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The Complexities of Chronic Illness

LIFE IS COMPLEX. Add a chronic illness to the mix, and those complexities seem to shoot off the scale.

Peter Drucker, management consultant, educator and author, once said that healthcare is “the most complex human organization ever devised.” The Affordable Care Act strongly supports that statement. Choosing a health plan on one of the marketplace exchanges to ensure the lowest possible cost to the consumer can be daunting. What’s worse is that with the advent of marketplace plans came specialty tiers that require exorbitant co-pays that often put medications out of reach for those who are treated with high-cost drugs. As we explain in our article “Navigating the ACA Marketplace Plans,” the basic cost of plans varies based on variables such as age and the state in which an individual lives. But those costs also change based on severity of illnesses, number and types of medications, etc. Making healthcare.gov easier to navigate for those with more complicated health situations will soon be possible with a cost calculator that is being created for the website. In the meantime, the National Health Council provides one specifically for individuals living with a chronic disease and their family caregivers. Even more hopeful is that many organizations are fighting to cap co-pays, with some states already adopting such laws.

Older individuals treated with immune globulin (IG) who are transitioning to Medicare face the complexity of understanding which plans will provide them with the best possible coverage for the drug. Every couple of years, we update our article “Transitioning IG Coverage to Medicare” to incorporate changes in Medicare rules and prices to help those new to the transition. Our article outlines who needs to apply and which Medicare plans pay for the IG drug, nursing and supplies. Again, many variables must be taken into account such as additional private plan coverage and site of care that determine how much out-of-pocket costs the consumer is responsible for.

At an annual checkup, most individuals rarely think twice about what doctors look for when evaluating lab tests. But, individuals with a serious illness like primary immunodeficiency (PI) who typically have spent years being ill without an accurate diagnosis usually feel differently. For PI patients, the complexity of their conditions warrants an understanding of how irregularities in routine lab tests may help to indicate problems (published in the June-July issue of IG Living). Now, in this issue’s article “Routine Primary Immunodeficiency Lab Reports: What Do They Mean?” Dr. Bob Geng, an immunologist, continues with a discussion of quantitative immunoglobulin and B and T cell flow cytometry panels that are used to diagnose various forms of PI.

As we discuss in our article “The Current Role of Hematopoietic Stem Cell Transplant in Primary Immunodeficiency Diseases,” a few types of PI are successfully cured with HSCT. The success of HSCT has been growing in recent years for many complex diseases, so patients with other forms of PI such as common variable immunodeficiency (CVID) wonder if, someday, HSCT will be a cure for them. To date, the only study conducted to evaluate the effectiveness of HSCT for CVID has resulted in 50 percent survival. As such, while HSCT is recommended only for CVID patients with a poor outlook, it is believed that it may one day become a viable treatment for some subsets of patients with CVID.

As always, I hope you gain insight from the information presented and enjoy this edition of IG Living.

Ronale Tucker Rhodes, MS
Where I Find Answers to Questions

By Abbie Cornett

I receive many requests from patients asking for help on a variety of issues — from health-related, reimbursement and access-to-care concerns, to how to connect with patient support groups. As IG Living’s patient advocate, I am focused on helping patients find answers. In search of the best possible solutions, I frequently refer to a number of trusted resources on a regular basis for guidance.

Because IG Living’s readers are patients with rare and chronic diseases treated with immune globulin (IG) therapy (immune deficiencies, autoimmune diseases and neuropathies, to name a few), I am fortunate to be able to reach out to highly specialized physicians whom I can rely on to help answer disease or side effect questions. These specialists include immunologist Terry Harville, MD, PhD; immunologist Roger Kobayashi, MD, PhD; and rheumatologist Marc Riedl, MD, MS. Exercise science specialist Matt Hansen, BSPTS, helps me with practical advice for how patients can safely improve their health by staying active.

When it comes to reimbursement issues, one of the most frequent questions I receive is: What happens when a patient transitions to Medicare? (See the updated “Transitionaling to Medicare” feature in this issue on page 26.) In addition to IG Living articles on the subject, some of the best resources are the Centers for Medicare and Medicaid Services (www.cms.gov/Medicare/Coverage/DeterminationProcess) and the official government Medicare site (www.medicare.gov/supplement-other-insurance/medigap/whats-medigap.html). Both websites offer very helpful coverage explanations.

Unfortunately, many patients often have issues with denials of coverage for IG. To better help them, I became familiar with the Healthcare Common Procedure Coding System (HCPCS) levels I and II (www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/index.html). Understanding coding is essential because a claim filed with an incorrect code will generate an automatic denial of the entire claim. Believe it or not, it has been reported that one out of five claims includes a coding error. This fall, these codes have once again been updated, and there is concern that the transition may lead to additional claims denials. Keeping abreast of these changes is important for both patients and their physicians.

For more complicated reimbursement issues and for help with appeals, I turn to specialists Michelle Greer, RN, MBA, and Leslie Vaughan, RPh. Both knowledgeable professionals at NuFACTOR Specialty Pharmacy, they have daily experience with IG patients and go out of their way to help any patient in need.

