April 2012

BioSupply Trends

Special Focus: SAFETY

Quarterly

Counterfeit Medications

Detecting & Defeating the Threat

Drug Shortages:
A "Tsunami" of Medical Risk

Daunting Safety Dangers
In the Healthcare Workplace

Proactive Screenings for Women

Lifelong Need For IG: Pros & Cons

Myths & Facts: Heart Disease

Two Decades of Unsurpassed Plasma Safety — Page 52

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----------

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#	67467-843-01	67467-843-02	67467-843-03	67467-843-04	

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Revised: September 2009

octapharma
For the safe and optimal use of human proteins

octagam®

Immune Globulin Intravenous (Human) 5% Liquid Preparation

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

Updated manufacturing process to enhance thromboembolic safety[3]

Validated pathogen safety

For more information, please contact us:

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To report suspected adverse reactions, contact Octapharma USA, Inc.
866-766-4860 or
FDA at 1-800-FDA-1088 or
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IMPORTANT SAFETY INFORMATION

Octagam® is contraindicated in individuals with intolerance to immunoglobulins, especially in immunoglobulin A (IgA) deficiency, when the patient has IgE mediated antibodies to IgA. Immune Globulin Intravenous (Human) (IGIV) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Other possible side effects with Octagam include: aseptic meningitis, hemolysis, transfusion-related acute lung disease (TRALI) and thrombotic events.

Immune Globulin Intravenous (Human) products have been reported to be associated with various minor reactions, such as headache, chills, backache, chest pain, fever, allergic reactions, arthralgia, dizziness, and changes in blood pressure, cutaneous reactions and/or nausea and vomiting. Cases of reversible aseptic meningitis and migraine and isolated cases of reversibly hemolytic anemia and reversible increases in liver function tests have been observed with Octagam. Immediate anaphylactic and hypersensitivity reactions are a remote possibility.

As with all medicine made from human plasma, the risk of spreading infections agents, including viruses, cannot be completely eliminated.

Some types of blood glucose testing systems falsely interpret the maltose contained in Octagam as glucose. This has resulted in falsely elevated glucose readings and, consequently, in the inappropriate administration of insulin, resulting in life-threatening hypoglycemia.

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

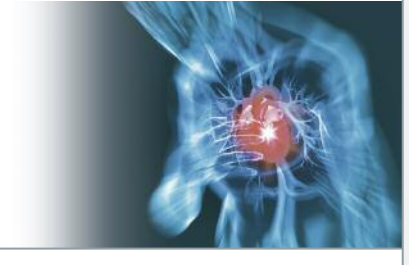
octapharma
For the safe and optimal use of human proteins

BioSupply Trends Quarterly

April 2012

Features

Special Focus: Safety



About BioSupply Trends Quarterly
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Danger Ahead: The Growing Safety Challenges

"THREAT," "CRISIS," "RISK" — these are some of the alarming adjectives used in our features for this safety-themed issue. With the number of counterfeit drug investigations having grown almost tenfold in the last five years, the number of prescription drug shortages nearly tripling from 2005 to 2010, and with recent indications that this threat is increasing rather than diminishing, keeping patients safe has never been more challenging.

The drug shortage crisis, referred to as a "tsunami of medical risk" in our feature article, has risen to an alarming level. While the causes of this crisis vary from manufacturing issues to economic factors, the impact is far-reaching.

Patients with curable conditions are at risk of not surviving due to difficult-to-access lifesaving medications, and many hospitals are forced to buy medicines from the so-called "gray market" where price-gouging is commonly practiced — sometimes up to 4,500 percent of the standard cost of drugs. The gray market also leaves patients and their healthcare providers vulnerable to compromised or counterfeit product because drugs are purchased outside authorized channels.

Counterfeit can mean many things from "fake," to "substandard" or "gray," but the deliberate misrepresentation of the safety and efficacy of a pharmaceutical product has a direct and potentially life-threatening consequence for patients, not to underscore the impact on public confidence. Though the FDA estimates that less than 1 percent of drugs on the U.S. market are counterfeit, that still amounts to as many as 40 million illicit products!

Our feature Counterfeit Drugs: A Growing Threat helps to define what counterfeit drugs are, the health risk they present, how they can infiltrate the supply chain and what is being done to stymie trafficking. It is truly alarming how sophisticated counterfeiters have become and how difficult it is to detect a fake. I would encourage all of our readers to become familiar with The Partnership for Safe Medicines (www.SafeMedicines.org) and to sign up for the organization's weekly emails. This site has many resources for healthcare professionals, specifically for physicians, pharmacists and nurses.

Safety is certainly a broad topic, but the focus from all stakeholders on the key areas where they have influence will collectively reduce risk for those who are the most vulnerable. From my perspective as an authorized biopharmaceutical distributor, this threat has always been present, and my top priority has been making the channel secure — a "patients first" philosophy. Now celebrating 24 counterfeit-free years, FFF has put in place systems and services that validate our Guaranteed Channel Integrity, defined by our commitment to purchase only from manufacturers and ship only to healthcare providers. This commitment is evidenced by safety innovations such as our Verified Electronic Pedigree system to validate our safe channel — an industry first — and our Lot-Track service that provides accurate product lot tracking and recall notification within four hours to those affected.

Healthcare practitioners can have an impact on the counterfeit issue by simply refusing to purchase products outside of an authorized distribution channel, even in times of shortage, and by verifying the pedigree of products when they are received.

We hope you enjoy this issue of *BioSupply Trends Quarterly*, and as always, we welcome your feedback to help us bring the greatest value to you and your practice.

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.

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Antihemophilic Factor/von Willebrand Factor Complex (Human), marketed as **Alphanate®**
Antithrombin III (Human), marketed as **Thrombate III®**
Coagulation Factor IX (Human), marketed as **AlphaNine® SD**
Factor IX Complex, marketed as **Profilnine® SD**
Immune Globulin Intravenous (Human) or **IVIG**
Immune Globulin Injection (Human)
Hyperimmune Globulin Therapy Products, marketed as **Hypermunes™**:
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- **Rh$_0$ (D) Immune Globulin** (Human) marketed as **HyperRHO® S/D**
- **Hepatitis B Immune Globulin** (Human) marketed as **HyperHEP B® S/D**
- **Immune Globulin** (Human) marketed as **GamaSTAN® S/D**

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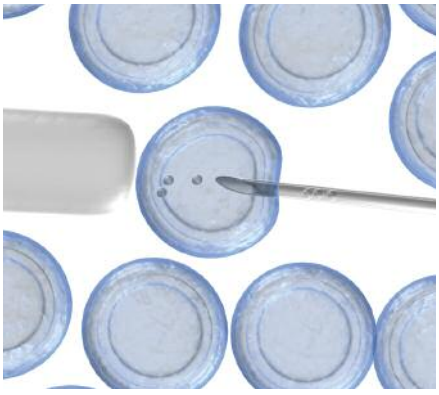
GRIFOLS

Court Rules for NIH in Stem Cell Research



On July 27, Royce Lamberth, chief judge of the District of Columbia District Court, ruled that the U.S. government can continue funding embryonic stem-cell research. His ruling threw out a 2009 lawsuit by researchers Dr. James Sherley of the Boston Biomedical Research Institute and Theresa Deisher, PhD, of AVM Biotechnology that challenged President Obama's 2009 order to expand funding for the research, for which he also called on the National Institutes of Health (NIH) to come up with guidelines to implement his order.

In August 2010, Lamberth ruled that the NIH guidelines violated the Dickey-Wicker Amendment, which prohibits federal funding for "research in which a human embryo or embryos are destroyed, discarded or knowingly subjected to risk or injury or death greater than that allowed for research on fetuses in utero." But a month after Lamberth's ruling, a three-judge appeals court panel lifted Lamberth's suspension while the lawsuit moved forward, and in April the panel sent the case back to Lamberth.

In dismissing the suit, Lamberth ruled that allowing federal funding for research using stem cells that were created using private funds is not a violation of the Dickey-Wicker Amendment. "This Court, following the D.C. Circuit's reasoning and conclusions, must find that defendants reasonably interpreted the Dickey-Wicker Amendment to permit funding for human embryonic stem-cell research because such research is not 'research in which a human embryo or embryos are destroyed,'" Lamberth stated in his opinion. ❖

New Rules Simplify Healthcare Paperwork

The U.S. Department of Health and Human Services has published a new rule for electronic funds transfers in healthcare that calls for simplified standards to be implemented for the format and data content of the transmission a health plan sends to its bank when it wants to pay a claim to a provider electronically and to issue a Remittance Advice notice.

The new rule, which became effective January 1 and must be complied with by all health plans covered under HIPAA by Jan. 1, 2014, will offer increased standardization of information and transmission formats so that healthcare providers can use one type of information request for all insurers rather than being required to use multiple systems. For instance, if a doctor submits an electronic analysis to a health plan regarding a patient's eligibility, certain plans may reply only yes or no, while others offer information that the physician needs to know at the point of service such as deductibles and patient copays. Under this rule, physicians will receive a more comprehensive response when they inquire about the status of a claim they have submitted.

Future administrative simplification rules will include a standard unique identifier for health plans, a standard for claims attachments, and requirements that health plans certify compliance with all HIPAA standards and operating rules.

According to an April 2010 study in *Health Affairs*, "Physicians spend nearly 12 percent of every dollar they receive from patients to cover the costs of filling out forms and performing other excessively complex administrative tasks. The study found that simplifying these systems could save four hours per week of professional time per physician and free up hours of support staff time every week — time that could be better spent on patient care."

The implementation of this rule and the HIPAA rule are projected to save the healthcare industry more than $16 billion over the next 10 years. ❖

Partnership for Patients Meeting Participant Goal

Nearly 4,500 organizations — including more than 2,000 hospitals — have pledged their support for Partnership for Patients, meeting the Obama administration's hospital goal in less than three months. Partnership for Patients aims to reduce preventable harm in hospitals by 40 percent in the next three years, including a reduction in the number of preventable in-hospital medication errors, central-line associated bloodstream infections, falls and other injuries. It also seeks to help patients heal successfully after discharge, targeting unnecessary return visits to reduce 30-day hospital readmissions by 20 percent over the next three years. According to the U.S. Department of Health and Human Services, the partnership has the potential to save up to $35 billion in healthcare costs, including up to $10 billion for Medicare. And, over the next 10 years, the partnership could reduce costs to Medicare by about $50 billion and result in billions more in Medicaid savings. ❖

New Rule Requires Plain Language in Describing Health Plan Benefits and Coverage

The U.S. departments of Health and Human Services, Labor and the Treasury together published new guidelines that will require health insurers and group health plans to provide consumers with clear, straightforward, consistent and understandable summary information regarding their health plans. The new rules also will make it simpler for employers and the nearly 150 million Americans with private health insurance plans to directly compare one plan with another.

Under the new guidelines, which go into effect in September, consumers must have access to two important documents to help them understand and evaluate their health insurance options: a short, easy-to-understand Summary of Benefits and Coverage (SBC); and a uniform glossary of terms commonly used in health coverage such as "deductible" and "copayment." Included in the SBC will be a new, organized plan comparison tool called coverage examples, which will demonstrate sample medical situations and describe how much coverage the plan will provide. The SBC must be provided to enrollees and clients at key periods in the registration process, such as during application and renewal.

The goals of the new plain language rule, which is part of the Affordable Care Act, are to ensure strong shopper information and to reduce paperwork and cost. A template for the SBC and the glossary can be viewed at cciio.cms.gov/resources/other/index.html#sbcug. ❖

Initiatives to Lower Medicaid Costs and Improve Care

The U.S. Department of Health and Human Services is launching two initiatives to help states save money and better coordinate care for the nine million Americans enrolled in both Medicare and Medicaid. The first, the Alignment Initiative, is an effort to more effectively integrate benefits under the two programs. Currently, lower-income seniors and people with disabilities must navigate two separate programs: Medicare for coverage of basic acute healthcare services and drugs, and Medicaid for coverage of supplemental benefits such as long-term care support and services, help with Medicare premiums and cost-sharing for those who need additional assistance.

The second initiative is a new process that provides faster state access to Medicare data to support care coordination, a tool that will help states seeking to coordinate care, improve quality and control costs for their highest-cost beneficiaries. For example, a state that wants to expand its long-term care and behavioral healthcare management program to serve low-income seniors and people with disabilities needs data on their Medicare-covered hospital, physician and prescription drug use. With Medicare data, states can identify high-risk and high-cost individuals, determine their primary health risks and provide comprehensive individual client profiles to its care management contractor to tailor interventions. More information on this initiative can be found at www.cms.gov/CMCSBulletins/CMCSB/list.asp#TopOfPage. ❖

Vaccines

FDA Approves First Quadrivalent Flu Vaccine

FluMist Quadrivalent
Influenza Vaccine Live, Intranasal

The U.S. Food and Drug Administration has approved the first vaccine that protects against four strains of the common flu, offering one additional layer of protection against the influenza virus. The FluMist Quadrivalent vaccine from AstraZeneca's MedImmune unit protects against two strains of influenza A and two strains of influenza B. The spray-based vaccine, which delivers weakened strains of the virus, is approved for people ages 2 to 49. All other flu vaccines on the market are trivalent vaccines, which contain two strains of influenza A and one strain of influenza B. ❖

Healthcare

U.S. Sets New Goals for a Healthier Nation

In October, the U.S. Department of Health and Human Services (HHS) released a list of critical health priorities for the coming decade designed to serve as a blueprint to help reach the Healthy People 2020 objective of improving the health of all Americans. The goals are designed to help policymakers at the federal, state and community level make priorities for the coming decade.

According to HHS Assistant Secretary for Health Howard Koh, MD, MPH, the top priorities are expanding access to medical care and increasing the number of Americans with their own primary care provider. Other goals include increasing the percentage of eligible Americans who are screened for colorectal cancer from the current 54 percent to 70 percent and the percentage of eligible women who have mammograms from 70 percent to 77 percent; increasing the percentage of people with high blood pressure and diabetes whose conditions are adequately controlled with medication; increasing the percentage of young teens who receive booster doses of the tetanus-diphtheria-acellular pertussis vaccine from 47 percent to 80 percent, and increasing the vaccination rate with two doses of the varicella vaccine in this age group from 37 percent to 90 percent; and increasing the number of Americans

who see a dentist regularly to around 49 percent, from a current rate of about 44 percent. For the first time, the goals include a section identifying social factors that help determine health. For instance, a major goal is to increase the percentage of students who graduate from high school with a regular diploma in four years from around 75 percent to 82 percent, a move made in recognition of the fact that higher education is closely linked to better health.

Koh, who presented the list of priorities at the annual meeting of the American Public Health Association, noted that over the previous decade, the average life expectancy of Americans has increased from 77 years to 78 years. And, three out of four health objectives identified by health officials to be met by 2010 were either met or substantial progress was made toward meeting them. ❖

FDA Approval

FDA Approves Advate to Treat Hemophilia A

The U.S. Food and Drug Administration (FDA) approved Baxter International Inc.'s Advate (antihemophilic factor [recombinant] plasma/albumin free method) for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A. Advate is the only antihemophilic factor approved in the U.S. for prophylactic use in both adults and children.

The approval is based on a Phase IV prophylaxis study, which demonstrated a statistically significant reduction in the median annual bleeding rate. Patients receiving on-demand treatment experienced 44 bleeds (per patient per year) compared with one bleed (per patient per year) while on either of the prophylactic regimens evaluated (a 98-percent reduction in annual bleed rate). Forty-two percent of study patients experienced zero bleeds during one year on prophylaxis. And, of the two prophylactic regimens approved for use, the dosing schedule of every three days (a pharmacokinetic-driven regimen based on patients' clinical response) offered some patients the option of fewer infusions over one year of treatment. ❖

Did You Know?

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

— Commonwealth Fund

Vaccines

2012 Vaccine Schedule for Children Is Released

The 2012 vaccine schedule for children and adolescents incorporates changes for the use of several vaccines adopted over the past year. The schedule, which was approved by the American Academy of Pediatrics, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices, and the American Academy of Family Physicians, contains three schedules: one for children from birth through 6 years, one for children and teens ages 7 through 18, and a catch-up schedule.

Among the most notable changes in the new schedule, the meningococcal vaccine guidance was changed to reflect Menactra's approval for children as young as 9 months old. Menveo can be administered in children as young as 2 years old. Also, recommendations were added for the routine administration of a booster dose of either vaccine, and for administration of either vaccine to children at increased risk for meningococcal disease.

Other changes include a routine recommendation of the human papillomavirus (HPV) vaccine for boys; the timing of doses of hepatitis B vaccine and hepatitis B immune globulin after administration of the birth dose of hepatitis B vaccine, which was clarified for infants weighing less than 4.4 pounds or for heavier infants who were born to mothers positive for hepatitis B surface antigen; the administration of a single dose of the tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine in children ages 7 to 10 who are not fully immunized, as a substitute for a single dose of tetanus and diphtheria (Td) vaccine in the catch-up series; the readministration of two doses of the measles, mumps and rubella (MMR) vaccine in infants ages 6 to 11 months who are traveling internationally, with the first dose administered at ages 12 to 15 months and the second dose administered at ages 4 to 6 years; and the modification to administer the second dose of the hepatitis A vaccine six to 18 months after the initial dose.

The footnotes in the schedule also were updated to note that the inactivated poliovirus vaccine is not routinely recommended for those 18 years and older. And the influenza footnotes reflect the recommendations for this year's flu season: Children ages 6 months to 8 years who did not receive at least one dose of the seasonal vaccine last year should receive two doses this year, separated by at least four weeks. Those who did receive one dose of the influenza vaccine last year need only one dose this year. ❖

FDA Approval

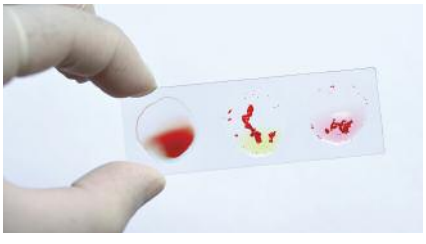
FDA Approves Pneumococcal Vaccine for Adults 50-Plus

The U.S. Food and Drug Administration (FDA) has approved Pfizer's Prevnar 13 for use in adults 50 years and older. Prevnar 13 can protect against 13 different strains of pneumococcal bacteria, including the most common type of pneumonia, Streptococcus pneumonia. Its approval was based on an accelerated time frame, with Pfizer agreeing to continue to study the effectiveness of the vaccine in adults. Adults ages 65 and older also are able to receive Merck & Co.'s Pneumovax vaccine. ❖

FDA Approval

FDA Approves Supplemental Test for Chagas Disease

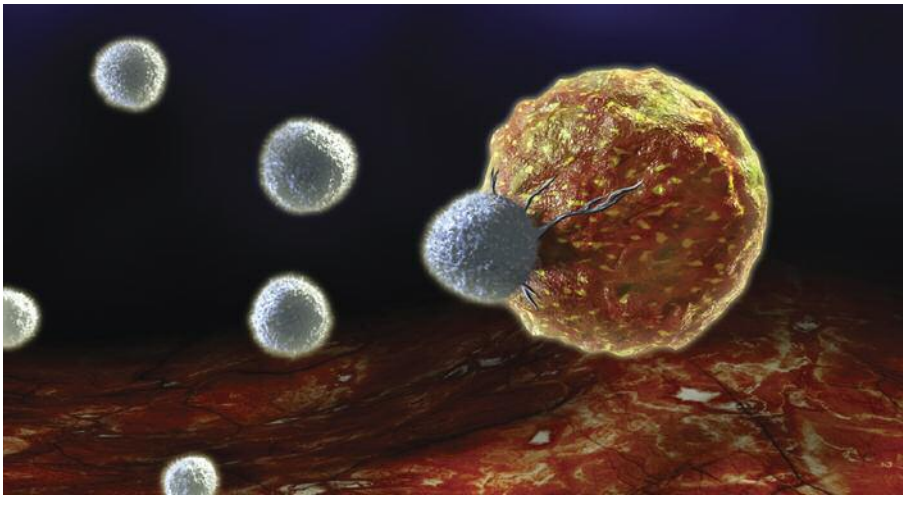
An additional, more specific test on human serum or plasma specimens found to be positive for antibodies to Trypanosoma cruzi (T. cruzi) has been approved by the U.S. Food and Drug Administration. T. cruzi causes Chagas disease, a serious and potentially fatal parasitic infection. The ESA Chagas [Trypanosoma cruzi (e. coli, Recombinant) Antigen], manufactured



by Abbott Laboratories, is an in vitro enzyme strip assay for the qualitative detection of antibodies to T. cruzi. While there are currently two donor screening tests licensed to detect antibodies to T. cruzi, this will be the first test licensed as a supplemental test. Chagas disease is spread mainly by bloodsucking insects infected with T. cruzi, but it also can be spread through blood transfusion, organ transplants and from mother to unborn child. ❖

Research

People with Job's Syndrome Have Impaired Immune Memory



A research team at the National Institute of Allergy and Infectious Diseases (NIAID) has found that people with Job's syndrome (also known as autosomal-dominant hyper-immunoglobulin E syndrome) have a lower number of immune memory cells, which makes them more susceptible to viral reactivation. The findings, which appear in the Nov. 23, 2011, issue of *Immunity*, provide a potential treatment strategy for people with Job's syndrome, as well as offer clues about how immune cells in healthy people control chronic viral infections.

