categorizes them according to different medical specialties," says Harris. "This allowed us to look at the data in new ways. For example, we had always heard that neurology was one of the most confusing fields when it came to genetic testing, so it's not surprising that we found over 30 percent of the available tests are within that specialty area. Correspondingly, we've had a tremendous response from physicians in that field, especially pediatric neurologists."

Harris says the platform offers an intuitive interface; within minutes, providers can easily identify the appropriate genetic tests for their patients, searching the database by gene or disorder — a process that previously could take up to two hours per test. The platform also allows side-by-side comparison of tests, and the company's partnerships with laboratories across the country enable physicians to order tests directly from the secure and HIPAA-compliant NextGxDx website. "By offering the ability to research tests based on patient symptoms, instantly compare tests across laboratories and determine existing institutional relationships, we can provide physicians with a single destination for discovering, comparing and ordering genetic tests," says Harris.

Leading with Confidence

Harris has a broad range of experience in scientific research, data analytics, product design and technology commercialization. Armed with these skills and a fascination with the burgeoning field of genetics, he has confidently stepped into a role that places him at the forefront of a rapidly advancing industry. As the leader of a flagship company within a cutting-edge field, Harris describes his leadership style as both inspirational and motivational. "Our company was the first to develop a web-based genetic testing marketplace and the first to implement tools that compare genetic testing products across multiple laboratories. That places us in a leadership position, and our long-range goal is to continue to innovate systems and methods that help patients get the appropriate test the first time," he states.

The NextGxDx management team, outside their offices in Franklin, Tenn. From left to right: Kevin McKnight, sales director; Dan Kauke, marketing director; Blake Blackshear, CTO; Mark Harris, PhD, CEO; Jud Schneider, PhD, scientific director; Julia Polk, acting CFO; Marshall Cottrell, developer; Jay Buford, SVP, business development.

In late 2012, NextGxDx explored the factors informing and shaping the genetic testing industry in the white paper *The Genetic Testing Landscape: Finding the Needle in the Haystack*. According to Harris, the paper provides an overview of the genetic testing industry, including the size of the industry, how genetic tests are used and how genetic information is communicated. It also outlines key strategies for the future of clinical integration of genetic testing and personalized medicine. The paper, authored by Schneider, NextGxDx's scientific director, establishes a robust analysis of genetic testing as it relates to the products currently available for clinical use. "As personalized medicine becomes a clinical reality, our goal is to provide accurate and relevant information for physicians to understand the scope and trajectory of the genetic testing industry and how it may impact their practices now and in the years ahead," says Harris.

While Harris' company is still in its first year of growth and expansion since its marketplace was launched, the ambitious entrepreneur already has his sights on future innovations: "Helping patients and their families diagnose their genetic disorders the first time — that's what drives us," says Harris. "The way we execute that mission is by becoming a one-stop shop for all genetic testing needs. Our technology is designed to eliminate the workflow and information barriers that hinder the genetic test ordering process. For example, as we look at patient out-of-pocket costs, we're researching ways of incorporating insurance eligibility tools into our online services that would provide guidance to the patient on how much the ordered test will cost them after insurance has paid. Our plan is to develop partnerships with other industry leaders to better link services like these through our single, consolidated platform." ❖

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

Depression: A Patient's Perspective

Deborah Gray lived with undiagnosed clinical depression until age 27. Today, the busy wife, mother and writer is proof there is a light at the end of the tunnel for those suffering from MDD.

BY TRUDIE MITSCHANG

AN ESTIMATED ONE in 10 adults suffers from major depressive disorder (MDD). There are various theories as to the cause of depression, including biological, psychological, social and spiritual explanations, although at least some genetic predisposition is likely in the majority of patients. There are also some common catalysts that seem to precede the onset of MDD, including loss, stress, isolation and trauma. For Deborah Gray, who has struggled with this debilitating illness since childhood, an incident that occurred when she was still a toddler stands out as the likely catalyst into what has become a lifelong battle. "My parents divorced when I was 2, and I essentially lost my father," she recalls. "I don't know if I would have suffered from depression without that early loss; I do know that the only picture of me as a child that shows me laughing was taken before my father left. Every picture taken afterward shows a solemn child who smiles only diffidently."

