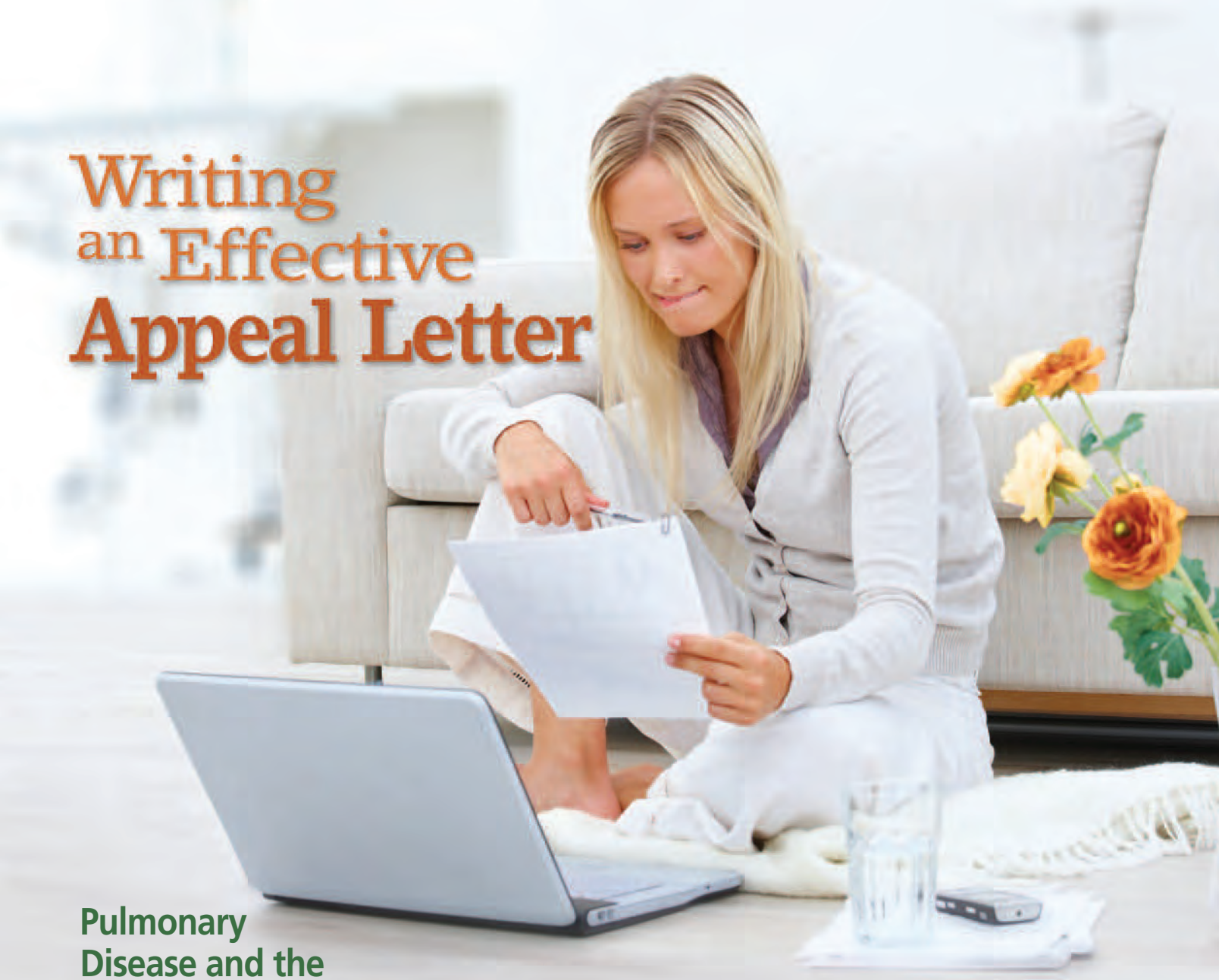
I.G. LIVING!
IMMUNE GLOBULIN COMMUNITY
www.IGLiving.com
December-January 2011



Writing an Effective Appeal Letter

Pulmonary Disease and the Immune Connection

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The Evolution of an Improved Antibody

Employment Rights: Reasonable Accommodations

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The PROOF is everywhere you look

GAMUNEX is the IGIV therapy supported by robust clinical trials

- Proven efficacy in more FDA-approved indications (CIDP, PI, and ITP)* than any other liquid IGIV[1]

Important Safety Information for GAMUNEX

Gamunex, Immune Globulin Intravenous (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).

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis and death. Patients predisposed to acute renal failure include patients with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentration available and the minimum rate of infusion practicable. While these reports of renal dysfunction and acute renal failure have been associated with the use of many of the licensed IGIV products, those containing sucrose as a stabilizer accounted for a disproportionate share of the total number. Gamunex does not contain sucrose. Glycine, a natural amino acid, is used as a stabilizer.

Gamunex 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.

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

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, and/or known or suspected hyperviscosity. Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIV therapy.

Gamunex 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.

In clinical studies, the most common adverse reactions with Gamunex were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection site reaction, nausea, pharyngitis, and urticaria (in PI); and headache, vomiting, fever, nausea, back pain, and rash (in ITP). The most serious adverse reactions 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. Talecris Biotherapeutics, Inc.

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 full Prescribing Information.

Evidence based. Patient proven.

gamunex®
immune globulin intravenous (human), 10% caprylate/chromatography purified

Talecris BIOTHERAPEUTICS

To get GAMUNEX call 1-888-MY-GAMUNEX (694-2686) USA Customer Service 1-800-243-4153 Clinical Communications 1-800-520-2807 Reimbursement *Help*line 1-877-827-3462

gamunex®

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

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GAMUNEX®, Immune Globulin Intravenous (Human), 10% Caprylate/Chromatography Purified, safely and effectively. See full prescribing information for GAMUNEX.

GAMUNEX (Immune Globulin Intravenous [Human], 10% Caprylate/Chromatography Purified) 10% Liquid Preparation

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 be associated with 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. GAMUNEX does not contain sucrose.**
- **Administer IGIV products at the minimum concentration available and the minimum infusion rate practicable.**

INDICATIONS AND USAGE

GAMUNEX is an immune globulin intravenous (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. Epinephrine should be 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.
- 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 GAMUNEX and other IGIV treatments, especially with high doses or rapid infusion.
- Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration.
- IGIV recipients should be monitored for pulmonary adverse reactions (TRALI).
- The product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

ADVERSE REACTIONS

- **PI** – Most common drug related adverse reactions during clinical trials were headache and cough.
- **ITP** – Most common drug related adverse reactions during clinical trials were headache, vomiting, fever, and nausea.
- **CIDP** – Most common drug related adverse reactions during clinical trials were headache and fever.

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

USE IN SPECIFIC POPULATIONS

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

Talecris BIOTHERAPEUTICS

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

08939392/08939393-BS
Revised: October 2008

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About *IG Living*

IG Living is the only magazine dedicated to bringing comprehensive healthcare information, immune globulin information, community and reimbursement news, and resources for successful living directly to immune globulin consumers and their healthcare providers.

IG Living, (ISSN 1949-4548), published bimonthly, is a community service provided by FFF Enterprises, 41093 County Center Drive, Temecula, CA 92591, (800) 843-7477 x1362, fax (951) 699-9655.

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All manuscripts should be submitted in MS Word, in Arial font. Manuscripts should be between 650 and 1,300 words in length, with unjustified margins and without any other formatting. Submission guidelines are available for download from the Contact Us page on www.IGLiving.com. Email manuscripts to editor@IGLiving.com. *IG Living* retains the right to edit submissions. The contents of each submission and their accuracy are the responsibility of the author(s) and must be original work that has not been, nor will be, published elsewhere, without the written permission of *IG Living*. A copyright agreement attesting to this and transferring copyright to FFF Enterprises will be required. Acceptance of advertising for products and services in *IG Living* in no way constitutes endorsement by FFF Enterprises.

Advertising in *IG Living*

IG Living Magazine is read by 30,000 subscribers who are patients who depend upon immune globulin products and their healthcare providers. For information about advertising in *IG Living*, download a media kit at www.igliving.com/Advertise.aspx. Or contact Cheryl Brooks at (800) 843-7477 x1177 or cbrooks@fffenterprises.com.

MATTHEW DAVID HANSEN, DPT, MPT, BSPTS
Physical Therapist and President, Allied Healthcare Staffing and Consulting Agency

Exercise for Arthralgia

"The reason individuals with autoimmune diseases experience inflammatory arthralgia is because their body doesn't respond normally to infection."

MARK T. HAGGARD
High School Teacher, Football Coach and Parent of PIDD Children

Reasonable Accommodations

"The bulk of chronically ill patients' rights rests on two pieces of legislation: the American with Disabilities Act (ADA) and the Family and Medical Leave Act (FMLA)."

TERRY O. HARVILLE, MD, PHD
Consultant and Medical Director, Special Immunology Laboratory, University of Arkansas for Medical Sciences

The Evolution of an Improved Antibody

"The process of generating a higher affinity or better antibody is known as "somatic mutation" (sometimes called "somatic hypermutation")."

JENNIFER KESTER
Health and Lifestyle Writer

The Connection Between Pulmonary Disease and Immune-Mediated Illness

"Even after a diagnosis, some PIDD patients continue to see a pulmonologist because of frequent pulmonary infections, as well as complications associated with the lungs."

KRIS MCFALLS
Patient Advocate, IG Living *magazine*

How to Write an Effective Appeal Letter

"The appeal should be packaged so that the insurer will be left with no questions and little chance but to grant the appeal and cover the treatment needed."

On- and Off-Label Uses and Clinical Trials of IG

"Many studies are currently being conducted to look at the efficacy of IG in non-FDA-approved indications."

Be a Part of *IG Living*'s Blog and Facebook Discussions!

IG Living isn't just a magazine; it's an interactive community of people with interesting stories.

Our blog: www.igliving.com/blogengine

Our Facebook page: www.Facebook.com/IGLivingMagazine

Connect with Other *IG Living* Readers through Monthly Teleforums!

IGL's Readers Group Teleforums allow readers to connect with others to share their experiences living with chronic diseases. Here's how you can participate:

- Email *IG Living* to be added to our email invitation list for the teleforums.
- *IG Living* will send you invitations to let you know when the two-per-month, hosted, toll-free teleforums will be held, as well as what topic relevant to the IG community will be discussed.
- The moderated, hour-long calls will be filled on a first-come, first-served basis and will be limited to 15 readers.

In addition to connecting with others, *IG Living's* patient advocate can help you determine if there's a patient organization support group in your area. Or, she can help you to start an IGL Readers Group of your own. To join a group or start one in your area, visit www.IGLiving.com and click on IGL Readers Groups.

Sign up for the Teleforums now by emailing **kmcfalls@IGLiving.com** or calling **(888) 433-3888, ext. 1349.**

I.G. LIVING!
IMMUNE GLOBULIN COMMUNITY

Our mission is to support the IG community through education, communication and advocacy

A community service from
FFF Enterprises, Inc.

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Temecula, CA 92591
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Editorial

Life's Unexpected Events

Sometimes, life doesn't always go as planned. That's what Stacy Henderson found out when her son, Andy Lutzenhiser, passed away in July, just months shy of their highly anticipated trip to California for the Disneyland Half Marathon Weekend. As part of the A-T Cure Team, Andy had been raising funds around the event to find a cure for ataxia telangiectasia (A-T), a disease he suffered from and then succumbed to at age 25. According to Stacy, this was the first of many of Andy's fundraising trips that she was going to attend with him. Instead, she joined the many other A-T Cure Team families supporting and running for the cause.

Stacy Henderson and her son, Taylor, supported the A-T Cure Team's fundraising efforts at the Disneyland Half Marathon Weekend, which raised $62,000 to find a cure for A-T. They are pictured with a poster of Andy and Cassy, Stacy's children who suffered from and succumbed to the disease.

However unexpected the trip was without Andy, his and others' efforts raised $62,000 at the event. "It was nice to meet the families and see what Andy and my daughter, Cassy, had worked so hard for for so many years," says Stacy. Cassy also suffered from A-T and passed away at age 21 in 2005.

Disease has a knack for throwing unexpected events our way. Some of these events are physical, life-threatening challenges, as in the case of Andy and Cassy and others affected by immune diseases; others' hurdles are sources of fear and frustration. In this issue, we take a look at both. One fearsome physical challenge that affects many with primary immune deficiencies is pulmonary disease. This disease is often hard to diagnose, but when it is, it is easily managed and treated. As antidote to some common frustrations, we also provide some in-depth advice about how to appeal an insurance claim denial. And, we discuss how patients can protect themselves when being denied employment.

All of the unexpected events we discuss in this issue are a cause of one thing: immune disease. And, it is only through the efforts of people like Andy and Cassy who get involved to find treatments and cures that we can hope to turn the tide on the unexpected.

Everyone can get involved. In this month's product directory, we highlight several organizations that need donations and volunteers to help support their cause. It is, after all, the season for giving. ◪

To your health,

Ronale Tucker Rhodes

Ronale Tucker Rhodes, MS, Editor

Faces of IG Living

There are many faces in the IG Living community, representing hundreds of immune-mediated diseases and countless medical and lifestyle issues. IG Living*'s magazine, website, Facebook page and blog are the ways in which our community can connect with one another. Be a part of the community by interacting with us. Your comments could lead you to others who share similar issues, and vice versa. Monday through Friday, we pose a new question on the* IG Living *Facebook page. Here is what some of our faces of IG Living are saying in response.*

IG Living

How long did you have symptoms before you were diagnosed? What was the key to getting a diagnosis?

Dale Manning Cook

It was 10 years before I was diagnosed. I was on antibiotics for sinus infections all the time and twice had pneumonia. My doctor sent me to be tested for allergies and I didn't have any allergies, so the allergist/immunologist ran blood work and that is when I was diagnosed. I also have low IgA and IgM.

Laura Guenther

I had symptoms since birth but wasn't diagnosed until my early teens. [The] doctors thought it was just very strange "severe, intractable asthma," with chronic lung and GI infections, "allergies," inflammatory bowel disease, etc. No one put it all together, but eventually I was diagnosed with almost no IgG and undetectable levels of IgM and IgA! I hope that with more awareness, physicians can start recognizing the signs earlier so that people can start treatment early and potentially prevent some of the complications due to repeated infections.

Shelli O'Donnell:

Does anyone know how many pints of plasma it takes for an infusion (say 40 grams)? Where are the plasma centers they get the plasma from? In the United States or out of the country?

IG Living

All plasma used for manufacturing immune globulin for U.S. patients is collected in the U.S. In fact, nearly 50 percent of the world's plasma is collected in the U.S. The amount of donation varies based on the donor's weight. Generally, each donation equals ¾ to 1¼ liter of plasma. It takes a minimum of 4,000 liters of plasma to start one batch. The number of grams produced from each batch varies depending on the product being produced.

IG Living

Have you ever wondered how IVIG is made? Did you know it takes nine months to go from the arm of a plasma donor to the arm of an IG patient? What do you think happens during that nine months?

Becky Wang

It's an amazing process. Part of the reason it takes so long (besides the cleaning/purification process) is the fact that the plasma has to be held for 60 days before anything can happen to it at all. In those 60 days, the plasma is tested for infectious agents. If you've never gotten to tour/visit a plasma center, especially if you're an IG recipient, you totally should!

Editor's Note: For detailed information on how plasma is donated, go to www.donatingplasma.org. For information on how IG is manufactured, go to page 14 of the January 2010 issue of BioSupply Trends Quarterly *at http://www.epaperflip.com/aglaia/viewer.aspx?docid=a77cc21c6d7448a2b6febcdbdb15363e.*

On- and Off-Label Uses and Clinical Trials of IG

By Ronale Tucker Rhodes, MS, and Kris McFalls

Immune globulin (IG) is used to treat a wide range of disorders. While the most common use of IG therapy is in treating primary immune deficiencies, its efficacy in numerous other disorders is well-documented. It is estimated that for every U.S. Food and Drug Administration (FDA)-approved indication, there are more than 10 non-FDA-approved indications. In certain neurological and dermatological disorders, IG is considered a first-line agent. In other areas, such as renal transplant and cardiology, it has established itself as an integral part of patient therapy. In the future, IG may be a potentially effective treatment for diseases and conditions for which there is currently no cure.

On-Label Indications

Marketing for IG is currently FDA approved for five indications: primary humoral immunodeficiency (PIDD); immune thrombocytopenia purpura (ITP); chronic inflammatory demyelinating polyneuropathy (CIDP); B-cell lymphocytic leukemia; and Kawasaki syndrome. While all IG products carry an indication for primary immunodeficiency, no one product carries an indication for all five.[1]

Off-Label Indications

The number of off-label uses for IG far exceeds that of labeled indications. Although IG has been proven useful for many disease states, the likelihood of manufacturers pursuing FDA approval for already treated indications is remote given the high cost of conducting trials without the benefit of increased marketing advantages. The sometimes tenuous and limited supply of IG, combined with the high costs of treatment, require best practice standards be used when deciding to treat with IG. Some diseases commonly treated off label with IVIG are Guillain-Barré syndrome, polymyositis, dermatomyositis, multifocal motor neuropathy, stiff person syndrome, relapsing-remitting multiple sclerosis and pemphigus.[2] Anecdotal reports suggest IVIG is effective in treating autoimmune neutropenia, autoimmune hemolytic

IG Products and Indications

Product	Manufacturer	On-Label Indications
Carimune NF	CSL Behring	Primary humoral immunodeficiency Immune thrombocytopenia purpura (ITP)
Flebogamma DIF 5%	Grifols	Primary humoral immunodeficiency
Flebogamma DIF 10%	Grifols	Primary humoral immunodeficiency
Gammagard Liquid	Baxter Healthcare Corp.	Primary immunodeficiency disorders associated with defects in humoral immunity
Gammagard S/D	Baxter Healthcare Corp.	Primary immunodeficiency (PIDD) B-cell chronic lymphocytic leukemia Immune thrombocytopenia purpura (ITP) Kawasaki syndrome
Gammaplex	Bio Products Laboratory	Primary humoral immunodeficiency
Gamunex-C	Talecris	Primary immunodeficiency (PIDD) Immune thrombocytopenia purpura (ITP) Chronic inflammatory demyelinating polyneuropathy (CIDP)
Hizentra	CSL Behring	Primary humoral immunodeficiency
Privigen	CSL Behring	Primary immunodeficiency (PIDD) Immune thrombocytopenia purpura (ITP)
Vivaglobin	CSL Behring	Primary humoral immunodeficiency

anemia, Evans syndrome and acquired hemophilia, especially when other therapeutic modalities fail.[3]

Indications Under Current Research

Many studies are currently being conducted to look at the efficacy of IG in non-FDA-approved indications. Three specific areas that are being explored, for which IG is not used as a standard of care, include Alzheimer's, secondary recurrent miscarriage and chronic regional pain syndrome.

Alzheimer's. IVIG appears to have promising effects for both reducing the risk of developing Alzheimer's, as well as improving the cognitive ability of those suffering from it. Results of a study presented at the International Alzheimer's Symposium in 2008 showed that the risk of developing Alzheimer's disease and related disorders (ADRD) may be reduced by about 40 percent in patients previously treated with IVIG.[4]

As of early 2009, several small clinical trials have shown promising results for treating Alzheimer's with IVIG.[5] In March 2010, results of a Phase 2 clinical trial suggests that treatment with IVIG is associated with a reduction in ventricular enlargement rates and cognitive decline in patients with mild to moderate Alzheimer's. In the study, uninterrupted treatment with IVIG for 18 months was associated with about half the rate of ventricular enlargement reflecting brain atrophy versus a placebo, along with better scores on neuropsychological testing. A pivotal Phase 3 study is now enrolling patients from 35 sites throughout the United States.[6]

Secondary recurrent miscarriage. Several clinical trials have been conducted to determine whether IVIG is an effective treatment for recurrent miscarriage. While clinical trials are still ongoing, one particular study consisted of a systematic review of randomized controlled trials, comparing all dosages of IVIG to a placebo or an active control. The study looked at eight trials involving 442 women that evaluated IVIG therapy used to treat recurrent miscarriage. The findings showed that, overall, IVIG did not significantly increase the odds ratio of live birth when compared with a placebo for treatment of recurrent miscarriage. However, there was a significant increase in live births following IVIG use in women with secondary recurrent miscarriage, while those with primary miscarriage did not experience the same benefit.[7]

Chronic regional pain syndrome (CRPS). Most recently, a small study found IVIG effective for alleviating CRPS, which causes chronic and often intractable pain, usually in the arm or leg, long after recovery from an illness. Researchers at the Pain Research Institute at the University of Liverpool in England administered a half gram of IVIG per kilogram of body weight to 13 people who had been suffering from CRPS between six and 30 months and who reported pain intensity of at least five on an 11-point scale for seven consecutive months. All had failed to achieve significant relief from other conventional treatments. After being treated with IVIG, five of the 12 subjects reported median pain scores at least two points lower, and three of the five reported pain scores at least 50 percent lower.[8]

Other diseases. There also are case reports and open label trials that show IVIG benefits some patients with rheumatoid arthritis, anti-neutrophil cytoplasmic antibody disorders, systemic sclerosis/scleroderma and Still's disease.[3]

The Future of IG

For now, IG continues to be used as a treatment for both FDA-approved and non-FDA-approved indications. But, the future of IG looks promising for its ability to treat a host of disease states. ■

RONALE TUCKER RHODES, *MS, is the editor of* IG Living *magazine, and* **KRIS MCFALLS** *is* IG Living*'s full-time patient advocate.*

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Safety

FDA Warns Against Using Stolen Inhalers

The U.S. Food and Drug Administration has issued a warning about Advair Diskus inhalers stolen in 2009 from a GlaxoSmithKline warehouse that have been found in some pharmacies, and is advising consumers not to use them. Advair Diskus, generically known as fluticasone propionate and salmeterol inhalation powder, is used to treat those who suffer from asthma and chronic obstructive pulmonary disease. Stolen pharmaceutical products such as these have risks because they may have been stored at incorrect temperatures and humidity levels, which can cause them to lose potency, and they may have been tampered with and may be contaminated.