The NIAID team examined patients with Job's syndrome to better understand how immune memory develops. Job's syndrome is a condition caused by a mutation in a gene for the protein STAT3, which aids in the development and specialization of specific types of immune memory T cells. The team observed that, when compared with healthy people, patients with Job's syndrome lack a major population of circulating memory T cells, which are thought to be a source for long-term T cell memory. These low numbers of central memory T cells are closely associated with these patients' increased susceptibility to varicella zoster virus reactivation, causing them to have a significantly higher chance of developing shingles at a young age (less than 50 years old) and of experiencing repeated episodes of shingles compared with healthy people. What's unique about this finding is that people with Job's syndrome do not typically experience severe chicken pox or have difficulty clearing the initial infection. This means that Job's syndrome is one of the few diseases that predisposes patients to developing shingles, but it does not affect their response to chicken pox.

Based on these findings, the researchers concluded that measuring circulating central memory T cells, or STAT3 function, could be a way to identify someone who is at greater risk for developing shingles or could benefit from the shingles vaccine. In addition, new therapeutics that boost the activity of STAT3 also could help protect people from VZV reactivation. Further study is needed, they said, to determine if young, otherwise healthy people who experience episodes of shingles have impaired memory T cells. In addition, more research is needed to better understand what level of immune memory is needed to protect people who have received the chicken pox vaccine from developing shingles. ❖

Counterfeit Drugs

Google Invests in Counterfeit Drug Fighting Technology

Eric Schmidt, executive chairman of Google, has invested $3.9 million in PharmaSecure, a mobile application used to verify medication authenticity using text messaging. PharmaSecure's anti-counterfeiting product uses SMS messaging to provide consumers with a method for verifying the authenticity of medication by typing a code on a medicine package into their phones and receiving an automated verification in response. Google is researching new applications to meet India's deadline of July 2012 by which all exported drugs are required to bear unique bar-codes and serial numbers.

In August, Google paid a $500 million fine to the U.S. Department of Justice for allowing illegal online pharmacies to advertise to U.S. consumers through its Adwords program. Illegal online pharmacies are notorious purveyors of counterfeit medications, according to a report issued by The National Association of Boards of Pharmacy in May 2011. According to the association, "One of the unfortunate consequences of our globalized marketplace … is the likelihood that those counterfeit and substandard drugs will make their way into medicine cabinets worldwide, as online sellers seek bargain prices from questionable distributors, and consumers neglect to question whether the substance they are buying is real medicine." ❖

Enhancing life's defenses

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

Positive efficacy outcomes
For PI patients receiving Gammaplex there were:

> No reports of Acute Serious Bacterial Infection[1]
> Just 0.75 days per year of subjects hospitalized[1]
> Only 8.73 days per subject year out of work/school/day care[1]

Low IgA levels
> The content of IgA is <10 µg/mL[1]

Convenient infusion schedule
> Infusion rate can be increased every 15 minutes to a maximum rate of 0.08 mL/kg/min[1]

Robust 3-step virus reduction
> An extremely low risk of viral transmission

Room temperature storage
> Gammaplex can be stored between 2°C and 25°C (36°F to 77°F) unopened for 2 years

Effective January 1, 2012, the permanent HCPCS "J" code for Gammaplex is **J1557**

For more information visit **www.gammaplex.com**

IMPORTANT SAFETY INFORMATION
Gammaplex is indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

WARNING: Renal dysfunction, acute renal failure, osmotic nephropathy and death may be associated with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable. See full prescribing information for complete boxed warning.

Gammaplex is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to human immune globulin and in patients with selective IgA deficiency and in patients with a history of hypersensitivity.

In patients at risk of developing renal failure, monitor urine output and renal function including blood urea nitrogen (BUN) and serum creatinine. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy. Thrombotic events may occur following treatment with Gammaplex and other IGIV products. Monitor patients with risk factors for thrombotic events, including a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known/suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with IGIV treatment. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. Hemolysis and hemolytic anemia can develop subsequent to IGIV treatments. Noncardiogenic pulmonary edema may occur in patients following IGIV treatment (i.e. transfusion-related acute lung injury [TRALI]). Monitor patients for pulmonary adverse reactions (TRALI). Test product and patient's serum for anti-neutrophil antibodies.

Gammaplex 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, the most common adverse reactions with Gammaplex were headache, fatigue, nausea, pyrexia, hypertension, myalgia, pain and vomiting.

Report adverse reactions to adr@bpl.co.uk

REFERENCES
1. BPL. US Prescribing Information, VSUS1PI, Sept. 2009.

Please see the Brief Summary of Prescribing Information, including boxed warning, on the reverse.

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Bio Products Laboratory
a commitment for life

For product information and inquiries, please call **(866) 398-0825** or email BPLinfo@LashGroup.com

December 2011 GPX/11/61 Printed in USA

Gammaplex®

Immune Globulin Intravenous (Human), 5% Liquid

BRIEF SUMMARY

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION PRIOR TO USE

INDICATIONS AND USAGE
Gammaplex®, Immune Globulin Intravenous (Human), 5% Liquid, is indicated for the replacement therapy of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.

CONTRAINDICATIONS
Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, is contraindicated in patients who have had an anaphylactic or severe systemic reaction to human immune globulin and in IgA-deficient patients with antibodies to IgA.

WARNINGS

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. 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 those who are overweight or are receiving known nephrotoxic drugs. Gammaplex does not contain sucrose. For patients at risk of renal dysfunction or failure, administer Gammaplex at the minimum infusion rate practicable.

See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections in the Package Insert for important information intended to reduce the risk of acute renal failure.

Because this product is made from human plasma, it may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob [CJD] agent that can cause disease. The risk has been reduced by screening plasma donors for prior exposure, testing donated plasma and inactivating or removing viruses during manufacturing. Despite these measures, Gammaplex carries an extremely remote risk of transmission of viral diseases. The physician should discuss the risks and benefits of this product with the patient, before prescribing it to the patient.

All infections suspected by a physician possibly to have been transmitted by this product should be reported to (866) 398-0825 or email BPLinfo@LashGroup.com on behalf of Bio Products Laboratory Ltd.

Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, should only be administered intravenously.

PRECAUTIONS
General
The product should be used promptly after piercing the cap. Any partially used or unused product should be discarded. Visually inspect each bottle before use. Do not use if the solution is cloudy or turbid. Solution that has been frozen should not be used.

Hypersensitivity
Severe hypersensitivity reactions may occur. In case of hypersensitivity, discontinue Gammaplex infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Renal dysfunction/failure
Ensure that patients with pre-existing renal deficiency are not volume depleted before infusion of IGIV. Periodic monitoring of renal function and urine output is particularly important in patients considered to be at increased risk of developing acute renal failure. Renal function, including blood urea nitrogen (BUN) and serum creatinine, should be assessed before administering Gammaplex and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing Gammaplex.

Information for patients: Patients should be instructed to report the following signs and symptoms to their healthcare professional: decreased urine output, sudden weight gain, fluid retention/edema, and/or shortness of breath (which may suggest kidney damage).

Hyperproteinemia, increased serum viscosity, and hyponatremia
Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV therapy. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies. For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion practicable.

Thrombotic events
Thrombotic events may occur following treatment with IGIV products. 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. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), hyperproteinemia or monoclonal gammopathies (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). For patients judged to be at risk of developing thrombotic events, administer Gammaplex at the minimum rate of infusion possible.

Aseptic meningitis syndrome (AMS)
Aseptic meningitis syndrome (AMS) may occur infrequently with Immune Globulin Intravenous (IGIV) treatment, usually beginning within several hours to 2 days after IGIV. AMS may occur more frequently with high doses (2 g/kg) and/or rapid infusion of IGIV. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis
IGIV products can contain blood group antibodies (hemolysins) that coat red blood cells (RBCs) in vivo with immune globulin, resulting in a positive direct antiglobulin test (DAT). Acute hemolysis has been reported with IVIG. Delayed hemolytic anemia can develop due to RBC sequestration. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests).

Transfusion-related Acute Lung Injury (TRALI)
Noncardiogenic pulmonary edema [Transfusion-related Acute Lung Injury (TRALI)] may occur in patients following IGIV treatment. Symptoms (fever, severe respiratory distress, pulmonary edema, hypoxemia but normal left ventricular function) typically appear within 1 to 6 hours following treatment. If TRALI is suspected, test for anti-neutrophil antibodies in both the product and the patient's serum (See WARNINGS AND PRECAUTIONS: Monitoring: Laboratory Tests). Management includes oxygen and appropriate ventilatory support.

Laboratory Tests
For appropriate monitoring, see previous sections on Renal, Hyperproteinemia, Hemolysis and TRALI.

Drug Interactions: Passive transfer of antibodies may transiently interfere with the immune response to live virus vaccines such as measles, mumps, rubella and varicella (SEE PATIENT COUNSELING INFORMATION IN PACKAGE INSERT).

Pregnancy Category C: Animal reproduction studies have not been conducted with Gammaplex. It is not known whether Gammaplex can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Gammaplex should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS
General
Gammaplex, Immune Globulin Intravenous (Human), 5% Liquid, contains no reducing carbohydrate stabilizers (e.g. sucrose, maltose) and no preservative.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of IGIV products.
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, dermatitis (e.g., bullous dermatitis).
Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs') test.
Gastrointestinal: Hepatic dysfunction, abdominal pain.
General/Body as a Whole: Pyrexia, rigors.

Primary Humoral Immunodeficiencies (PI)
In a multicenter, open-label, non-randomized clinical study, 50 subjects with primary humoral immunodeficiency received 703 infusions with Gammaplex. Doses ranged from 279 to 799 mg/kg every 21 days (mean dose 465 mg/kg) or 28 days (mean dose 458 mg/kg), for up to 12 months. At some time during the study, all 50 subjects had an adverse event (AE) and in twenty-four subjects (48.0%) it was considered product-related.

The temporally associated AEs that occurred in more than 5% of subjects during a Gammaplex infusion or within 72 hours after the end of an infusion, *irrespective of causality* are given in the table below:

Adverse Event	Subjects (%) [n=50]	Infusions (%) [n=703]
Headache	18 (36%)	53 (7.5%)
Sinusitis	8 (16%)	9 (1.3%)
Pyrexia	7 (14%)	10 (1.4%)
Nausea	6 (12%)	7 (1.0%)
Pain	5 (10%)	5 (0.7%)
Chills	3 (6%)	5 (0.7%)
Fatigue	3 (6%)	9 (1.3%)
Hypertension	3 (6%)	4 (0.6%)
Insomnia	3 (6%)	3 (0.4%)
Nasal congestion	3 (6%)	3 (0.4%)
Upper respiratory tract infection	3 (6%)	5 (0.7%)
Vomiting	3 (6%)	3 (0.4%)

Five subjects (10%) experienced seven serious AEs. Two of these serious AEs were considered related to Gammaplex treatment (thrombosis and chest pain). Three other subjects withdrew from the study due to the following AEs: paresthesia, bronchospasm and pregnancy.

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

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December 2011 US/Gx/1211/0001

Research

Combined IVIG Treatment Effective to Treat Kawasaki Disease

Researchers from Kitasato University School of Medicine in Japan found that combining intravenous methylprednisolone pulse and intravenous immunoglobulin (IVIG) to treat patients with Kawasaki disease appears safe and effective. The researchers looked at data on 122 patients with Kawasaki disease who were randomly assigned to either the combined treatment or IVIG alone. Fever abated more quickly in 19 of 22 patients in the combined group compared with six of 26 patients in the IVIG group. In addition, coronary artery dimension z scores of 2.5 or more at one month were higher in the IVIG group than in the combined treatment group. Adverse events of the combination therapy included hypothermia, bradycardia and hypertension in some patients; however, these events were transient and not serious in either group. "Approximately 15 percent to 20 percent of patients with [Kawasaki disease] are not responsive to initial IVIG treatment, and these patients are at a higher risk for coronary artery lesions," the researchers wrote. "It is important to identify these patients because they might benefit from more aggressive initial treatment." ❖

Research

More Evidence of an Autism Immune Component

A recent study shows that specific autoantibodies found in a modest proportion of mothers with an autistic child may provide more evidence of an immune component related to autism. The study is an expansion of an earlier one at the Medical Investigation of Neurodevelopmental Disorders (MIND) Institute at the University of California, Davis, which demonstrated that 12 percent of women with an autistic child had unusual antibodies not present in mothers of typically developing children or those with other intellectual developmental disorders. That finding raised the hypothesis that the antibodies, which are immunoglobulin G that cross the placenta, might be interacting with the fetal brain, leading to disregulation of development (and, ultimately, to autism).

In the recent study, researchers tested the effects of the antibodies in pregnant Rhesus monkeys. The monkeys were injected over a six-week period with either purified autoantibodies to fetal brain proteins from the blood of the mothers of children with autism or with autoantibodies from mothers with typically developing children. They found that the offspring of monkeys injected with the IgG of mothers of children with autism showed distinctive autistic characteristics, including social impairment and stereotypic behaviors across several behavioral testing paradigms. While the social impairment was subtle and did not reach the level of social impairment consistent with autism, the sterotypy was profound. "Given that [stereotypy] is one of the clinical signs of autism, we thought this was intriguing," said David G. Amaral, PhD, research director at the MIND Institute. "The ability to reproduce this effect in an animal model was strong evidence that these antibodies may have a disease-causing effect."

Dr. Amaral and his colleagues have replicated these findings in two independent studies and are currently extending their analysis to a magnetic resonance imaging (MRI) study of brain development in the treated monkeys. In other prior research by the MIND Institute investigators, a substantial proportion of boys with autism have been shown to have precocious brain growth during early childhood, and the MRI studies are designed to determine if similar patterns of brain development occur in the treated Rhesus monkeys. If confirmed, the findings could lead to screening tests for pregnant mothers and, perhaps, to preventive measures for certain types of autism. ❖

Vaccines

UNICEF Lists Vaccine Prices to Drive Down Cost

In a move to spark price competition as costs rise, UNICEF is publicizing how much drugmakers are charging it for vaccines. In May, UNICEF posted on its website the actual prices that it has paid individual drugmakers for 16 vaccines purchased over the last decade, hoping to cut prices so that the organization can vaccinate more children and save more lives.

Last year, UNICEF spent $757 million to provide 2.5 billion doses of vaccines to 99 countries, reaching about 58 percent of the world's children. Its price list shows significant disparities, with Western drugmakers often charging UNICEF double what companies in India and Indonesia charge. ❖

Research

Albumin Can Be Grown in Rice

Scientists in China have successfully grown human serum albumin (HSA) in rice, which has been successfully used to grow other human proteins. Using a species of rice called Oryza sativa, the scientists used a bacterium to deliver the gene for making HSA into the rice plants, and after a few generations of breeding, the plants were making HSA reliably. The research team, based mainly in Wuhan, China, ran several tests to compare the rice and human versions of HSA, and both types had the same molecular mass, amino acid sequence and overall shape, among other similarities. Both versions were able to bind to the blood-thinning drug warfarin and to the painkiller naproxen. In rats with liver cirrhosis, the rice-derived HSA helped the animals eliminate excess abdominal fluid. The researchers also were able to extract the protein from rice in an efficient manner. Their two-day purification process captured about 46 percent of the protein in the plant, resulting in a yield of 2.75 grams of HSA from every kilogram of rice, enough to make commercial production feasible.

HSA is a protein that helps transport certain hormones, steroids and fatty acids in the bloodstream, and it is used to treat people with hemorrhagic shock, patients with serious burns and other medical conditions. It is also hoped that HSA can be put to use in other ways, such as delivering drugs or oxygen within the body. The worldwide demand for HSA exceeds 500 tons per year. The study was reported on October 31 in the *Proceedings of the National Academy of Science*. ❖

Research

Immunotherapy May Help to Treat Alzheimer's

Canadian scientists are working on an intravenous treatment for Alzheimer's that could halt the progression of the disease and improve cognitive functions. Vancouver researcher Neil Cashman and colleagues have discovered a biomarker on toxic molecules called amyloid beta (a-beta) oligomers, which are catalysts in the brain degeneration of Alzheimer's. Their industry partner, Cangene Corp., a Winnipeg-based biopharmaceutical company, is developing antibodies designed to attack the toxic molecules without harming healthy ones. If successful, the antibodies could be used as an immune therapy for Alzheimer's, or as a preventive vaccine, according to Dr. Cashman, scientific director of PrioNet Canada, a network of centers conducting research into neurodegenerative disorders. The next step is to test the treatment on mice engineered to develop Alzheimer's. The mice studies will be completed at the University of British Columbia and at a lab in Milan, Italy. It is expected to be four years before there will be an experimental treatment for clinical trials in humans. ❖

Clinical Trials Update

Baxter International has initiated a Phase III clinical trial to evaluate the safety and effectiveness of **BAX 111**, an investigational recombinant von Willebrand factor for the treatment and prevention of bleeding episodes in patients with von Willebrand disease. BAX 111 is the first recombinant von Willebrand product in clinical development.

Inovio Pharmaceuticals Inc. has achieved best-in-class immune responses in a Phase I clinical study of **Pennvax-B** for the prevention of HIV subtype prevalent in the U.S. and Europe.

Biondvax Pharmaceuticals Ltd. has received the approval of the Ethics (Helsinki) Committees of the Institutional Review Boards of both the Hadassah Clinical Research Center at Hadassah University Hospital in Jerusalem and the Tel Aviv Sourasky Medical Center to perform a Phase II clinical trial to evaluate the safety, immunogenicity and priming potential of its universal influenza vaccine, the **Multimeric-001**.

Data from **Pfizer**'s final Phase III study of its rheumatoid arthritis pill, **tofacitinib**, shows it to be as effective as Humira with no sign of new safety concerns.

Results of **Sanofi-Aventis**' Phase III GetGoal clinical trial, which assessed the efficacy and safety of **lixisenatide**, found that the monotherapy, administered once daily, significantly improved glycemic control with a pronounced postprandial effect, as well as demonstrated an acceptable safety profile in patients with type 2 diabetes. Lixisenatide is a GLP-1 receptor agonist monotherapy in patients with type 2 diabetes.

GlaxoSmithKline has started a Phase III trial that will test intravenous **zanamivir** against Roche's Tamiflu as a treatment for patients hospitalized with influenza. The trial, which will measure the time to clinical response in patients with confirmed flu, aims to enroll 462 patients in 20 countries and will take approximately three years to complete.

Research

Study Suggests Obesity Hinders Flu Vaccine

A new study suggests that overweight people benefit less from the flu vaccine than those of normal weight, and the heavier they are, the lower their immune response to the shot over time. In the study, researchers gave 74 people a combination vaccine against three strains of the flu in the 2009-10 season and measured their antibody response one month after the shot and then a year later. A third of the group, mostly made up of women, were normal weight, one-third were overweight and one-third were obese. After one month, overweight people had produced about the same level of antibodies as those of normal weight. But, 11 months later, more than half of the obese patients had a fourfold or greater decrease in antibodies, a drop seen in just 25 percent of the normal-weight subjects. The study, published online in October in the *International Journal of Obesity*, found that the activity of CD8+ T cells, white blood cells that help fight flu infection, also decreased as body mass index increased.

The study is ongoing in an effort to determine whether body mass index correlates with actual rates of laboratory-confirmed influenza in people who have been vaccinated. "We have a stronger flu vaccine for elderly populations because their immune response is not as robust," said the study's senior author, Melinda A. Beck, professor of nutrition at the University of North Carolina. "Maybe we need stronger vaccines for obese people as well." ❖

The first human clinical trial phase to test techniques to develop a vaccine for **celiac disease**, and which can be applied to creating treatments for other autoimmune diseases such as type 1 diabetes, has started in Australia.