Diagnosis: A Long and Winding Road

A painfully shy child who sought refuge in reading, Deborah withdrew further as a teen. In college, her depression worsened, and she found herself lagging socially and academically. In desperation, she visited a walk-in clinic of a local hospital and came away with a diagnosis of PMS and a mandate to begin journaling. Discouraged, Deborah graduated weeks later with no diagnosis and minimal hope for the future. "After graduation, I found a job, but I was barely making it through the workday. I would do only what was absolutely necessary — there was no joy, motivation or sense of accomplishment. Though I wasn't suicidal, I couldn't imagine life five years down the road," says Deborah.

The stigma of depression left Deborah Gray suffering for 20 years with MDD before she was diagnosed.

A turning point came when Deborah was 27; after reading the book *Darkness Visible* by William Styron, she says she realized the author perfectly described what she'd been experiencing for two decades. "He articulated beautifully all of the feelings of loneliness and despair I'd been fighting for the past 20 years," she explains.

Deborah made an appointment with the head of psychiatry at a nearby hospital, where she was finally diagnosed with depression and prescribed a treatment plan that included a regimen of talk therapy and antidepressants. Initially, Deborah declined the medication, wary of side effects, but later reconsidered when talk therapy alone failed to work. "Six months after my diagnosis, I began taking Norpramin. In six weeks, I experienced a complete one-eighty," says Deborah. "Small things that used to require all my energy, like taking a walk, became effortless, and I could express my emotions in therapy."

Deborah remained on Norpramin for the next 10 years, until she learned she was pregnant in 2002 and was advised to wean herself off her medication. "I was shocked when I didn't experience any depression during my pregnancy, and as soon as I gave birth to my son, Lawrence, I began taking Wellbutrin to avoid any bouts of postpartum depression."

Breaking the Silence

Today, with the help of medication and weekly therapist visits, Deborah says the majority of her days are good ones. The stigma of depression had left her suffering in silence for years, and she was compelled to help others who might be suffering in silence, too. Deborah started a popular and well-respected depression website, Wing of Madness, to help educate, support and advocate for those dealing with MDD. "I am still dealing with depression and probably will be for the rest of my life," she says. "Sometimes it's still a struggle to find the motivation to do household chores, like making a simple set of curtains for our kitchen. The difference is now I use my support system of doctors, family and friends to keep me healthy." ❖

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

Depression: A Physician's Perspective

Major depressive disorder is a prevalent condition, but with swift and appropriate treatment, the chance of recurrence can be minimized.

Dr. Gus Alva is focusing on the latest treatments for major depressive disorder to find better therapies for this prevalent disease.

GUS ALVA, MD, is the medical director of ATP Clinical Research (a premiere private clinical research company specializing in neuropsychiatric investigations) in Costa Mesa, Calif. He also is a forensic psychiatric consultant for the Orange County Superior Court and a diplomate of the American Board of Psychiatry and Neurology.

Dr. Alva has served as a principal investigator since 1995, conducting investigations of myriad neuropsychiatric conditions, including Alzheimer's, depression, anxiety disorders, bipolar disorder and psychotic conditions. As a clinician and investigator, Dr. Alva's focus is on the genetics, neuroimaging and latest treatments available. He has published numerous articles, and presents at both national and international meetings and conferences.

BSTQ: What are the most common misconceptions about major depressive disorder (MDD)?

Dr. Alva: Most people don't realize how prevalent MDD is. It actually falls just behind hypertension in terms of how frequently it is diagnosed. The other misconception is that MDD is somehow linked to a character flaw or weakness; MDD is a medical problem requiring medical intervention. The truth is, medical treatment can restore an individual's ability to function normally following an MDD diagnosis.

BSTQ: What is your typical treatment approach for MDD?

Dr. Alva: You have to tailor the treatment to the individual patient, and, unfortunately, finding the right approach often requires trial and error. Sometimes individuals will respond to psychotherapy alone, but often we find there is a synergy between medication and therapy, and when done simultaneously, the outcome can be very positive. The challenge we face with medications that treat MDD is that a lot of the traditional options present numerous unwanted side effects such as weight gain and sexual dysfunction. Thankfully, there are many newer medications and treatment options in the pipeline that promise better results with fewer side effects. The bottom line is: It's never a cookie-cutter approach.