Two lots were stolen, totaling 25,600 inhalers. The lot numbers include 9ZP2255-NDC0173-0696-00 and 9ZP3325-NDC0173-0697-00. Patients who have products with these lot numbers should stop using them, contact GlaxoSmithKline's customer response center at (888) 825-5249, and follow up with their physician or pharmacist to obtain a proper replacement.

Research

IVIG Study for CIDP Announced

Octapharma AG will conduct its largest study of intravenous immune globulin (IVIG) to treat chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The double-blind, placebo-controlled, randomized, multicenter, adaptive, two-stage Phase II/III dose-finding study will investigate the efficacy and safety of Octapharma's novel 10% IVIG in the treatment of CIDP and, together with results from additional ongoing and upcoming studies, will support its regulatory filing in Europe and the U.S. The study is one more study of a series to investigate Octapharma's new 10% IVIG for a range of neurologic and hematological conditions, including immune thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), Kawasaki disease and CIDP.

Insurance

New York Law Prohibits Drug Specialty Tiers

The state of New York has passed a new law that prohibits commercial health insurance plans from creating specialty tiers within their prescription drug formularies. According to the law, the justification for the ban on specialty tiers is as follows:

As the cost of prescription drugs continues to climb, health insurance plans in California, Minnesota, Maryland and Alabama have created new specialty tiers to increase the copayments that consumers pay. Instead of a three-tiered drug formulary structure used by most plans (where Tier 1 is for generics, Tier 2 is for brand-name preferred drugs, and Tier 3 is for brand-name non-preferred drugs), some plans have begun to add fourth and fifth tiers for the most expensive medications. These additional tiers assign a percentage of the cost of the medication as coinsurance, as opposed to a set dollar amount used in the other three tiers. An example might be $10 for Tier 1 generics, $25 for Tier 2 brand-name preferred drugs, and $50 for Tier 3 brand-name non-preferred drugs.

In the states allowing specialty tiers, medications placed in Tiers 4 and 5 are typically assigned a coinsurance payment of between 20 percent and 35 percent. Therefore, a patient being treated for multiple sclerosis (MS), for example, could have a monthly copayment that could reach $775. People living with chronic illnesses, such as MS, rheumatoid arthritis and hemophilia, or people with a life-threatening condition, such as HIV, breast or colorectal cancers, leukemia and non-Hodgkin's lymphoma, are the patients who are most affected.

According to the New York law, specialty tiering is contrary to the original purpose of insurance, which is to spread the cost. Instead, it creates a structure where those who are most sick pay more, which is an unlawful discriminatory practice.

Medicine

Gamunex-C Approved for Subcutaneous Administration

The U.S. Food and Drug Administration (FDA) has approved Talecris Biotherapeutics' Gamunex-C (immune globulin injection [human] 10% caprylate/chromatography purified) for subcutaneous administration in the treatment of primary immunodeficiency (PIDD). Gamunex-C can be administered subcutaneously and intravenously, whereas Talecris' previously FDA-approved Gamunex can be administered intravenously only. Intravenous (IV) delivery for both products is FDA-approved to treat PIDD, chronic inflammatory demyelinating polyneuropathy (CIDP) and idiopathic thrombocytopenic purpura (ITP). Gamunex-C has labeling and packaging information that describes both IV and subcutaneous routes of administration. Gamunex has labeling and packaging information that describes only IV administration.

"The FDA approval of Gamunex-C is important because it provides another option for patients with primary immunodeficiency and their healthcare professionals when they are considering the various treatment modalities," says Fred Modell, cofounder of the Jeffrey Modell Foundation. "We consider it significant for patients to have multiple modes of delivery so they can select the option that best suits their individual needs."

Medicine

Cangene to Manufacture New IVIG Product

Cangene Corp. has announced that it is developing an intravenous immune globulin (IVIG) product — a product that was included, but unidentified, in the company's pipeline for the past two years. According to a Cangene press release, the company is currently scaling up its manufacturing processes for clinical trials, which are expected to begin in 2011. The process of manufacturing the IVIG product will incorporate a different platform technology for plasma fractionation than the one the company uses for its specialty hyperimmune products, such as WinRho SDF and HepaGam B. Cangene is also building an inventory of the source plasma needed for the manufacture of IVIG to be used in clinical trials. Source plasma differs from the specialty plasma the company uses to manufacture its hyperimmune products because it has not been selected for the presence of specific antibodies.

"The potential uses of [IVIG] continue to expand. We believe this product has great potential for us and that it would be a good addition to our hospital-based commercial product lineup," says Dr. John Langstaff, Cangene's president and CEO. "We are also working with some new technology for manufacturing this product, which may in turn be used for future products."

Medicine

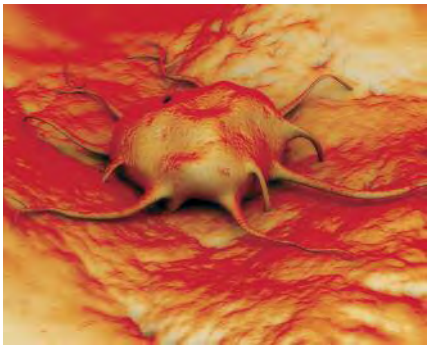
Hizentra Shelf Life Extended to 24 Months

The U.S. Food and Drug Administration has approved a supplemental biologics license application (sBLA) to extend the shelf life of Hizentra, immune globulin subcutaneous (human) 20% liquid, from 18 months to 24 months. Hizentra is the first and only 20 percent subcutaneous immune globulin (SCIG) approved in the U.S., as well as the first and only SCIG that may be stored at room temperature. Hizentra is indicated for the treatment of primary immunodeficiency.

The sBLA was based on a study that assessed the product's physicochemical, biological and immunological parameters over 24 months' storage under controlled conditions at 77 degrees Fahrenheit. Data generated from the study support that when Hizentra is stored at room temperature (up to 77 degrees Fahrenheit) and protected from lights, it is stable for up to 24 months.

Research

Scleroderma, Cancer Linked in Study



Researchers at Johns Hopkins University School of Medicine have found that patients with a certain type of scleroderma may get cancer and scleroderma simultaneously. The small study, which examined blood and tumor samples from 23 patients with both scleroderma and cancer, looked for specific immune markers in each patient to determine which type of antibodies the patients made. Those with antibodies called anti-RNA polymerase I/III had the most closely related onset of cancer and scleroderma; patients got both diseases within two years of one another. However, the reasons for the apparent link are not understood, and it is not known whether cancer could be causing scleroderma or if scleroderma could be causing cancer.

Scleroderma is a complex autoimmune disease, with visible symptoms affecting the skin, or invisible symptoms affecting internal organs. For some people living with scleroderma, it affects both. The study was published online in the journal *Arthritis and Rheumatism*.

Medicine

Octagam Withdrawal Issued for All Lots

Octapharma USA has initiated a voluntary withdrawal of all lots of Octagam (immune globulin intravenous [human] 5% liquid preparation) from the U.S. marketplace due to an unusually high number of thromboembolic events that have been associated with people being administered the drug. This follows an initial announcement in August of a voluntary withdrawal of selected lots of Octagam 5%, which reported at least nine events in which blood clots dislodged and traveled through the body, causing injury and pain to patients.

According to Octapharma USA, while the company has not received any reports of thromboembolic events since its initial voluntary market withdrawal, "the Food and Drug Administration and Octapharma agree that until a root cause analysis of the previously reported thromboembolic events can be determined, the most prudent course of action is to suspend further administration of Octagam 5%."

The company requests that customers quarantine all lots of Octagam 5% and then contact the Octapharma customer service department at (201) 604-1141 to return the product.

This withdrawal is for Octagam only. Octapharma's Albumin (Human) and Wilate, Von Willebrand Factor/Coagulation Factor VIII Complex (Human), are unaffected and are readily available in all sizes for purchase.

Medicine

FDA Approves Grifols' Flebogamma 10% DIF IVIG

Grifols has obtained U.S. Food and Drug Administration approval for its next generation of intravenous immunoglobulin (IVIG) 10% concentration, under the name Flebogamma 10% DIF. Flebogamma DIF (double inactivation and filtered) is a polyvalent IVIG that incorporates two specific viral inactivation methods and the additional safety step of nanofiltration at 20 nanometers. These processes produce higher yields of the product to maximize the amount of life-saving medicine that can be produced from each plasma donation.

With this approval, Grifols is the first company in the U.S. to offer patients and clinicians two concentrations of liquid IVIG (5% and 10%).

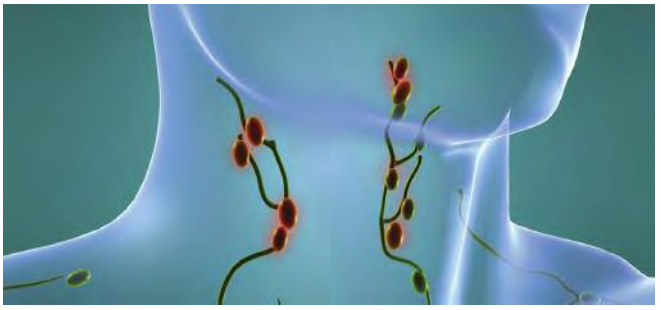
People and Places in the News

The Neuropathy Association has added **Edward Hines Jr. VA Hospital** to its network of Neuropathy Centers of Excellence, which now totals 15 centers across the U.S. The Neuropathy Center at Hines Jr. VA Hospital serves the veterans community in Chicago and the surrounding region.

Allostera Pharma has appointed **Christopher Henney**, PhD, as chairman of its board of directors. Henney, an immunologist, is the co-founder of Immunex, Icos and Dendreon.

The Evolution of an Improved Antibody

By Terry O. Harville, MD, PhD



IGG IS PERHAPS the most important antibody that our immune systems produce. As noted in my previous column, it is the only type of immunoglobulin that can pass through the placenta, making it very important for the developing fetus and during the neonatal period.

The Adaptive Production of IgG

IgG typically is produced after the immune system has been stimulated by an encounter with a specific antigen. An antigen is a protein to which our immune systems respond. It usually is thought of in a negative perspective, since it may be a protein from a pathogen such as an influenza virus, representing an offending agent to which our immune systems respond in order to protect us. But, an antigen triggering a response also can be a protein from a cancer cell to which our immune systems respond. And, indeed, there has been recent success in using cancer antigens from melanoma for stimulating immunity, which has resulted in remission of disease.

Therefore, IgG can be considered to be produced in an "adaptive" context. For example, a bacterial infection begins, causing white bloods cells, such as neutrophils, monocytes and tissue dendritic cells, to respond by engulfing and then digesting the bacteria. During digestion, bacterial proteins (potential antigens) are converted into shorter pieces called peptides. Then, via dendritic cells that have migrated to lymph nodes, these peptide antigens stimulate T and B lymphocytes that have receptors, which specifically recognize the processed bacterial antigen.

As previously discussed, each B lymphocyte will produce its own unique antibody (through a process of gene recombinations to be discussed later). During the initial development, the antibody expresses the IgM antibody class on its cell surface. Yet, while IgM has a weaker affinity for an antigen than IgG and is not as specific as IgG, a B lymphocyte with cell surface IgM is somewhat capable of recognizing a specific antigen and can be stimulated in the presence of an antigen presenting cell (APC), such as a dendritic cell or a specific T lymphocyte. Therefore, in a lymph node, specific interactions occur as dendritic cells present the antigen, and a B lymphocyte and T lymphocyte recognize the antigen, thus transmitting signals back and forth to cause stimulation. When the B lymphocyte receives the signals, it begins to undergo changes. In particular, the genes that produce the IgM antibody are reactivated, inducing a transformation that further changes the antibody genes' DNA sequences.

An Evolutional Process

All of this occurs in an attempt to produce a "better" antibody for binding to the specific antigen, which is a remarkable example of Darwinism, or evolution's "selection of the fittest." And, it works. It begins with an initial antibody that can bind somewhat to the specific antigen, and then changes as the initially recombined genes occur, resulting in the emergence of a much, much better antibody. The process of generating a higher affinity or better antibody is known as "somatic mutation" (sometimes called "somatic hypermutation"). And, while this process ensues, another event occurs: The initial IgM undergoes what is known as "class-switch" to IgG (more on this later). This evolution from a naive B lymphocyte with cell surface expression of IgM to a stimulated B lymphocyte, which has "class-switched" to IgG production, can be detected three or so days after the beginning of an infection. And, significant amounts of IgG in the serum that are produced by the activated B lymphocyte may be detected some seven to 10 days after the infection begins, and these amounts may continue to increase, reaching peak levels two to six weeks after an infection occurs (i.e., after the initial antigen stimulation exposure).

Next issue, we'll continue our discussion on antibodies and immunoglobulin. ◪

TERRY HARVILLE, *MD, PhD, is medical director of the Special Immunology Laboratory at the University of Arkansas for Medical Sciences, and a consultant for immunodeficiencies, autoimmunities and transplantation.*

How to Write an Effective Appeal Letter

Appealing denials of insurance coverage for expensive therapies, such as immune globulin, can be time-consuming and frustrating, but patients can succeed by following the proper steps.

By Kris McFalls

Not much can make a person's heart skip a beat more than the arrival of a letter or explanation of benefits (EOB) statement from the insurance company that denies a claim, leaving the patient on the hook for tens of thousands of dollars. Because immune globulin (IG) therapy is such an expensive treatment, the best way to avoid receiving such a shock is for the patient to request authorization before treatment begins. In fact, most private insurers require prior authorization before they will agree to pay for treatment. Even with prior authorization, however,

insurance companies reserve the right to review medical records after the fact and can still deny claims. In either case, an appeal will need to be filed, and the process and the tools to appeal either a denial of authorization or denial of a claim are identical.

Don't Give Up: Appeal

Filing an appeal can be stressful and frustrating for even the healthiest people. For those with a chronic illness, having to fight for lifesaving treatment on top of battling disease can be a daunting task. Many people would rather give up than continue fighting a system with so much red tape and so little transparency. According to Advocacy for Patients with Chronic Illness Inc., "although 94 percent of insurance denials are never appealed, approximately 70 percent of those that are appealed are granted. Clearly, then, the odds are good for a successful outcome for the patient who appeals."

A Proper Approach for Appeal

To help ensure a successful appeal, proper steps need to be followed. Be forewarned: A person should never take the seemingly easy route when filing an appeal. For example, when an insured calls to inquire about a denial, insurance companies often offer to start the appeal right away over the phone. As tempting as that can be, don't! Jennifer Jaff, attorney and former executive director of Advocacy for Patients with Chronic Illness Inc., gives this piece of advice: "Even though a denial letter will invite the insured to initiate an appeal by calling the insurance company to inform it of the intent to appeal, individuals should *never* appeal by phone, nor should they simply send a note without medical records and other documentation to back up the appeal. Instead, the appeal should be packaged so that the insurer will be left with no questions and little chance but to grant the appeal and cover the treatment needed."

Before the Appeal Is Filed

Before writing an appeal letter, it's important to gather some information.

Coding errors. An American Medical Association study revealed that one out of five medical claims contains errors. Several of those errors pertain to coding. Immune globulin therapy requires several components, such as supplies, nursing and the immune globulin itself, and each of these components requires a separate code. For instance, in the case of nursing, the first hour of care is one code and each additional hour is a separate code. Additionally, the diagnosis and site of treatment have specialized codes. If any of the codes are wrong or do not mesh with the other codes, the entire claim or authorization request will be denied automatically. Individuals should double-check that the proper codes were used when the claim was filed. (See the listing of manufacturer sites of reference for code numbers and reimbursement questions on page 16.)

Treatment policies. It used to be that a doctor could write a script for a diagnosis, and treatment would be given, no questions asked. That is no longer the case. Insurers have specific policies for specific disease states. And, they have medical policies listing the medical criteria each patient must meet to justify treatment. If a patient is denied treatment, the medical policy detailing the medical criteria must be provided free of charge. So, prior to filing an appeal, the insurer's policy should be checked. Many insurers now have these policies available for viewing via the Internet.

An American Medical Association study revealed that one out of five medical claims contains errors.

Plan types. There is a difference between a fully insured and self-funded insurance plan. This difference will help to determine how an appeal is processed, what an individual's rights are, and if a plan is governed by state laws or by the Employee Retirement Income Security Act (ERISA).

- Fully insured plans are governed by state regulations. Monthly premiums are paid by an employer to an insurance company, and the insurance company determines the benefits and pays the claims. So, an appeal will be made to the insurance company itself.
- Self-funded plans are common for large companies and are governed by ERISA. The employer hires an insurance company to administer the plan, but the employer actually pays the claims. And, the employer has the right to make exceptions and pay a claim an insurer has denied. So, in some cases, an appeal can be made directly to the employer's human resources department, which can choose to overrule the denial.

In addition, under the healthcare reform law, which went

into effect in September 2011, those covered under self-funded plans now have the right to ask an independent review organization to review the denial of coverage and consider whether to overturn the insurer's or plan's decision. However, this change does not apply to "grandfathered" plans, those that existed on the day when healthcare reform was signed into law that do not substantially modify their character (benefits package, copays, deductibles, etc.). The change applies only to plans that do make modifications, and requires them to comply with all of the provisions of the new law, including the expanded right to appeal.

Submitting the package. When making an appeal, it is important for a complete package to be submitted. A complete package includes:

- Name, date of birth, subscriber number and contact information
- Letter of medical necessity from the prescribing doctor detailing the diagnosis and need for treatment
- Lab reports and test results detailing how the patient fits the medical criteria (It is not enough to state that a patient is weak or that the patient called complaining of an infection. Weakness must be explained, and infections need to be validated. For instance, instead of stating that a patient is weak, it should be explained that the patient can no longer stand without assistance. In the case of infections, cultures and radiology reports are hard evidence that cannot be ignored.)
- Doctor's notes detailing treatments that have been tried and failed
- Peer-reviewed articles supporting immune globulin as a treatment for the disease (See website listings on page 17.)

Although 94 percent of insurance denials are never appealed, approximately 70 percent of those that are appealed are granted.

The timeline. Nothing will lose an appeal faster than not sticking to the allotted timeline. On average, most insurance companies require appeals to be made within 30 days. But, in some cases, the timeline for an appeal can be as long as 360 days or as short as 14 days. Each company's timeline is different, and it can be found on the back of the EOB statement.

Keeping a journal can assist individuals to file an appeal within the allotted timeline. It can be used to track when letters are received, as well as to list the names, dates and times of people spoken to. This can be especially helpful because dates can be tricky. Many insurers date the letters of denial on the date they write the letter, which is usually at least a week before the letter is received. Therefore, the envelope with the postmark should be kept as proof of the date of receipt.

Return receipt. Last, the entire appeal package should be submitted Certified Mail Return Receipt, requiring the recipient at the insurance company to sign for the document and the post office to provide notification of receipt to the sender.

IVIG Coding and Reimbursement Websites

Several of the immune globulin manufacturers have websites that list codes to make an insurance claim for IVIG treatments, as well as answer general reimbursement questions.