Tolerx Inc. has initiated a Phase III clinical trial to further evaluate **otelixizumab** in autoimmune new-onset type 1 diabetes. The new trial, called DEFEND-2 (Durable-Response Therapy Evaluation for Early or New-Onset Type 1 Diabetes) immediately follows successful completion of enrollment in the initial Phase III clinical trial, DEFEND-1, with results from DEFEND-1 expected in the first half of 2011.

Avila Therapeutics Inc., a biotechnology company developing targeted covalent drugs, has initiated a Phase I clinical trial to assess the safety, tolerability and pharmocokinetic profile of **AVL-292**, a novel, orally available covalent drug that targets Bruton's tyrosine kinase (Btk).

Sanofi-Aventis and its wholly owned subsidiary, **BiPar Sciences**, have published the final Phase II data for the investigational drug **iniparib** (BSI-201), demonstrating significant clinical benefit in women with matastatic triple negative breast cancer when it is administered in combination with chemotherapy agents gemcitabine/carboplatin.

VentiRx Pharmaceuticals' experimental treatment for cancer passed its initial clinical trial in 33 patients. The drug, **VTX-2337**, which is designed to stimulate the innate immune system to fight tumors in tandem with standard cancer treatments, was found to be safe and well-tolerated in the study and showed increasing signs of activity as doses escalated.

St. Louis University, St. Louis, Mo., has launched a human clinical trial to test the safety of a new vaccine to induce an immune response against **tuberculosis** (TB). While there is an existing vaccine that can protect people from developing some of the worst complications of the disease, there is not yet one to prevent people from getting infected with TB.

Results from a Phase III clinical trial examining the efficacy and safety of **Novo Nordisk**'s **recombinant factor XIII** (FXIII) compound for the prevention of bleeds associated with congenital FXIII deficiency showed that treatment with monthly injections significantly decreased the number of bleeding episodes requiring treatment compared with the control group.

A Phase I clinical trial of a brain tumor vaccine, called **IMA950**, is being conducted in the United Kingdom at the **Beatson West of Scotland Cancer Centre** in Glasgow to determine whether it is effective in helping the body's immune system fight glioblastoma, a deadly and common form of brain cancer.

Octapharma is conducting a multicenter Phase II trial to test the first **recombinant Factor VIII** derived from a human cell line for previously treated patients with severe hemophilia A.

Product Recall

Povidine Iodine Prep Pads Are Voluntarily Recalled

On March 16, H&P Industries Inc., the parent company of the Triad Group of Hartland, Wis., voluntarily recalled all lots of povidine iodine prep pads. The recalled products all were distributed in the United States and include those pads made by H&P Industries and packaged under the names Cardinal Health, Medical Specialties, VHA, Triad, Triad Plus, North Safety and Total Resources. According to the recall notice, the pads may be contaminated with Elizabethkingia meningoseptica, an organism that has caused rare but serious infections in humans, including meningitis in newborn infants, pneumonia in patients on ventilators, and necrotizing fasciitis, more commonly known as flesh-eating bacteria disease. However, there have been no reported illnesses from the contaminated pads as of this writing.

This recall comes more than two months after H&P Industries issued a global recall of hundreds of millions of contaminated alcohol prep pads and wipes because of potential contamination with a rare bacteria called Bacillus cereus. This contamination was found after children in Colorado came down with bloodstream infections caused by the organism and a Colorado hospital cultured the pads and found the potentially life-threatening bacteria. A 2-year-old boy in Houston died from bacterial meningitis after becoming infected with the bacteria.

Specific customers distributing povidine iodine prep pads and selling them at the wholesale and hospital level are being notified by certified mail with instructions on how to return the product. Consumers who have any of these types of products in their possession should not use the product and should return it to the place it was purchased for a full refund. Or, they can call customer service at H&P Industries Inc. from Monday through Friday between the hours of 8:30 a.m. and 4 p.m. central time at (262) 538-2900 to be issued a return authorization number and return arrangements.

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program at www.fda.gov/medwatch/report.htm or by calling (800) 323-0178. ❖

One of these medicines is fake.
Can *you* tell which?

In today's global environment, it doesn't matter if you live in the United States, Europe, Asia, or Africa—**everyone is at risk from unsafe drugs.** Counterfeit drugs defraud consumers and deny patients therapies that can alleviate suffering and save lives. Unfortunately, in some cases, these drugs have caused great harm and fatalities.

Join Us For Interchange 2012

PARTNERSHIP FOR SAFE MEDICINES INTERCHANGE 2012

On September 28, The Partnership for Safe Medicines will host a conference with leading drug safety experts to discuss the latest information about the dangers of counterfeit drugs.

When
Friday, September 28, 2012

Where
National Press Club
Washington, D.C.

Contact
Tara Goodin
(202) 591-4041
tara@safemedicines.org

To learn more about the Interchange 2012, please visit www.SafeMedicines.org.

The Partnership for SAFEMEDICINES

Together, we can protect the safety of our prescription drugs.

Reimbursement FAQs

Some commonly held misunderstandings about reimbursement are clarified.

Can a patient with primary immunodeficiency disease (PIDD) be reimbursed for subcutaneous immunoglobulin (SCIG) treatment through Medicare Part D? Historically, SCIG has been reimbursed through Medicare Part B.

By statute, SCIG falls under Medicare Part B. However, some drug plans, including Medicare Advantage Plans with prescription drug coverage, allow PIDD patients to access SCIG utilizing the prescription benefit. Patients should be advised, however, that unlike Part B, the drug plans do not reimburse for the cost of supplies or the pump. Additionally, if the IG product falls under the specialty tier in the drug plan, the patient could be charged up to a 33 percent coinsurance fee. For stand-alone Part D plans, patients also could be subject to paying 100 percent of the cost of the drug when they fall into the doughnut hole. ❖

Can a patient request a change in a subcutaneous immune globulin (SCIG) prescription if the insurance company charges a copayment for every different vial size needed to fill that prescription?

While a separate copayment for different vial sizes of IG has not been a widespread problem, as health plans continue to move IG to the prescription benefit, it may become so.

In the retail pharmacy arena, it is common for patients to be charged a separate copay for each drug with a different national drug code (NDC) number. Every drug is required to be labeled with a unique NDC number for each strength of the medication, even if it is the same formula. Retail pharmacists usually can figure out a way to fill a prescription without using two different strengths of the medication. However, IG dosing is not as simple as, for instance, antibiotic dosing. This is because optimal dosing for many diseases treated by IG has not yet been established, and patient dosing varies greatly based on the individual patient's weight and disease state. Therefore, it is nearly impossible for manufacturers to produce every possible dosage in their manufacturing process.

So far, patients have been able to overcome this issue by contacting their health plan's case manager or pharmacy benefit manager to request an override so they are charged only one copay. Additionally, patients and doctors can request information about how the IG can be billed as part of the major medical benefit. If the IG can be billed through a clinic or under the home infusion benefit, it likely will fall back under the major medical portion of the healthcare plan. ❖

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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.

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The Growing Threat of Counterfeit Drugs

Fake medicines are a serious threat to public health due to their growing involvement in the medical supply chain. But organizations across the world are working to stymie trafficking of these illegal and dangerous drugs.

By Ronale Tucker Rhodes, MS

The deaths in January of more than 100 Pakistani heart patients, as well as the ongoing treatment of 300 more, at the Punjab Institute of Cardiology hospital underscores the seriousness of the counterfeit drug crisis across the globe. Similar to many other counterfeit drug incidents that have been growing at an alarming rate, these patients were prescribed substandard medicine. What's atypical and even more unsettling about this incident, however, is that the medicines, one of which was contaminated and all of which contained the toxic ingredient pyrimethamine (used for the treatment of malaria), are known to have been manufactured by three pharmaceutical companies. One company's license had long expired, yet it continued to manufacture the contaminated drugs in bulk and supply them to government hospitals and open markets.[1]

According to the U.S. Food and Drug Administration (FDA), the number of counterfeit drug investigations has grown almost tenfold in the last five years.[2] An ABC news report in February reported that the FDA recently shut down a number of websites that purported to sell drugs for heart disease, epilepsy and anxiety. They listed for sale more than 40 prescription drugs, including Depakote, Zoloft, Lipitor and Xanax — all of which turned out to be fakes. "A lot of these drugs are ordered over the Internet from what appear to be legitimate pharmacies and are shipped directly to the patients by the counterfeiters," said the U.S. Customs and Border Protection's Therese Randazzo.[3]

The FDA estimates that less than 1 percent of drugs on the U.S. market are counterfeit; however, that is still as much as a one-in-100 chance of obtaining an illicit product. In addition, of the four billion prescriptions filled in the U.S. each year, as many as 40 million may be filled with counterfeits.[2]

Counterfeit Drugs Defined

"Counterfeit," "fake," "substandard" and "gray" are words often used interchangeably to refer to counterfeit medicines. Yet, each of these words has a specific definition. Known as spurious/falsely-labeled/falsified/counterfeit (SFFC) medicines, the World Health Organization (WHO) defines counterfeit, or fake, drugs as those that are "deliberately and fraudulently mislabeled with respect to identity or source." Substandard drugs are defined as "genuine drug products which do not meet quality specifications set for them." However, if substandard drugs are knowingly produced to make an unlawful product, they too are considered counterfeit. And, the gray pharmaceutical market is defined as one in which illicit profiteers are outwardly marketing competitive brands without regular approval. While gray pharmaceuticals are rarely counterfeit, per se, they are often substandard, and they have all of the negative consequences of a counterfeit drug, including circumventing health regulations, undercutting public confidence and providing an easy source of income for criminals.[2]

All kinds of medicines are counterfeited — both branded and generic. According to Margaret A. Hamburg, MD, FDA commissioner of food and drugs: "They may contain too much, too little or the wrong active ingredient, and they could contain toxic ingredients. They also can increase the likelihood of drug resistance, and they may prevent patients from getting the real medical products that they need to alleviate suffering and save lives."[4] Indeed, according to the ABC news report, a series of raids all over the world have uncovered counterfeit pill-making operations. In Ecuador, boric acid, used to kill cockroaches, was one of the ingredients going into pills. In Montreal, counterfeiters used lead-based wall paint to give pills the well-known blue color used in real Viagra. In Colombia, drugs were made using Sheetrock and rat poison. In Hungary, investigators found pills that contained speed.[3]

According to the U.S. Food and Drug Administration, the number of counterfeit drug investigations has grown almost tenfold in the last five years.

The most popular medicines targeted by counterfeiters are those used to treat chronic conditions. These range from hypertensive drugs to diabetes medicines. In fact, the more expensive the drug, the more profitable the margins for counterfeiters because these medicines often consume a significant proportion of individual or family income, so chronically ill people seek places to purchase at a cheaper cost.[5]

Antibiotics, corticosteroids, erectile dysfunction drugs, cancer drugs and antiretrovirals for HIV/AIDS also are among those most counterfeited. In terms of number of incidents, the top therapeutic areas for counterfeits are cardiovascular, central nervous system, cytostatic, anti-infective, musculoskeletal and alimentary, according to Pharmaceutical Security Institute (PSI) Chief Executive Thomas Kubic.[6]

The latest criminal trend is the importation, repackaging and sale of difficult-to-counterfeit drugs, including biological formulations. Biologics are particularly difficult to detect because they are typically administered through injections and, therefore, cannot be discerned by taste. An example of this occurred in November 2009 when illegally imported

human immunoglobulin (IG) vials from a company in Mumbai were seized. Because the product contained IG, it appeared that the vials were imported from a lesser producer in China and repackaged under a leading brand name. And, they were being offered at 25 percent less than the market price.[2]

A Growing Public Health Risk

Worldwide, the massive increase in counterfeit drug sales has risen to more than $75 billion, an increase of more than 90 percent from 2005.[2] It is now thought that the counterfeiting trade has become more lucrative than the narcotics business.[6] According to WHO, in some countries around the world, counterfeit prescription drugs comprise as much as 70 percent of the drug supply, and they have been responsible for thousands of deaths in some of the world's most impoverished nations. Peter Pitts, president of the Center for Medicine in the Public Interest and former FDA associate commissioner, estimates that counterfeit drugs may grow by 20 percent annually in coming years. And, if this estimate is correct, the counterfeit pharmaceutical industry could generate as much cash as the world's fourth-largest healthcare company, AmerisourceBergen, with revenues of approximately $79 billion in 2011.[7]

The results of this can be tragic. In her speech at the Partnership for Safe Medicines Interchange 2010 in October 2010, Dr. Hamburg recounted many incidents over the past several years, including:[4]

- In Haiti, Panama and Nigeria, many children died due to cough syrup and teething medication poisoned with diethylene glycol.
- In 2008, adulterated heparin caused injury and some deaths in patients throughout the world.
- In early 2010, patients received counterfeit over-the-counter diet pills that had an ingredient that is found in a prescription diet pill, causing great risk for patients with cardiac conditions.
- In the summer of 2010, the FDA found that patients were using insulin from the same lot numbers stolen months before — insulin believed to have been stored or handled improperly, thereby compromising its potency.

Infiltrating the Supply Chain

Counterfeiting stems from a variety of factors, including an increased number of imported drugs, theft, growing sophistication among counterfeiters and lack of regulatory oversight. "Today, nearly 40 percent of the drugs Americans take are imported, and nearly 80 percent of the active ingredients in the drugs on the American market come from overseas sources," explains Dr. Hamburg. "As a result, the supply chain — from raw material to finished product — has become more complex and mysterious, involving a web of repackagers and distributors in a variety of locations." This proliferation, she adds, can infiltrate the drug supply.[4] Add to this the growing size and sophistication of counterfeit rings, as well as increased involvement of organized transnational criminals and even international terrorist groups, including the Russian mafia, Colombian drug cartels, Chinese triads, Mexican drug gangs and even Hezbollah and al Qaeda, who are finding counterfeiting pharmaceuticals an appealing source of illicit revenue since the legal implications are routinely much lower in comparison to illicit narcotics trafficking.[2]

While counterfeiting occurs all over the world, the United Nations Office for Drugs and Crime reports that it occurs more often where regulatory capacity is low. For instance, surveys of anti-infective medications in Asia and Africa have found as much as 60 percent of local drug supplies with active ingredients outside of medicinal limits. In fact, a recent WHO study found that less than 20 percent of the organization's member states are thought to have a well-developed drug regulation system. This lack of regulatory mechanisms makes it easy for counterfeiters to access legitimate channels of distribution.[2]

And, once drugs are on the market, there is even less oversight in most areas of the world. This is because far more effort by drug regulatory systems in most countries is spent on pre-marketing approvals rather than on post-market monitoring.[2]

The most popular medicines targeted by counterfeits are those used to treat chronic conditions.

Detecting a Fake

Because the burden of detection and reporting lies primarily with the pharmaceutical companies, most have taken steps to mark their medications so they can be identified against counterfeit versions. Some of the methods used to differentiate genuine medications include holograms, embossing, special ink and two-dimensional bar codes. However, many of these methods have proved to be easily copied by counterfeiters, such as invisible ink, which can be easily reproduced with any standard printer. And, some of these methods require special training to read the marking and to be able to tell a genuine from a fake. To overcome this, MPedigree launched a program that allows codes from medications to be sent through a text message for free. The program then checks whether or not the medication is genuine and notifies the requester. In addition, one of the latest methods is Cryptoglyph, which places an

invisible dot pattern over an entire package or label that is impossible to erase or duplicate.[8]

Unfortunately, physicians and consumers can still easily be fooled by a counterfeit medication. One reason it is so difficult to detect counterfeit medicines is that they appear strikingly similar to the genuine products. But, there are ways to detect counterfeit drugs. Packaging that is unsealed, labels that are changed or anything that is open inside an outer package should be looked for. The batch number on the outside of the package should match the number on the inside of the package. In addition, packaging should be compared with other packaging for the same drug. While the packaging may look identical, upon close inspection, there may be a different color on the logo or design on the box. The appearance of the drug also should match; if it looks different, it could be counterfeit. And beware of price. Anything dramatically cheaper could be counterfeit. Last, physicians should be cautious about a drug if patients report not feeling right or that the medication isn't working.[9]

Measures to Stymie Trafficking

According to Dr. Hamburg, the FDA has taken a number of significant steps since the heparin contamination crisis in 2008 to prevent similar situations from occurring. It has developed "risk models to help identify drug ingredients at risk of economically motivated adulteration so it can target its efforts." It also has developed "standards for track and trace systems that enable the identification of these products and facilitate efforts to recall them." It has established "overseas posts in China, India, Europe and Latin America, and it is currently doing so in the Middle East." It has established a "standard for unique identifiers for packages of drugs that creates a 'license plate' for individual packages of drug products as they travel through the supply chain." And, it has established a new "Drug Integrity and Security Program based in the Office of Compliance in the FDA's Center for Drug Evaluation and Research, which will focus on issues such as counterfeiting, economically motivated adulteration, diversion, cargo theft and other supply chain threats."[4]

Bills were introduced both in the House and the Senate in 2011 to increase the penalties for trafficking in counterfeit drugs. Both versions of the proposed Counterfeit Drug Penalty Enhancement Act of 2011 (H.R. 3468 and S. 1886) would amend the law that criminalizes the use of counterfeit marks on or in connection with goods or services and would increase the maximum punishment for an individual counterfeiter from five years to 20 years in prison. The Senate approved the bill in a unanimous voice vote on March 6, and as of this writing, the legislation heads to the House. And, a similar measure was introduced in October as part of H.R. 3261, the Stop Online Piracy Act (or SOPA bill), aimed primarily at shutting down websites that traffic in goods that infringe on copyright or trademark rights. The SOPA provision would clarify that the counterfeit law applies to drugs, but it would only enhance the penalties in cases involving serious bodily harm, death or counterfeit military goods or services.[10]

Bills were introduced both in the House and the Senate in 2011 to increase the penalties for trafficking in counterfeit drugs.

A Worldwide Problem

Counterfeit drug trafficking is an extremely dangerous problem that impacts both developed and undeveloped nations. Many organizations are implementing procedures to detect these counterfeits, and government is pushing to enact laws to punish those who are profiting from this crime. However, in the end, it will take the cooperation of all countries working together to solve this growing threat to global public health. ❖

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

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

INDICATIONS AND USAGE

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- None known.

USE IN SPECIFIC POPULATIONS

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

DOSAGE AND ADMINISTRATION

For Intravenous Use after Reconstitution

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

Dosage in von Willebrand Disease

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

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

Dosing Schedule

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

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

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

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

Treatment guidelines apply to all VWD types

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

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

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

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

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

HOW SUPPLIED/STORAGE AND HANDLING

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

Shelf life

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

PATIENT COUNSELING INFORMATION

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

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For the safe and optimal use of human proteins

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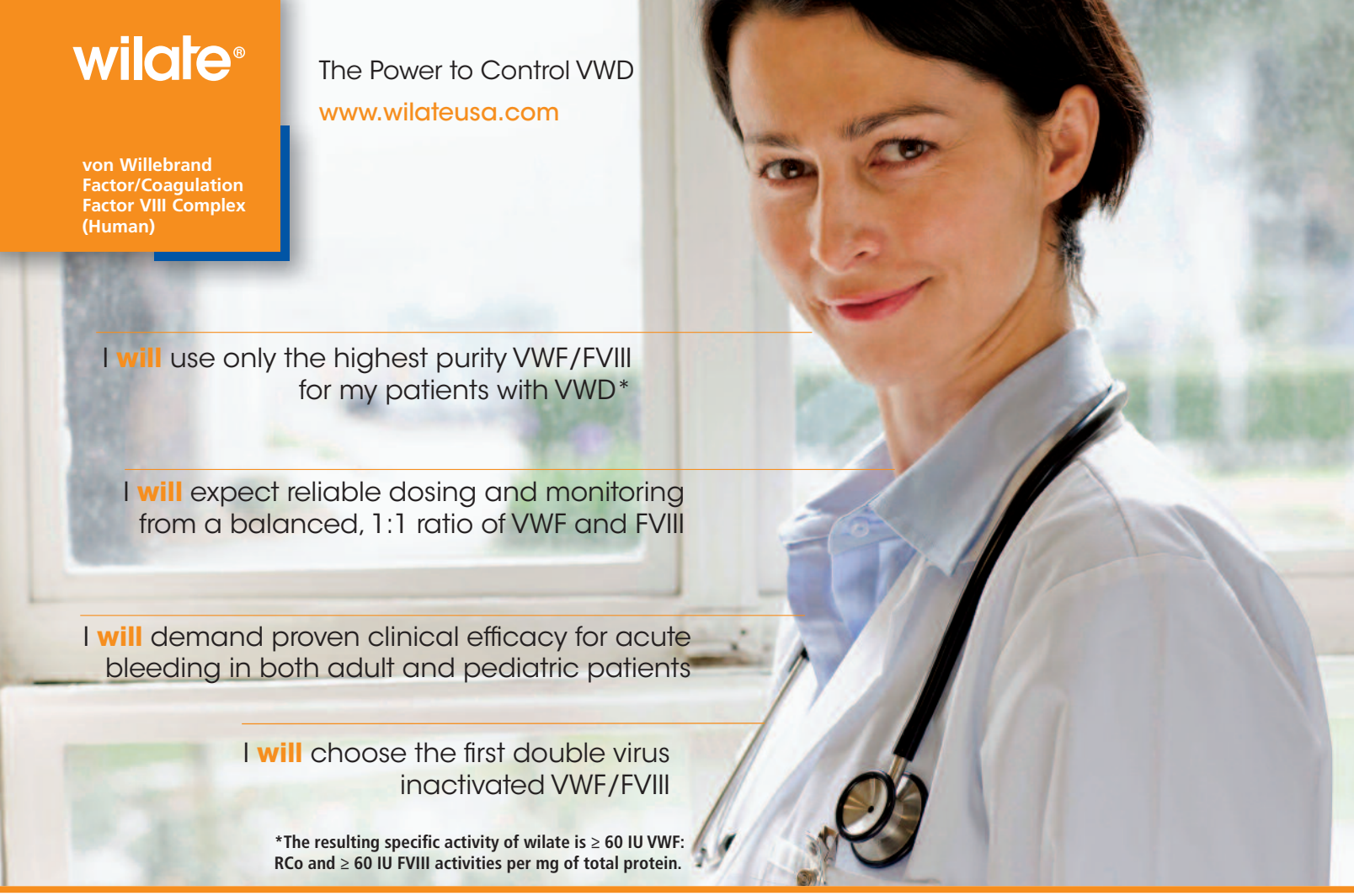

I **will** use only the highest purity VWF/FVIII for my patients with VWD*

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.**

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.