BSTQ: Can MDD be cured?

Dr. Alva: MDD is considered a chronic recurrent problem. After a patient has one episode of MDD, they have a 50 percent chance of another episode. The odds keep rising, and after a third episode of MDD, the chances of recurrence are better than 90 percent. That's why we always encourage patients to seek appropriate treatment as soon as symptoms present themselves.

BSTQ: What is your opinion of experimental drugs like ketamine for the treatment of MDD?

Dr. Alva: Ketamine is an anesthetic medicine that was developed nearly 50 years ago. Recently, research has demonstrated that ketamine may be administered intravenously in doses far below those used for surgery to provide rapid relief from symptoms of depression and anxiety, although it is still considered experimental. Because ketamine use can result in psychotic episodes and other negative side effects, I think there are safer treatments for dealing with MDD. One that has been approved by the U.S. Food and Drug Administration since 2008 is called transcranial magnetic stimulation (TMS). TMS uses magnetic fields to stimulate nerve cells in the brain to improve symptoms of depression. TMS may be tried when other depression treatments have failed.

BSTQ: In addition to medication and therapy, are there any lifestyle changes recommended for the treatment of MDD?

Dr. Alva: Lifestyle changes are always important. A Mediterranean-style diet is helpful — what's good for the body is also good for the brain. It's also proven that exercise releases endorphins that act as opiates and improve mood. We look at a patient's current diet and activity levels and make recommendations as part of a total treatment plan.

BSTQ: Tell us about some of your recent clinical trials.

Dr. Alva: Currently, our focus is on augmentation strategies. A lot of studies show that adding a second medication to an existing medication — what we call augmenting agents in MDD — can be very effective. There also are a couple of new antidepressants in the pipeline that may offer additional aid to individuals who have not successfully responded to previous medications. ❖

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

BioResearch

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

Albumin Infusion Cuts Renal Impairment and Mortality Risk in Patients with Spontaneous Bacterial Peritonitis

Noting that albumin administration has been reported to reduce renal impairment and mortality in patients with spontaneous bacterial peritonitis (SBP), U.S. and Italian investigators performed a meta-analysis of randomized controlled trials to quantify this effect. A total of four trials involving 288 patients were identified and included in the analysis.

Albumin was compared with no albumin in three trials and with an artificial colloid in the fourth trial. No evidence of statistically significant heterogeneity or publication bias was found in any of these studies. The incidence of renal impairment was 44 of 144 (30.6%) in control group subjects, compared with 12 of 144 (8.3%) in groups given albumin. The pooled odds ratio for renal impairment after albumin therapy was 0.21 (95% confidence interval [CI], 0.11 to 0.42).

Control group mortality was 51 of 144 (35.4%), compared with 23 of 144 (16.0%) among patients who received albumin. The pooled odds ratio for decreased mortality after albumin infusion was 0.34 (95% CI, 0.19 to 0.60). "Based on our quantitative findings and the clear benefits demonstrated, it seems prudent to treat all SBP patients with albumin, regardless of whether they are high-risk or low-risk for poor outcome," the study's lead author said.

Salerno F, Navickis RJ and Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol *2013 Feb;11(2):123-30.*

Subcutaneous Immunoglobulin Is a Potential Alternative to Intravenous Immunoglobulin in CIDP

Hypothesizing that administration of subcutaneous immunoglobulin (SCIG) in patients is feasible, safe and effective, Danish investigators randomized 30 adult patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) on maintenance therapy with intravenous immunoglobulin (IVIG) to either SCIG at a dose corresponding to their pre-study IVIG dose or to subcutaneous saline given twice weekly or three times weekly for 12 weeks at home.

At the start and end of the trial, as well as two weeks before, isokinetic strength performance of four predetermined and weakened muscle groups was measured. Overall disability sum score (ODSS), 40-meter walking test (40-MWT), nine-hole-peg test, neurological impairment score (NIS), Medical Research Council (MRC) score and grip strength were also evaluated.