Coding sites:

CSL Behring: *www.cslbehring-us.com/Products/Universal-Billing-Codes*
Gammagard: *www.gammagard.com/healthcare-professionals/ordering-and-reimbursement/suggested-coding.html*
Privigen: *www.privigen.com/professional/ordering-privigen/privigen-coding.aspx*

Reimbursement sites:

CSL Behring: *www.cslbehring-us.com/physicians-and-healthcare-professionals/reimbursement-resource-center.htm*
Grifols: *http://www.grifolsusa.com/en/web/international/results?p_p_auth=Kt32SDgj&p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-2&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=178368&_101_type=content&_101_groupId=10192&_101_urlTitle=reimbursement-poli-1&redirect=%2Fen%2Fweb%2Finternational%2Fresults%3Fq%3Dreimbursement*
Octapharma: *www.octapharma.com/en/about-octapharma/corporate-profile/subsidiaries/octapharma-usa-inc/octapharma-usa-inc.html*

Writing the Appeal Letter

The appeal letter should be formally written, devoid of any personal ranting and raving. Personal information should be in the heading of the letter, and should include the individual's name, contact information, subscriber identification number, date of birth and the reference or claim number of the denial.

The first paragraph of the letter should clearly and succinctly state the reason for writing the letter. For instance: "I am appealing the decision of denial for treatment of (insert disease) with immune globulin. ABC insurance wrongfully denied my claim stating (denial reason). I disagree with ABC's decision of (the reason).

The next paragraph should clearly state what the facts are, and each fact should be referenced. Bullet points work well to outline main points and how they correlate with the insurance criteria. For instance, a patient with a primary immune disease may want to list immune levels and chronic recurring bacterial infections with poor response to antibiotics as bullet points. Then, under each bullet point, further detail can be provided.

Example:

• ABC policy: For a diagnosis of CVID, patient must have an IgG level of 400 or less.

— My IG levels clearly fall within the parameters for a diagnosis of common variable immune deficiency (CVID).

The appeal letter should be formally written, devoid of any personal ranting and raving.

— My IgG level of 395, as shown on 123 lab report, is clearly within the range in ABC's stated policy. See attached 123 lab report dated xx-xx-xxxx.

• ABC Policy: Patient must show evidence of serious recurrent bacterial infections despite adequate treatment.

— I have had pneumonia three times in the past 12 months, requiring six courses of oral antibiotics and one hospitalization for intravenous antibiotics.

— Attached is Good Sam hospital's chest X-ray report confirming pneumonia dated xx-xx-xxxx.

— Attached is Dr. Smith's office note dated xx-xx-xxxx showing poor response to antibiotics, as well as the doctor's note ordering intravenous antibiotics.

— Attached is Good Sam hospital's note regarding my hospital stay for treatment.

Websites for Peer-Reviewed IVIG Treatment Articles

Autoimmune diseases: *www.advocacyforpatients.org/resources.html*

IVIG Tool Kit: *www.aaaai.org/practice-resources/management-tools-and-technology/ivig-toolkit.aspx*

Neurology: *www.neurology.org*

PIDD Journal of Allergy and Clinical Immunology (JACI): *www.aaaai.org/members/jaci.stm*

The facts section of the letter should conclude by referencing current medical literature. For example: "Treating CVID with IG is clearly the standard of treatment as supported in peer-reviewed articles. As stated in Dr. Smith's article, titled 'Treatment of CVID with IG,' immunoglobulin replacement therapy is the only ..."

Once the facts have been presented, the consequences from lack of treatment should be stated. For instance, a person with chronic demyelinating polyneuropathy (CIDP) might write: "Lack of treatment with IVIG will result in decreased mobility, increased dependency and an overall increase in healthcare needs. Treatment with IVIG is the most prudent way to regain lost motor skills and improve my overall health, thus decreasing my chances of severe or permanent disability."

The closing paragraph should reiterate the need for treatment and request a positive solution without delay. A person with CIDP might write: "Treating my CIDP with IVIG is reasonable and medically necessary. ABC insurance should immediately reverse its decision of non-coverage based on medical necessity to prevent further regression."

Good Reason to Appeal

Despite the legwork required and the frustration of filing an appeal for a denial of authorization or claim, it's in the best interest of a patient to do so. By following the guidance in this article to file the appeal properly, there's a 70 percent chance of success. ■

KRIS MCFALLS *is* IG Living*'s full-time patient advocate.*

Editor's note: This article was updated on August 16, 2013.

Exercise for Arthralgia

One of the most effective treatments for joint pain is a program that combines range-of-motion, stretching, strength training and aerobic exercise.

By Matthew David Hansen, DPT, MPT, BSPTS

The term "arthralgia" comes from the Greek *arthro-* (joint) and *-algos* (pain). Arthralgia, or joint pain, can be caused by injury, allergic reactions, degenerative causes, infection and illness. Individuals with an immune disorder who suffer from arthralgia are typically diagnosed with inflammatory arthralgia. However, according to the Medical Subject Headings created by the United States National Library of Medicine, the term "arthralgia" is a misnomer because it should be used only when a condition is not inflammatory; when it is inflammatory, the term "arthritis" should be used. Nonetheless, for the purposes of this article, and to avoid confusion with the non-related condition of osteoarthritis, the term "inflammatory arthralgia" will be used to refer to joint pain that is a result of an immune disorder.

It is not unlikely that someone suffering from inflammatory arthralgia also could be dealing with osteoarthritis and would benefit from understanding the difference between the two conditions. Osteoarthritis (aka degenerative arthritis)

is the most common form of arthritis, caused by the loss of cartilage (the "cushion" that sits between the bones of joints), and becomes more prevalent as people age. Repetitive use over the years of commonly affected joints can irritate the cartilage and lead to pain and swelling. If the cartilage completely wears out between two joint surfaces, friction between the bones leads to increased pain and loss of joint mobility. Pain from osteoarthritis is worse after activity and at the end of the day, while stiffness in the morning or after inactivity usually lasts only a few minutes. On the other hand, stiffness from inflammatory arthralgia tends to last more than an hour. Joints on both sides of the body usually are involved, with the smaller joints of the hands and feet most affected. In addition, redness, swelling and warmth near the joint is more prominent than with osteoarthritis.

The Role of Autoimmune Disease

Several of the most common autoimmune diseases associated with inflammatory arthralgia include rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's disease and mixed connective tissue disease.

The reason individuals with autoimmune diseases experience inflammatory arthralgia is because their body doesn't respond normally to infection. Here's why: When the body's inflammatory response is working properly, increased blood flow to the surrounding injured or infected area creates an environment that is bathed in the enzymes needed for tissue repair and the leucocytes (white blood cells) used to fight infection. Once their mission has been accomplished, the swelling leaves the area, along with the cell debris, recruited enzymes and white blood cells. But, in the case of inflammatory arthralgia, the body views its own tissues as the foreign invader, and a chronic inflammatory response ensues as immune cells attack the joint capsule and/or synovial membrane, ligaments, blood vessels, tendons and muscles surrounding a joint.

Unless the inflammatory process can be stopped, tissue will be destroyed and fibrous scarring will occur in the areas of greatest damage. Scar tissue is not pliable, and as a consequence, frequently has a severe impact on one's functional movement. With decreased movement comes the risk of bone and muscle atrophy (wasting), muscle imbalance and possible related dislocations or subluxations (partial dislocations) of the joint surfaces, and eventual complete immobility of the joint (ankylosis).

The Role of Exercise

Though it may be difficult to imagine that any type of exercise could be good for joint arthralgia, especially for those who moan and groan their way out of bed in the morning, lack of movement actually adds to disabling joint pain and stiffness. The right type and amount of exercise can help to reduce inflammation and pain, prevent the buildup of scar tissue, strengthen the muscles around the joints, maintain bone strength, improve daily stamina, control body weight, contribute to a good night's sleep and improve self-esteem.

Individuals who haven't been active for a while should start slowly and ease into exercise. Overdoing it can aggravate joint structures and cause more inflammation and pain. Therefore, if patients' condi-

tions get worse after exercise and if symptoms continue, a doctor should be contacted. When approved by a doctor, applying superficial heat like a warm towel, hot pack, heating pad or warm shower to a joint for 15 to 20 minutes before exercise — or when patients feel particularly stiff — can help to relax the body, relieve pain and possibly reduce the chance of a flare-up (i.e., acute inflammation). If joints are able to tolerate the cold, applying a bag of frozen vegetables or an ice pack wrapped in a towel for 10 to 15 minutes immediately following exercise also can help to reduce pain and swelling. Those who have Raynaud's syndrome, a condition not uncommon in people with inflammatory arthralgia that causes the blood vessels in the fingers and toes to constrict when exposed to cold, should probably not use ice.

One of the best things that people with inflammatory arthralgia can do to preserve the movement that they have is to just keep moving.

Range of Motion and Stretching

One of the best things that people with inflammatory arthralgia can do to preserve the movement they have is to just keep moving. That advice may seem obvious, but there will be many days when it is the last thing that they want to do. Range-of-motion exercises that are performed in a non-weight-bearing position should normally be performed two to three times daily. For example, to "range" elbows, they should be bent toward the body (i.e., flexed) and then extended as far as they can in each direction without increasing pain. Knees can be ranged by sitting in a chair and extending them up into the air, then returning them to a position slightly under the seat, as tolerated; this is considered a non-weight-bearing exercise because patients are not standing while bending their knees and thereby not applying the additional force of their body weight through the joints. Exercises should be repeated slowly for three to five minutes for each joint that is being targeted (e.g., shoulders, hips, ankles, wrists, etc.).

Stretching involves moving a joint and its surrounding muscles to the end of — or slightly beyond — their normal range of motion and holding the position for at least 30 seconds. Many people are accustomed to holding a stretch for shorter periods of time; however, scientific research has demonstrated that at least a 30-second hold is needed to produce lasting effects. Because inflammatory arthralgia can cause different deformities over time, and even some conditions that should not be stretched (e.g., joint dislocations), a doctor and/or physical or occupational therapist should inspect patients' joints before prescribing a particular program.

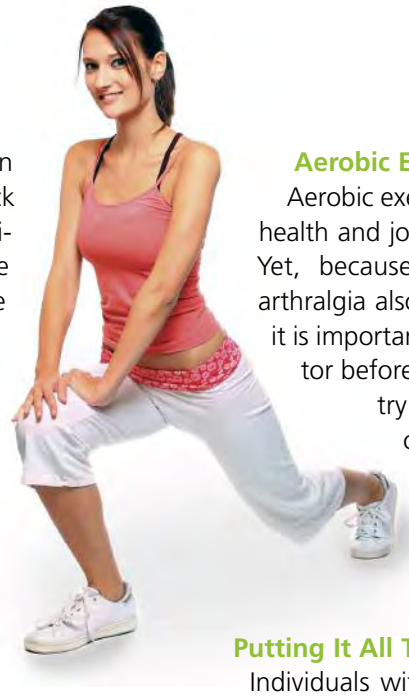
Strengthening Exercises

Strengthening exercises can help to build the muscles that surround a joint, thus reducing the load put through the joint and its structures. In general terms, there are two types of strengthening exercises: isometric and isotonic. Isometric exercises involve simply contracting a particular muscle group in place, holding it against gravity without moving, or pushing it against an immovable object (e.g., a wall). The joints do not move during isometric exercises, so they may be a good place to start for people who experience significant joint pain. Isometric exercises are convenient because most of them can be performed at the same time as everyday tasks, without anybody else being the wiser. For example, knee muscles can be exercised while sitting in a business meeting, etc., by extending one leg out in front, contracting the thigh muscles for 10 seconds and relaxing for 10 seconds, and then repeating the pattern three to five times on each side.

The opposing hamstrings can be exercised by bending the knee so that the heel is pressed against the sofa or chair leg and then pulled into the surface, following the same pattern described above. Finally, the calf musculature behind and below the knee can be targeted by rising up onto tiptoes (while still sitting with knees bent) and squeezing. Similar activities can be performed all the way up and down the body to work different muscle groups. The length and amount of contractions just need to be adjusted to meet patients' fitness levels.

Isotonic exercises involve moving a joint through its range of motion against resistance (gravity and/or an external weight like a dumb-

bell). The muscle groups targeted above can be exercised by standing with the back against the wall and working the quadriceps by bending just enough to make the tip of the toes disappear from site before returning to a fully upright position. Individuals also can sit in a chair and straighten out one of their knees in the air in front of them (with or without an ankle weight for added resistance). The hamstrings can be exercised by either lying on the stomach or holding onto the back of a chair while standing, and then bending one of the knees so that the heel is lifted up off the ground. One of the best exercises for the calf muscles (gastroc-soleus complex) is to perform toe raises. Toe raises are performed by holding onto the back of a chair or a stair railing, raising up onto the balls of the feet so that the heels are off of the ground, pausing for two seconds, and then returning to the starting position. Enough resistance should be added so that individuals are able to comfortably perform three to five sets (groups) of eight to 10 repetitions of each exercise, every other day. This is a typical prescription for an intermediate load on muscles, although a therapist can help to tailor-fit each individual's program.



Strengthening exercises can help to build the muscles that surround a joint, thus reducing the load put through the joint and its structures.

Isotonic exercises are widely thought to be more effective for functional movement than isometric exercises, because they work the muscle through its different lengths/positions. However, during joint flares or when inflammatory arthralgia is advanced, isotonic exercises can cause more pain than isometric activity. There really aren't any universally prohibited exercises for inflammatory arthralgia; nevertheless, patients should be careful with any high-impact activity that puts a lot of stress on the joint (e.g., heavy weightlifting, jogging, squeezing objects with their hands, jumping repeatedly or climbing lots of stairs).

Aerobic Exercise

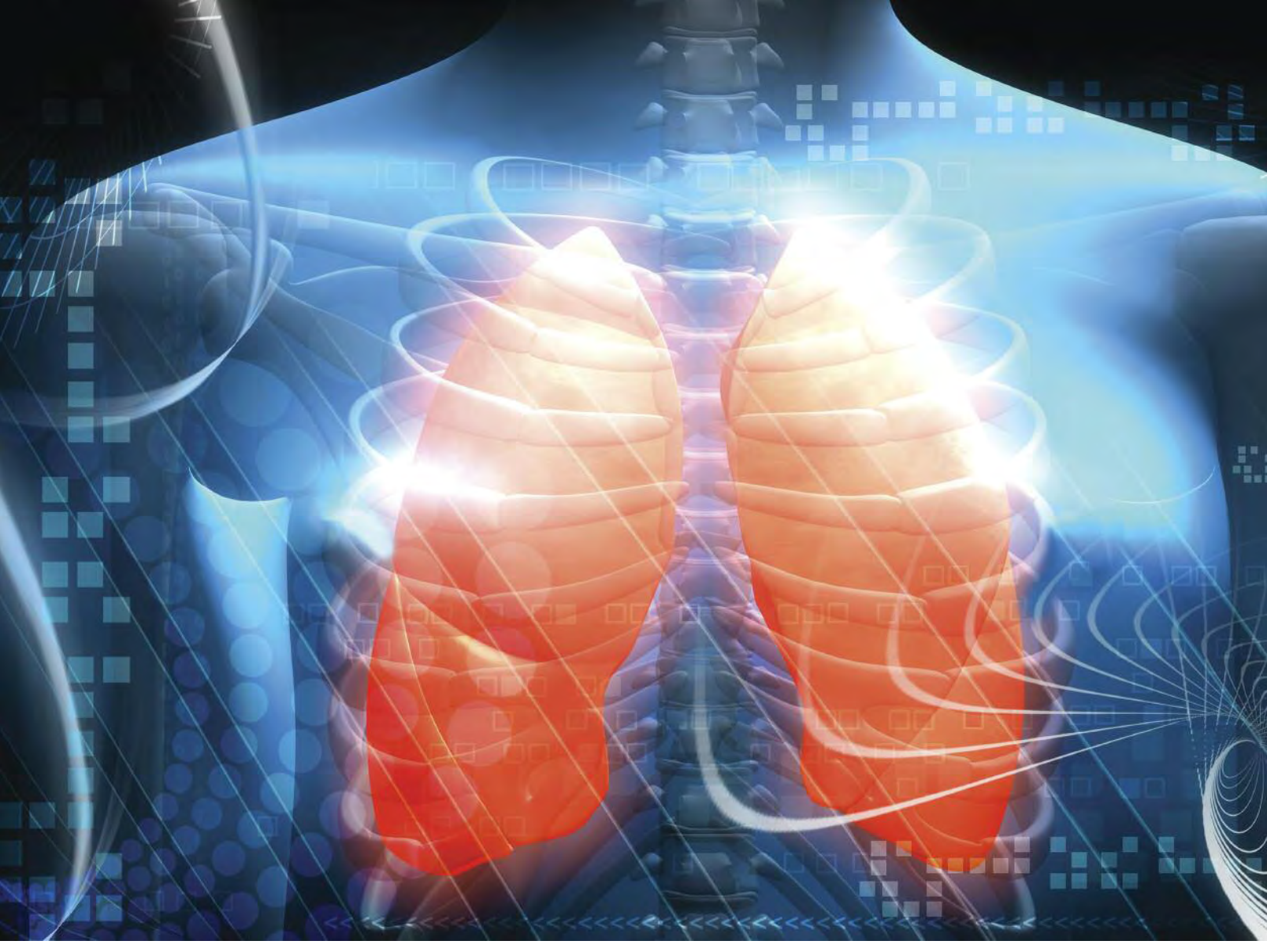
Aerobic exercise can improve patients' cardiovascular health and joint symptoms by controlling body weight. Yet, because many diseases causing inflammatory arthralgia also can affect the heart, lungs and kidneys, it is important that patients get clearance by their doctor before beginning activity. If cleared, they should try to work their way up to 20 to 30 minutes of low-impact aerobic exercise three to five times a week. Some examples of good activities are swimming and water aerobics, walking and bicycling (especially on a stationary recumbent bike).

Putting It All Together

Individuals with inflammatory arthralgia will likely feel overwhelmed with starting an exercise program, especially one that involves range-of-motion and/or stretching exercises two to three times daily, strengthening exercises every other day, and aerobic exercises three to five times a week. But, it is important for these individuals to understand that any movement is better than no movement. If it helps, they can begin by making just the range-of-motion and/or stretching exercises part of their normal day, and incorporating them into activities that they are already doing (eating meals, watching TV, reading, etc.). Once they have been able to successfully do that, some isometric or isotonic exercises can be added into the routine, eventually designating several 20- to 30-minute blocks during the week when they can do their aerobic exercise, even if it's just a walk around the neighborhood.

When looking for a place to exercise, local hospitals, clinics, health clubs and community centers sometimes offer exercise programs for people with physical limitations. And, whether individuals continue to exercise during flare-ups is up to them and their doctors, but in most cases, they should still be able to perform non-weight-bearing range-of-motion exercises just to keep moving. That's the key: Just keep moving.

MATTHEW DAVID HANSEN, *DPT, MPT, BSPTS, is a practicing physical therapist in Washington state and president of an allied healthcare staffing and consulting agency. He completed his formal education at the University of Utah, Salt Lake City, and has additional training in exercise and sports science, motor development and neurological and pediatric physical therapy.*

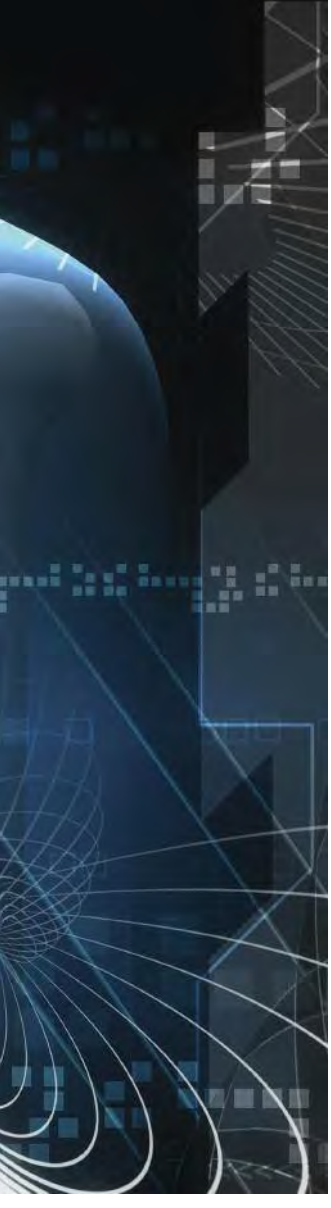


The Connection Between Pulmonary Disease and Immune-Mediated Illness

By Jennifer Kester

Breathing problems due to pulmonary disease are often a cause of immune and autoimmune diseases, and can lead to serious complications if not diagnosed and treated early.