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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 Highlights of Prescribing Information on adjacent page

Date of preparation: December 2011

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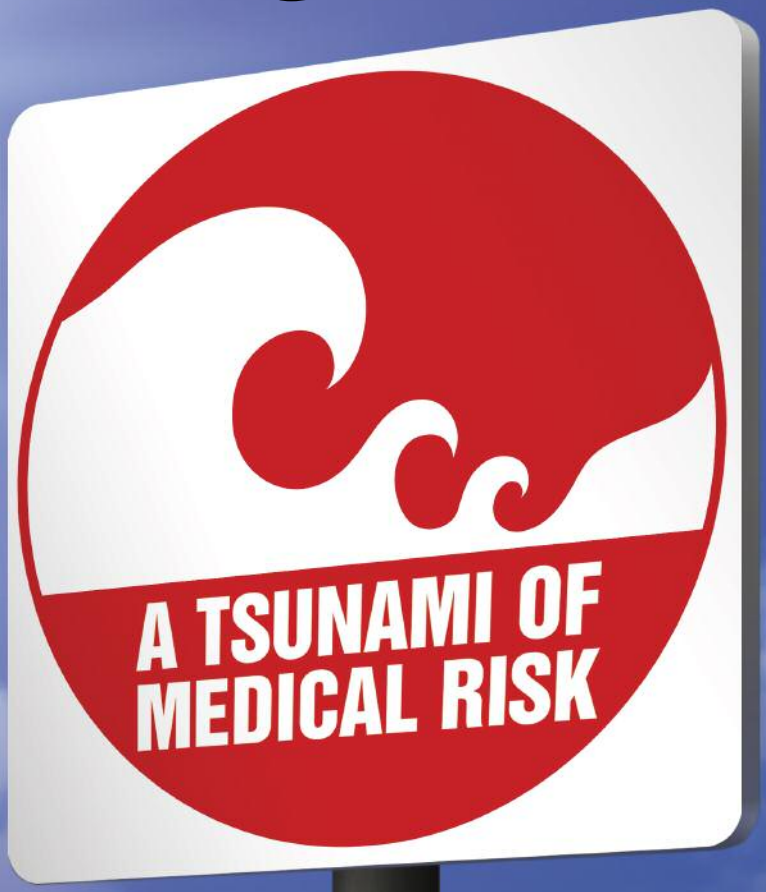
The Drug Shortage Crisis



The drug shortage crisis has been referred to as "a tsunami of medical risk," and there is no sign that the problem will disappear in the near future.

By Ronale Tucker Rhodes, MS

Imagine finding out you have a type of cancer that can be cured with medication but that medicine is in short supply. So while your prognosis should be excellent, there is a chance you won't survive if you can't get the medicine. The problem is that this scenario isn't imaginary. It's happening all the time at an increasing rate in this country. It is estimated that between July 2010 and September 2011, there were 15 deaths due to drug shortages either because the right drug wasn't available or because of dosing errors or other problems when administering or preparing alternative medications.[1]

Between 2005 and 2010, the number of prescription drug shortages in the U.S. nearly tripled from 61 to 178. And, shortages are becoming more severe and more frequent.[2] What types of drugs are involved? They run the gamut from infection-fighting medications for tuberculosis, herpes encephalitis, neurosyphilis, etc.,[3] to those used in surgeries and those prescribed to treat cancer, attention deficit disorder, blood pressure — you name it. As of January, drugs on the short supply list totaled almost 300.[1]

Lawrence A. Solbert Jr., MD, PhD, chair of the American Society of Hematology's Committee on Practice, called the increase in national drug shortages "a tsunami of medical risk."[4] Because of the shortages, many hospitals are forced to buy medicines from the so-called "gray market vendors" that practice price-gouging sometimes to the tune of up to 4,500 percent of the standard cost of drugs — drugs that could be tainted because they are sold outside authorized channels.[5]

There are many reasons cited for shortages, with no single entity on which the problem can be blamed. What is certain, however, is the need to turn this growing tide around. In 2011, two pieces of legislation were proposed in Congress, which are still pending. And, most recently in October, President Obama issued an executive order to target critical drug shortages.

Why a Shortage?

While there is general agreement on the different causes of drug shortages, those reasons vary depending upon the source. According to Commander Jouhayna Saliba, senior regulatory program manager for the U.S. Food and Drug Administration (FDA) Drug Shortage Program in the Center for Drug Evaluation and Research: "There are a number of different factors contributing to the current shortage of sterile injectables and other drugs, including manufacturing issues and economic factors. Some companies have decided to discontinue making their products for business reasons, others have had problems with their raw-material suppliers, and some have experienced manufacturing deficiencies that compromise the safety and efficacy of their products."[6]

Saliba explained that, many times, companies voluntarily stop production or suspend production of critical drugs when manufacturing problems occur so that they can resolve them, and oftentimes this takes considerable amounts of time. In other situations, companies will continue to manufacture the product, but this depends upon the level of risk, and the FDA looks at the "risk-benefit balance on a case-by-case basis in order to be flexible in addressing shortages and to mitigate any risk to patients." If a manufacturer is unable to resolve a shortage involving a critical drug, the FDA will search for overseas companies that are willing to import the drug until the shortage is resolved.[6]

But manufacturing is only part of the drug shortage problem. Almost all drug shortages are in the generics market, where profit margins are low. Many buyers are third-party payers, such as insurance companies, pharmaceutical benefit managers and government health programs, who have a strong incentive to drive the prices of these products down as low as possible. According to Mandy L. Gatesman, PharmD, of Virginia Commonwealth University of Richmond, and Thomas J. Smith, MD, of Johns Hopkins, "The main cause of drug shortages is economic. If manufacturers don't make enough profit, they won't make generic drugs." With only a half dozen companies making the vast majority of injected generics, that means other companies are needed to fill the void. But those companies are discouraged by the lengthy and expensive process of setting up new manufacturing lines and getting FDA approval.[7,8]

It is estimated that between July 2010 and September 2011, there were 15 deaths due to drug shortages.

Compounding this economic problem is Medicare's "statutory price inflexibility," which has established a 6 percent ceiling on price increases in any six-month period. This provides little incentive for manufacturers to produce more of a drug when there is a shortage. And, as part of the Medicare Modernization Act, reimbursement was set at 6 percent above the average wholesale price of a drug, which makes reimbursement less than the cost of administration in some cases.[7]

A further reason for shortages is theft of prescription drugs from warehouses or during shipment, which is on the upswing. During 2010, approximately $185 million of prescription drugs was stolen in the U.S. These thefts, accounting for the rise in

value of pharmaceutical products by 350 percent since 2007, are being sold on the street or repackaged and resold to medical suppliers with potentially dangerous consequences.[9]

The Gray Market Result

When a drug shortage occurs, so does price gouging, fueled by gray market vendors, part of the so-called "parallel market," that sell drugs outside authorized channels. Drug manufacturers typically distribute medicines through authorized national suppliers. But, sometimes, third-party suppliers are able to buy drugs. While not all third-party suppliers are unscrupulous, this is where the bad ones enter the market to sell the drugs at an inflated cost to hospital pharmacists who are desperate for those drugs to treat their patients. This is also the practice of gray market suppliers who sell stolen pharmaceuticals.

A new study released by Premier, a North Carolina-based alliance of 2,500 hospitals and 73,000 other healthcare sites in the U.S., quantified the effect of price gouging amid the worst-ever drug shortage in U.S. history. In 2010, 211 vital drugs were reported in short supply, according to the University of Utah Drug Information Service, which tracks the problem. Then, at the end of July 2011, 180 drugs shortages were logged, and estimates had predicted that the number would double by the end of the year, which it has.

There are many reasons cited for shortages, and there is no single entity on which the problem can be blamed.

According to the Premier study, during a two-week period in 2011, 42 of Premier's acute care hospitals reported receiving 1,745 unsolicited offers from drug suppliers selling vital medications that were in short supply. "The marketing offers were often in the form of emails and fliers that contained language such as: 'We only have 20 of this drug left and quantities are going fast,'" says the Premier report. Eighteen gray market providers offered the drugs, 96 percent of which were double the normal price, 45 percent of which were 100 times the normal price, and 27 percent of which were at least 20 times the normal price. The drug with the highest markup was labetalol, a blood pressure medication that has been in shortage since 2010. Normally priced at $25.90 per unit, it was being offered for $1,200 a unit, a 4,533 percent increase. "It did sort of

surprise us," says Mike Alkire, Premier's chief operation officer. "There are a lot of people who take advantage of issues like this in the market."[5]

Who sells to gray market suppliers and who buys from them? According to Amanda Forster, a spokeswoman for Premier, it's not clear. But, many hospitals contend they won't buy from these sources.

Legislation in the Works

Currently, there is a bill pending in Congress called the Preserving Access to Life-Saving Medications Act (S. 296 and H.R. 2245). The bill defines a drug shortage as a "period of time when the total supply of such drug available at the user level will not meet the demand for such drug at the user level." Specifically, the bill would "require all drug manufacturers, including those who share the market with others, to notify the FDA of any discontinuance, interruption or adjustment in the manufacture of a drug that may result in a shortage." And if the manufacturer plans to discontinue the drug, it must notify the FDA at least six months in advance. In addition, the FDA must be notified of other disruptions in manufacturing or in the supply chain as soon as the manufacturer becomes aware of the problem, but within six months. Manufacturers who do not comply with the reporting requirements are subject to civil monetary penalties of up to $10,000 for each day the violation continues, not to exceed $1.8 million. The bill also would require the FDA to publish information relating to manufacturing problems and drugs experiencing an actual shortage on its website. And it would require the FDA to

implement evidence-based criteria for identifying drugs vulnerable to a shortage. For medically necessary drugs deemed vulnerable to a shortage, the FDA would be required to collaborate with manufacturers to establish continuity of operations plans to address drug shortages. Last, the bill would require the FDA to provide an annual report to Congress followed by a report every five years on the actions taken to address and prevent drug shortages. As of this writing, the bill has been referred to the Subcommittee on Health.[10]

Another pending bill attempts to bring medical theft under the Racketeer Influenced and Corrupt Organizations (RICO) law, which was originally developed to prosecute organized crime. Introduced by six Democrats, the bill would increase penalties for stealing medical products, give police extra tools, including wiretaps, to track thieves, and give law enforcement officials more leeway to pursue and punish criminals who steal prescription pharmaceuticals.[9]

In October, President Obama issued an executive order to help stem the nation's shortage of lifesaving drugs. The order, the first since 1985 by a president to affect the functions of the FDA, directs the FDA to broaden reporting of potential shortages of certain prescription drugs and to expedite regulatory reviews that can help prevent or respond to shortages. Under the order, the FDA will work with the Department of Justice to examine whether potential shortages have led to illegal price gouging or stockpiling of lifesaving medications. The order also directs the FDA to expand its current efforts to expedite review of new manufacturing sites, drug suppliers and manufacturing changes to help prevent shortages. President Obama also announced that he supports bipartisan legislation that addresses the prescription drug shortage.[11]

Unfortunately, there is no sign that drug shortages will disappear in the future.

Is There Hope?

Is there hope for patients whose survival depends upon getting the scarce medication they need? Unfortunately, there is no sign that drug shortages will disappear in the future. Despite President Obama's executive order, many of the problems with drug shortages are outside of the FDA's authority, which the president has acknowledged. In short, says Scott Gavura, a pharmacist who works in the Ontario (Canada) cancer system and author of the Science-Based Pharmacy blog, no one "owns" the supply issue…, and there is no single organization responsible for ensuring this complicated supply process, once started, isn't interrupted. "The supply chain that links the chemical synthesis to the administration to the patient is intricate, to put it mildly," explains Gavura. "This process involves companies that manufacture the active pharmaceutical ingredient, to the company that packages it for administration, to the pharmaceutical company that sells and distributes the product," the regulators who verify manufacturing standards, the wholesalers who distribute the drug, and the group purchasers who consolidate purchasing among hospitals or HMOs, insurers and public payers.[12]

Addressing such a complicated problem requires a variety of considerations, including regulatory changes, manufacturing adjustments and ways to hinder theft, hoarding and diversion to the gray market. Current legislative proposals alone are likely not enough, and the possibility of the Centers for Disease Control and Prevention stockpiling critical-care drugs as it does for many other drugs is an alternative. It appears that a multipronged approach on several fronts will bring about the most effective solutions to the escalating drug shortage crisis. ❖

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Risky Business

By Trudie Mitschang

From bloodborne pathogens to biological dangers, healthcare workers face a daunting number of safety hazards. Proper training, increased awareness and more stringent safeguards can help minimize the risks.

When you think of dangerous lines of work, occupations like mining, firefighting and law enforcement come readily to mind. That's why it is surprising to note that in 2010, the healthcare and social assistance industry reported more injury and illness cases than any other private industry sector — 653,900 cases in all.[1]

Healthcare workers face a number of serious safety and health hazards, including physical injury and chemical and biological threats. From bloodborne pathogens and ergonomic pitfalls, to chemical exposures and needlesticks, the healthcare professions can indeed be hazardous to one's health. This problem has drawn increased attention in recent years; the healthcare workforce was a focus last year of the U.S. Department of Labor's annual report about workplace injuries and illness. "We remain concerned that more workers are injured in the healthcare and social assistance industry sector than in any other, including construction and manufacturing, and this group of workers had one of the highest rates of injuries and illness at 5.2 cases for every 100 workers," Labor Secretary Hilda L. Solis stated in a report on the occupational risks in healthcare.[2]

Back Injuries: A Risk for Nurses

When it comes to back injuries, construction workers, warehouse drivers or delivery personnel might be expected to suffer the highest number of on-the-job injuries. In fact, it is nursing that leads the list with the highest incidence of back injuries, and the second highest number of all types of nonfatal work-related injuries in the U.S.[3]

A closer look at the day-to-day tasks involved with nursing sheds some light on this statistic: The two main risk factors for back injury among nurses are lifting and transferring patients, and repetitive movements like bed-making. During a typical shift, an average hospital staff nurse will lift 20 patients into bed and transfer five to 10 patients from bed to a chair. Since patients typically weigh in excess of 100 pounds, the load is significantly above the weight that would be considered safe for a typical industrial worker performing this degree of lifting.

"When I was a labor and delivery nurse, my patient and her unborn child went into distress after the epidural had been administered," says Stephanie McBride, RN. "When the midwife left to get the doctor, I instinctively went to help the patient reposition onto her hands and knees. She was deadweight due to the epidural, and I ended up with two herniated discs and a hairline fracture. The next day, I couldn't move." McBride sustained her back injuries two years ago, and although she is in chronic pain, at only 32 years old she is fearful of the potential risks of corrective back surgery. Her injuries forced her to forgo the more physical rigors of the labor and delivery room; she now works as an oncology nurse.

As with many in the hospitality field, bed-making also increases the risks of back injury because of the bending and stretching involved in repetitively changing sheets. The good news is there are several ways that hospitals, care facilities and nursing professionals can minimize the risk of back injury.[4] These include:

- using lifting assistance devices to help lift and move patients from bed to seat, including gait belts, walkers, bed rails and hydraulic lifts
- using appropriate equipment to reduce patient handling activities, such as powered beds, height-adjustable chairs, and powered wheelchairs
- promoting improved and consistent ergonomics training for nurses and health aides to encourage good work postures and proper twisting and/or bending techniques.

Needlesticks and Scalpel Safety

The unfortunate reality is that anyone who works regularly around sharp instruments is at some risk of injury, no matter how many safeguards are in place. Needlestick injuries are a common event in all healthcare environments, particularly when drawing blood, administering an intramuscular or intravenous drug, or performing other procedures involving sharp instruments. These injuries also commonly occur during needle recapping and as a result of failure to place used needles in approved sharps containers. Surgical procedures also put healthcare workers at risk of needlesticks; a surgical needle may inadvertently penetrate the glove and skin of the surgeon or assistant. Penetrating accidents of the surgeon or assistant with the scalpel or other sharp instruments also are common threats.

While flesh wounds can be painful and sometimes serious, the real threat with needlesticks is the potential transmission of viruses from the source to the recipient. Generally, needlestick injuries themselves cause only minor bleeding or trauma, but the risk of viral infection remains, especially if the patient is a carrier of hepatitis B (HBV), hepatitis C (HCV) or human immunodeficiency virus (HIV). According to the Occupational Safety and Health Administration (OSHA), approximately eight million healthcare workers are at risk of occupational exposure to bloodborne pathogens.[5]

In 2010, the healthcare and social assistance industry reported more injury and illness cases than any other private industry sector.

Diane Mawyer, RN, is someone whose life was forever changed by a needlestick injury that infected her with HCV. She tells her story in a compelling nine-minute video that has been widely viewed on YouTube. Although the incident happened more than 20 years ago, Mawyer has endured three organ transplants and still struggles with life-altering health challenges. "When I was exposed, very little was known about HCV and the risks associated with needlestick injuries and exposure to bloodborne pathogens," said Mawyer. "But with our growing understanding of HCV, it is crucial that we be proactive in screening and diagnosis. If my hepatitis C had been identified earlier, there's a good chance that my organ transplants could have been avoided."[6]

According to a 2006 study of needlestick injuries and safety devices, the majority of U.S. nurses surveyed report being accidentally stuck by a needle while working; nearly half (47 percent) of all nurses in the survey were stuck by a contaminated

Real-Life Workers with Life-Changing Injuries

- Nurse working in an intensive care unit was stuck by an intravenous catheter used on a patient with end-stage AIDS; she was infected with HIV as a result. (*Advances in Exposure Prevention*: Vol.7, No.7, 2005, p.25)
- Nurse was infected with hepatitis C (HCV) from a blood exposure sustained at work. (*Advances in Exposure Prevention*: Vol.5, No.2, 2000, p.13)
- Laboratory worker acquired West Nile virus infection from a cut to his thumb from a scalpel blade. (*Advances in Exposure Prevention*: Vol.6, No.5, 2003, p.59)
- Firefighter/paramedic was infected with HIV; he sustained massive blood and body fluids exposures on a number of occasions during his nine years as a paramedic. (*Advances in Exposure Prevention*: Vol.6, No.1, 2002, p.14)
- Surgeon was diagnosed with HCV infection from an occupational sharps injury. (*Advances in Exposure Prevention*: Vol.6, No.5, 2003, p.49)
- Eleven U.S. and Canadian veterinary schools reported multiple scalpel/knife cuts. (Langley, R.L. et al. [1996]: A Survey of Peronsland Occupational Health and Safety Training for U.S. and Canadian Veterinary Schools. *Journal of Agromedicine*, Vol.3, No.4, December 1996, pp.23-25)
- A survey of dental students showed that the majority of injuries were from needlesticks and mishaps with hand instruments. (Wood, A.J., et al. [2006]: Student Occupational Exposure Incidence: Perception Versus Reality. *Journal of Dental Education*, 70[10]: 1081-1088)

needle. Of the nurses reporting needlesticks, some were stuck multiple times.[7]

"Healthcare workers like Ms. Mawyer are on the frontlines every day looking out for our health and safety, and we need to do more to protect them," said Murray Cohen, PhD, MPH, CIH, chairman of the Frontline Healthcare Workers Safety Foundation, in an article on safety issues and healthcare workers. "By addressing the need for appropriate prevention measures, disease screening and post-exposure therapy guidelines…, we hope to urge government, private employers and benefit providers to take action to protect workers from the debilitating effects of HCV."[8]

The majority of U.S. nurses surveyed report being accidentally stuck by a needle while working.