SCIG therapy was well tolerated in all 14 patients who received it. Six patients complained of mild side effects at the injection site. In the SCIG group, there was an increase in isokinetic muscle strength of 5.5 ± 9.5% ($P < 0.05$) as compared with a decline of 14.4 ± 20.3% ($P < 0.05$) in the placebo group; the difference between the two groups was statistically significant ($P < 0.01$). Grip strength, ODSS, NIS, MRC and 40-MWT all improved following SCIG versus saline. The authors concluded that SCIG therapy is feasible, safe and effective, and seems an attractive alternative to IVIG.

Markvardsen LH, Debost JC, Harbo T, et al. Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy. Eur J Neurol *2013 Jan 7 [Epub ahead of print].*

Recombinant and Plasma-Based Factor VIII Products Confer Similar Risks of Inhibitor Development

To address whether the type of factor VIII (FVIII) product administered or switching among products is associated with the development of clinically relevant inhibitory antibodies in previously untreated children with severe hemophilia A, investigators at 29 European hemophilia treatment centers evaluated 574 consecutive patients born between 2000 and 2010. Data were collected on all infusions of plasma-based FVIII and first-, second- and third-generation recombinant FVIII products for up to 75 exposure days or until development of inhibitors.

Inhibitory antibodies developed in 177 of the 574 children (32.4%); 116 had a high-titer inhibitor, defined as a peak titer of at least 5 Bethesda units per milliliter. Plasma-derived FVIII products conferred a risk of inhibitor development that was similar to the risk with recombinant products (adjusted hazard ratio, 0.96; 95% confidence interval [CI], 0.62 to 1.49). As compared with third-generation full-length recombinant products (derived from the full-length complementary DNA sequence of human factor VIII), second-generation full-length products were associated with increased inhibitor risk (adjusted hazard ratio, 1.60; 95% CI, 1.08 to 2.37). The content of von Willebrand factor (vWF) in FVIII products and switching among products were not associated with the risk of inhibitor development.

The investigators concluded that recombinant and plasma-derived FVIII products confer similar risks of inhibitor development, and neither wWF content nor switching among products is associated with the risk of inhibitor development.

Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. New Engl J Med *2013 Jan 17;368:231-9.*

BioResources

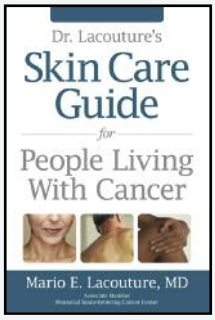
Recently released resources for the biopharmaceuticals marketplace.

HealthCare Lean — The Team Guide to Continuous Improvement

Author: Lawrence M. Miller

HealthCare Lean relays the fundamental tools and practices needed for hospitals and healthcare workers to work together in teams to increase efficiency, improve quality of care, eliminate waste, cut costs and increase satisfaction of staff and patients. The book is organized into three parts: Getting Organized, Improving Performance and Improving Teamwork. Specific chapters include the stages of team development, clarifying decision styles, motivation and human performance, leading effective meetings, giving and receiving feedback, improving team dynamics and more. The author's expertise is derived from 35 years of hands-on experience creating change in the culture of hundreds of organizations, including the North Carolina prison system in which he established one of the first applications for behavioral analysis in the correctional setting.

www.managementmeditations.com



Dr. Lacouture's Skin Care Guide for People Living with Cancer

Author: Mario E. Lacouture, MD

While this book is written for cancer patients, it can be used as a reference for physicians prescribing treatments that can cause side effects that affect the skin, hair and nails. Written by a leading authority on dermatologic conditions that result from anti-cancer medications, the author offers clear, practical suggestions for preventing, treating and living through these skin, hair and nail changes, including information about the rashes, blisters and cracked, itching or dry skin that may come with cancer treatment; tips for caring for the nails; the risks for hair loss; how to stay safe in the sun; and even cosmetics that are right for patients.