Since she was a child, Melissa Hauser frequently got sick. She suffered from repeated sinus infections and respiratory infections, and she came down with pneumonia at least once a year. Then, in 2005, she contracted pneumonia and she never healed. After checking out of the hospital, she landed right back there, and when she got off antibiotics, she had to go right back on them. In one month, she was forced to go on a hospital respirator three times. The problem: None of her doctors could



pinpoint the reason for her chronic health issues.

That changed when Hauser started college and she switched to a pulmonologist, a lung specialist, closer to her school, rather than continuing to see the one near her home in Vernon, Conn. When she met her new doctor, she told him she "felt compromised," the 27-year-old recounts about that meeting. "I told him my symptoms, [and] then he did a blood test." After years and countless tests that came back inconclusive, his simple blood test revealed that her hunch was right: She was diagnosed with hypogammaglobulinemia, which for Hauser, who had low immunoglobulin (IG) levels, was classified as a common variable immune deficiency (CVID).

What Is Pulmonary Disease?

According to a 2010 report from the American Society of Hematology, one in 25,000 to 50,000 people have CVID. Since it is a disorder that damages the immune system, patients can't fight off infections, making them prone to recurrent sinus and lung problems. Pulmonary disease is one of the more serious CVID complications, and it is one of the leading causes of death for those with CVID. Also known as chronic obstructive pulmonary disease (COPD), pulmonary disease causes an airflow blockage that makes it hard to breathe. Emphysema, chronic bronchitis and, in some cases, asthma all are types of pulmonary diseases.

Although her diagnosis wasn't optimal, Hauser was relieved. "You know your body when something isn't right," she says. But, until then, all the doctors she saw didn't believe her when she tried to explain something was really wrong. "I was told: 'You don't know what you're talking about,' 'No, that's all in your head' and 'You are making it up.'" Even now, many doctors don't really understand. "If you're not a classic textbook case, [or] if you don't fit," says Hauser, "the doctors automatically think 'It must be in your head; you must be making it up.'"

PIDD and Pulmonary Complications

Like Hauser, some patients with an undiagnosed primary immune deficiency disease (PIDD) initially visit a pulmonologist to seek treatment for what they believe are breathing problems, only to learn they have PIDD. Pulmonologists are more likely to be aware of the possibility that a patient with recurrent respiratory problems could have immunodeficiencies, says Dr. Les Szekely, a pulmonary specialist at Doylestown Hospital, which is located about an hour north of Philadelphia. "We check for it a lot because it's sort of on our mind," he says.

Pulmonologists are more likely to be aware of the possibility that a patient with recurrent respiratory problems could have immunodeficiencies.

"Once you've seen it and you've diagnosed it, treated it and had success, it sticks in the back of your mind." Szekely says that immunodeficiencies are rare — he has only six patients who are prescribed IVIG — but he suspects that there are many more out there. "There are a lot of people who just aren't diagnosed," he explains.

Even after a diagnosis, some PIDD patients continue to see a pulmonologist because of frequent pulmonary infections, as well as complications associated with the lungs. These PIDD patients are those who suffer from chronic bronchitis; asthma; granulomas (small areas of chronically inflamed tissue, such as from an infection), particularly chronic granulomatous disease, an immunodeficiency disorder resulting from an inability of phagocytes, like white blood cells, to kill harmful microbes; and bronchiectasis, in which the airways widen and become flabby and scarred.

Autoimmune Diseases and Pulmonary Complications

Some patients with autoimmune diseases who are treated with IG also have pulmonary complications, which require them to seek out a specialist. Those who have chronic inflammatory demyelinating polyneuropathy (CIDP) experience decreased muscle tone and activity, which

increases the risk of lung infections. People with Guillain-Barré syndrome (GBS) can suffer serious breathing difficulties with the onset of the disease. And, in more severe GBS cases, a ventilator may be necessary. In cases of myositis, one of the complications that can arise is refractory interstitial lung disease, a chronic condition that is unresponsive to treatment, causing swelling and scarring of the lung, affecting patients' ability to breathe.

For some autoimmune diseases, a pulmonologist is the primary specialist that a patient sees. One example is Wegener's granulomatosis, which causes blood vessels and other tissues to become inflamed, thus limiting blood flow to the organs and destroying normal tissue. Because one of the main organs affected in Wegener's granulomatosis is the respiratory tract, it's necessary for patients to see a pulmonologist. Another condition that requires a pulmonologist's care is sarcoidosis, which is the growth of clumps of inflammatory cells in different areas of the body — the lungs being one of the most common places.

Even people with severe asthma who don't have an immune disease also may be primarily treated by a pulmonologist. Research shows that patients with severe refractory asthma often respond to IG treatments.

Testing for Pulmonary Disease

For those with immune-mediated conditions, pulmonologists run a battery of tests to check for pulmonary diseases. The most basic is a blood test, such as what was done in Hauser's case, in which doctors check immunoglobulin levels. A CT scan of the chest gives a better look at the lungs and thoracic lymph nodes than a simple X-ray. Pulmonary function tests are able to measure how well the lungs work, including how they expand and how much oxygen they can hold. One common test uses a spirometer, an instrument that patients breathe into, which gauges the air entering and leaving their lungs.

Some patients with autoimmune diseases who are treated with IG also have pulmonary complications, which require them to seek out a specialist.

Pulmonologists also look at oxygen saturation levels by measuring the amount of O_2 that is carried by the red blood cells. One method of measuring O_2 uses a pulse oximeter, a device that shines a light on the fingernail bed and calculates the amount of oxygen in the blood. This works because blood cells reflect different levels of light based upon the amount of oxygen they are carrying. Another form of testing doctors use is sputum, or phlegm, cultures. The pulmonologists check the mucus to see what types of organisms are colonized or causing an infection in the chest.

Treating Pulmonary Disease

IG is a common therapy for pulmonary disease, but there also are other therapies. To assist with breathing, asthma inhalers and nebulizers can be used. A pulmonologist also may prescribe corticosteroids to reduce swelling in the breathing tubes. If there is an infection in the lungs, antibiotics are usually recommended by the doctor. And, those who have difficulty getting rid of secretions in the chest are given devices to help break up the mucus and bring it up. Szekely says this is important for PIDD patients because leaving the chest congested with mucus can lead to pneumonia. Last but not least, patients with severe COPD and low oxygen levels may receive supplemental oxygen, which comes in portable devices and does not require a hospital stay.

Hauser's lung function is poor, and she is in constant

need of supplemental oxygen. She uses a concentrator, a machine that takes oxygen out of the air and condenses it for use by the patient. She also has portable oxygen tanks for when she leaves her home.

To further deal with her illness, Hauser is on intravenous immunoglobulin (IVIG). According to a 2006 report from the *Cleveland Clinic Journal of Medicine*, regular IV infusions help reduce the rate of infection and protect pulmonary function. Hauser started with once-a-month treatments, but the benefit wore off after a week, so two years ago, she changed to a weekly low-dose IVIG treatment. Each week, she devotes a full day out of her schedule to receive the treatment: She drives an hour to her doctor to receive the infusion, which takes six hours, and then drives an hour back home. "There are times when I don't want to do this, but you know you need the IVIG to survive," she says. "It's a double-edged sword: You need it and it keeps you healthy, but there are definitely things you have to give up."

One of the things Hauser had to give up was her aspiration to become a nurse, since being around sick patients jeopardizes her health. Then, after graduating from college in 2009, she wanted to get her doctorate in biology to conduct research, but that wasn't possible with her constant illnesses. Her frequent infections and other health issues also made it difficult for her to hold down a job. But, she hasn't given up on pursuing her dream of working in the medical field and is taking online classes to learn medical animation. "I know that there are some people who say, 'I wish I wouldn't have to work,'" she explains. "But I want to work; I pray for the day I can work a 20-hour week."

IG is a common therapy for pulmonary disease, but there also are other treatments.

Hauser still struggles to find the right combination of medicine to alleviate her symptoms. To help her breathe, she uses DuoNeb, a solution that she inhales every four hours through a nebulizer. She also takes a medication that breaks up mucus. Aside from her pulmonary problems, Hauser suffers from gastrointestinal ailments and joint pain, as well as severe migraines that get so bad she's been forced to go to the emergency room to seek relief.

"I found out that I have a bunch of health issues that doctors don't seem to be able to figure out," she says of her non-lung-related ailments. "Finding a doctor [who] will put them all together is really hard."

Szekely recommends that those who suspect they might have a pulmonary issue should get it checked out. "A thorough evaluation by a pulmonary specialist would be advised — it's a different look, it's a different approach," he says. "If you are having problems, seeing a respiratory specialist won't hurt. If you have pulmonary problems and aren't currently managed adequately or think you have any respiratory issues, seeing a pulmonologist would be a good idea."

Early Diagnosis Is Key

Hauser says the keys to avoiding major pulmonary problems are early diagnosis and proper treatment. "The longer you go without treatment and diagnosis, the more lasting effects [there are]," she says. "When you get respiratory infections that frequently, you get scarring in your lungs. The amount of infections I had caused my lung function to go down."

She tells people to go with their gut feeling if they think they might have a condition like hers. "My biggest piece of advice is trust yourself and advocate for yourself," she says. "A doctor can't tell you how you feel. You know your body best." ◪

JENNIFER KESTER *is a San Diego-based writer and editor specializing in health and lifestyle issues.*

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  - ≥ 6.2 log reduction through 4% PEG precipitation and ≥ 5.5 log reduction through 20 nm nanofiltration of an experimental agent considered a model for the vCJD and CJD agents [3]

Please see reverse for Important Safety Information and Black Box Warning.

(1) Data on file, Instituto Grifols, S. A.
(2) Berger M. et al. Efficacy, Pharmacokinetics, Safety and Tolerability of Flebogamma® 10% DIF, a high purity human intravenous immunoglobulin in primary immunodeficiency. J Clin Immunol 2010; 30 (2): 321-9.
(3) Diez JM, et al. Capacity of the manufacturing process of Flebogamma® DIF, a new human high purity intravenous immunoglobulin, to remove a TSE model-agent. Biologicals (2010), doi:10.1016/j.biologicals.2010.08.003.

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Important Safety Information

Flebogamma® 10% DIF is a human immune globulin intravenous (IGIV) that is indicated for the treatment of primary immune deficiency (PI), including the humoral immune defect in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott - Aldrich syndrome.

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Use of immune globulin intravenous (IGIV) products, particularly those containing sucrose, has 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 those receiving known nephrotoxic drugs** (*see Warnings and Precautions [5.2]*). **Flebogamma® 10% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Flebogamma® 10% DIF at the minimum infusion rate practicable** (*see Dosage and Administration [2.3], Warnings and Precautions [5.2]*).

Flebogamma® 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to the administration of human immune globulin and in IgA deficient patients with antibodies to IgA and a history of hypersensitivity. In case of hypersensitivity, discontinue Flebogamma® 10% DIF infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

In patients at risk for developing acute renal failure, monitor renal function, including blood urea nitrogen, serum creatinine, and urine output.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma® 10% DIF therapy.

Thrombotic events may occur during or following treatment with Flebogamma® 10% DIF. Monitor patients at risk for thrombotic events, including those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and known or suspected hyperviscosity.

Aseptic meningitis syndrome (AMS) may occur infrequently with Flebogamma® 10% DIF treatment. AMS may occur more frequently following high doses and/or rapid infusion of IGIV.

Flebogamma® 10% DIF may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis.

Non-cardiogenic pulmonary edema [Transfusion-Related Acute Lung Injury (TRALI)] may occur in patients following Flebogamma® 10% DIF treatment. If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient serum.

All patients, but especially individuals receiving Flebogamma® 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events.

Because Flebogamma® 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for Flebogamma® 10% DIF.

The most common adverse reactions (reported in ≥ 5% of clinical trial subjects) occurring during or within 72 hours of the end of an infusion were headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema. The most serious adverse reactions observed with Flebogamma® 10% DIF were back pain, chest discomfort, and headache (2 patients); and chest pain, maculopathy, rigors, tachycardia, bacterial pneumonia, and vasovagal syncope (1 patient).

Please refer to enclosed Flebogamma® 10% DIF full prescribing information for full prescribing details, including comprehensive adverse event profile and black box warning.

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BRIEF SUMMARY
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INDICATIONS AND USAGE
Flebogamma® 10% DIF is a human immune globulin intravenous (IGIV) that is indicated for the treatment of primary immune deficiency (PI), including the humoral immune defect in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott - Aldrich syndrome.

DOSAGE AND ADMINISTRATION
The recommended dose of Flebogamma® 10% DIF for patients with PI is 300 to 600 mg/kg body weight (3.0 to 6.0 mL/kg), administered every 3 to 4 weeks.

The infusion of Flebogamma® 10% DIF should be initiated at a rate of 0.01 mL/kg body weight/minute (1.0 mg/kg/minute). If there are no adverse drug reactions, the infusion rate for subsequent infusions can be slowly increased to the maximum rate of 0.08 mL/kg/minute (8 mg/kg/minute).

Ensure that patients with pre-existing renal insufficiency are not volume depleted. For patients judged to be at risk for renal dysfunction or thrombotic events, administer Flebogamma® 10% DIF at the minimum infusion rate practicable, and consider discontinuation of administration if renal function deteriorates.

CONTRAINDICATIONS
Flebogamma® 10% DIF is contraindicated in patients who have had a history of anaphylactic or severe systemic reactions to the administration of human immune globulin and in IgA deficient patients with antibodies to IgA and a history of hypersensitivity.

WARNINGS AND PRECAUTIONS

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- **Use of immune globulin intravenous (IGIV) products, particularly those containing sucrose, has 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 those receiving known nephrotoxic drugs** *(see Warnings and Precautions [5.2])*. **Flebogamma® 10% DIF does not contain sucrose.**
- **For patients at risk of renal dysfunction or failure, administer Flebogamma® 10% DIF at the minimum infusion rate practicable** *(see Dosage and Administration [2.3], Warnings and Precautions [5.2])*.

- Weigh the potential risks and benefits of Flebogamma® 10% DIF against those of alternative therapies in all patients for whom Flebogamma® 10% DIF is being considered.
- Before prescribing Flebogamma® 10% DIF, the physician should discuss risks and benefits of its use with patients.

Hypersensitivity
Severe hypersensitivity reactions may occur. In case of hypersensitivity, discontinue Flebogamma® 10% DIF infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions.

Renal Dysfunction/Failure
Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of Flebogamma® 10% DIF and at appropriate intervals thereafter. If renal function deteriorates, consider discontinue use of Flebogamma® 10% DIF.

In patients who are at risk of developing renal dysfunction because of pre-existing renal insufficiency or predisposition to acute renal failure, administer Flebogamma® 10% DIF at the minimum rate of infusion practicable.

Hyperproteinemia
Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving Flebogamma® 10% DIF therapy. It is clinically critical to distinguish true hyponatremia from a pseudo-hyponatremia that is temporally or causally related to hyperproteinemia with concomitant decreased calculated serum osmolarity or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity and a higher risk of thrombotic events.

Thrombotic events may occur during or following treatment with Flebogamma® 10% DIF. Monitor patients at risk for thrombotic events, including those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization, and known or suspected hyperviscosity.

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 Flebogamma® 10% DIF at the minimum rate of infusion practicable *(see Dosage and Administration [2.3])*.

Aseptic Meningitis Syndrome (AMS)
AMS may occur infrequently with Flebogamma® 10% DIF treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae (3-4).

AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting (*see Patient Counseling Information* [17]). Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series and elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination to patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis.
AMS may occur more frequently following high doses (2 g/kg) and/or rapid infusion of IGIV.

Hemolysis
Flebogamma® 10% DIF may contain blood group antibodies that can act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis (5-6). Delayed hemolytic anemia may develop subsequent to Flebogamma® 10% DIF therapy due to enhanced RBC sequestration (7), and acute hemolysis, consistent with intravascular hemolysis, has been reported.

Monitor patients for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after Flebogamma® 10% DIF infusion, perform appropriate confirmatory laboratory testing (*see Patient Counseling Information* [17]).

Transfusion-Related Acute Lung Injury (TRALI)
Non-cardiogenic pulmonary edema may occur in patients following Flebogamma® 10% DIF treatment (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 (*see Patient Counseling Information* [17]). If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.

Infusion Reactions
All patients, but especially individuals receiving Flebogamma® 10% DIF for the first time or being restarted on the product after a treatment hiatus of more than 8 weeks, may be at a higher risk for the development of fever, chills, nausea, and vomiting. Careful monitoring of recipients and adherence to recommendations regarding dosage and administration may reduce the risk of these types of events (*see Dosage and Administration [2.3]*).

Transmissible Infectious Agents
Because Flebogamma® 10% DIF is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for Flebogamma 10% DIF. All infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Biologicals at 1-888-474-3657. Before prescribing or administering Flebogamma® 10% DIF, the physician should discuss the risks and benefits of its use with the patient (*see Patient Counseling Information* [17]).

Monitoring: Laboratory Tests
- Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of Flebogamma® 10% DIF and at appropriate intervals thereafter.
- 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, because of the potentially increased risk of thrombosis.
- If signs and/or symptoms of hemolysis are present after an infusion of Flebogamma® 10% DIF, perform appropriate laboratory testing for confirmation.
- If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

Interference with Laboratory Tests
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. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

Adverse Reactions
The most common adverse reactions (reported in ≥ 5% of clinical trial subjects) occurring during or within 72 hours of the end of an infusion were headache, chills, fever, shaking, fatigue, malaise, anxiety, back pain, muscle cramps, abdominal cramps, blood pressure changes, chest tightness, palpitations, tachycardia, nausea, vomiting, cutaneous reactions, wheezing, rash, arthralgia, and edema. The most serious adverse reactions observed with Flebogamma® 10% DIF were back pain, chest discomfort, and headache (2 patients); and chest pain, maculopathy, rigors, tachycardia, bacterial pneumonia, and vasovagal syncope (1 patient).

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

In a multicenter, open-label, non-randomized, historically controlled clinical study, 46 individuals with primary humoral immunodeficiency received infusion doses of Flebogamma 10% DIF at 300 to 600 mg/kg body weight every 3 weeks (mean dose 469 mg/kg) or 4 weeks (mean dose 457 mg/kg) for up to 12 months (*see Clinical Studies [14.1]*). Routine pre-medication was not allowed. Of the 601 infusions administered, 130 infusions (22%) in 21 (47%) subjects were given pre-medications (antipyretic, antihistamine, or antiemetic agent) because of experience with consecutive infusion-related adverse reactions.

One subject experienced four serious adverse events (AEs, bacterial pneumonia, subcutaneous abscess and two episodes of cellulitis) and withdrew from the study. Two other subjects who participated in the study discontinued prematurely due to AEs (back pain/chest pain/headache; and chills/tachycardia). Three subjects experienced four serious non-related AEs (drug abuse/depression; hernia; and sinusitis).

Forty-five (98%) subjects experienced at least 1 AE irrespective of the relationship with the product, and these subjects reported a total of 723 AEs. Thirty-eight subjects (83%) had an adverse reaction at some time during the study that was considered product-related. Of the 21 subjects receiving pre-medications, 12 (57%) subjects reported adverse reactions during or within 72 hours after the infusion in 48 of the 130 pre-medicated infusions (37%).

Table 2. Treatment-related Adverse Events Occurring in ≥ 5% of Subjects with PI during a Flebogamma® 10% DIF Infusion or within 72 Hours after the End of an infusion

Adverse Event	Subjects (%) [N=46]	Infusions (%) [N=601]
Headache	24 (52%)	67 (11%)
Rigors	17 (37%)	37 (6%)
Pyrexia	15 (33%)	27 (5%)
Tachycardia	10 (22%)	18 (3%)
Hypotension	9 (20%)	11 (2%)

Adverse Event	Subjects (%) [N=46]	Infusions (%) [N=601]
Back pain	8 (17%)	27 (5%)
Myalgia	8 (17%)	17 (3%)
Body temperature increased	4 (9%)	6 (1%)
Nausea	4 (9%)	6 (1%)
Pain	4 (9%)	8 (1%)
Chest discomfort	3 (7%)	4 (1%)
Chest pain	3 (7%)	5 (1%)
Infusion site reaction	3 (7%)	4 (1%)
Pain in extremity	3 (7%)	3 (0.5%)

The total number of adverse events occurring during or within 72 hours after the end of an infusion, *irrespective of causality*, was 359, excluding non-serious infections.