The Centers for Disease Control and Prevention (CDC) estimates that hospital-based healthcare personnel sustain an average of 1,000 sharps injuries per day.[9] Scalpel blade injuries account for 7 percent to 8 percent of those injuries. In an article on sharps safety published by the Joint Commission on Accreditation of Healthcare Organizations, Jerry Gervais, CHFM, CHSP, associate director, Standards Interpretation Group of the Joint Commission, said: "It's very unfortunate that injuries such as these occur, and it's not just clinicians who are at risk. Other potential victims include maintenance, laundry and housekeeping personnel."[10]

Gervais noted that one of many protective measures that can be implemented to protect healthcare providers includes putting needles and scalpel blades in self-sealing containers and then sending them to an approved medical destruction site regulated by the federal Environmental Protection Agency to ensure they are disposed of properly.

Of course, all the safeguards in the world are no match against medical personnel noncompliance. While the reasons for noncompliance can be varied and complex, Mary J. Ogg, MSN, RN, CNOR, sharps expert with the Association of periOperative Registered Nurses (AORN), said oftentimes physicians may be hesitant to adopt practices that decrease the incidence of sharps injuries if hard numbers supporting best practices are not provided. Ogg notes that AORN developed a 30-slide educational PowerPoint presentation that demonstrates the effectiveness of the practices with supporting data.[11] "Surgeons are more receptive to seeing evidence rather than just being told they should do this," she explained. "The AORN toolkit on sharps injuries and needlesticks also includes a letter from retired surgeon Mark Davis, MD, that explains when a physician ignores best practices for preventing injuries, he or she puts every member of the surgical team at risk." Ogg recommends using data and testimony from other respected physicians to convince providers that the prevention practices are worthwhile and necessary.

Minimizing Chemical Hazards

Exposure to potentially hazardous chemicals is a fact of life for healthcare workers. Chemicals are encountered in the course of diagnostic and therapeutic procedures; in laboratory work; in preparation and cleanup activities; and sometimes even in emanations from patients. Despite the constant threat of such exposures, this problem has historically received minimal attention from those involved in occupational health and safety research and regulation.

Exposure to potentially hazardous chemicals is a fact of life for healthcare workers.

Numerous chemicals found in hospitals may be toxic or irritating to workers who come in contact with them. Chemical exposure can come in the form of airborne dusts, vapors or gases; they may also enter the body by absorption through the skin. Some of the more common potential chemical exposure risks for healthcare workers include formaldehyde used for preservation of specimens for pathology; ethylene oxide, glutaraldehyde and peracetic acid used for sterilization; and numerous other chemicals used in healthcare laboratories. In terms of specific risks, glutaraldehyde is known as a potent sensitizer that causes occupational asthma. Many of the drugs used to treat cancer are themselves known carcinogens. Ethylene oxide, a cold sterilizing agent, is a carcinogen and a reproductive toxin that causes miscarriage. Cleaning agents and materials and their methods of use are increasingly implicated in asthma. Despite the existence of OSHA chemical hazard communications, most healthcare workers are unaware of the risks of these agents and the appropriate control measures needed to prevent injury.[12]

Danger in the Air

The harsh, disinfectant odor common in hospitals is considered a necessary irritant required to keep bacteria at bay. But for those who are exposed to the resulting poor indoor air quality on a regular basis, the longer-term health consequences can be troublesome. Many traditional cleaning products, floor strippers and disinfectants present a variety of human health and environmental concerns, and may contain chemicals that cause cancer, reproductive disorders, respiratory ailments (including occupational asthma), eye and skin irritation, central nervous system impairment, and other human health effects.[13] In addition, some of these products contain persistent bioaccumulative toxins (PBTs), and are classified as hazardous waste, or otherwise contribute to environmental pollution during their manufacture, use or disposal. Hospitals and clinics hoping to minimize employee exposure to such chemicals are encouraged to explore some of the environmentally friendly options that are becoming increasingly available, especially as "green" cleaning products become more and more mainstream.

According to an abstract published by the U.S. National Library of Medicine National Institutes of Health, decreasing chemical exposure in the healthcare setting will require a multipronged approach. Suggestions include recognizing healthcare as a "high-hazard" employment sector; fortifying voluntary safety guidelines to the level of enforceable regulation; "potent" inspections; treating hazardous pharmaceuticals like the chemical toxicants they are; and protecting healthcare workers at least as well as workers in other high-hazard sectors.[13] ❖

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Proactive Screenings for Women's Health

By Trudie Mitschang

In recent years, the medical specialty of women's health has evolved beyond the basics of childbirth, breast cancer and bone density tests to encompass a spectrum of proactive screenings designed to prevent disease and prolong life.

The past four decades have birthed a virtual transformation within the field of women's healthcare. Traditionally, diagnostic exams or screenings for many life-threatening diseases were performed only after symptoms developed. Unfortunately for many women, the first sign of trouble often showed up as a catastrophic health event such as a stroke or heart attack. Healthcare providers are well aware that early detection is the most effective way to fight debilitating and chronic disease, but the key to early diagnosis and the detection of risk factors begins with raising patient awareness about the need for specific screenings.

"The U.S. Preventive Task Force has come out with new guidelines for certain screening tests," says Sue Romanick, MD, board certified in internal medicine and rheumatology, with a practice in Bellevue, Wash. "I tell women it's a good idea to work with your doctor to find out which annual screenings you need while also making the right lifestyle choices, including a healthy diet, regular exercise and stress modification. All of these decisions can help tip the balance in your favor when it comes to staying disease-free."

The Weaker Sex?

While women may not literally be the "weaker sex," the fact remains that women experience life-altering conditions like diabetes and heart disease differently than their male counterparts. Women also tend to suffer from certain diseases at a higher rate than men, including osteoarthritis, obesity, depression and fibromyalgia. Statistically, women are more prone to autoimmune conditions like Sjogren's syndrome, lupus and hypothyroidism as well. Understanding these gender differences can help clinicians develop studies and screenings that address the unique needs of the female population.[1]

Greater awareness of women's health concerns has led to increased attention on female-focused research. The National Institutes of Health now requires women and minorities to be included in the research it supports, and the U.S. Food and Drug Administration (FDA) encourages that women be included in drug and device testing. To support this effort, regional women's health coordinators have been appointed to focus on inclusion at state and local levels, and a National Women's Health Resource Center (NWHRC) has been established to provide easier access to women's health information by telephone and on the Internet.[2]

Gaps in knowledge regarding women's health concerns are increasingly being filled through more targeted research; to date, 18 National Centers of Excellence in Women's Health have been established around the country to foster research, clinical services and education on women's health issues, as well as to enhance the career development of women in academic medicine.[3] New recommendations for medical education curricula are also being developed to help ensure that future physicians are sensitive to gender differences in the etiology, treatment and prevention of disease for women of all ages.[4]

Promoting Patient Awareness

In 2012 alone, almost half a million women will die of cardiovascular disease.[5] To put that in perspective, the number is nearly equivalent to the entire population of the state of Wyoming. Although statistics like this are widely publicized, there is still ample misinformation and lack of awareness among patients and providers; while heart disease is the No. 1 killer of American women, only 13 percent of women in the United States see heart disease as the greatest threat to their health. Even more surprising, less than one in five physicians know that more women than men die of heart disease each year.[6] "There are far too many women dying of heart disease in their 60s, when no one expects to die because that's too young in this country," says Cindy Pearson, executive director of the National Women's Health Network. "There are (also) women, who, for many years, are really ill with heart disease — being out of breath, not being able to walk up one flight of stairs … because heart disease impairs their ability to get around."[7]

Greater awareness of women's health concerns has led to increased attention on female-focused research.

Thanks to organizations like Susan G. Komen and its ubiquitous pink ribbons, breast cancer awareness is at an all-time high, but misperceptions still abound. Two of the most common false beliefs are that mammograms can detect 100 percent of all breast cancers, and that breast cancer does not afflict young women. Studies show that up to 10 percent of breast cancers do not show up on a mammogram, either because they are located in a part of the breast that is difficult to include in the image, or they are hidden by normal breast tissue. And while only 5 percent of all breast cancer cases occur in women under 40 years old, the disease can strike at any age, depending on a woman's risk factors. On the bright side, a recent study in the *New England Journal of Medicine* found that advances in breast cancer screenings contributed significantly to the 20 percent reduction in the U.S. breast cancer death rate between 1975 and 2000. The study also found that

Women's Health Fast Facts

- One woman in eight who lives to age 85 will develop breast cancer during her lifetime.
- Breast cancer is the leading cause of death in women between the ages of 40 and 55.
- The American Cancer Society estimates that about 213,000 women in the U.S. are diagnosed with invasive breast cancer each year.
- In 2003, 41,566 females in the U.S. died of breast cancer.
- In 2003, all cardiovascular diseases combined claimed the lives of 483,842 females, with coronary heart disease accounting for 233,886 deaths.
- One in three female adults has some form of cardiovascular disease.
- Sixty-four percent of women who died suddenly of coronary heart disease had no previous symptoms.

Source: American Heart Association, American Cancer Society, National Cancer Institute

when breast cancer is detected early and confined to the breast, the five-year survival rate is nearly 100 percent.[7]

According to the American Cancer Society guidelines, all women should begin cervical cancer screening about three years after they begin having vaginal intercourse, but no later than 21 years of age. Screening should be performed annually with the regular Pap test or every two years using the newer liquid-based Pap test. Older women experiencing menopause are encouraged to be aware of the signs and symptoms of uterine cancer, and if risk factors exist, may opt for a yearly endometrial biopsy. Likewise, colon cancer screenings are recommended yearly after the age of 50, or more often based on the patient's personal and family history.

When it comes to conditions like cardiovascular disease and cancer, one thing is certain: A woman's best line of defense is through regular, proactive screenings and examinations as prescribed by her physician; early detection saves lives.

Advanced Diagnostics on the Rise

Breakthroughs in diagnostic technology have given physicians improved tools for detecting disease earlier, making more confident diagnoses and providing more personalized treatment. For example, when it comes to breast cancer, traditional screening mammography has long been considered the gold standard. In recent years, digital mammography has emerged and is allowing radiologists to manipulate images for a more accurate assessment and diagnosis. A recent study sponsored by the National Cancer Institute suggests digital mammography detects up to 28 percent more cancers than traditional mammography for women under the age of 50 or for those with dense breasts.

Other technologies such as magnetic resonance imaging (MRI), ultrasound and the hybrid positron emission tomography/computed tomography (PET·CT) also are valuable tools for diagnosing breast cancer. MRI, for example, can help physicians better examine abnormalities first detected by mammography, can detect abnormalities in women with breast implants, and can provide accurate assessments of the breast tissue in younger women. Additionally, breast ultrasound technology elastography, in which images are acquired on high-end ultrasound devices equipped with additional software and hardware, is expected to enable physicians to accurately distinguish characteristics of breast lesions, which may reduce reliance on invasive breast biopsy procedures.

A recent Mayo Clinic study of nearly 1,000 women showed that new gamma-ray cameras detected three times as many tiny tumors (as small as two-fifths of an inch in diameter) as standard mammography in women with dense breasts. This development gives high-risk women another early-detection option besides mammograms and more expensive MRIs.[8]

Although the most talked about, breast cancer is not the only cancer impacting women. Other types of female-specific cancers such as ovarian and uterine cancer also can be detected through proactive screenings, although risk factors should often be evaluated first to ensure an accurate assessment.

"Screening for cancer saves lives, yet the numbers of Americans getting screened fall below recommended target levels," says Dr. Romanick. "There can be controversy surrounding certain screening tests such as the CA-125 for ovarian cancer, a test some women are now asking for during annual exams. As with other cancers, we now know that it's important to consider risk factors first. For example, if you've had a certain cancer before, or if ovarian cancer already runs in your family, or let's say that you've had a condition such as endometriosis, then your provider may opt to do additional screenings." Romanick says typical screenings would include looking for gene mutations (BRCA 1 and BRCA 2), in addition to having repeated CA-125 testing over time while looking to see how the values are changing rather than looking at one isolated value.

Heart disease, too, can be detected with advanced imaging technologies to help pinpoint the disease in its earliest stages. Scanners such as the CT angiography, in which multiple CT scans are used to produce a three-dimensional image of the heart, can be highly effective, but advised only if specific risk factors are present. Several studies have suggested that expensive

tests for biomarkers that are sometimes indicative of heart disease, including C-reactive protein, a sign of systemic inflammation, are not cost-effective in generally healthy patients. More sophisticated tests such as these are often advised only in patients with known heart risks.

Benefits of Blood Panel Testing

Imaging technology is not the only type of screening recommended when assessing a woman's risk factors for disease. Blood panel tests also can identify a variety of red flags. "In addition to a complete blood panel, which assesses the complete blood count, lipid panel and liver enzymes, I am a big believer in blood testing to assess and then correct the hidden epidemic of diabetes, believed to be an underlying cause of dementia, fatty liver disease, depression, mood disorders, nervous system dysfunction and kidney failure," says Ann Louise Gittleman, PhD, CNS. "To monitor for this condition, the tests I would absolutely request include an insulin response test, hemoglobin A1c and NMR profile to measure the size and number of low-density lipoprotein, high-density lipoprotein and triglycerides, the latter being a major red flag for heart disease, especially among women."

Breakthroughs in diagnostic technology have given physicians improved tools for detecting disease earlier.

Gittleman, a best-selling author and expert on women's health, asserts that lifestyle changes are still probably the largest contributor to long-term health for women. "The most important lifestyle change I recommend is to cut sugar from the diet. Sugar, including excessive fruit, fruit juices, sweeteners and processed and refined carbohydrates, triggers the production of insulin, the fat-promoting hormone. Curtailing its intake is critical to obtaining and maintaining a healthy weight."

Women and the Affordable Care Act

The Affordable Care Act, which was passed by Congress and signed into law by President Obama on March 23, 2010, is poised to have a potentially large impact on the future of health screenings for women. Under the Affordable Care Act, women's preventive healthcare such as mammograms, screenings for cervical cancer, prenatal care and other services are covered with no cost-sharing for new health plans. For women who have traditionally declined screenings due to financial restraints, this is good news.

As of September 2010, new health plans are required to cover the services recommended by the U.S. Preventive Services Task Force (UPSTF), an independent panel of prevention and primary care experts that routinely assesses and makes recommendations for clinical preventive care. Current UPSTF recommendations for preventive screenings for diseases such as breast and cervical cancer, colorectal cancer and chlamydia, as well as bone density tests, testing for high cholesterol and high blood pressure, obesity screening, annual influenza vaccinations, and smoking cessation treatment all are covered under the new guidelines.[9]

Over the last decade, there has been heightened interest and awareness regarding women's health issues. Stakeholders from medical, government and patient sectors have weighed in to create strategic plans that will improve the health, longevity and quality of life for future generations of women. Critical gaps in medical research are being addressed, and while there is much that still needs to be done, great strides have been made to ensure that proactive screenings for the diseases that impact women are utilized to their full advantage. This increased focus can go a long way toward better equipping 21st-century healthcare providers with the improved diagnostic tools and resources needed to prevent disease and prolong life. ❖

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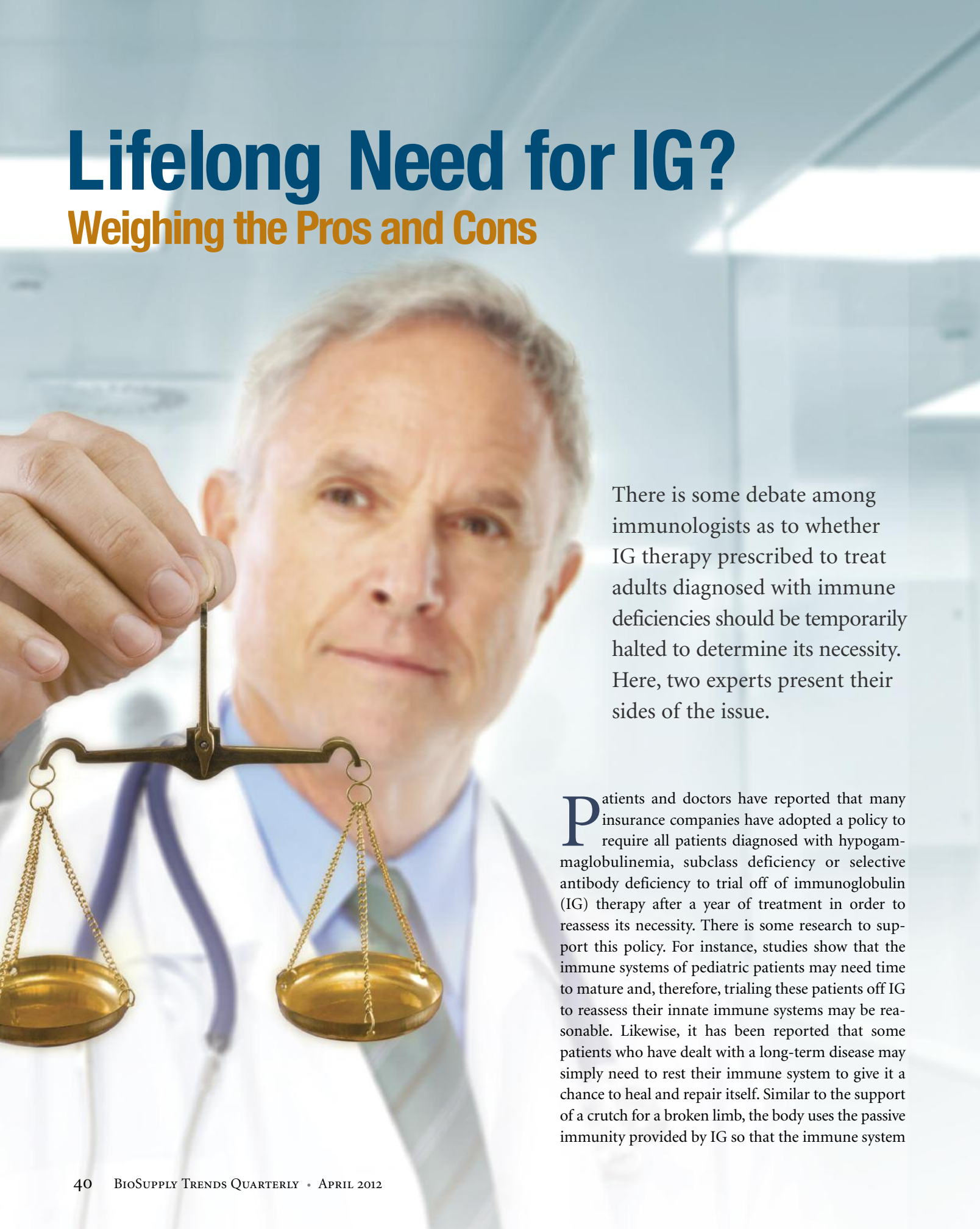
Lifelong Need for IG?

Weighing the Pros and Cons



There is some debate among immunologists as to whether IG therapy prescribed to treat adults diagnosed with immune deficiencies should be temporarily halted to determine its necessity. Here, two experts present their sides of the issue.

Patients and doctors have reported that many insurance companies have adopted a policy to require all patients diagnosed with hypogammaglobulinemia, subclass deficiency or selective antibody deficiency to trial off of immunoglobulin (IG) therapy after a year of treatment in order to reassess its necessity. There is some research to support this policy. For instance, studies show that the immune systems of pediatric patients may need time to mature and, therefore, trialing these patients off IG to reassess their innate immune systems may be reasonable. Likewise, it has been reported that some patients who have dealt with a long-term disease may simply need to rest their immune system to give it a chance to heal and repair itself. Similar to the support of a crutch for a broken limb, the body uses the passive immunity provided by IG so that the immune system

can rest and repair itself. Regardless, even expert clinical immunologists have a difference of opinion on the subject. Therefore, having a one-size-fits-all approach may not be in the best interest of the patient.