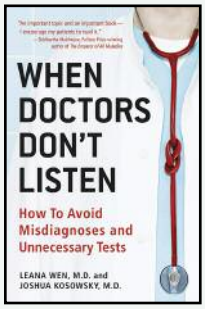
www.DrLacoutureSkinCare.com

Understanding the U.S. Biosimilars Pathway

Author: U.S. Food and Drug Administration

Understanding the U.S. Biosimilars Pathway is the roadmap to the new biosimilars market in the United States. The report analyzes the U.S. Food and Drug Administration's (FDA) draft guidance for drugmakers and provides insight into what that guidance means in practical terms. The report addresses the FDA definition of a biological product; products not suitable for 351(k); principles of biosimilarity demonstration; interchangeability and substitution; reference products (outside U.S. comparators and reference standards); formulation, delivery device and container/closure; presentations, conditions of use and strength; biosimilar structure, deliberate modifications and expression systems; quality considerations and specifications; nonclinical studies; clinical testing; extrapolation; drift of biosimilar before, during and after development; labeling and naming; and pharmacovigilance. The report is available from FDAnews in print or PDF format for $377.

www.fdanews.com/conference/detail?eventId=3183



When Doctors Don't Listen: How to Avoid Misdiagnoses and Unnecessary Tests

Author: Leana Wen, MD

In *When Doctors Don't Listen*, Dr. Leana Wen, an emergency physician at Brigham & Women's and Massachusetts General and a clinical fellow at Harvard Medical School, teaches patients they need to advocate for their own health by doing one simple thing: asking for a diagnosis when they go to see their doctor. The book could be used as a guide by physicians to better communicate with their patients with its 8 Pillars to Better Diagnosis, including: tell your story, even if your doctor is steering you away from a narrative and toward the chief complaints; practice your pitch before going, including writing it out; make the differential diagnosis together by keep asking what else could be going on; evaluate with your doctor the likelihood of each possible diagnosis; use common sense to confirm the working diagnosis (a working diagnosis should be reached at the end of every visit) and make sure it makes sense.

us.macmillan.com/ThomasDunne.aspx

BioProducts

Medication Reminder App

MediSafe Project is a mobile health app that reminds individuals when it's time to take their medication, as well as their families, friends and caretakers, by sending alerts when there is a missed dose. The cloud-synced mobile app is designed to help families prevent emergencies caused by over- or underdosing medications, as well as a way to lower hospitalization and mortality rates, promote sustainable behavior changes that prolong health, decrease long-term healthcare costs and help pharmaceutical companies understand patients' barriers to medication compliance. The app's dashboard features anonymous demographics, geolocation, patient behaviors, physician trends and other market aspects. For instance, it can show which demographics have higher noncompliance for a drug compared with the general population, the doctors or areas that have the lowest prescription rates within a city, competitive drugs patients are switching to, etc. The MediSafe Project app is available for all Android devices and is compatible with iPhones and iPads as an alpha version.

MediSafe Project Ltd., (972) 54-466-4242 (Israel), www.medisafeproject.com

Patient Engagement Solution

Nurseline MD's DoctorDirect patient engagement solution is designed to reduce operational costs while increasing patient satisfaction. The system allows patients the flexibility to communicate with providers any time of day, night or weekend, and providers can monitor incoming requests during business hours, with the flexibility to monitor off-hours if desired. DoctorDirect notifies providers instantly when a message is received and viewed, as well as when a response occurs. Providers can use any device such as a PC, laptop or mobile phone. And information is stored encrypted in the system with messages viewable only by the patient and provider. All data are transferred over the Internet using SSL extended validation encryption; the green address bar (https) verifies the secure connection.

Nurseline MD, (865) 748-3747, www.nurselinemd.com/DoctorDirectProvider.aspx

Health Records App

BlueButton is a set of smartphone and tablet apps based on Humetrix mobile technology for patient-controlled automated access, download and transfer to healthcare providers of Blue Button (federal government) and other records. At the point of care, the direct iBlueButton record exchange is a two-way communication (patient to provider and provider back to patient) delivered by a secure real-time proximity "push" in between a patient's phone using the iBlueButton or the iBlueButton Veterans App and a provider's tablet using the iBlueButton Pro App. With the iBlueButton Pro App, providers can exchange health records with patients; access other iPad apps and transfer files, including images; retrieve patient records with a built-in file management system; create visit notes for patients; record a log of patient exchanges; email records to patients; and print any recorded exchange stored within the app.