Table 3 lists the AEs that occurred in greater than 5% of subjects during a Flebogamma® 10% DIF infusion or within 72 hours after the end of an infusion, *irrespective of causality*.

Table 3. Adverse Events Occurring in ≥ 5% of Subjects with PI during a Flebogamma® 10% DIF Infusion or within 72 Hours after the End of an infusion, *Irrespective of Causality*

Adverse Event	Subjects (%) [N=46]	Infusions (%) [N=601]
Headache	28 (61%)	71 (12%)
Pyrexia	17 (37%)	27 (5%)
Rigors	17 (37%)	37 (6%)
Back pain	13 (28%)	29 (5%)
Cough or Productive cough	12 (26%)	5 (1%)
Nausea	12 (26%)	8 (1%)
Hypotension	10 (22%)	13 (2%)
Tachycardia	10 (22%)	19 (3%)
Myalgia	9 (20%)	17 (3%)
Diarrhea	8 (17%)	2 (0.3%)
Infusion site reaction	8 (17%)	8 (1%)
Pharyngolaryngeal pain	7 (15%)	3 (1%)
Nasal congestion	7 (15%)	2 (0.3%)
Postnasal drip	7 (15%)	4 (1%)
Arthralgia	6 (13%)	2 (0.3%)
Conjunctivitis	6 (13%)	2 (0.3%)
Pain	6 (13%)	10 (2%)
Vomiting	6 (13%)	0 (0%)
Dizziness	5 (11%)	3 (1%)
Fatigue	5 (11%)	1 (0.2%)
Urinary tract infection	5 (11%)	4 (1%)
Chest pain	5 (11%)	4 (1%)
Ear pain	5 (11%)	1 (0.2%)
Pain in extremity	5 (11%)	2 (0.3%)
Dyspnea	5 (11%)	0 (0%)
Rhinorrhea	4 (9%)	1 (0.2%)
Wheezing	4 (9%)	4 (1%)
Body temperature increased	4 (9%)	6 (1%)
Neck pain	4 (9%)	2 (0.3%)
Sinus pain	4 (9%)	1 (0.2%)
Chest discomfort	4 (9%)	4 (1%)
Crackles lung	4 (9%)	2 (0.3%)
Abdominal pain	3 (7%)	2 (0.3%)
Dyspepsia	3 (7%)	1 (0.2%)
Toothache	3 (7%)	0 (0%)
Gastroesophageal reflux disease	3 (7%)	0 (0%)
Lymphadenopathy	3 (7%)	3 (1%)
Respiratory tract congestion	3 (7%)	0 (0%)
Fall	3 (7%)	1 (0.2%)
Hypertension	3 (7%)	4 (1%)

In this study, the upper bound of the 1-sided 95% confidence interval for the proportion of Flebogamma® 10% DIF infusions associated with one or more AEs was 37.8% (total infusions: 208; actual proportions: 34.6%). The average percent of infusions with AEs during or within 72 hours after the end of an infusion for each individual subject was 36.7% and the upper bound of the 1-sided 95% confidence interval was 43.9%.

AE reporting was based upon a clinical protocol precluding pre-medication against AEs. Pre-medication could be utilized only after the first 2 infusions only in those patients that exhibited adverse events.

Forty-three of the 46 subjects enrolled in this study had a negative Coombs test at baseline. Of these 43 subjects, 10 (23.3%) developed a positive Coombs test at some time during the study. However, no subjects showed evidence of hemolytic anemia.

Post-marketing Experience

Because adverse reactions are reported voluntarily post-approval from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. The following adverse reactions have been identified during post approval use of intravenous immune globulins, including Flebogamma 5% (see References [15]).

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), Transfusion-Related Acute Lung Injury (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 multiformae, dermatitis (e.g., bullous dermatitis)
Hematologic	Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs) test
Musculoskeletal	Back pain
Gastrointestinal	Hepatic dysfunction, abdominal pain
General/Body as a Whole	Pyrexia, rigors

DRUG INTERACTIONS

Passive transfer of antibodies may transiently impair the immune response to live attenuated virus vaccines such as measles, mumps, and rubella. Inform the immunizing physician of recent therapy with Flebogama® 10% DIF so that appropriate measures may be taken (*see Patient Counseling Information* [17]).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been performed with Flebogamma® 10% DIF. It is also not known whether Flebogamma® 10% DIF can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Flebogamma® 10% DIF should be given to a pregnant woman only if clearly needed. Immunoglobulins cross the placenta from maternal circulation increasingly after 30 weeks of gestation.

Nursing Mothers

Use of Flebogamma® 10% DIF has not been evaluated in nursing mothers.

Pediatric Use

Three (3) pediatric patients with primary humoral immunodeficiency (two between the ages of 6 and 10, and one 16 year old) were included in the clinical evaluation of Flebogamma® 10% DIF. This number of subjects is too small to establish safety and efficacy in the pediatric population (*see Clinical Studies [14]*).

Geriatric Use

Use caution when administering Flebogamma® 10% DIF to patients over 65 years of age who are judged to be at increased risk for developing certain adverse reactions such as thromboembolic events and acute renal failure (*see Boxed Warning, Warnings and Precautions [5.2]*). Do not exceed the recommended dose, and infuse Flebogamma® 10% DIF at the minimum infusion rate practicable.

One (1) patient with primary humoral immunodeficiency at or over the age of 65 was included within the clinical evaluation of Flebogamma® 10% DIF. This number of geriatric patients was too small for separate evaluation from the younger patients for safety or efficacy (*see Clinical Studies [14]*).

HOW SUPPLIED/STORAGE AND HANDLING

Flebogamma® 10% DIF is supplied in single-use, individually laser etched vials containing the labeled amount of functionally active IgG.

The following presentations of Flebogamma® 10% DIF are available:

NDC Number	Fill Size	Grams Protein
61953-0005-1	50 mL	5g
61953-0005-2	100 mL	10g
61953-0005-3	200 mL	20g

Each vial has an integral suspension band and a label with two peel-off strips showing the product name and lot number.

DO NOT FREEZE.

When stored at room temperature (up to 25 ºC [77 ºF]), Flebogamma® 10% DIF is stable for up to 24 months, as indicated by the expiration date printed on the outer carton and container label.

Keep Flebogamma® 10% DIF in its original carton to protect it from light.

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Let's Talk!

By Trudie Mitschang

If your life depends on immune globulin, this column is for you! Here, we have an opportunity to network and share our experiences about all of the ramifications of our illnesses, and to learn from one another. If you have a question, comment or experience to share for a future column, email it to us at editor@IGLiving.com.

As most of our readers know, immune globulin (IG) is a therapeutic plasma product that requires specialized training to administer. Even nurses who are highly experienced at placing intravenous (IV) lines may not understand how much different IG is and why it requires more care than other IV medications. Unfortunately, many hospitals, infusion clinics and homecare providers often don't take that into consideration when hiring a nurse to deliver IG. This month, we sat down with Heather Lawson, a registered nurse with seven years of experience administering IG infusions, to find out what she's learned and what tips she offers patients to help infusions go more smoothly.

Trudie: Tell us about your nursing background.

Heather: I've been a nurse for 12 years, including several years in the emergency room (ER). After becoming a mom, I transitioned into the home healthcare environment. Because of my ER training, I was good at performing IV sticks, so I got a lot of those assignments early on. Today, I have seven IG patients that I treat regularly.

Trudie: How did you come to specialize in IG infusions?

Heather: The first time I was assigned to an IG patient, I had never even heard of gammaglobulin, and since I don't like to be ignorant, I immediately began looking for information. I was overwhelmed by how specialized this drug is and how little I knew, so I made it my mission to become educated.

Trudie: How do you suggest healthcare providers and nurses educate themselves?

Heather: The Internet remains a good place to start, and of course, *IG Living* is a great resource. I also refer people to the Immune Deficiency Foundation and Jeffrey Modell Foundation websites. Many of the brochures and pamphlets are downloadable and free.

Trudie: What are some important tips you've learned about IG product handling?

Heather: The average IG product has a shelf life of 24 to 36 months and needs to be kept at about 77 degrees Fahrenheit, depending on the product. Some products are kept in the refrigerator, but it's important to make sure [those are] brought to room temperature prior to infusion. I have my patients take the product out [of the refrigerator] the night before, since we generally start infusing first thing in the morning.

Trudie: What have you learned about the differences in various IG products?

I think patients need to feel empowered to ask questions and request a change of product if they have a bad reaction.

Heather: The main thing is that IG is not "one size fits all." For example, some products contain stabilizers that have a high sugar content, which can cause a surge in glucose levels. This can be dangerous if you have renal issues or are diabetic.

Trudie: Side effects can be trouble-

some for many IG patients. Any tips on helping infusions go more smoothly?

Heather: I think patients need to feel empowered to ask questions and request a change of product if they have a bad reaction. I've seen some patients come down with wicked migraines while using some IG products, and then do fine with another. In general, when it comes to side effects, the biggest issue for people is the rate at which a product is administered. I have patients who have no side effects because we slowed their infusion rate down and kept them well hydrated. Some people don't understand that it's not OK to feel debilitated 72 hours after an infusion; sometimes all you have to do is slow the rate down. So what if it takes all day? It's better than being sick all day.

Trudie: What else affects a patient's response to their infusion?

Heather: I've found that premedication can make a big difference for some people. Many doctors prescribe antihistamines and NSAIDs and, of course, recommend drinking lots of water prior to the administration of IG. This can prevent side effects. If a significant reaction occurs, the doctor, nurse and pharmacist need to be informed. A reaction can occur up to 72 hours later.

Trudie: What are some of the greatest challenges you face as an infusion nurse?

Heather: Doing damage control and establishing trust. In this line of work, building relationships is important; my patients are like family members to me. My goal is to make the experience as stress-free as possible. I don't wear scrubs to work because I don't think people need

to be reminded they are sick. I want to create a relaxed atmosphere so they feel they can open up. Sadly, every patient has a challenging story. With immune diseases, no one ever gets diagnosed quickly, finds a great doctor and moves on with their lives. So that's why it's so important to connect with others who can relate. Support groups and online resources can really help.

Trudie: How can patients begin to become their own advocates?

Heather: Never let any one individual stick you more than two or three times while attempting an infusion. If that happens, ask for a more experienced nurse. If you have infusions performed on your hands, running them under warm water beforehand can help prep the veins. Also, ask for the smallest needle possible, and make sure your infusion sites are alternated each time. If you are in a clinic setting, talk to other patients and find out which nurses they recommend.

Trudie: How can IG patients find a qualified infusion nurse?

Heather: In addition to asking directly about their experience with IG infusions, it's important to find a nurse who listens to you. You have to be your own advocate. If you have a home healthcare company and you are not comfortable with the nurse they send, you can request someone else. If you like the nurse, but the nurse is not educated to your satisfaction, ask them if they are willing to learn about your disease state. Stop worrying about hurting people's feelings; worry about what is best for you.

TRUDIE MITSCHANG *is a staff writer for* IG Living *magazine.*

Transitions

By Ronale Tucker Rhodes, MS

Immune globulin (IG) is a miraculous therapy, and no one knows this better than patients who receive it for an immune-mediated disease. Indeed, without IG, these individuals would fail to make the transition from living in a constant state of illness, struggling to survive, to a healthy, happy lifestyle. That is what this column is about — the unique and sometimes extraordinary stories of people of all ages whose lives have positively transitioned with the help of IG. We want to hear your stories! Email us at editor@igliving.com.

Not a Victim; Just Victorious

IN 1987, BRENDA Kulczak came down with a stiff neck that just wouldn't go away. She attributed it to stress caused by raising a small child and a possible problem with her marriage. But even after her divorce, the stiff neck turned into symptoms that kept getting worse. "The worst was feeling spasms in my lower back, which felt like contractions," explains Brenda. "I would have to grab onto countertops and hold tight and remember what it was like having a baby and tell myself to breathe through it." Then, her pain got so bad that she was unable to walk. Even after Brenda's diagnosis many years later, it was only when she took control of her own prescription for good health that she began to lead a normal and active life.

A Long Road to Diagnosis

Before Brenda's symptoms advanced, she got pregnant for a third time, but she had a miscarriage. The OB-GYN told her that her uterus was causing the back pain and recommended a hysterectomy. "That was after my two boys were born," says Brenda. "None of it made sense to me, but I thought maybe she was right." So, at age 35, she underwent a hysterectomy. But, for no reason; it didn't work and the spasms persisted. "I thought: 'I should have gone with my gut and never had the hysterectomy,'" says Brenda. "I'm a lot smarter now."

After that, Brenda was in pain for years before being diagnosed. She took muscle relaxants, she saw a chiropractor, she went to a pain center, where they recommended killing the nerve in her left leg that was sending the pain to her brain, and she got Botox injections. Eventually some of the treatments did damage to her left leg.

Brenda is a medical technologist and was working in a reference lab blood bank in Atlanta when the spasms worsened. She'd seen numerous doctors and continued to undergo numerous procedures, but still no diagnosis. The worst, says Brenda, is "when I couldn't sit down, lie down or do anything other than having someone hold me tight because my muscles were so contracted."

Then, in 2001, she saw neurologist No. seven, who considered that she might have "a one-in-a-million disease" and proceeded to test her for glutamic acid decarboxylase antibodies and islet cells, and the results came back positive. Her diagnosis: stiff person syndrome (SPS).

Brenda (right) believes in staying positive and taking one day at a time.

Diagnosed But Still Diseased

Brenda was first treated with Solu-Medrol intravenous, which worked. "It was like the miracle drug, and I was so happy," she exclaims. First told that she would be on the drug for only four months and then she'd go into remission, she unfortunately learned that four months became six months and then the rest of her life.

While contending with her health problems, Brenda had remarried. She and her husband, Chris, began researching the disease and found a study that was being conducted by the National Institutes of Health (NIH). For two years, she was evaluated and donated blood and spinal fluid. In 2003, the NIH recommended she be switched from Solu-Medrol to intravenous immune globulin (IVIG). "I couldn't tell the difference between the two treatments," says Brenda, "but thank goodness I have good insurance through my husband, who is also a medical technologist in a hospital whose insurance covered the cost of my treatments."

Yet, even though IVIG was making her feel better, that didn't put an end to her SPS symptoms. One day at work, she had her first "tin man" fall. "One minute you're fine, and all of a sudden your brain says, 'What do you think you're standing on?'" explains Brenda. "I couldn't feel from my waist down." She knew she was falling. Trying to protect the blood tubes in her hand, "I bounced off of every biohazard can and drawer that was in the way, landed on my right elbow, which caused a fractured radial head, hit my head on the tile floor, and then regained movement in my legs." That was before she understood that tin man falls were a part of SPS. "The nurses and doctors I worked with thought I had blacked out, but I knew I hadn't," she says. It would be the first of 10 different falls she unexpectedly had since being diagnosed with SPS.

She also was still experiencing spasms, some of which would occur while she was driving. She had already had two car accidents due to the spasms and medication that caused her fatigue. But, when she totaled her third car after starting IVIG, she decided to call it quits: "I told my boss I wouldn't be back."

Even after Brenda's diagnosis many years later, it was only when she took control of her own prescription for good health that she began to lead a normal and active life.

Taking Matters into Her Own Hands

"Doctors say it's a debilitating disease and things will never get better," says Brenda. "But, that's not true.... I just knew that there was no way I was giving up and this was the way it had to be. I had two children to live for and I was going to try to find a way to be as good as I was before this disease." So she started listening to her body and trying unconventional treatments. "I got my mind set right and did whatever I had to do — neuromuscular therapy, acupuncture, chiropractic, etc. — even though some of it wasn't covered by insurance," says Brenda. "We spent a lot of money trying to make me walk without a cane."

While living in Atlanta, she saw an OB-GYN who recommended she try a B12 shot to help with fatigue. "As a medical technologist, I questioned it since I'm not B12-deficient," says Brenda. But, she tried it and the fatigue got better. "I've been giving myself B12 shots for seven or eight years, and my neurologist actually believes in it now. I don't know if she'd prescribe it to anyone else, but she does prescribe it for me."

Brenda also began to notice how her condition was so different in the summer than in winter. "During the summers, I was a normal person," she explains. "I'd be at the gym, or I could walk a certain distance at work with no pain." Then, when the cold weather came, things would get worse. She'd have to start using a cane again and had trouble walking up curbs. "I knew there was a difference between warm and cold weather, and I kept telling my family I was moving to Hawaii or Aruba," says Brenda. When her husband got tired of seeing how sore she was in the winter months, he found a job

in the North Port, Fla., area and they relocated.

Now, instead of taking sea salt baths to help her muscles relax, she soaks in the Gulf waters and enjoys the heat from the sun. She also has changed her diet. "I've learned through kinesiology and acupuncture that I have to eat foods that help me with my condition," says Brenda, who explains that her diet is gluten-, sugar-, wheat- and yeast-free, and she eats no fried food. She also gave up beef and pork and eats more fish, chicken and vegetables. "The key is to stay as natural as possible," she says. "It just changes the way I feel."

Exercise also is once again a big part of her life. Currently, she goes to the gym three days a week,

Exercise is once again a big part of Brenda's life, including yoga, Pilates, cardio workouts, swimming and scuba diving.

beginning with a 30- to 45-minute cardio workout, usually on the elliptical trainer (she avoids the treadmill because "it moves me instead of me moving it"), and then finishes with a 30-minute abdominal class and an hour and a half of yoga and sometimes Pilates. She's also a swimmer and a scuba diver, although she says it took a while to get a doctor to sign off on her diving papers because of all the medications she's on. "I didn't start doing all this exercise on my own," says Brenda. "It took help and time to get there. That's where the neuromuscular therapy, massage and acupuncture came in."

According to Brenda, exercise has improved her self-confidence and makes her feel normal. And because of it, she no longer relies on the cane as much. When she feels bad, she calls it an anxiety attack, which can occur when crossing a parking lot or walking into a large room. "I'll just stop and do some yoga breathing, bend down and talk to myself," she explains. "I reset the breaker. I think of my body as an electrical switch in the house, and I restart it. I also say to myself, 'Angels wings; God is walking with me and will not let me fall.'"

One day in 2005, while lying by her pool, she said, "I'm over this." She called the local hospital to see if they could use someone to cover lunch and breaks and was hired. She now works two days a week, five hours each day. "My disease took away the job that I went to college for — what I dreamed about doing since middle school, as well as my biweekly paycheck," says Brenda. "I love being a blood banker. Those few hours I get to work makes a difference mentally and financially."

A Continuous Journey to Better Health

Brenda has the support of her husband and two boys: Chase, who is 18 and just started college, and Joshua, who is 24 and due to have his first child in March. But, her disease has taken its toll on them all. "Chase told his counselors that he never knew me as normal, which made me feel sad," says Brenda. "All those days on the tennis courts, riding bikes, playing baseball and basketball when he was 4 years old. I think he was just too young to remember."

Exercise has improved her self-confidence and makes her feel normal.

Now, however, she's getting back to normal. Brenda believes it's about staying positive and taking one day at a time — trying to see progress each day. "I couldn't walk from my house to the mailbox because I got freaked out about walking on the concrete," she explains. Now, she tricks her brain, and she's able to not only make that walk, she also can ride her bike for five miles.

Her recommendation to others with diseases like hers: "Be happy where you're at at this point in your journey; just never stop going. I'm not looking backward like I used to. I'm not mad anymore because I have this. I have a motto that says, 'I'm not a victim, but I'm victorious.'" ■

RONALE TUCKER RHODES, *MS, is the editor of* IG Living *magazine.*

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Ask Kris

By Kris McFalls

Have a question? Kris McFalls, *IG Living*'s patient advocate, is eager to find answers. Email them to editor@IGLiving.com. Your confidential information will not be used for any purpose but to communicate with you about your questions.

Mark: Why don't more patients take advantage of the "hardship" programs that specialty pharmacies have? I know a specialty pharmacy cannot advertise or promote that they have such a program, but most all have them. I'm always amazed at how many patients don't know about these programs, let alone take advantage of them.

Kris: Good question! Financial hardship or charity care, as it is referred to by the federal government, is meant to be an exception and not the rule, even for highly expensive medications. In general, it is expected that most patients should be able to afford their out-of-pocket expenses. But, for the exceptional need, each company is required to set its own qualifying guidelines, which are based on patient income. In addition to charity care applications, patients also may be required to apply for their state Medicaid program. This may reduce the financial burden for the patient, in addition to ensuring the patient's needs meet state and federal guidelines. Depending on the charity program, some patients who do not qualify for Medicaid may still be eligible for some charity care due to their financial situation.