For this article, we invited two expert immunologists to present their analyses, pro versus con, on the issue of whether adults diagnosed with these immunodeficiency diseases should trial off IG after a period of therapy.

Argument in Favor of Lifelong IG Treatment

By Francisco A. Bonilla, MD

Many clinical immunologists stipulate that following a correct diagnosis of antibody deficiency (or combined immunodeficiency) in adults, IgG replacement therapy should be lifelong. The reason for this is that these forms of immune deficiency are 1) genetically determined and unlikely to resolve spontaneously, 2) usually have a constant or gradually worsening clinical course over time, and 3) there is usually unequivocal evidence through experience regarding the benefit of IgG replacement for improving the course of the disease.

The most prevalent form of antibody deficiency in adults is common variable immunodeficiency (CVID), which may have its onset at any age. CVID is properly diagnosed when it is found that patients have a reduced number of two or more antibody classes (must include IgG with low IgA and/or IgM) and a clear impairment of antibody formation in response to vaccination, infection or both. In CVID patients, there are no well-described cases of resolution of the disease, and there is abundant evidence of the effectiveness of IgG therapy for reducing infections and improving other manifestations. Even after a period of relative clinical wellness, in properly diagnosed patients, it is expected that cessation of IgG therapy will result in a rapid waning of IgG levels, and a markedly increased risk of infection or worsening of chronic lung disease, etc. These complications may lead to an irreversible worsening of function that never would have occurred if therapy had not been temporarily halted, and does not return to baseline with its resumption.

Other antibody deficiency disorders in adults include X-linked agammaglobulinemia and various forms of hyper-IgM syndrome. Combined deficiencies include Wiskott-Aldrich syndrome, and additional forms of hyper-IgM syndromes, as well as others. These diseases almost always are diagnosed in childhood, but many individuals will survive into adulthood with appropriate therapy, including IgG. Some patients may receive bone marrow transplantation in infancy for immunodeficiency. Many may fail to properly reconstitute B cell function and have persistent antibody deficiency. In all of these situations, spontaneous improvement in the course of the disease is not expected, and IgG therapy must be lifelong. Inappropriate cessation of therapy would expose these patients to the same risks described above.

Milder forms of antibody deficiency have been described in adults. These include hypogammaglobulinemia that does not meet criteria for CVID, IgG subclass deficiency with or without associated IgA deficiency and/or defects of specific antibody production, and defects of specific antibody production with normal immunoglobulins. These remain controversial as diagnoses of "true" immunodeficiency, and the natural histories of these "disorders" are less well-understood, and the role of IgG therapy in their management is less well-substantiated. For these reasons, many clinicians argue that IgG replacement is not indicated for these patients at all, and it should never be used. That being the case, then, IgG therapy is to be used only for those diseases described above for which therapy is expected to be lifelong, and for which interruption of therapy could be expected to have dire adverse consequences.

IgG replacement in properly diagnosed immunodeficient adults should never be discontinued.

Thus, IgG replacement in properly diagnosed immunodeficient adults should never be discontinued.

Argument in Favor of a Trial Discontinuation of IG Treatment

By Ricardo U. Sorensen, MD

Before discussing situations in which IG therapy may be discontinued, it is important to first consider the initial indications for IgG replacement therapy. These are largely based on the immunodeficiency with which each patient is diagnosed. If the immunodeficiency involves a deep decrease in IgG concentrations, as in agammaglobulinemia, hyper-IgM syndrome and in many patients with common variable immunodeficiency (CVID), there is little doubt that IG therapy is indicated and that there are no reasons to ever discontinue IG treatment.

Discontinuing IG therapy should be considered only if patients have had a sufficiently long period of well-being on IG therapy.

Second, it is important to consider the clinical severity, which refers mostly to the severity and frequency of infections. Clinical severity may vary even for some patients with agammaglobulinemia and CVID. And, an occasional X-linked agammaglobulinemic patient may have a very mild clinical course, and therefore, they may not be diagnosed until adulthood. Still, the need for treatment is rarely questioned if the patient came to clinical attention due to unusual or recurrent infections. However, some patients with CVID and many patients with immunologically milder forms of hypogammaglobulinemia need a clear assessment of their infection history as the need for IG therapy is considered.

If infections have already led to comorbidities like bronchiectasis or severe chronic sinus disease, these complications may become the strongest indication for long-term treatment, even if the immunologic severity is mild (e.g., mild hypogammaglobulinemia, IgG subclass deficiency with normal total IgG concentrations, or specific antibody deficiencies with normal immunoglobulins). Again, in these situations, IG therapy should be indicated and not discontinued.

So, when is a trial discontinuation of IG therapy warranted? There are several situations when this may be appropriate.

First, the need to continue treatment may no longer be present in patients who may have started therapy early in life. This is because the transient nature of an immune deficiency is not apparent at the time of initiation of therapy, despite a diagnosis of hypogammaglobulinemia stemming from significant infections that are affecting quality of life and the cost of medical care. Some of these patients could retrospectively be diagnosed with a transient hypogammaglobulinemia of infancy. In patients treated for hypogammaglobulinemia in the first years of life that do not have very low B lymphocytes, such as in an agammaglobulinemic patient, it is important to monitor IgM and IgA concentrations during IG therapy. Ideally, IgG trough levels also should be carefully monitored by keeping the dose of IgG per kilo and the interval of infusion constant. If the patient has improved clinically and the concentrations of immunoglobulins increase over time, a trial discontinuation of IG therapy should be considered.

There also are antibody and combined immunodeficiencies in which a limited period of IG therapy should be considered as part of the initial therapeutic plan. This includes some patients with IgG subclass deficiency and most patients with specific antibody deficiencies and normal immunoglobulin concentrations. In these patients, a limited period of IG therapy of one to two years should be planned from the start. This is recommended not so much to see if IG therapy works, since a well-designed treatment with appropriate concomitant management of infections will almost always be effective. Discontinuation of therapy is indicated because there is a reasonable expectation that, after a period of time, IgG replacement may no longer be needed.

An indication of IG therapy for a limited period of time also is almost always appropriate when IG is used as concomitant treatment for patients receiving a stem cell transplant or gene therapy. In many cases, these treatments offer a permanent cure for a primary immunodeficiency, enabling the patient to produce their own antibodies.

Another situation in which discontinuation of IG therapy should be considered is if there is an unclear indication for IG therapy when it is initiated at any age. For instance, patients may have been prescribed IG therapy without solid evidence

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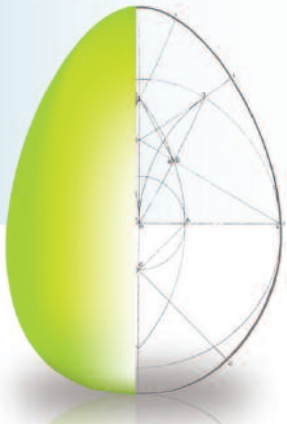

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Important Safety Information

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. Also monitor patients with risk factors for thrombotic events; 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). There have been reports of IVIg-related hemolysis, hemolytic anemia, and pulmonary adverse events, including transfusion-related acute lung injury (TRALI). Avoid high-dose regimen where fluid volume is of concern.

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 PVG10-11-0014 10/2011

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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 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.[2]

5.4 Thrombotic Events

Thrombotic events may occur following treatment with IGIV products, including Privigen.[3-5] 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 (triglycerides), 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]*).

5.5 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]

Hemolysis, possibly intravascular, occurred in two subjects treated with Privigen in the ITP study (*see Adverse Reactions [6]*). These cases resolved uneventfully. Six other subjects experienced hemolysis in the ITP study as documented from clinical laboratory data.

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

The high-dose regimen (1 g/kg/day for 2 days) used to treat patients with chronic ITP is not recommended for individuals with expanded fluid volumes or where fluid volume may be of concern (*see Dosage and Administration [2.2]*).

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

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of an immunodeficiency or without a sufficiently documented history of infections. In these cases, patients may be re-evaluated, in some cases as a result of a request for a second opinion about the need to continue lifelong IG therapy. However, before discontinuing treatment, it would be appropriate to measure mature B lymphocytes and memory B lymphocytes by flow cytometry. If they are clearly below normal numbers, it is very likely patients will suffer from a recurrence of infections after discontinuing IG treatment. If treatment is discontinued, careful observation is advisable to avoid infections that may cause secondary damage.

In all of these situations, infections need to be monitored during IG therapy to ensure successful treatment. However, since the absence of infections is the main goal of IG therapy, this fact alone should not be an indication for discontinuation of therapy. Discontinuing IG therapy should be considered only if patients have had a sufficiently long period of well-being on IG therapy. This usually requires at least one and up to two years of treatment to allow mucosal surfaces to heal and normal clearing functions altered by recurrent or severe infections to be restored.

If no clinical improvement occurs with IG treatment, it is necessary to examine why this generally very effective therapy has failed. If failure to improve is due to an inappropriate indication for IG therapy, then it should be discontinued.

The decision to discontinue IG therapy should be made by the treating or consulting immunologist in agreement with the patient. And, each time IG therapy is discontinued, there should be a period of at least four months prior to re-evaluating the need to restart it. The decision to restart IG therapy should be based more on the return of well-documented infections than on the depth of the immunological abnormality. This is because the presence of infections that improve on IG therapy and that return upon discontinuation of therapy is an indirect but very strong proof of a functional antibody deficiency.

The decision to discontinue IG therapy should be made by the treating or consulting immunologist in agreement with the patient.

When there is a justifiable reason to stop IG therapy, it can be stopped at once, because the long IgG half-life will actually provide for a slow decrease in available circulating IgG over several months. Tapering off IG therapy by giving smaller doses of IgG or prolonging the interval between infusions is usually not done. It is recommended by many clinicians to discontinue IG therapy in the spring, when many patients experience a decreased number of infections even without treatment.

A Debate Among Shades of Gray

As these two experts so expressly convey in their analyses, this issue of lifelong need for IG is far from black and white. Instead, whether pro or con, the grays in their lines of thinking come across explicitly: Determining when to treat primary immunodeficiency patients with IG must be based upon a proper diagnosis, severity of infections, patient response and the doctors' expertise.

No doubt, this debate represents just one of many differences of opinion that patients and immunologists will have concerning treatment with IG therapy. In the relatively young field of study of primary immunodeficiencies, the understanding of how and why IG treatment is and is not effective will continue to evolve. ❖

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Editor's note: This article refers to both IG and IgG. To clarify: IG is used when referring to the immune globulin therapy (the drug used to treat an immune deficiency). IgG is used when referring to the specific antibody found in the body that immune deficient patients are lacking.

if you spot it, you can stop it

Name: Joseph Miller Age: 62 years

Model is used for illustrative purposes only.

Symptoms[1,2]:

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

Labs[1,3]:

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

Treatments[1]:

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

Diagnosis: ACQUIRED HEMOPHILIA

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

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

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

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

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

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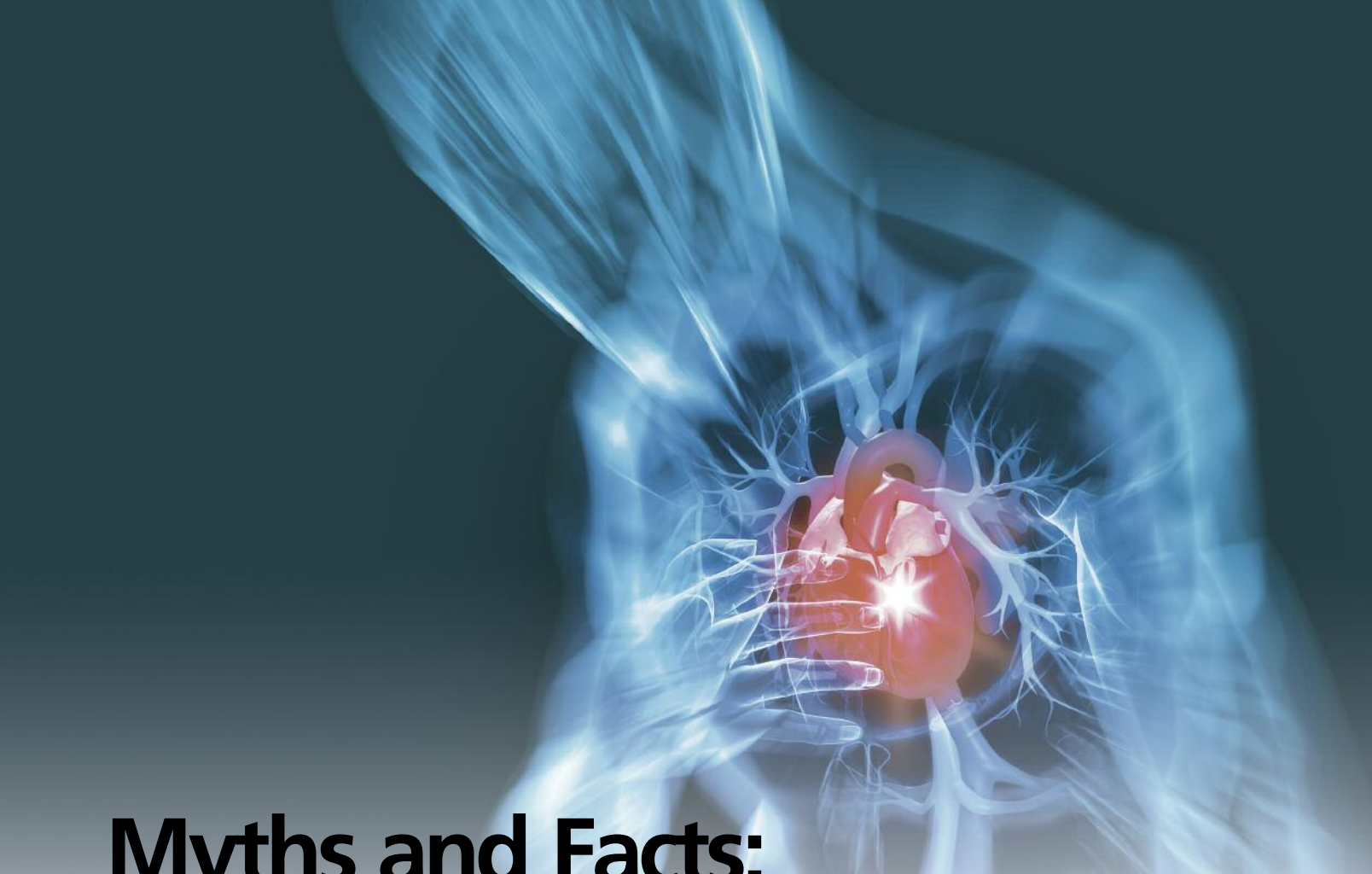

Myths and Facts: Heart Disease

Little is known about this No. 1 killer in the world, despite its prevalence and growing rates among all populations.

By Ronale Tucker Rhodes, MS

On average, every 39 seconds, a person in the U.S. dies from a heart attack, which totals more than 2,500 people dying each day. Every year, about 785,000 Americans have a first heart attack, and another 470,000 who have already had one or more heart attacks have another attack. Heart disease is the No. 1 killer in the world, causing more deaths than all forms of cancer combined. And, it does not discriminate. It occurs in all ethnicities, in both sexes and at all ages. What's more, it's expensive: In 2010, coronary heart disease alone was projected to cost the U.S. $108.9 billion, which includes the cost of healthcare services, medications and lost productivity.[1,2]

With such alarming statistics, it's safe to say that almost every individual in the U.S. has likely been affected by heart disease in some way — whether they have suffered a heart attack themselves or they have a family member or friend who has heart disease. Yet, since heart disease has touched so many lives, it makes one wonder why more is not known about this deadly killer. The answer, says Dr. Ralph Sacco, president of the American Heart Association, is that "there's a lack of awareness of what ideal cardiovascular health really is." People think they're healthier than they are, which makes them less likely to take steps to reduce their risk of heart disease.[2] Added to this is a widespread lack of awareness of the facts about heart disease.

Separating Myth from Fact

Myth: All heart disease results in heart attacks.

Fact: Heart disease is an umbrella term that includes conditions such as coronary artery disease, heart attack, cardiac arrest, congestive heart failure and congenital heart diseases. The most common cause of heart disease is coronary artery disease, which is a blocked or narrowed coronary artery that supplies the heart with blood.[3] In 2008, 405,309 people died from coronary artery disease.[1]

Myth: All heart attacks are the same.

Fact: There are actually two types of attacks that can occur due to heart disease. The first is a heart attack (myocardial infarction), which occurs when blood supply to the heart muscle stops and the heart muscle dies. The second is a sudden cardiac arrest, which occurs when the heart suddenly stops pumping due to an electrical problem in the heart. It's possible for a heart attack and a sudden cardiac arrest to occur simultaneously.[3]

Myth: Heart disease affects only older adults.

Fact: The risk of heart disease does increase with age, and heart disease in general and angina and coronary disease in particular occur more often in people over the age of 54, with incidence rates increasing even more sharply for people over the age of 64.[4] However, the roots of heart disease often begin as early as childhood. In fact, one in three Americans has cardiovascular disease, which includes young and middle-aged people.[5]

Myth: Heart disease doesn't affect children.

Fact: With the growing prevalence of obesity in children, more and more are experiencing heart disease. Cardiac arrest strikes an estimated 5,920 children each year, and most unexpected deaths in young athletes are the result of heart disease. In fact, heart disease accounts for up to one death per 100,000 high school athletes.[2] In addition, other childhood diseases, such as Kawasaki disease and acute rheumatic fever, can be the main causes of acquired heart disease in children in the U.S.[3]

Myth: Heart disease primarily occurs in men.

Fact: Not anymore. Since 1984, more women than men have died each year from heart disease, and the gap between men's and women's survival continues to widen. Worldwide, 8.6 million women die from heart disease each year, accounting for a third of all deaths in women. Eight million women in the U.S. are currently living with heart disease, and 435,000 American women have heart attacks annually, 83,000 of whom are under age 65 and 35,000 of whom are under age 55. Under age 50, women's heart attacks are twice as likely as men's to be fatal, with 267,000 women dying each year from heart attacks. What may be surprising to many is that heart attacks kill six times as many women as breast cancer does.[6]

Myth: The symptoms of a heart attack are easy to detect.

Fact: In a 2005 survey, 92 percent of respondents recognized chest pain as a symptom of a heart attack. Yet, only 27 percent were aware of all the major symptoms.[1] Although it's common to have chest pain or discomfort, a heart attack may cause even subtle symptoms, including shortness of breath, nausea, feeling lightheaded, and pain or discomfort in one or both arms, the jaw, neck and back. In addition, leg pain felt in the muscles could be a sign of peripheral artery disease (PAD), which results from blocked arteries in the legs caused by plaque buildup. People with PAD have a fivefold increased risk of a heart attack.[5]

It's also common for people not to experience any symptoms of a heart attack. In fact, research suggests that 25 percent of heart attacks go unrecognized, and they are discovered only later when a routine ECG is performed. But, individuals shouldn't assume that with regular checkups, their doctor will order tests for heart disease. Simple heart tests, such as a CT scan that can detect plaque buildup in the arteries at an early, easily treatable stage, are not routinely recommended.[2]

Heart disease is the No. 1 killer in the world, causing more deaths than all forms of cancer combined.

Myth: The symptoms of a heart attack are the same in men and women.

Fact: While both men and women can experience the classic symptoms of a heart attack such as chest pain and cold sweat, women typically have subtler and less-recognizable symptoms such as abdominal pain, achiness in the jaw or back, nausea and shortness of breath. Half of women have no chest pain at all.[2] And two-thirds of deaths from heart attacks in women occur in those who have experienced no history of chest pain.[3]

A common symptom of a heart attack in women is unusual tiredness. Kathy Magliato of St. John's Health Center in Santa Monica, Calif., and author of *Heart Matters: A Memoir of a Female Heart Surgeon*, says that too often, women "blow off" their symptoms, mistaking them for indigestion or a sign of being out of shape. "The No. 1 way women present with heart disease is dead," she adds. "They don't come in with chest pain or fatigue. It's sudden cardiac death."[2]

Myth: It's OK to drive someone to the hospital while they are experiencing heart attack symptoms.