Humetrix, (858) 259-8987, humetrix.com/ibb.html

Rescue Inhaler with GPS Sensor

Asthmapolis is a rescue inhaler topped with a GPS sensor that maps patients' location every time they take a puff and sends that information back to their doctor. It is designed to provide healthcare providers with an accurate picture of when and where patients' asthma symptoms are occurring and how often they are using their medications. Using the Asthmapolis provider dashboard, healthcare providers can remotely monitor the asthma symptoms of their patients and easily identify those with uncontrolled asthma and low controller medication adherence. The device also provides customizable alerts so providers can be notified if a patient's condition worsens. In July, Asthmapolis received clearance as a medical device from the U.S. Food and Drug Administration. Since then, the company has signed contracts to manage asthma patients for a Medicaid managed-care organization and a hospital.

Asthmapolis, (608) 251-0470, www.asthmapolis.com

BioDashboard

IVIG Reimbursement Calculator

Medicare Reimbursement Rates*
Rates are effective April 1, 2013 through June 30, 2013.

Product	Manufacturer	HCPCS	ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$66.24
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$71.03
GAMMAGARD LIQUID	Baxter BioScience	J1569	$75.65
GAMMAGARD S/D	Baxter BioScience	J1566	$66.24
GAMMAKED	Kedrion	J1561	$76.46
GAMMAPLEX	Bio Products Laboratory	J1557	$74.43
GAMUNEX-C	Grifols	J1561	$76.46
OCTAGAM	Octapharma	J1568	$62.99
PRIVIGEN	CSL Behring	J1459	$72.15

* Hospital outpatient and physician office settings

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

2013-2014 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, trivalent, 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, trivalent, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90656
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, trivalent, split virus, when administered to children 6-35 months of age, for intramuscular use	90657
FLUCELVAX	0.5 mL prefilled syringe	Influenza virus vaccine, derived from cell cultures, subunit, preservative and antibiotic free, for intramuscular use	90661
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
FLUMIST QUADRIVALENT	0.2 mL nasal spray	Influenza virus vaccine, quadrivalent, live, intranasal use, when administered to individuals 2-49 years of age	90672
FLUARIX QUADRIVALENT	0.5 mL prefilled syringe	Influenza virus vaccine, quadrivalent, split virus, preservative free, when administered to individuals 3 years of age and older, for intramuscular use	90686
AFLURIA	5 mL multi-dose vial	Influenza virus vaccine, trivalent, 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

gamunex®-C
immune globulin injection (human), 10%
caprylate/chromatography purified

Evidence based. Patient proven.

Product Features

FDA approved indications[1]:

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Primary immunodeficiency (PI) for both IV and SC administration
- Idiopathic thrombocytopenic purpura (ITP)

Product properties[1]:

- No sugar
- Optimal pH of: (4.0-4.5)
- IgA content: average of 46µg/mL
- Only trace amounts of sodium
- Close to physiologic osmolality: (258 mOsm/kg)

Easy to use[1]:

- Latex-free packaging
- Tamper-evident vials (cap overwrap)
- Vials available in 1, 2.5, 5, 10, and 20 g
- Long 3-year shelf life; room temperature storage*

* Up to 6 months at any time during 36-month shelf life.

Important Safety Information

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 preexisting 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 Acute 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).

Please see adjacent page for brief summary of Gamunex-C full prescribing information.

1. GAMUNEX-C package insert. Research Triangle Park, NC: Grifols Therapeutics Inc.; 2010.

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

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

GRIFOLS

FLU SEASON?

Got it Covered.

FLU SEASON IS UNPREDICTABLE...

Take Control with MyFluVaccine.com

CHOICE
All Flu Vaccines from All Manufacturers

CONVENIENCE
Secure **YOUR** best delivery dates.

SAFETY
With Guaranteed Channel Integrity™

LOG ON TODAY
and take control of your flu vaccine supply!

MyFluVaccine™
A PROGRAM OF FFF ENTERPRISES

800.843.7477 | MyFluVaccine.com

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