As you point out, it is important to remember that providers cannot advertise their charity care options. Doing so could result in their facing a legal charge of providing a financial incentive to lure a patient to sign on for service. If this charge is substantiated, the provider and any employees involved could be punished by fines, jail time and loss of Medicare provider licensure. Facing these very serious penalties, most companies and their employees choose not to even dabble in any gray area. Therefore, it is often standard company protocol to not mention charity programs unless the information is requested. Providers are often much more comfortable talking about charity care after a patient broaches the subject.

Financial hardship or charity care, as it is referred to by the federal government, is meant to be an exception and not the rule, even for highly expensive medications.

Charity care also is harder to get these days. This is because over the past few years, reimbursement rates have steadily decreased, leaving providers scrambling for ways to cut costs in order to stay in business. One such cost-cutting option includes lowering the qualifying income threshold for charity care. In other words, patients' income levels must be lower now to qualify for charity care assistance. Remember, every dollar given to charity care is money that is not collected. A company cannot remain solvent if it is not collecting money owed. And, although there may be some small tax advantage for charity care, it is not an immediate credit and still does not translate into daily cash flow.

While reimbursement rates are declining, patient needs are increasing. Rising out-of-pocket expenses through higher copayments, deductibles and coinsurance are reasons we may be hearing more about this issue as more patients struggle to make ends meet. Even so, some patients are just not comfortable sharing their personal financial information to qualify for help. Applying for charity care and/or Medicaid requires patients to reveal quite a bit of private information, along with proof of income in some cases. And, some patients are just not willing to make these disclosures, even if it means reducing their financial responsibilities.

The combined demands on the providers and the patients lead to quite a storm for all involved. I'm not sure what the answer is. I just know that we need to keep asking the questions. ■

KRIS MCFALLS *has two adult sons with chronic diseases treated with IG. She is formerly a physical therapist assistant, and currently is* IG Living*'s full-time patient advocate.*

With Hope On My Side

By Ever Fecske

SOMETIMES HOPE IS hard to find. On rare occasions, I have to look so deep within myself for even an ounce of hope that I think I may drown. I don't want to feel hopeless, because the loneliness that accompanies it negatively affects my health. Yet, as hard as it may be sometimes, I know that I have to have hope on my side to help me be healthy.

Since my diagnosis six years ago, having hope is what has allowed me to cope. More than anything, I have believed that my doctors and I would find a way for me to live a life as close to normal as possible. I have taken a lot of the responsibility for my quality of life. For example, taking prednisone is enough to challenge any sense of hope I may feel, but I refuse to give in to that feeling. I have continued to hope for a normal future, despite all my confusion and questions, and a body and face I don't recognize. With hope, I have created goals for myself. I have cut out magazine clippings of what I hope for, from individual words like "faith," "love" and "courage," to pictures of tropical places, beautiful clothes and healthy food. I have filled myself with visions of hope.

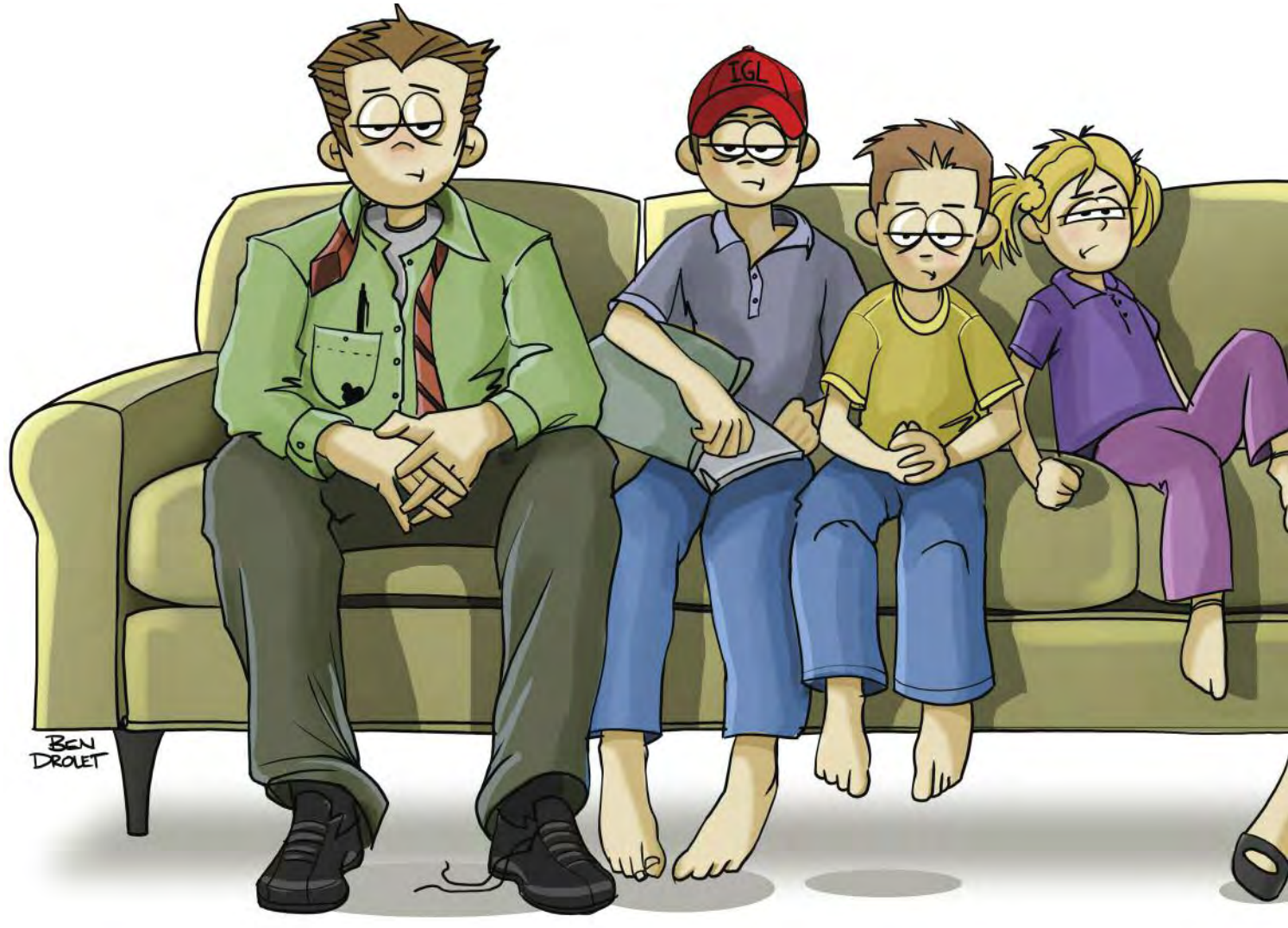
I have made it a priority to visualize my healthy body and what I will do when I accomplish my optimum health. I see myself lying on a beach in a bikini — with no prednisone in sight. I imagine having the energy to run to Starbucks and drink a coffee without any difficulty breathing. I envision my life without the stress of leaving my house in fear of not finding a public restroom in time. Oh, what a world that would be!

It is so important for hope to be a part of everyday life. Just as important is having faith that hope will be found. Recently, I received results of a CT scan of my lungs. After being on prednisone for five years to try to keep my life-threatening lung disease from taking over, we decided to try one last treatment. Just two months later, I've been told by my doctor that my lungs are showing "significant improvement." This is mostly the result of the hard work my doctors and I have put into finding a solution to this scary prognosis — and of having been resilient and always hopeful! It has been a long five years, and without hope, I may have given up a long time ago. Hope is what has helped me continue to believe that there is something out there that will work.

Sometimes, life for people with a chronic illness can feel like an uphill climb. We push and push ourselves to keep hiking. We may be out of breath and in pain (and, gosh, are the shoes ugly!), but once we get to the top and look over to the other side, it all seems worth it; we climbed with purpose and with hope.

I truly believe that when we have hope, we are more likely to take chances on things that may be scary. My new treatment has a lot of potentially damaging side effects, such as brain damage, but I am being fearless because I know hope is on my side. This is a chance I can take to overcome this lung disease, and to live a long and relatively normal life. So far, so good. So, never give up hope; it's what makes life worth living. I hope you all find what you are hoping for! ◪

EVER FECSKE *was diagnosed with CVID and interstitial lung disease in 2004. She is a fashion design student, loves spending time with her fiancé, family and bulldog, Dunkin, and can't get enough of writing, cake decorating and anything that sparkles!*



If the Name Fits…

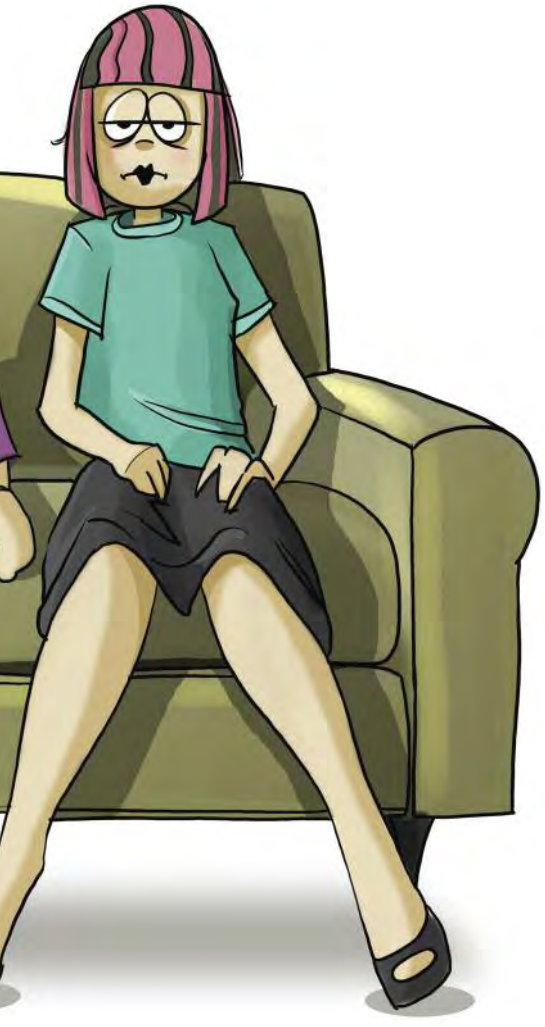
By Cheryl L. Haggard

"WHAT A PERFECT last name for a family with immune issues: Haggard!" my BFF (best friend forever) recently teased me as I blew my nose. Then she did something that came very close to threatening our BFFness: She flipped her Palm Pilot phone-thinga-majig, bounced my last name off a satellite in cyberspace and somehow found the definition for "haggard."

"How perfect is that!" she squealed with delight while thrusting her phone-thing into my direct line of vision. "I mean, come on, Cheryl! You have got to read this!"

Sure enough, Webster defines haggard as "untamed or wild in appearance" (which explains my pink and black hair); or, "having a worn or emaciated look" (which describes what our chronically ill family looks like after a lengthy romp through the local McHamburger joint's germ-infested PlayPlace).

I did manage a gratuitous chuckle for my buddy. And for the record, my brilliant friend was not the first to point out the similarity of Haggard our last name and haggard the definition. In fact, the more physicians I



collect, the more ridiculous the name game gets! Not even I could conjure up this stuff. For example, Dr. Payne is my dentist and Dr. Care is my hand specialist (except he doesn't seem to care when shoving steroids into your carpal tunnel). Then, there is Dr. Mark Hannibal. He's our tried-and-true immunologist who has endured many laughs at his surname's expense. While Hollywood's rendition of a fictional Dr. Hannibal Lecter in "Silence of the Lambs" savored supping on his patients, our Dr. Hannibal won't even touch the hospital's daily special.

So, when it came to naming our children, Mark and I threw caution to the wind, ignored familial suggestions and picked names we liked. Mark and I weren't the norm. In fact, the 21st-century generation of parents with whom Mark and I are associated didn't just pick names that sounded good. No, this cerebral pack of parents studied names from every possible angle. These studious baby namers knew the Greek, Hebrew and Latin root of their son Elliot and daughter Emma. Frankly, the only name that meant anything to us when our kids were babies was what antibiotic was going to kill the streptococcus taking residence in their maxillaries.

This namesake business didn't interest us until one of our infusion nurses asked us what the kids' names meant. So, in between the kids' immune globulin infusions and a sinus wash or two, I made time to research our offspring's given titles. That was when I was sure our kids would be in therapy for the rest of their lives.

The name of our firstborn, Calvin, means "bald one" in Gaelic (which is furthest from the truth, as he inherited my thick straight hair). Upon finding this out, Calvin asked if he was too young to join the hair-of-the-month club.

Caleb means "dog" in Hebrew, which is so perfect for our middle guy. If it wasn't for his furry friends past and present, I don't know how we would get through Caleb's infusions and surgeries.

Then there's our Molly. Despite being derived from the name "Mary," the name seems to be associated more with animals than people. When calling for Molly at the park one day, 10 cocker spaniels and 12 Labrador retrievers came running my way.

I gave up taking it personally when I'd tell someone about my Molly and they'd chime in innocently about their favorite (insert pet type here) Molly. Why? Because my mother-in-law recently told me about a horse she rode in her childhood named — say it with me — Molly. Even in the throes of birthing my sweet daughter, I asked my obstetrician, "What do you think of the name Molly?"

"I love it!" Dr. McGee responded enthusiastically.

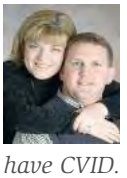
"I guess so," I sputtered in pain. "Why do you like the name Molly?"

"It's the name of my Irish setter."

So, to come full circle with this name thing, I decided to investigate my name, which means (cough) "womanly" (gag) and "tiny" (boohoo, not after having three kids and numbing the sting of their diagnoses by gorging on Ho Hos!).

Finally, there's Mark. Arthurian legend has it that Mark was a king (only a history teacher like my Mark would know such *Jeopardy!* trivia). Oh, and I can't forget St. Mark from the Bible, but let's keep my Mark's sainthood our little secret, eh?

Frankly, all this name stuff my BFF got me started on seems so trivial compared with real-life struggles with chronic illnesses and the inability to pronounce the names of the bugs that got us sick with the illnesses in the first place! Therefore, you can call me anything you want. Just don't call me late for supper. ◪



CHERYL L. HAGGARD *is a stay-at-home mom and has three children, two of whom have CVID. She and her husband, Mark, also operate Under the Hood Ministries at www.underthehoodministries.org.*

Reasonable Accommodations

Patients with chronic illness have specific employment rights, designed to protect them in the workplace.

By Mark T. Haggard

WHEN CONSIDERING the legal rights of chronically ill patients, insurance issues often top the list of concerns. What are not as readily considered are employment rights. Without a job that provides insurance coverage and, hence, access to intravenous immune globulin (IVIG), insurance issues mean little to many immune-mediated patients. Three individuals recently discovered just how important it is to understand their rights when it comes to employment — rights that you as a chronically ill patient also may need to know.

The first individual is Cleve, who was preparing to graduate from law school and who was determined to become a military lawyer. But, when Cleve made his intentions known, an Army representative informed him that he could not join because of his inflammatory bowel disease. Cleve then contacted an attorney, who demanded a reason why a person with an immune deficiency should not be allowed to join the military. The Army's answer: Suppressive agents in his medication did not allow him to be properly vaccinated for certain stations around the world.

The second individual is Barry, a corrections officer with ulcerative colitis. Barry underwent surgery to create an ostomy, a section of the bowel that is pulled through the abdominal wall for discharging waste. When he was

cleared by his own surgeon to return to work, the Department of Corrections physician would not allow him to come back. Barry was told that the ostomy would not allow him to restrain an inmate, and that he now required a bulletproof vest, as well as numerous other "special accommodations."

Then, there is Kyle, a security guard with Crohn's disease who was continually disciplined for leaving his post because he needed frequent access to a bathroom.

For help in their efforts to preserve their jobs, each of these men contacted Jennifer Jaff, the founder and executive director of Advocacy for Patients with Chronic Illness, Inc. What they found out is that the bulk of their — and other chronically ill patients' — employment rights rest on two pieces of legislation: the Americans with Disabilities Act (ADA) and the Family and Medical Leave Act (FMLA).

The Americans with Disabilities Act

The ADA defines a person with a disability as one who has a "physical impairment that substantially limits one or more life activities." Proper immune function qualifies as a life activity. That being the case, the law specifies two things: First, it prohibits the discrimination of those who have disabilities when being hired. Second, it states that employers must provide "reasonable accommodations" for employees with a disability.

But, "there is nothing automatic about ADA," warns Jaff. There is no list of accommodations to which an employer or an employee can point. Instead, employees need to educate their employers about their disease and negotiate with them for reasonable accommodations. For instance, if you work in an area where there is greater exposure to pathogens, your employer should make accommodation.

The trickiest issue for employees is the need for them to perform the "essential functions of the job." If they cannot perform the essential functions, then they are no longer protected. For immune deficient employees, the main issue is attendance: Being at work is an essential function of the job and absences may be counted against you.

Family Medical Leave Act

The FMLA allows 12 weeks of unpaid leave for medical issues at home.

Employees who have worked for more than 12 months for a company that employs more than 50 employees qualify for FMLA. Employees must be granted leave if they have a medical certification stating that they, or a dependent, have a serious health condition. The FMLA requires that the company continue to cover employees' health insurance during their leave and that they be returned to an "equivalent" job to what they had before they left. If they fail to return from medical leave, however, employees may be subject to returning the expense of the benefits that the company paid for them.

The trickiest issue for employees is the demand for them to perform the "essential functions of the job."

When taking medical leave, you must explain to your employer in advance that you are taking leave under FMLA. If it is an emergency and you fail to inform you employer as soon as possible, you should tell your employer you want to use FMLA as soon as possible. The onus is on the employer to let employees know that they have a right to FMLA; if you have not been informed of that right, you may be retroactively granted leave.

The problem with FMLA is with those recently hired (less than one year on the job) and those employed by small businesses (fewer than 50 employees). Employer education, good communication once on the job and a written contract similar to FMLA might suffice to keep an employee at work for a small company.

For patients and caregivers of those with a chronic illness, it is good to know that leave under FMLA does not have to be taken in one 12-week block. Leave can be taken a bit at a time, for instance, for an infusion every three weeks, for an occasional doctor's appointment or for an emergency sinus surgery.

Cleve, Barry and Kyle

Cleve's, Barry's and Kyle's stories, as well as others, are documented in Jaff's book, *It's Hard to Be Sick in America: Stories of Chronic Illness*. Despite the intervention of then-Sen. Hillary Clinton, Cleve's case was not considered because the military is exempt from ADA. For security guard Kyle, rather than simply make "reasonable accommodations," the company fired him at the cost of a hefty severance package. Corrections Officer Barry's case was taken to the Department of Corrections, the governor, and finally the head of employee health services. Barry was allowed to return to work after the Corrections Department was educated concerning his ostomy.

Knowing How to Navigate

As you navigate through life, managing a disease that you did not ask for, it is important to understand what your rights are in each circumstance. As Jaff states, "Patients need the tools to manage their disease as a whole, not just some subset of it." These tools, provided through the ADA and the FMLA, give you the appropriate rights. Knowing these rights and having "reasonable accommodations" can allow you to have a much better quality of life. ■

MARK T. HAGGARD *is a high school teacher and football coach, and has three children, two of whom have CVID. He and his wife, Cheryl, also operate Under the Hood Ministries at www.underthehoodministries.org.*

Resources

If you have an employment concern and feel that you have been discriminated against because of an immune disorder, you do have recourse. If you believe that your rights under the ADA have been violated, you may file a complaint with the U.S. Equal Employment Opportunities Commission or your state's fair employment practices agency. If you believe that you have been denied medical leave in accordance with the FMLA, you may file a complaint with the Department of Labor. Further help can be obtained through the Advocacy for Patients with Chronic Illness website at www.advocacyforpatients.org. Although those in the organization will not get involved in litigation, they can connect you with someone in your area who will.

A Time to Give Back to Our Community

By Kris McFalls

THIS TIME OF year tends to be one of reflections about the blessings in our lives. When counting our blessings at *IG Living*, we place our readers at the top of our list. Many of the diseases you face are so uncommon that they fall into the rare disease category. And, having a rare disease can leave you feeling isolated and thirsting for information. Therefore, one of our goals at *IG Living* is to provide a forum where we can all come together to create a larger, connected and better-educated community in support of one another.

Our quest to build a stronger community has led us to learn more about some wonderful nonprofit organizations that cannot survive without our support. It is through these organizations that many of our readers find friendship, acceptance and understanding.