Fact: In that same 2005 survey mentioned earlier, those 27 percent of people who were unaware of all the major symptoms of a heart attack also didn't know to call 9-1-1 when experiencing symptoms.[1] It takes only four to six minutes after a cardiac arrest before a person experiences brain death and then complete death. Indeed, the survival rate outside a hospital is less than 1 percent to 2 percent.[3]

Myth: Heart disease is hereditary, so people whose parents don't have it won't get it either.

"The No. 1 way women present with heart disease is dead."

Fact: People can't change their genes. It's true that heart disease is genetic. A person with both a first-degree relative (a parent or sibling) and a second-degree relative (uncle or grandparent) who suffer from heart disease before age 60 is nearly 10 times more likely to suffer from heart disease early in life.[3] But that doesn't mean that risk can't be mitigated with a healthy lifestyle.

Myth: Heart disease can't be prevented.

Fact: Heart disease can be prevented. Most importantly, cholesterol and blood pressure need to be kept within the recommended levels. A healthy cholesterol level is lower than 200, and a normal blood pressure range is a diastolic reading of less than 80 and a systolic reading of less than 120. The American Heart Association recommends that individuals start getting their cholesterol checked at age 20. For those without heart disease, lowering cholesterol and blood pressure levels can reduce the risk from it developing. Lowering cholesterol and blood pressure levels also can have a positive effect on those who already have heart disease, including reducing the risk of dying from heart disease, having a nonfatal heart attack, and needing heart bypass surgery or angioplasty.[1]

The chances of developing heart disease also can be prevented by exercising regularly, maintaining a healthy weight and not smoking. In fact, 53 percent of U.S. adults between 2005 and 2008 who were inactive, 34 percent who were obese, 32 percent who had high blood pressure, 21 percent who smoked, 15 percent who had high cholesterol and 11 percent who had diabetes were at risk of developing heart disease.[1]

Myth: Diabetics who keep their blood sugar level in control aren't at increased risk of having a heart attack.

Fact: Even diabetics whose blood sugar levels are under control are at risk of heart disease. This is because diabetes causes inflammation that can damage blood vessels.[2]

Myth: Exercise is unsafe for people who have experienced a heart attack.

Fact: Heart attack survivors should exercise as soon as possible after an attack. Those who are regularly active and make other heart-healthy changes live longer than those who don't.[5]

Myth: Heart disease is curable with treatment.

Fact: There is no magic pill or procedure that will cure heart disease, but it is treatable. Treatments vary, from lifestyle changes to medication, surgery and other medical procedures. Whether mild or severe, lifestyle changes will be needed, including eating a low-fat and low-sodium diet, getting at least 30 minutes of moderate exercise on most days of the week, quitting smoking and limiting alcohol intake. If lifestyle changes aren't enough, doctors will prescribe medications such as diuretics, angiotensin-converting enzyme (ACE) inhibitors or beta blockers to lower blood pressure; daily aspirin therapy to thin the blood; and statins or fibrates to lower cholesterol.

Medical procedures or surgery also may be needed to clear blockages in the heart. A common procedure is angioplasty, which is performed by placing a catheter in an artery in the arm or groin, threading a small balloon to the blocked artery and inflating it to reopen the artery. During angioplasty, a small metal coil called a stent is often placed in the artery to help keep the artery open. If needed, coronary bypass surgery is performed, which involves using a vein from another part of the body (usually the leg) to bypass the blocked section of the artery.[7]

Dispelling the Myths Now

Today, more than 79,400,000 Americans have one or more forms of heart disease. Understanding the risks of developing this deadly disease and how to deal with it once it has developed can mean the difference between life and death. ❖

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Human Plasma Products: Two Decades of Unsurpassed Safety

Quality is never an accident; it is always the result of intelligent effort. — John Ruskin

By KEITH BERMAN, MPH, MBA

THANKS TO DONOR screening and blood testing, the risk of a potentially serious infection from transfused blood is lower today than it has ever been. Bacteria transmitted through platelet transfusions now account for the most meaningful risk; a non-negligible proportion of the approximately one in 3,000 contaminated units result in sepsis or death. At the other extreme, the theoretical risk of acquiring an HIV infection through blood transfusion is estimated at one in 1.5 million; the last reported case of HIV acquired from a blood transfusion was in 2008.[1] While the U.S. Centers for Disease Control and Prevention characterizes most of these risks as "rare," "extremely rare" or "extremely remote," the agency still cautions that "a wide variety of organisms, including bacteria, viruses, prions, and parasites, can be transmitted through blood transfusions."[2]

With this in mind, consider the safety record of human plasma derivatives — immunoglobulins, coagulation factor concentrates, albumin, fibrin sealants and others. Those familiar only with the fact that each of these is purified from many thousands of pooled units of donor plasma may be surprised to learn that we are fast approaching two decades without a single reported infection* transmitted to any U.S. patient through any licensed plasma-derived product.

The significance of this extraordinary safety record should particularly resonate with those who practiced in the 1970s.

*In 1995, a single production lot of a factor VIII concentrate was implicated in the infection of three hemophilia A patients (Morbidity and Mortality Weekly Report, 1996 Jan 19;45[2]:29-32). The FDA is not aware of a definitive cause of that contamination event (personal communication, R. Chapelle, FDA/CBER, Feb. 17, 2012).

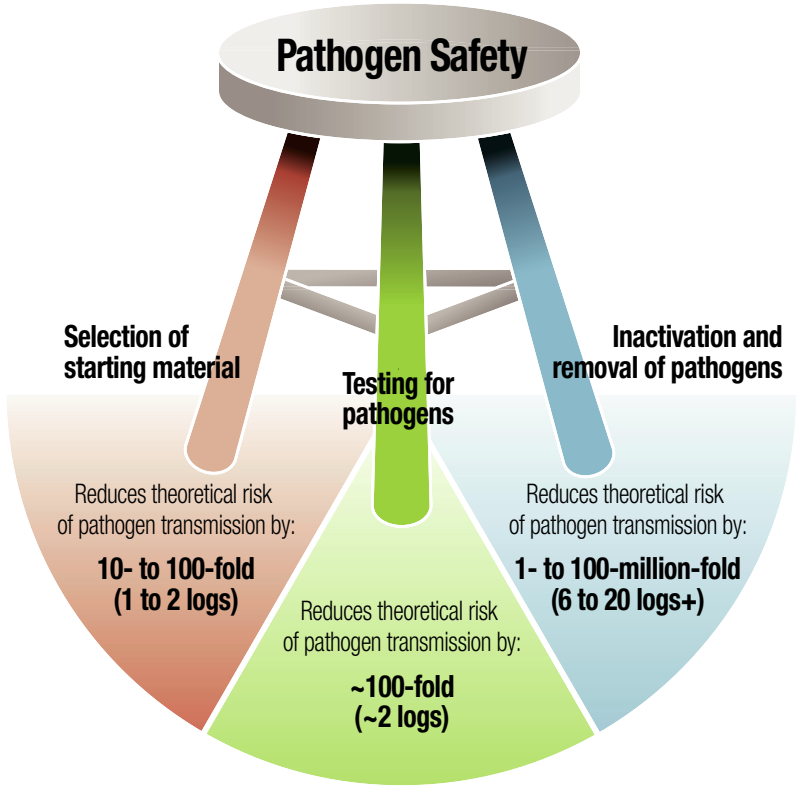
In those days, hepatitis B and C viruses would eventually infect most persons with severe hemophilia through contaminated factor VIII and IX concentrates. Then, in the early 1980s, HIV, a previously unknown lipid-enveloped virus, found its way into transfused patients through the blood supply and infected nearly half of all persons with severe hemophilia, again through contaminated factor concentrates.

How did the entire plasma products industry turn this grim situation around? How, since the early 1990s, has this industry supplied vast quantities of dozens of therapeutic proteins administered to millions of patients with a completely unblemished pathogen-related safety record?

The "Safety Tripod"

The answer lies in a continuing collaboration between industry and drug safety regulators to innovate, validate and, finally, incorporate measures that collectively have driven down pathogen contamination risks to extraordinarily low levels. Because they conveniently fall into three categories, these measures are known as the "safety tripod" (see Figure 1).

Figure 1: The Pathogen Safety Tripod



The three measures that collectively have driven down pathogen contamination risks to extraordinarily low levels are known as the "safety tripod."

Selection of starting material. Before plasma is accepted for further processing, the potential donor is subjected to a screening questionnaire to try to assure that he or she is in good health and to rule out personal or medical history associated with increased risk of exposure to one of the "big three" viruses (HIV or hepatitis B or C) or to the infectious prion thought to be responsible for about 200 cases of variant Creutzfeldt-Jakob disease (vCJD) in Europe.

Pathogen testing. Testing occurs in two successive stages (see Table 1). First, individual donor plasma units are screened for HIV and hepatitis B and C viruses using conventional viral antigen and antibody screening tests. Plasma units are then aggregated into mini-pools and tested again for the "big three" viruses, as well as the non-enveloped viruses hepatitis A and parvovirus B19, using nucleic acid amplification testing (NAT). NAT can detect exceedingly small numbers of viral particles in the rare event that a plasma unit that tested negative by serological tests was collected during the very brief "window period" following donor infection and prior to appearance of enough antiviral antibody or antigen load to be detected by routine serological tests.

Once each donor plasma unit is "released" by passing these screening tests, each plasma unit is pooled with thousands of other units into a single

production batch, which undergoes further processing into purified therapeutic proteins.

While donor selection and pathogen testing dramatically reduce the chance of a contaminated unit entering the plasma pool, just as importantly, these two steps act to assure that only a very minimal amount, or "load," of any pathogen might conceivably escape testing and end up in the plasma pool. Unlike blood and blood components intended for transfusion, the goal here of donor screening and plasma testing is not merely to mitigate infectious risks. These two legs of the safety tripod most importantly act to limit any potential pathogen load that slips through so that downstream inactivation and removal steps can readily and completely eliminate it.

Pathogen inactivation and removal. Over more than 60 years of widespread clinical use — including four decades prior to the availability of pathogen screening — human albumin has never transmitted hepatitis. Nor has a single case of HIV ever been associated with albumin administration, even in the early 1980s before HIV had even been identified.

Table 1. Plasma Screening Tests for HIV and Hepatitis Viruses

Each donor plasma unit	Plasma mini-pools prior to processing
Hepatitis B virus Hepatitis B surface antigen (HBsAg) Anti-hepatitis B core antigen (anti-HBc)*	Hepatitis B virus Hepatitis B virus DNA (NAT)†
Hepatitis C virus Anti-hepatitis C antibody	Hepatitis C virus Hepatitis C virus RNA (NAT)
Human immunodeficiency virus (HIV) Anti-HIV 1 and 2 antibody	Human immunodeficiency virus (HIV) HIV RNA (NAT)
	Parvovirus B19 B19 DNA (NAT)
	Hepatitis A virus Hepatitis A virus DNA (NAT)

* performed only on recovered plasma from whole blood donations
† nucleic acid amplification testing

plasma. Numerous subsequent studies confirmed that heat treatment of the final albumin solution bottles at 60 degrees Celcius for 10 hours — simple pasteurization — eliminated any risk of jaundice, later understood to be caused by hepatitis viruses.[3]

It was not until the early 1980s that scientists identified ways to stabilize factor VIII and factor IX concentrates so that heat treatment could similarly be employed to inactivate hepatitis viruses. Before the introduction of this first virus inactivation procedure in 1984, most persons with severe hemophilia eventually acquired hepatitis B and hepatitis C (then called "non-A, non-B hepatitis") through infusions of factor concentrates.

Most modern manufacturing processes incorporate two steps that are effective in reducing any potential lipid-enveloped virus load that might slip past donor selection and donation testing. The industry defines effectiveness as resulting in a minimum of four logs of viral reduction (i.e., at least a 10,000-fold reduction). Thus, two such steps together achieve at least a 100 million-fold viral reduction potential. It is this extraordinary designed-in margin of safety that ultimately accounts for plasma products' unblemished safety record with respect to HIV, hepatitis B and C and other lipid-enveloped viruses.[4]

These inactivation and removal steps (see Table 2) can vary for different products. Some of these, including pasteurization and affinity chromatography, effectively clear both lipid-enveloped and smaller non-enveloped viruses, while others better target one or the other. For all products, these as well as other steps throughout the protein purification process have been carefully validated to show how each contributes to getting the job done (see Figure 2).

Today, the manufacturing processes for every licensed therapeutic protein derived from human donor plasma

The reason for albumin's perfect pathogen safety record traces back to World War II.

The reason for this perfect pathogen safety record traces back to World War II, when stabilizers were added to albumin to improve the protein's physical integrity during military shipment to hot desert regions. It was soon recognized that albumin stabilization would allow the application of heat to inactivate infectious agents present in donor

Table 2. Common Means of Viral Clearance in Manufacture of Plasma Products

Inactivation
Solvent-detergent treatment
Pasteurization
Vapor heat treatment
Dry-heat treatment
Low pH incubation
Caprylate incubation
Removal
Nanofiltration (20 or 35 nm pore size)
Column chromatography methods
Caprylate precipitation/depth filtration
Cold ethanol fractionation

include definitive pathogen reduction steps that have all but eliminated every known threat to our blood supply. This is the leg of the safety tripod that is properly credited for the extraordinary safety record of plasma products over the last two decades.

But What About the Unknown Pathogen?

With the safeguards currently in place, the risk of being infected through a licensed plasma product by known blood-transmissible viruses now arguably compares favorably with the chance of being struck by lightning. But what happens when a virus or other type of "emerging pathogen" comes along that we don't yet know of, or for which we don't have a valid test to screen donors?

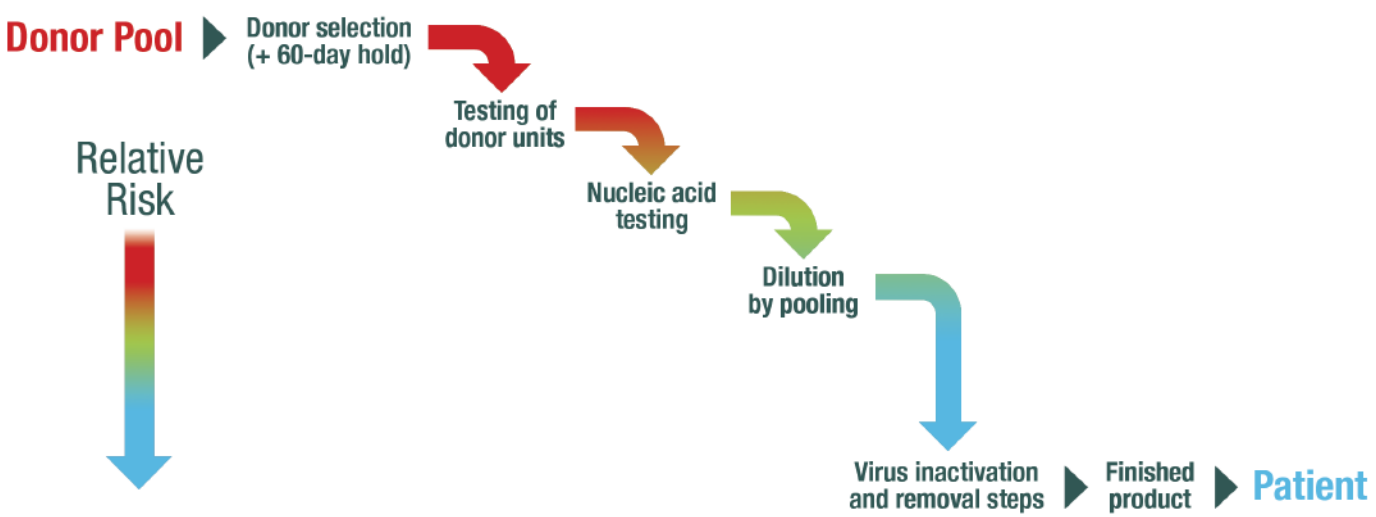
In fact, this important question has already been put to the test.

Endemic to Africa and the Middle East for decades before the initial U.S. outbreak in 1999, the lipid-enveloped West Nile virus (WNV) is an avian zoonosis transmitted to humans through a mosquito vector. Roughly one in every 140 infected people progresses to develop encephalitis, meningitis or acute flaccid paralysis. A handful of WNV infections through a blood transfusion have been reported, beginning in 2002 when 23 cases were confirmed in patients transfused with platelets, red blood cells or fresh frozen plasma from 16 viremic blood donors. While national blood donor screening was initiated in 2003, it has not eliminated the risk of WNV transmission through transfusions.[5]

Each year during its transmission season, thousands of Americans are infected with WNV. A few of these individuals might inadvertently donate plasma during the early viremic phase before they become symptomatic. But through testing and experience, we also know this: 1) WNV is efficiently inactivated by pasteurization, solvent-detergent treatment and other validated virus inactivation methods, and 2) in the 12 years since that first outbreak, no cases of WNV infection have been reported through administration of a plasma product.

For these two reasons, the U.S. Food and Drug Administration (FDA) exempts source plasma intended for fractionation from the WNV screening requirement that applies to transfused blood components, which cannot be similarly subjected to dedicated

Figure 2: Pathogen Safety Measures from Donor to Patient



Source: Adapted from information provided by the Plasma Protein Therapeutics Association (PPTA)

pathogen inactivation.

The confidence of the FDA in this principle of preemptive pathogen reduction to eliminate WNV is supported by the lack of a single reported infection after more than a decade and millions of doses of plasma products.

Preemptive Pathogen Reduction: Powerful Protection

For a second equally compelling example of the preemptive pathogen reduction principle, consider the prion responsible for vCJD, a uniformly fatal neurodegenerative disease first identified in the United Kingdom in 1996 and contracted directly through consumption of cattle sick with bovine spongiform encephalopathy. Epidemiologists have concluded that three of the 217 cases of vCJD reported worldwide were linked to blood transfusion from an infected donor.[6] To this day, there is no mass screening test available for blood or plasma donors, yet not a single case of vCJD has ever been traced to administration of a U.S.-licensed human plasma product.

filtration and affinity chromatography, for example — each contribute to prion clearance and reduction in infectivity.[7,8,9] Similar studies are conducted with both enveloped and non-enveloped viruses.

It is uncertain whether the infectious prion responsible for vCJD has ever found its way into a plasma pool sent for fractionation. All we know is that, consistent with the prion study findings, there has never been a single documented instance of the transmission of either vCJD or classical CJD by any therapeutic human plasma-based product.

The capability of preemptive pathogen reduction built into each plasma product manufacturing process will undoubtedly be challenged again by future emerging pathogens. But with the combination of this proven, robust preemptive pathogen reduction and constant vigilance by industry and drug regulators, it's safe to say that plasma products can be prescribed with more confidence than ever. ❖

With the safeguards currently in place, the risk of being infected through a licensed plasma product by known blood-transmissible viruses now arguably compares favorably with the chance of being struck by lightning.

Manufacturer-conducted studies in which prion-infected material was spiked into various process intermediates have documented how individual protein purification steps — precipitation,

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

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- 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.

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- 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.

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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.

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"Producing efficacious plasma therapies makes a significant difference in our patients' quality of life. That's what motivates me and makes me feel good about what we do every day. It's an honor to be in this profession." — Gregory Rich, president and CEO of Grifols North America

BY TRUDIE MITSCHANG

GREGORY RICH has long maintained a collaborative leadership style that invites input from colleagues throughout the organization he leads. This "open-door policy" has served him well during his nearly decade-long tenure as president and CEO of Grifols North American operations. It also positioned him as the perfect person to lead the corporate transition following the company's acquisition of Talecris Biotherapeutics last June. "Once the transition teams were in place, we recognized there was tremendous potential to grow and learn from one another as we pursued our goal of creating a unified team, while building on the successes we achieved as separate companies," he says. "Our goal, then and now, is to build on the exceptional customer service and quality operations that our patients and customers have come to expect from both Grifols and Talecris. This is a very exciting time for us."

The company's new commercial operations have been divided into three divisions: immunology, hematology and pulmonology. According to Grifols S.A. President Victor Grifols, the union of the two biopharmaceutical leaders served to strengthen Grifols' commitment to providing life-saving therapies to patients with rare, chronic diseases. By all accounts, the move has created a significantly expanded global footprint for Grifols that will ultimately increase the quantity of products and choices available to the patients who need them.

With a global presence in more than 90 countries, Grifols had long established itself as a standard-bearer within the plasma therapies industry.

With a global presence in more than 90 countries, Grifols had long established itself as a standard-bearer within the plasma therapies industry. Since the Talecris acquisition, Grifols has become the world's third-largest producer of plasma protein therapies; the combined 2010 U.S. sales for both companies were more than €2.3 billion or approximately $3.1 billion. "We bring a 70-year history, a pioneering spirit, a wealth of knowledge, and tried-and-true commitment to the community now as a larger company that will meet a broader range of patient needs," says Rich. "The patient community can take comfort in the fact that Grifols is a company that has been around a long time, and they can now count on us establishing an even stronger presence in the U.S."

A Patient-First Philosophy

Rich has more than 30 years of experience in the plasma industry associated with Grifols; since his appointment as CEO in 2003, he and his team have been

instrumental in driving the company's profitability in the U.S. Under his leadership, Grifols has grown and expanded without losing sight of its mission to meet the unique needs of chronically ill patients. One of the distinctive ways Grifols demonstrates that commitment is through a variety of patient assistance programs, including temporary assistance to patients in emergent financial need, patients without insurance coverage and those seeking coverage, and patients struggling to meet co-pay requirements. "Many of the patients who use our products face problems in obtaining and maintaining adequate health insurance," says Rich. "The many avenues Grifols offers for obtaining patient assistance demonstrates our ever-growing commitment to helping those in need." Patients living with various disease states, including hemophilia, primary immune deficiency disease (PIDD) and Alpha-1 lung disease, are among those who can benefit from Grifols' programs.

When asked to gaze into the proverbial corporate crystal ball, Rich says Grifols plans to continue investing in the future to meet the needs of patients in the U.S. and worldwide.

An Eye on Expansion

A few years ago, Grifols began construction on a state-of-the-art intravenous immune globulin (IVIG) facility in Los Angeles, which it expects to be fully operational by 2013. The facility is currently undergoing the required industrial validation process, and represents a $55 million investment that will substantially increase the company's manufacturing capacity for its IVIG products. "The new facility will further position Grifols as a proactive source of health innovation along with its corporate traits of persistent growth, partnership, character and cultural diversity," Rich says.

The Los Angeles facility will utilize the same proprietary technologies and process flow designs employed at the company's existing IVIG production facility in Barcelona, Spain. It will serve as a twin of that pioneering facility, which the U.S. Food and Drug Administration licensed in 2007. A key component of Grifols' multiyear global growth plan to meet demand for plasma therapies, the new Los Angeles facility will follow the recent securing of FDA approval of the company's state-of-the-art bulk processing and aseptic filling facility in the same city.

When it comes to promoting safety within the company and the industry, Grifols prioritizes education and training for its employees. Grifols formed the Academy of Plasmapheresis in Glendale, Ariz., — a combination state-of-the-art donor center and training facility — as part of its long history of continuous improvement and commitment to education. "We utilize this facility to train our plasma operations employees throughout the U.S.; last year, we trained over 550 employees in that facility," Rich says. "We acquired the facility with the building next door to have an opportunity to expand the Academy when needed, and now with the acquisition complete, we have substantially increased our donor staff and training needs."

When asked to gaze into the proverbial corporate crystal ball, Rich says Grifols plans to continue investing in the future to meet the needs of patients in the U.S. and worldwide. "We've been around for 70 years, and we plan to be here for succeeding generations for another 70 — and 70 beyond that."

Like many who work in industries that supply life-sustaining products to the chronically ill, Rich continually gains perspective and inspiration from interacting with those on the receiving end of the company's multifaceted global operations: "I've been in this industry a long time, and I've had [the] opportunity to attend international conferences and meet with patients around the world. Doing so has helped me see firsthand that producing efficacious plasma therapies makes a significant difference in the quality of life of our patients. That's what motivates me and makes me feel good about what we do every day. ❖

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

Life Interrupted

High school athlete Jessica Hayes was healthy, active and had no family history of blood disorders. Her sudden-onset diagnosis of acquired hemophilia demonstrates the unpredictable nature of this rare and often life-threatening disease.

by TRUDIE MITSCHANG

Jessica Hayes, a senior in high school and captain of the basketball team, was in the middle of an intense practice session when she experienced her first symptoms of sudden-onset acquired hemophilia.

HEMOPHILIA IS A blood disorder that is passed down genetically and is frequently diagnosed at birth. In extremely rare cases, hemophilia can be acquired later in life, with symptoms that sneak up suddenly and that are often difficult to diagnose. This type of hemophilia is known as acquired hemophilia (AH), and it is believed to occur in up to one case per million persons per year. However, given the likelihood of misdiagnosis, that figure could be underestimated. In patients with AH, the body starts producing antibodies that fight its own blood-clotting proteins. AH also is characterized by sudden bleeding in patients without a previous personal or family history of hemophilia. Although many AH patients are older, with the greatest number of incidences occurring between 60 and 80 years of age, the disease can strike young adults and even teens.[1] Just ask Jessica Hayes.

A Difficult Diagnosis

An active and athletic high school senior, Jessica was captain of her basketball team and in the middle of intense practice sessions for the upcoming tournament season when symptoms of AH first appeared. Jessica remembers coming home from practice and noticing an unusual number of bruises peppering her shins. Since her chosen sport involves frequent contact with other players, the bruises were not cause for immediate alarm. But when they persisted, eventually worsening into raised, painful lumps, Jessica's mother insisted she see a doctor.

"During that first round of doctor visits, they ran blood tests for anemia. When everything came back negative, we were told it was probably just a bad case of muscle fatigue," recalls Jessica. "At the doctor's advice, I ignored the symptoms and continued to play basketball. At one point, I got hit in the knee with the ball and developed a lump so huge and painful I asked for a prescription pain medication. That's when my mom really stepped in as my advocate; after multiple trips to the ER and a still undiagnosed bleed in my thigh, she demanded a consultation with a doctor from Children's Hospital Orange County (CHOC)."

After seeing a specialist at CHOC, Jessica was admitted into the hospital, eventually meeting with a hematologist and pulmonologist. Following a battery of additional tests, Jessica was finally diagnosed with AH. The diagnosis was just the beginning of a frightening three-week hospital stay and a future prognosis that would put an end to the athletic aspirations of this active and ambitious teen; AH patients are strongly advised to avoid activities that risk injury or trauma to the body.

"After my diagnosis, I was admitted to the cancer wing and I remember being really frightened," Jessica says. "This disease was so rare and we were trying to learn as much as we could, but the first few days were dreadful — doctors kept trying different medications to see which ones worked best. My vitals had to be checked every four hours, giving me no time to sleep. Plus, I felt like I had literally been yanked right out of my life — basketball and my friends were my

Fortunately for Jessica, her diagnosis at CHOC allowed her to quickly receive the knowledgeable care she needed.

Symptoms of AH

Because of its rarity, acquired hemophilia (AH) is frequently misdiagnosed, resulting in unnecessarily high mortality rates. The most common symptoms are

- bleeding into the skin
- bleeding into soft tissues
- bleeding inside the body, in tissues or organs
- bleeding following surgery
- bleeding after childbirth

AH is diagnosed with laboratory tests that measure clotting time of blood and Factor VIII levels.

life, and within the blink of an eye, everything I loved was gone."

Almost all known cases of AH are characterized by autoantibodies that either disrupt the functioning of coagulation factor VIII or that clear this clotting factor from the plasma, resulting in unpreventable bleeding. Doctors suspect a bout with strep throat may have been the catalyst that triggered the antibodies in Jessica's body to go haywire. Her lumpy bruises and accompanying pain were the result of bleeding into the skin and musculature. In her case, testing was done to measure the levels of clotting factors VIII, IX, XI and XII. Test results determined Jessica's factor VIII levels were below 1 percent at the time of her diagnosis.

Devising a Treatment Plan

Treating AH has a twofold objective, the first being to control the affected bleeding areas, and the second to remove the inhibitor causing the disorder.[2] Because of the rarity of the disease, patients diagnosed with AH are encouraged to seek care from specialized hemostasis units with experience treating AH. Fortunately for Jessica, her diagnosis at CHOC allowed her to quickly receive the knowledgeable care she needed; CHOC employs pediatric subspecialty faculty skilled in providing comprehensive, multidisciplinary evaluation and treatment for hematologic diseases.

In Jessica's case, she was put on a twice-daily regimen of NovoSeven, an FDA-approved bypassing agent for the treatment of AH manufactured by Novo Nordisk, in addition to a twice-daily regimen of steroids. She responded well, and she was discharged with a peripherally inserted central catheter (PICC) line in her arm, with instructions to continue her treatment plan at home. Unfortunately, Jessica's PICC line became infected after only three days of home infusions, sending her back to the hospital. "I was still holding out hope that I would be well in time for softball season," Jessica recalls. "After that second infection, I knew that would not be an option."

Jessica's downtime in the hospital afforded her ample time to peruse college applications and possible scholarship opportunities; as an AH patient, she was now a candidate for several educational grants. Jessica was fortunate. An essay she penned about her experience with AH diagnosis and treatment garnered her two $2,500 academic scholarships. SevenSECURE, a program of Novo Nordisk, awards the Professor Ulla Hedner Scholarship to high school seniors and college or vocational students to help pay for tuition or school expenses.

"Being hospitalized allowed me to understand the concept of dedication and commitment in a new sense that most of my peers could not fully grasp," says Jessica. "It taught me that if you are going to put your time into something, you better give it your all. There is no promise or guarantee that whatever it is you are working on, whether it [is] learning to do something new or getting a college degree, will still be waiting for you tomorrow."

Optimistic About the Future

Jessica did not fit the typical AH patient profile in many ways. Statistically, AH patients tend to be elderly with other underlying health complications such as heart disease, hypertension or diabetes. Of those patients, 20 percent tend to suffer a relapse of AH between one week to 14 months following immunosuppressive therapy. But of those who relapse, 70 percent achieve another remission following a second round of therapy.[1] To date, the odds have been in Jessica's favor. Diagnosed two years ago, she is now a business administration major at San Diego State University, where she remains symptom-free, at least for the time being.

"Life is a series of unexpected events that are going to challenge you, your character and your skills, and how you respond to them ultimately determines your success," says Jessica. "The events I experienced in my life were and still are an uphill battle, but I am determined to not let them alter my potential accomplishments in life." ❖

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

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BioResearch

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Over Half of U.S. Hemophilia Treatment Centers Do Not Follow NHF Guidelines for Factor VIII Prophylaxis in Severe Hemophilia A

Factor VIII prophylaxis every other day (qod) or three times weekly is recommended by the National Hemophilia Foundation to prevent joint bleeds in children with severe hemophilia A. An email survey of U.S. hemophilia treatment centers (HTCs) was conducted to help define actual current prophylaxis practices.

Of 62 HTCs that responded, prophylaxis is initiated on a three times weekly schedule in 29 HTCs (46.8 percent), twice weekly in 13 HTCs, and once weekly in 20 HTCs (32 percent). Central venous catheters are used to infuse factor prophylactically at 55 HTCs (89 percent). In 19 of the 62 responding HTCs (31 percent), central venous catheters are used in 100 percent of children initiating prophylaxis, while they are avoided altogether at seven other HTCs (11 percent).

Prophylaxis is initiated in 56 of the 62 responding HTCs (90 percent) after one or more bleeds, but after the first bleed in only 28 HTCs (25 percent). Despite a recommended standard of three times weekly prophylaxis, more than half of surveyed HTCs do not follow these guidelines, and nearly one-third initiate prophylaxis on a once weekly schedule to delay or avoid the need for central venous access.

Ragni, MV, Fogarty, PJ, Josephson, NC, et al. Survey of current prophylaxis practices and bleeding characteristics of children with severe haemophilia A in U.S. haemophilia treatment centres. Haemophilia, *2012 Jan;18(1):63-8.*

Inhibitors Don't Differ for Previously Untreated Patients Given Plasma-Derived and Recombinant Factor VIII: Systematic Review

A number of studies have examined the impact of plasma-derived or recombinant factor VIII (FVIII) replacement therapy on inhibitor antibody development in hemophilia A patients, with conflicting results. In order to shed light on this controversial issue, Italian investigators at the University Hospital of Parma performed a systematic review and meta-analysis of published prospective studies evaluating the incidence rate of inhibitors in previously untreated patients (PUPs) with severe hemophilia A.

Data from a total of 800 patients enrolled in 25 prospective studies published between 1990 and 2007 were included in this review, which incorporated selective criteria for assessment of study quality. Overall, the inhibitor incidence rate did not differ significantly between recipients of plasma-derived and recombinant FVIII concentrates (respective weighted means: 21 percent; 95% confidence interval [CI], 14-30 versus 27 percent; 95% CI, 21-33). Similarly, high-titer inhibitors did not differ significantly between patients treated with plasma-derived (weighted means: 14 percent; 95% CI, 8-25) or recombinant FVIII concentrates (weighted means: 16 percent; 95% CI, 13-20).

The main conclusion of this systematic review is that administration of a plasma-derived or recombinant FVIII product does not appear to influence the inhibitor rate in PUPs with severe hemophilia A.

Franchini, M, Tagliaferri, A, Mengoli, C, et al. Cumulative inhibitor incidence in previously untreated patients with severe hemophilia A treated with plasma-derived versus recombinant factor VIII concentrates: A critical systematic review. Critical Reviews in Oncology/Hematology, *2012 Jan;81(1):82-93.*

Trend Toward Better Responses in Subarachnoid Hemorrhage Patients Treated with 25% Human Albumin: Pilot Study

Human albumin is known to exert a neuroprotective effect in animal models of cerebral ischemia and humans with various intracranial pathologies. Encouraged by those findings, researchers at five U.S. and Canadian centers investigated the safety and tolerability of 25% human albumin in patients with subarachnoid hemorrhage (SAH), with the goal of providing necessary information for a future definitive efficacy trial in SAH. The "Albumin in Subarachnoid Hemorrhage" (ALISAH) Pilot Clinical open-label, dose-escalation study evaluated four daily dosage tiers: 0.625 g/kg (tier 1), 1.25 g/kg (tier 2), 1.875 g/kg (tier 3) and 2.5 g/kg (tier 4). The maximum tolerated dose of albumin was based on the rate of severe heart failure and anaphylactic reaction, as well as functional outcome at three months. Treatment was administered daily for seven days.

A total of 47 adult subjects were enrolled: 20 in tier 1, 20 in tier 2 and seven in tier 3. No patients were enrolled in tier 4. Doses ranging up to 1.25 g/kg/day were tolerated by patients without major dose-limiting complications. Clinical outcomes trended toward better responses in subjects enrolled in tier 2 (1.25 g/kg) compared with tier 1 (odds ratio [OR], 3.0513; 95% confidence interval [CI], 0.6586-14,1367), and compared with the International Intraoperative Hypothermia for Aneurysm Surgery Trial cohort (OR, 3.1462; CI, 0.9158-10.8089).

The investigators concluded that albumin in doses ranging up to 1.25 g/kg/day for seven days was tolerated by patients with SAH without major complications and may be neuroprotective. Based on these results, planning of a Phase III, randomized, placebo-controlled trial (ALISAH II) to test the efficacy of albumin is under way, with sponsorship from the National Institute of Neurological Disorders and Stroke.

Suarez, JI, Martin, RH, Calvillo, E, et al. The Albumin in Subarachnoid Hemorrhage (ALISAH) multicenter pilot clinical trial: Safety and neurologic outcomes. Stroke, *2012 Jan 19 [Epub ahead of print].*

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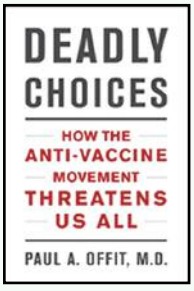

Deadly Choices: How the Anti-Vaccine Movement Threatens Us All

Author: Paul A. Offit

How anyone came to view vaccines with horror is rooted in one of the most powerful citizen activist movements in U.S. history. It has created a silent, dangerous war in which on one side are parents, bombarded with stories about the dangers of vaccines, now wary of immunizing their sons and daughters, and on the other side are doctors, scared to send kids out of their offices vulnerable to illnesses like whooping cough and measles — the diseases of their grandparents. In *Deadly Choices*, infectious disease expert Paul Offit relates the shocking story of anti-vaccine America — its origins, leaders, influences and impact. Providing a vigorous and definitive rebuttal of the powerful anti-vaccine movement, the book offers strategies to keep us from returning to an era when children routinely died from infections.

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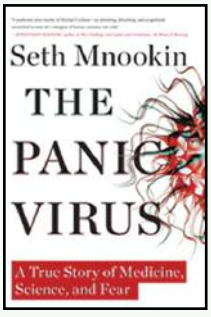
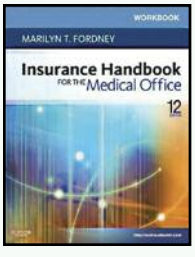


The Panic Virus: A True Story of Medicine, Science, and Fear

Author: Seth Mnookin

In *The Panic Virus*, Seth Mnookin draws on interviews with parents, public health advocates, scientists and anti-vaccine activists to tackle a fundamental question: How do we decide what the truth is? The fascinating answer helps explain everything from the persistence of conspiracy theories about 9/11 to the appeal of talk-show hosts who demand that President Obama "prove" he was born in America.

books.simonandschuster.com/Panic-Virus/Seth-Mnookin/9781439158647



Insurance Handbook for the Medical Office, 12th ed.

Author: Marilyn Takahashi Fordney

This book gives physician office personnel real-life practice in insurance billing and coding. Corresponding to the chapters in Fordney's Insurance Handbook for the Medical Office, 12th edition, this workbook provides realistic, hands-on exercises that help apply concepts and develop important critical-thinking skills. Study tools include chapter overviews, key terms, chapter review exercises, and workbook assignments. A companion Evolve website includes patient simulations for additional practice in real-world billing.

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FDAnews Guide to International Pharma Regulation: 2012 ed.

Author: U.S. Food and Drug Administration

This book is the one-stop authority for quick, accurate answers to emerging changes in inspection practices, changes to quality manufacturing requirements, developing biosimilars approvals pathways, new labeling and marketing regulations, changing product registration requirements, pricing and reimbursement debates, anti-counterfeiting measures, and dozens more key topics in drug regulation worldwide.

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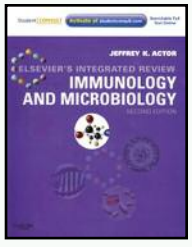

Elsevier's Integrated Review Immunology and Microbiology

Author: Jeffrey K. Actor, PhD

This book merges basic science and clinical skills. It is a title in the popular Integrated Review Series focusing on the core knowledge in immunology and microbiology, while linking that information to related concepts from other basic science disciplines. Case-based questions at the end of each chapter enable readers to gauge their mastery of the material, and a color-coded format allows them to quickly find the specific guidance they need. Online access via www.studentconsult.com — included with the book's purchase — allows readers to conveniently access the book's complete text and illustrations online, as well as relevant content from other Student Consult titles. This concise and user-friendly reference provides crucial guidance for the early years of medical training and United States Medical Licensing Examination preparation.

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BioDashboard

CALCULATOR

IVIG Reimbursement Calculator

Medicare Reimbursement Rates
Rates are effective April 1, 2012 though June 30, 2012.

Product	Manufacturer	HCPCS	Hospital Outpatient ASP+4% (per gram)	Physician Office ASP+6% (per gram)
CARIMUNE NF	CSL Behring	J1566	$61.83	$63.02
FLEBOGAMMA 5% & 10% DIF	Grifols	J1572	$69.86*	$69.86
GAMMAGARD LIQUID	Baxter BioScience	J1569	$78.89	$80.41
GAMMAGARD S/D	Baxter BioScience	J1566	$61.83	$63.02
GAMMAKED	Kedrion	J1561	$73.79	$75.21
GAMMAPLEX	Bio Products Laboratory	J1557	$74.59*	$74.59
GAMUNEX-C	Grifols	J1561	$73.79	$75.21
OCTAGAM	Octapharma	J1568	$67.97	$69.28
PRIVIGEN	CSL Behring	J1459	$68.75	$70.08

*ASP + 6% (pass-through drug)

Calculate your reimbursement online at www.FFFenterprises.com.

REFERENCE TABLES

IVIG/SCIG Reference Table

Product	Indications	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/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
PIDD Primary immune deficiency disease

2012-2013 Influenza Vaccine

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

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

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GAMUNEX®-C

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2003

WARNING: ACUTE RENAL DYSFUNCTION and FAILURE

See full prescribing information for complete boxed warning.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Talecris BIOTHERAPEUTICS

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

08939771/08939782-BS
Revised: October 2010

The PROOF is everywhere you look

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

Important Safety Information for GAMUNEX-C

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

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

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

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

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

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

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

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

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

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

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

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

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

Reference: 1. Data on file, Grifols.

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

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

gamunex®-C

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