With that in mind, we would like to encourage all of our readers to support the organizations that are always there for us. These organizations rely on the generosity of others to continue their missions. Even if a financial donation is not possible, a note of thanks is always appreciated. Many well-deserving organizations are listed in our resource directory. But, in this issue of *IG Living*, we have chosen to highlight a few of the national nonprofit organizations.

KRIS MCFALLS *is the full-time patient advocate for* IG Living *magazine.*

Directory of Charities

Cure JM Foundation

Cure JM was founded in 2003 by Harriet Bollar, Shari Hume and Lisa Felix, grandmother and mothers (respectively) of children diagnosed with juvenile myositis (JM). Cure JM seeks to raise awareness and research money in hopes of curing juvenile dermatomyositis and juvenile polymyositis.

Mission statement: As its name implies, the Cure JM Foundation, a 501(c)(3) nonprofit organization, was created specifically to find such a cure, while also providing support and information for families suffering from JM.

www.curejm.com, (760) 487-1079, info@curejm.com

GBS-CIDP Foundation International

The GBS-CIDP Foundation was founded in 1980 by Estelle and Robert Benson after Robert was diagnosed with Guillain-Barré syndrome. The foundation started with eight people around a kitchen table and has grown to tens of thousands of members throughout several countries.

Mission statement: To improve the quality of life for individuals and families worldwide affected by GBS, CIDP and variants by providing a network for all patients, their caregivers and families; providing public and professional educational programs designed to heighten awareness

and improve the understanding and treatment of GBS, CIDP and variants; and expanding the foundation's role in sponsoring research and engaging in patient advocacy.
www.gbs-cidp.org, (866) 224-3301, info@gbs-cidp.org

Immune Deficiency Foundation (IDF)

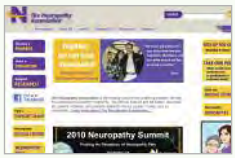
Soon after her son was born with a primary immune disease, Marcia Boyle founded the Immune Deficiency Foundation (IDF) to create educational resources and programs for people affected by primary immune disease. IDF hosts both national and regional patient meetings throughout the United States. The next national conference, which will celebrate IDF's 30th anniversary, will be held in Phoenix, Ariz., June 23-25.

Mission statement: IDF is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.
www.primaryimmune.org, (800) 296-4433, idf@primaryimmune.org

Jeffrey Modell Foundation (JMF)

The Jeffrey Modell Foundation (JMF) was established by Vicki and Fred Modell in memory of their son Jeffrey, who died at the age of 15 from pneumonia due to an underlying primary immunodeficiency disease.

Mission statement: The foundation is dedicated to early and precise diagnosis, meaningful treatments and, ultimately, cures of the ever-increasing known primary immunodeficiency diseases. JMF's focus is to affirm its absolute commitment to clinical and basic research in order to better understand and treat primary immunodeficiencies; to serve as a national and international source for the dissemination of information and education into the diagnosis and treatment of genetic immunodeficiencies; to serve as a tireless, compassionate advocate on behalf of patients and families to assure their access to excellent and comprehensive care; to promote public awareness of the primary immunodeficiency diseases through programs involving our lawmakers, as well as lay, scientific and medical communities; and to affirm its commitment to turn pain, despair and suffering of immunodeficient children and adults into comfort and hope.
www.jmfworld.org, (866) 463-6474, info@jmfworld.org



Neuropathy Association

The Neuropathy Association was started in 1995 by people suffering from disorders that affect the peripheral nerves. Current membership is more than 50,000 with over 120 support groups spread throughout the United States. The organization lists 15 centers of excellence on its website.

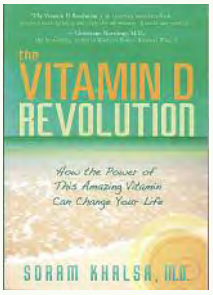
Mission statement: The Neuropathy Association's mission is to help and heal people with peripheral neuropathy through awareness, education, support, advocacy and research.
www.neuropathy.org, (212) 692-0662, info@neuropathy.org

The Myositis Association (TMA)

The Myositis Association (TMA) was originally organized as the Inclusion Body Myositis Association by Betty Curry, an inclusion body myositis patient. TMA strives to provide information, support, advocacy and research for all forms of myositis. Local support groups known as KIT (Keep In Touch) can be found in several locations throughout the United States. TMA also hosts an annual national patient meeting that is usually held in September.

Mission statement: TMA's mission is to find a cure for inflammatory and other related myopathies, while serving those affected by these diseases.
www.myositis.org, (800) 821-7356, TMA@myositis.org

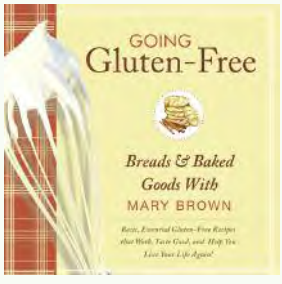
Book Corner



The Vitamin D Revolution

Author: Soram Khalsa, MD
Publisher: Hay House Inc.,
www.hayhouse.com

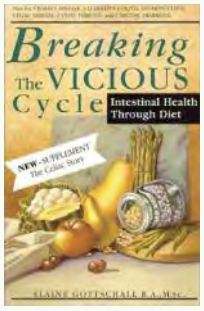
Recent groundbreaking medical research has made a connection between vitamin D deficiency and 17 types of cancers, including breast, colon and prostate. In this book, Soram Khalsa, MD, sheds new light on the power of vitamin D, revealing the consequences of vitamin D deficiency, which has reached epidemic proportions in North America. He also shares insights from his Beverly Hills medical practice, where he normalizes his own patients' vitamin D levels for their optimal health and well-being. A glossary and an appendix titled *Vitamin D Scientists' Call-To-Action Statement* are also included.



The New Eating Right for a Bad Gut

Author: James Scala, PhD
Publisher: The Penguin Group,
www.penguin.com

Leading nutritionist Dr. James Scala has completely revised and updated this handbook to include the latest breakthroughs in treating ilietis, colitis, Crohn's disease, nervous stomach and irritable bowel disease. Chapter topics include developing a personal testing program to identify foods that cause, aggravate or relieve flare-ups, keeping a food and lifestyle diary, explaining how food allergies affect IBD, what to do if an individual is lactose-, alcohol- or sugar-intolerant, the dos and don'ts of food selection, IBD and children, a drug-free diet and nutrition program, and more.

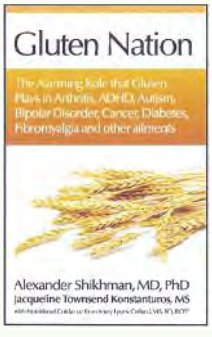


Breaking the Vicious Cycle

A Patient and Her Doctor Negotiate a Life with Chronic Illness

Author: Elaine Gottschall
Publisher: Kirkton Press Ltd.,
www.breakingtheviciouscycle.info/book/the_book.htm

Breaking the Vicious Cycle looks at the relationships between food and intestinal disorders such as Crohn's disease, ulcerative colitis, diverticulitis, celiac disease, cystic fibrosis of the pancreas and other forms of chronic diarrhea. It includes a discussion of the cycle of events occurring in the intestine of those with problems, and how the Specific Carbohydrate Diet can break this cycle and permit the body to regain normal functioning. The latest edition contains a new chapter titled *About Autism*, which reviews some of the research dealing with the gut-brain axis in child developmental disorders. A complete recipe section offers an assortment of simple, quick and gourmet-type recipes, based on the scientific principle underlying the Specific Carbohydrate Diet.



Gluten Nation

Author: Alexander Shikhman, MD, PhD, and Jacqueline Townsend Konstanturos, MS
Publisher: Restorative Remedies,
www.restorativeremedies.com

Gluten Nation explores the many ways that gluten can wreak havoc in the lives of the more than 20 million Americans who are gluten sensitive, most of whom don't know it. Along with case studies based on true stories and the science of gluten sensitivity, the book will give readers a clear step-by-step path to getting started on a gluten-free diet. Included are recipes that are gluten-free.

For a more comprehensive list of resources, visit the Resources page at www.IGLiving.com.

General Resources

Other Organization Websites

These organizations provide information about various disease states, which can be found by conducting a search of the disease state name.

- Advocacy for Patients with Chronic Illness: www.advocacyforpatients.org
- Alliance for Plasma Therapies (fair access to plasma therapies): www.plasmaalliance.org
- American Autoimmune Related Diseases Association (AARDA): www.aarda.org
- American Chronic Pain Association (ACPA): www.theacpa.org
- Band-Aides and Blackboards: www.lehman.cuny.edu/faculty/jfleitas/bandaides
- Cleveland Clinic: www.clevelandclinic.org/health
- eMedicine from WebMD: emedicine.medscape.com
- FamilyDoctor.org: www.familydoctor.org
- Johns Hopkins Medicine: www.hopkinsmedicine.org
- KeepKidsHealthy.com (pediatrician's guide to children health and safety): www.keepkidshealthy.com.
- Kids Health (medical and emotional impact of caring for an ill child): www.kidshealth.org/parent/system/ill/seriously_ill.html
- Mayo Clinic: www.mayoclinic.com
- National Committee for Quality Assurance (detailed report cards on health plans, clinical performance, member satisfaction and access to care): www.ncqa.org.
- National Institute of Neurological Disorders and Stroke (NINDS): www.ninds.nih.gov/disorders/disorder_index.htm
- National Institutes of Health: www.niams.nih.gov/hi/topics/pemphigus/pemphigus.htm
- National Organization for Rare Disorders (disease-specific support groups and virtual communities for patients and caregivers): www.rarediseases.org
- Office of Rare Diseases Research: rarediseases.info.nih.gov
- Patient Advocate Foundation (patient access to care, maintenance of employment and financial stability): www.patientadvocate.org

PSI

The nonprofit Patient Services Incorporated, www.patientservicesinc.org, specializes in health insurance premium, pharmacy co-payment and co-payment waiver assistance for people with chronic illnesses. (800) 366-7741

- WebMD (medical reference): www.webmd.com

IG Manufacturer Websites

- Baxter: www.baxter.com
- CSL Behring: www.cslbehring.com
- Grifols: www.grifolsusa.com
- Octapharma: www.octapharma.com
- Talecris: www.talecris.com

Disease-State Resources

Ataxia Telangiectasia (A-T)

Websites

- A-T Children's Project: www.atcp.org

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Websites

- GBS/CIDP Foundation International: www.gbs-cidp.org
- The Neuropathy Association: www.neuropathy.org

Evans Syndrome

Online Peer Support

- Evans Syndrome Research and Support Group: www.evanssyndrome.org

Guillain-Barré Syndrome (GBS)

Websites

- GBS/CIDP Foundation International: www.gbs-cidp.org
- The Neuropathy Association: www.neuropathy.org

Online Peer Support

- GBS & CIDP Discussion Forum – UK Bulletin Board (For Ireland and England): www.gbs.org.uk/cgi-bin/ikonboard3/ikonboard.cgi
- GBS/CIDP Foundation International Discussion Forums: www.gbs-cidp.org/forums.
- GBS Support Group and Chat Room – UK: www.jsmarcussen.com/gbs/uk/chat.htm

Idiopathic Thrombocytopenic Purpura (ITP)

Websites

- ITP Support Association – UK: www.itpsupport.org.uk
- National Heart, Lung and Blood Institute: www.nhlbi.nih.gov/health/dci/Diseases/Itp/ITP_WhatIs.html
- Platelet Disorder Support Association: www.pdsa.org

Kawasaki Disease

Websites

- American Heart Association (how the disease affects the heart): www.americanheart.org/presenter.jhtml?identifier=4634
- Kawasaki Disease Foundation: www.kdfoundation.org
- KidsHealth: http://kidshealth.org/parent/medical/heart/kawasaki.html

Mitochondrial Disease

Websites

- United Mitochondrial Disease Foundation: www.umdf.org

Multifocal Motor Neuropathy (MMN)

Websites

- The Neuromuscular Center at Washington University: www.neuro.wustl.edu/neuromuscular
- The Neuropathy Association: www.neuropathy.org

Multiple Sclerosis (MS)

Websites

- All About Multiple Sclerosis: www.mult-sclerosis.org/index.html
- Multiple Sclerosis Association of America: www.msaa.com
- Multiple Sclerosis Foundation: www.msfacts.org
- National Multiple Sclerosis Society: www.nationalmssociety.org

Online Peer Support

- Friends with MS: www.FriendsWithMS.com
- MSWorld's Chat and Message Board: www.msworld.org

Myasthenia Gravis (MG)

Websites and Chat Rooms

- Myasthenia Gravis Foundation of America (MGFA): www.myasthenia.org

Online Peer Support

- Autoimmune Information Network Inc.: www.aininc.org

Myositis

Websites

The Myositis Association

The mission of The Myositis Association, www.myositis.org, is to find a cure for inflammatory and other related myopathies, while serving those affected by these diseases. (703) 299-4850

- International Myositis Assessment and Clinical Studies Group: https://dir-apps.niehs.nih.gov/imacs/index.cfm?action=home.main

Cure JM Foundation www.curejm.com

The Cure JM Foundation
www.curejm.com
(760) 487-1079

Online Peer Support

- Juvenile Myositis Family Support Network: www.curejm.com/family_support/index.htm
- Myositis Association Community Forum: www.myositis.org
- Myositis Support Group: www.myositissupportgroup.org
- Myositis Support Group – UK: www.myositis.org.uk

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS)

Websites

- Guide to P.A.N.D.A.S. Syndrome: www.pandas-syndrome.webs.com
- P.A.N.D.A.S. Network: pandasnetwork.org
- Behavioural Neurotherapy Clinic – Australia: www.adhd.com.au/PANDAS.htm

Pemphigus and Pemphigoid

Websites

- The International Pemphigus and Pemphigoid Foundation: www.pemphigus.org

Peripheral Neuropathy (PN)

Websites

The Neuropathy Association

The Neuropathy Association, www.neuropathy.org, is devoted exclusively to all types of neuropathy, which affects upwards of 20 million Americans. The Association's mission is to increase public awareness of the nature and extent of PN, facilitate information exchanges about the disease, advocate the need for early intervention and support research into the causes and treatment of neuropathies. (212) 692-0662

- Neuropathy Action Foundation: www.neuropathyaction.org

Online Peer Support

- Calgary Neuropathy Support Group: www.calgarypners.org

Primary Immune Deficiency Disease (PIDD)

Websites

The Immune Deficiency Foundation (IDF), www.primaryimmune.org, is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research. (800) 296-4433

Jeffrey Modell Foundation

The Jeffrey Modell Foundation, www.info4pi.org, is dedicated to early and precise diagnosis, meaningful treatments and, ultimately, cures for primary immunodeficiency. (212) 819-0200

- The National Institute of Child Health and Human Development (NICHD), www.nichd.nih.gov, is part of the National Institutes of Health. Go to the "Health Information and Media" tab on the website and do a search under
- American Academy of Allergy, Asthma & Immunology: www.aaaai.org
- International Patient Organization for Primary Immunodeficiencies (IPOPI): www.ipopi.org
- Michigan Immunodeficiency Foundation: www.midf.org

- National Institute of Child Health and Human Development (NICHD) (Click on "Health Information and Media" tab and search for "primary immunodeficiency": www.nichd.nih.gov
- New England Primary Immunodeficiency Network: www.nepin.org
- Rainbow Allergy-Immunology: www.uhhospitals.org/tabid/132/Default.aspx
- Team Hope (for families and patients in New England): www.teamhope.info

Online Peer Support

- IDF Common Ground: www.idfcommonground.org
- IDF Discussion Forum: my.primaryimmune.org/forum
- IDF Friends: my.primaryimmune.org
- Jeffrey Modell Foundation Message Board: www.info4pi.org
- Rhode Island peer group: http://health.groups.yahoo.com/group/RhodeIslandPIDD

Scleroderma

Websites

- Scleroderma Center: http://scleroderma.jhmi.edu
- Scleroderma Foundation: www.scleroderma.org
- Scleroderma Research Foundation: www.srfcure.org

Online Peer Support

- CureZone.com: curezone.com/forums/f.asp?f=404
- International Scleroderma Network: www.sclero.org/support/forums/a-to-z.html

Stiff-Person Syndrome (SPS)

Websites

- American Autoimmune Related Diseases Association Inc.: www.aarda.org
- Autoimmune Information Network Inc.: www.aininc.org
- Living with Stiff Person Syndrome (personal account): www.livingwithsps.com

Other Resources

Education and Disability Resources

- Americans with Disabilities Act of 1990: www.ada.gov
  Provides protection for people with disabilities from certain types of discrimination, and requires employers to provide some accommodations of the disability.
- Continuation of Health Coverage — Consolidated Omnibus Budget Reconciliation Act (COBRA): www.dol.gov/dol/topic/health-plans/cobra.htm
- DisabilityInfo.gov: www.disabilityinfo.gov
  U.S. Federal government's disability-related information and resources.
- Individuals with Disabilities Education Improvement Act of 2004: http://idea.ed.gov/explore/home
- National Disabilities Rights Network: www.ndrn.org
  This website offers a search tool to find resources in your state to assist with school rights and advocacy.
- Social Security: www.ssa.gov/disability
- U.S. Department of Education Website: www.ed.gov
  This federal government website offers a parents section titled "My Child's Special Needs."
- U.S. Department of Health and Human Services, Office of Civil Rights: www.hhs.gov/ocr/office/news/2008/discrimdisab.html
  Spells out your rights under Section 504 of the Rehabilitation Act.

Medical Research Studies

- ClinicalTrials.com: www.clinicaltrials.com
  This site has a registration form to request that you be notified about recruitment for future studies.
- ClinicalTrials.gov: www.clinicaltrials.gov
  A registry of federally and privately supported clinical trials conducted in the United States and around the world.

Food Allergies

- Allergic Disorders: Promoting Best Practice: www.aaaai.org
- American Partnership for Eosinophilic Disorders: www.apfed.org
- Food Allergy and Anaphylaxis Network: www.foodallergy.org
- National Institutes of Health, National Institute of Allergy and Infectious Diseases (2004). Food Allergy: An Overview (NIH Publication No. 04-5518): www.niaid.nih.gov/topics/foodallergy/Pages/default.aspx
- Sicherer, S.H. (2006). "The Complete Peanut Allergy Handbook: Understanding and Managing Your Child's Food Allergies," Johns Hopkins Press.
- World Allergy Organization: www.worldallergy.org

Product Information

- Influenza and the influenza vaccine: www.cdc.gov/flu or call (800) CDC-INFO: (800) 232-4636
- IVIG Carimune NF: www.carimune.com
- IVIG Flebogamma: www.grifolsusa.com/pdfs/flebo_14Jun05.pdf
- IVIG Gammagard Liquid: www.gammagardliquid.com
- IVIG Gammagard S/D: www.immunedisease.com
- IVIG Gamunex: www.gamunexconnexions.com
- IVIG Octagam: www.octapharma.com
- IVIG Privigen: www.privigen.com
- SCIG Hizentra: www.hizentra.com
- SCIG Vivaglobin: www.vivaglobin.com

Pump and Infusion Sets Websites

- EMED Corporation: www.safetymedicalproducts.com
- Graseby Marcal Medical: www.marcalmedical.com
- Intra Pump Infusion Systems: www.intrapump.com
- Micrel Medical Devices: www.micrelmed.com
- Norfolk Medical: www.norfolkmedical.com
- Repro Med Systems, Inc: www.rmsmedicalproducts.com
- Smith Medical: www.smiths-medical.com/brands/cadd

Have something to add to these pages? Please send your suggestions for additions to the IG Living Resource Directory to editor@IGLiving.com.

CSL Behring

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Hizentra, Immune Globulin Subcutaneous (Human), 20% Liquid

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

1 INDICATIONS AND USAGE

Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

4 CONTRAINDICATIONS

Hizentra is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80.

Hizentra is contraindicated in patients with hyperprolinemia because it contains the stabilizer L-proline (*see Description [11]*).

Hizentra is contraindicated in IgA-deficient patients with antibodies against IgA and a history of hypersensitivity (*see Description [11]*).

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur to human immune globulin or components of Hizentra, such as polysorbate 80. In case of hypersensitivity, discontinue the Hizentra infusion immediately and institute appropriate treatment.

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 Hizentra. Hizentra contains ≤50 mcg/mL IgA (*see Description [11]*).

5.2 Reactions Reported to Occur With IGIV Treatment

The following reactions have been reported to occur with IGIV treatment and may occur with IGSC treatment.

Renal Dysfunction/Failure

Renal dysfunction/failure, osmotic nephropathy, and death may occur with use of human immune globulin products. 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 Hizentra and at appropriate intervals thereafter.

Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk of developing acute renal failure.[1] If renal function deteriorates, consider discontinuing Hizentra. 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 or use concomitant nephrotoxic medicinal products, or those who are over 65 years of age), administer Hizentra at the minimum rate practicable.

Thrombotic Events

Thrombotic events may occur with use of human immune globulin products[2-4]. Patients at increased risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, hypercoagulable disorders, prolonged periods of immobilization, and/or known or 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 Hizentra at the minimum rate practicable.

Aseptic Meningitis Syndrome (AMS)

AMS may occur with use of human immune globulin products.[5] The syndrome usually begins within several hours to 2 days following IGIV treatment. AMS is characterized by signs and symptoms including severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently show pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, with elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.

Conduct a thorough neurological examination, including CSF studies, to rule out other causes of meningitis in patients exhibiting signs and symptoms of AMS. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae.

Hemolysis

Hizentra can contain blood group antibodies that may act as hemolysins and induce *in vivo* coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin (Coombs') test result and hemolysis.[6-8] Delayed hemolytic anemia can develop subsequent to immune globulin therapy due to enhanced RBC sequestration, and acute hemolysis, consistent with intravascular hemolysis, has been reported.[9]

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

Transfusion-Related Acute Lung Injury (TRALI)

Noncardiogenic pulmonary edema may occur in patients administered human immune globulin products.[10] TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Typically, it occurs within 1 to 6 hours following transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

Monitor Hizentra recipients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and patient's serum.

5.3 Transmissible Infectious Agents

Because Hizentra 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). 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 Hizentra.

Report all infections thought to be possibly transmitted by Hizentra to CSL Behring Pharmacovigilance at 1-866-915-6958.

5.4 Laboratory Tests

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

6 ADVERSE REACTIONS

The most common adverse reactions (ARs), observed in ≥5% of study subjects receiving Hizentra, were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, vomiting, pain, and fatigue.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, AR rates observed in clinical studies of a product cannot be directly compared to rates in the clinical studies of another product and may not reflect the rates observed in clinical practice.

The safety of Hizentra was evaluated in a clinical study for 15 months in subjects with PI who had been treated previously with IGIV every 3 or 4 weeks. The safety analyses included 49 subjects in the intention-to-treat (ITT) population. The ITT population consisted of all subjects who received at least one dose of Hizentra (*see Clinical Studies [14]*).

Subjects were treated with Hizentra at weekly doses ranging from 66 to 331 mg/kg body weight during the wash-in/wash-out period and from 72 to 379 mg/kg during the efficacy period. The 49 subjects received a total of 2264 weekly infusions of Hizentra.

No deaths or serious ARs occurred during the study. Two subjects withdrew from the study due to ARs. One subject experienced a severe injection-site reaction one day after the third weekly infusion, and the other subject experienced moderate myositis. Both reactions were judged to be "at least possibly related" to the administration of Hizentra.

Table 2 summarizes the most frequent adverse events (AEs) (experienced by at least 4 subjects), *irrespective of causality*. Included are all AEs and those considered temporally associated with the Hizentra infusion, i.e., occurring during or within 72 hours after the end of an infusion. Local reactions were the most frequent AEs observed, with injection-site reactions (i.e., swelling, redness, heat, pain, and itching at the site of injection) comprising 98% of local reactions.

Table 2: Incidence of Subjects With Adverse Events (AEs)* (Experienced by 4 or More Subjects) and Rate per Infusion, *Irrespective of Causality* (ITT Population)

AE (≥4 Subjects)	All AEs*		AEs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate†) of AEs (n=2264 Infusions)	Number (%) of Subjects (n=49)	Number (Rate†) of AEs (n=2264 Infusions)
Local reactions‡	49 (100)	1340 (0.592)	49 (100)	1322 (0.584)

Table 2: (Continued)

AE (≥4 Subjects)	All AEs*		AEs* Occurring During or Within 72 Hours of Infusion	
	Number (%) of Subjects (n=49)	Number (Rate†) of AEs (n=2264 Infusions)	Number (%) of Subjects (n=49)	Number (Rate†) of AEs (n=2264 Infusions)
Other AEs:				
Headache	13 (26.5)	40 (0.018)	12 (24.5)	32 (0.014)
Cough	8 (16.3)	9 (0.004)	5 (10.2)	6 (0.003)
Diarrhea	7 (14.3)	8 (0.004)	5 (10.2)	6 (0.003)
Fatigue	6 (12.2)	6 (0.003)	4 (8.2)	4 (0.002)
Back pain	5 (10.2)	11 (0.005)	4 (8.2)	5 (0.002)
Nausea	5 (10.2)	5 (0.002)	4 (8.2)	4 (0.002)
Abdominal pain, upper	5 (10.2)	5 (0.002)	3 (6.1)	3 (0.001)
Rash	5 (10.2)	7 (0.003)	2 (4.1)	3 (0.001)
Pain in extremity	4 (8.2)	7 (0.003)	4 (8.2)	6 (0.003)
Migraine	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Pain	4 (8.2)	5 (0.002)	3 (6.1)	4 (0.002)
Epistaxis	4 (8.2)	6 (0.003)	2 (4.1)	3 (0.001)
Pharyngolaryngeal pain	4 (8.2)	6 (0.003)	2 (4.1)	2 (<0.001)
Arthralgia	4 (8.2)	5 (0.002)	2 (4.1)	3 (0.001)

* Excluding infections.
† Rate of AEs per infusion.
‡ Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

The ratio of infusions with temporally associated AEs, including local reactions, to all infusions was 1338 to 2264 (59.1%; upper 95% confidence limit of 62.4%). Excluding local reactions, the corresponding ratio was 173 to 2264 (7.6%; upper 95% confidence limit of 8.9%).

Table 3 summarizes the most frequent ARs (i.e., those AEs considered by the investigators to be "at least possibly related" to Hizentra administration) experienced by at least 2 subjects.

Table 3: Incidence of Subjects With Adverse Reactions (Experienced by 2 or More Subjects) to Hizentra and Rate per Infusion (ITT Population)

Adverse Reaction (≥2 Subjects)	Number (%) of Subjects (n=49)	Number (Rate*) of Adverse Reactions (n=2264 Infusions)
Local reactions†	49 (100)	1338 (0.591)
Other ARs:		
Headache	12 (24.5)	36 (0.016)
Vomiting	3 (6.1)	3 (0.001)
Pain	3 (6.1)	4 (0.002)
Fatigue	3 (6.1)	3 (0.001)
Contusion	2 (4.1)	3 (0.001)
Back pain	2 (4.1)	3 (0.001)
Migraine	2 (4.1)	3 (0.001)
Diarrhea	2 (4.1)	2 (<0.001)
Abdominal pain, upper	2 (4.1)	2 (<0.001)
Nausea	2 (4.1)	2 (<0.001)
Rash	2 (4.1)	2 (<0.001)
Arthralgia	2 (4.1)	2 (<0.001)

* Rate of ARs per infusion.
† Includes injection-site reactions as well as bruising, scabbing, pain, irritation, cysts, eczema, and nodules at the injection site.

Table 4 summarizes injection-site reactions based on investigator assessments 15 to 45 minutes after the end of the 683 infusions administered during regularly scheduled visits (every 4 weeks).

Table 4: Investigator Assessments* of Injection-Site Reactions by Infusion

Injection-Site Reaction	Number† (Rate‡) of Reactions (n=683 Infusions§)
Edema/induration	467 (0.68)
Erythema	346 (0.50)
Local heat	108 (0.16)
Local pain	88 (0.13)
Itching	64 (0.09)

* 15 to 45 minutes after the end of infusions administered at regularly scheduled visits (every 4 weeks).
† For multiple injection sites, every site was judged, but only the site with the strongest reaction was recorded.
‡ Rate of injection-site reactions per infusion.
§ Number of infusions administered during regularly scheduled visits.

Most local reactions were either mild (93.4%) or moderate (6.3%) in intensity.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and 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 postmarketing use of IGIV products[11]:

- *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

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

7 DRUG INTERACTIONS

7.1 Live Virus Vaccines

The passive transfer of antibodies with immunoglobulin administration may interfere with the response to live virus vaccines such as measles, mumps, rubella, and varicella (*see Patient Counseling Information [17]*).

7.2 Serological Testing

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

8.3 Nursing Mothers

Hizentra has not been evaluated in nursing mothers.

8.4 Pediatric Use

Hizentra was evaluated in 10 pediatric subjects (3 children and 7 adolescents) with PI. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels.

Hizentra was not evaluated in neonates or infants.

8.5 Geriatric Use

Of the 49 subjects evaluated in the clinical study of Hizentra, 6 subjects were 65 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger subjects.

15 REFERENCES

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Kankakee, IL 60901 USA
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

Vivaglobin®
Immune Globulin Subcutaneous (Human)

Manufactured by:
CSL Behring GmbH
35041 Marburg, Germany
US License No. 1765

Distributed by:
CSL Behring LLC
Kankakee, IL 60901 USA

CSL Behring

℞ **only**

Before prescribing, please consult full prescribing information, a brief summary of which follows:

INDICATIONS AND USAGE

Vivaglobin® Immune Globulin Subcutaneous (Human), is indicated for the treatment of patients with primary immune deficiency (PID).

CONTRAINDICATIONS

As with all immune globulin products, Vivaglobin® Immune Globulin Subcutaneous (Human) is contraindicated in individuals with a history of anaphylactic or severe systemic response to immune globulin preparations and in persons with selective immunoglobulin A (IgA) deficiency (serum IgA < 0.05 g/L) who have known antibody against IgA.

WARNINGS

Patients who receive immune globulin therapy for the first time, who are switched from another brand of immune globulin, or who have not received immune globulin therapy within the preceding eight weeks may be at risk for developing reactions including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock. Such patients should be monitored for these reactions in a clinical setting during the initial administration of Vivaglobin® Immune Globulin Subcutaneous (Human).

If anaphylactic or anaphylactoid reactions are suspected, discontinue administration immediately. Treat any acute anaphylactoid reactions as medically appropriate.

Vivaglobin® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Vivaglobin® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the CJD agent. The risk that such plasma-derived products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture (see **DESCRIPTION** section for virus reduction measures). Stringent procedures utilized at plasma collection centers, plasma-testing laboratories and fractionation facilities are designed to reduce the risk of virus transmission. The primary virus reduction steps of the Vivaglobin® manufacturing process are pasteurization (heat treatment of the aqueous solution at 60°C for 10 hours) and ethanol - fatty alcohol / pH precipitation. Additional purification procedures used in the manufacture of Vivaglobin® also potentially provide virus reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated. Any infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 1-800-504-5434 (in the US and Canada). The physician should discuss the risks and benefits of this product with the patient.

During clinical trials, no cases of infection due to hepatitis A, B, or C virus, parvovirus B19, or HIV were reported with the use of Vivaglobin®.

PRECAUTIONS

General-Administer Vivaglobin® Immune Globulin Subcutaneous (Human), subcutaneously. **Do not administer this product intravenously.** The recommended infusion rate and amount per injection site stated under **DOSAGE AND ADMINISTRATION** should be followed. When initiating therapy with Vivaglobin®, patients should be monitored for any adverse events during and after the infusion.

Laboratory Tests - After injection of immunoglobulins, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, D may cause a positive direct or indirect antiglobulin (Coombs') test.

Drug Interactions - Immunoglobulin administration can transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps and rubella. The immunizing physician should be informed of recent therapy with Vivaglobin® Immune Globulin Subcutaneous (Human), so that appropriate precautions can be taken.

Vivaglobin® should not be mixed with other medicinal products.

Pregnancy Category C - Animal reproduction studies have not been conducted with Vivaglobin® Immune Globulin Subcutaneous (Human). It is also not known whether Vivaglobin® can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity. Vivaglobin® should be given to a pregnant woman only if clearly needed.

Pediatric Use - Vivaglobin® was evaluated in 6 children and 4 adolescents in the US and Canada study and in 16 children and 6 adolescents in the non-IND study. There were no apparent differences in the safety and efficacy profiles as compared to adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of Vivaglobin® was not studied in pediatric subjects under two years of age.

Geriatric Use - The clinical study of Vivaglobin® Immune Globulin Subcutaneous (Human), did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

In clinical studies, administration of Vivaglobin® Immune Globulin Subcutaneous (Human), has been shown to be safe and well tolerated in both adult and pediatric subjects. Reactions similar to those reported with administration of other immune globulin products may also occur with Vivaglobin®. Rarely, immediate anaphylactoid and hypersensitivity reactions may occur. In exceptional cases, sensitization to IgA may result in an anaphylactic reaction (see **CONTRAINDICATIONS**).

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly, and appropriate treatment and supportive therapy should be administered.

In the US and Canada clinical study, the safety of Vivaglobin® was evaluated for 15 months (3-month wash-in/wash-out period followed by 12-month efficacy period) in 65 subjects with PID. The most frequent adverse reaction was local reaction at the injection site. Table 5 summarizes the most frequent adverse events by subject reported in the clinical study, and Table 6 summarizes the most frequent adverse events by infusion.

Table 5: Most Frequent Adverse Events by Subject *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 10% of subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	31 (48%)
Gastrointestinal disorder	24 (37%)
Fever	16 (25%)
Nausea	12 (18%)
Sore throat	11 (17%)
Rash	11 (17%)
Allergic reaction	7 (11%)
Pain	6.7 (10%)†
Diarrhea	6.7 (10%)†
Cough increased	6.7 (10%)†

*Excluding infections

† Due to missing subject diary information, values listed are estimates.

Table 6: Most Frequent Adverse Events by Infusion *Irrespective* of Causality* in the US and Canada Study

Adverse Events (≥ 1% of infusions) (Number of Infusions: 3656)	**No. of Adverse Events** (Rate**)
Adverse Events at the Injection Site	1789 (49%)
Mild	1112 (30%)
Moderate	601 (16%)
Severe	65 (2%)
Unknown Severity	11 (< 1%)
Non-Injection Site Reactions	
Headache	159 (4%)
Gastrointestinal disorder	40.3 (1%)†

*Excluding infections

**Rate = number of reactions/infusion

†Due to missing subject diary information, values listed are estimates.

Table 7 summarizes the most frequent related adverse events by subject reported in the clinical study, and Table 8 summarizes the most frequent related adverse events by infusion.

Table 7: Most Frequent Related Adverse Events by Subject* in the US and Canada Study

Related Adverse Event (≥ 2 subjects)	**No. of Subjects (% of total)**
Adverse Events at the Injection Site	60 (92%)
Non-Injection Site Reactions	
Headache	21 (32%)
Nausea	7 (11%)
Rash	4 (6%)
Asthenia	3 (5%)
Gastrointestinal disorder	3 (5%)
Fever	2 (3%)
Skin disorder	2 (3%)
Tachycardia	2 (3%)
Urine abnormality	2 (3%)

*Excluding infections

Table 8: Most Frequent Related Adverse Events by Infusion* in the US and Canada Study

Related Adverse Event (≥ 2 AEs) (Number of Infusions: 3656)	**No. of AEs (Rate**)**
Adverse Events at the Injection Site	1787 (49%)
Non-Injection Site Reactions	
Headache	59 (1.6%)
Rash	9 (0.2%)
Nausea	9 (0.2%)
Nervousness	4 (0.1%)
Asthenia	3 (0.1%)
Gastrointestinal disorder	3 (0.1%)
Skin disorder	3 (0.1%)
Urine abnormality	3 (0.1%)
Fever	2 (0.1%)
Dyspnea	2 (0.1%)
Gastrointestinal pain	2 (0.1%)
Tachycardia	2 (0.1%)

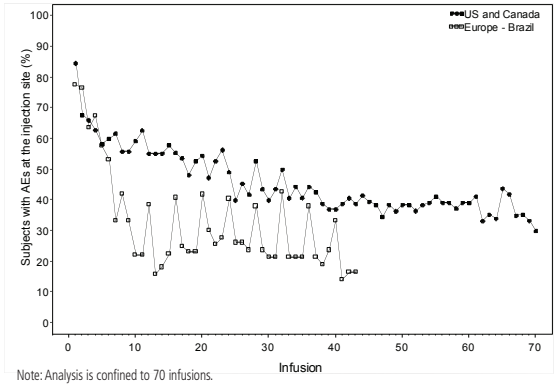
*Excluding infections

**Rate = number of reactions/infusion

In the non-IND Europe and Brazil clinical study, the safety of Immune Globulin Subcutaneous (Human), Vivaglobin® was evaluated for 10 months in 60 subjects with PID. The adverse events and their rates reported in this study were similar to those reported in the US and Canada study, with two notable exceptions for the related adverse events. These events were 59 episodes of headache (1.6%) and 2 episodes of fever (0.1%) in the US and Canada study and no episodes of headache and 18 episodes of fever (0.8%) in the Europe and Brazil study.

Local (Injection Site) Reactions - Local injection site reactions consisting of mostly mild or moderate swelling, redness and itching, have been observed with the use of Vivaglobin®. No serious local site reactions were observed. The majority of injection site reactions resolved within four days. Additionally, the number of subjects reporting local injection site reactions decreased substantially after repeated use (see Figure 1). Only three subjects in the US and Canada study and one subject in the Europe and Brazil study discontinued due to local site reactions.

Figure 1: Subjects Reporting Local Site Reactions By Infusion



Note: Analysis is confined to 70 infusions.

After administration, discard any unused solution and administration equipment in accordance with biohazard procedures.

HOW SUPPLIED

Vivaglobin® Immune Globulin Subcutaneous (Human), is supplied in single-use vials containing 160 mg IgG per mL. The following dosage forms are available:

NDC 0053-7596-01	3 mL carton
NDC 0053-7596-03	Box of ten 3 mL vials
NDC 0053-7596-10	10 mL carton
NDC 0053-7596-15	Box of ten 10 mL vials
NDC 0053-7596-20	20 mL carton
NDC 0053-7596-25	Box of ten 20 mL vials

STORAGE

Store in the refrigerator at 2 - 8°C (36 - 46°F). Vivaglobin® Immune Globulin Subcutaneous (Human), is stable for the period indicated by the expiration date on its label. Do not freeze. Keep vials in storage box until use.

Based on April 2009 revision

If you live with primary immunodeficiency disease (PIDD)…

Make the leap to Hizentra

Ready-to-use Sub-Q Ig therapy

- Room temperature storage—no refrigeration required
- Hizentra can be infused in approximately 2 hours*
- From the maker of Vivaglobin®, Immune Globulin Subcutaneous (Human)

Ask your doctor about Hizentra today.
For more information, visit **www.Hizentra.com**

Important Safety Information

Hizentra and Vivaglobin are indicated for the treatment of patients with primary immunodeficiency (PI).

If you have a history of anaphylactic or severe systemic response to immune globulin preparations or selective immunoglobulin A deficiency, check with your physician as neither Vivaglobin nor Hizentra should be used. If your physician suspects you are having anaphylactic or anaphylactoid reactions, treatment will be discontinued. Because Hizentra contains the stabilizer L-proline, you cannot be treated with Hizentra if you have hyperprolinemia.

Hizentra and Vivaglobin are 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 separate clinical trials for Hizentra and Vivaglobin, the most frequent adverse event was injection-site reaction, consisting of mild or moderate swelling, redness, and itching. With Vivaglobin, no serious local site reactions were observed, and reactions tended to decrease substantially after repeated use. Other adverse events with Vivaglobin, irrespective of causality, included headache, gastrointestinal disorder, fever, nausea, sore throat, and rash.

Adverse reactions to Hizentra, observed in 5% or more of clinical trial subjects, were local injection-site reactions, headache, vomiting, pain, and fatigue.

Your physician will monitor for reactions associated with IVIg treatment that might occur with Hizentra, including renal dysfunction/failure, thrombotic events, aseptic meningitis syndrome (AMS), hemolysis, and transfusion-related acute lung injury (TRALI).

Patients receiving Ig therapy for the first time, receiving a new product, or not having received Ig therapy within the preceding eight weeks may be at risk for developing reactions, including fever, chills, nausea, and vomiting. On rare occasions, these reactions may lead to shock.

Ig administration could impair the effect of live virus vaccines, such as measles, mumps and rubella. Before getting any vaccination, inform your doctor that you are being treated with Hizentra or Vivaglobin.

In their clinical studies, Hizentra and Vivaglobin were effective in pediatric patients without specific pediatric dose adjustments. With either treatment, no overall differences in safety or efficacy have been observed in patients over 65 or in pediatric patients.

Please see brief summary of full Prescribing Information for Hizentra and Vivaglobin, including Patient Product Information, on previous pages.

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.

*In a clinical study, the median length of a weekly infusion ranged from 1.6 to 2 hours.

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