Frequently, when patients contact me, they have just been diagnosed, and they are looking for information about their disease, as well as support from people who understand what they are going through. There are several national patient organizations that I frequently refer patients to for help: the Immune Deficiency Foundation (primaryimmune.org), the GBS-CIDP Foundation International (www.gbs-cidp.org), the Neuropathy Action Foundation (www.neuropathyaction.org), The Myositis Association (www.myositis.org), the Jeffrey Modell Foundation (www.info4pi.com) and the National Organization for Rare Disorders (rarediseases.org). These empowering organizations provide educational opportunities for patients to learn about their disease, and they can put patients in touch with support groups in their area.

Helping patients understand their conditions and therapies is paramount to me and those who contribute their expertise to IG Living. Together, we will continue to work to provide the information patients need to receive the care they deserve.

ABBIE CORNETT is the patient advocate for IG Living magazine.
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CLINICAL BRIEF

The Current Role of Hematopoietic Stem Cell Transplant in Primary Immunodeficiency Diseases

By Michelle Greer, RN

THE LIST OF diseases for which hematopoietic stem cell transplant (HSCT) is a treatment option has been growing over the last several years, and it includes primary immunodeficiency diseases (PIs). With more than 100 types of PI, treatment options vary depending on the type and severity, as well as overall prognosis. HSCT (also known as bone marrow transplant [BMT]) is used to treat certain forms of PI, and it is becoming much more successful due to better tissue typing and matching of donors, less toxic chemotherapy, better virus detection and treatment, improved supportive care and graft-versus-host disease (GVHD) prophylaxis. However, HSCT does come with its share of risks, and it is a treatment option that should be carefully considered and discussed between patients and their physicians.

What Is HSCT?

A stem cell is the most basic cell in any organism that has the potential to become a specific type of cell. A hematopoietic stem cell is a stem cell in the blood. Immunoglobulins are made from B lymphocytes, also known as B cells, that mature in the bone marrow. They play a key role in the immune system, serving as protection against anything foreign entering the system. Immunoglobulins, which are also called antibodies, are produced in response to antigens (something foreign in the system). There are five types of immunoglobulins — IgG (the most prevalent), IgA, IgM, IgE and IgD — each of which serves a specific function in the immune system. When the body does not produce sufficient amounts of one or more immunoglobulins or other blood cells that play a role in immunity, the result is an immune deficiency. If the cause can be identified, treated and corrected, this is usually a secondary immune deficiency. If the cause is simply an inherent defect in the system’s ability to produce sufficient amounts, this is known as a primary immune deficiency.

HSCT may be warranted in PIs that are extremely rare such as severe combined immunodeficiency (SCID), chronic granulomatous disorder and Wiskott-Aldrich syndrome. Once the decision to undergo HSCT is made, the process is relatively simple, but it can involve side effects and complications that can impact the ultimate success of the transplant. Compliance with pre- and post-transplant protocols is also essential to the success and overall outcome.

The goal of HSCT is to destroy the blood cells in the immune system that include the defect or disease and then to rebuild a normal and healthy immune system from stem cells from either bone marrow or peripheral blood cells. Transplants can either be from one’s own tissue and cells, known as autologous, or from a matched donor, known as allogeneic. Typically for PI, a suitable donor is located. Finding a suitable donor is probably the No. 1 barrier to undergoing HSCT. Once a donor is located, the immune system is ablated with maximally tolerated chemotherapeutic agents chosen by the transplant physicians based on the underlying condition that is the reason for the transplant. For example, someone with a malignancy would receive a different chemotherapy regimen than someone with PI. Donor cells are then administered via a relatively short infusion.

After HSCT, complications, mainly involving potential for infections and GVHD, can arise while the immune system is rebuilding itself. To prevent infections, prophylactic medications, including antifungals, antibiotics, vaccinations and intravenous immune globulin (IVIG), are given. GVHD occurs in allogeneic transplants when the donor cells attack the patient’s body.
HSCT for CVID

While not routinely considered, there are some instances in which HSCT may be considered for patients with common variable immunodeficiency (CVID), the most common form of PI. Typically, CVID patients are treated with IG therapy for life because, in most cases, it is effective in maintaining sufficient antibody levels to protect from infection and any complications. However, those with CVID have a 20 percent to 30 percent chance of developing autoimmune diseases, and, in some cases, autoimmune diseases are diagnosed before CVID. CVID patients also have an increased incidence of lymphoma and, less common, stomach cancer. In these cases, HSCT may be warranted.

Only one study has been conducted on HSCT for CVID. The multicenter retrospective study demonstrated that HSCT in patients with CVID was beneficial in most surviving patients; however, there was a high mortality associated with the procedure. Of 25 patients, aged 8 years to 50 years at the time of transplantation, there was an overall survival rate of 48 percent, and an 83 percent survival rate for patients undergoing transplantation for lymphoma. In 92 percent of surviving patients, the condition constituting the indication for HSCT resolved, and in 50 percent of surviving patients, IG therapy was stopped. The major causes of death were treatment-refractory GVHD accompanied by poor immune reconstitution and infectious complications. The study authors concluded that HSCT “should only be considered in carefully selected patients in whom there has been extensive characterization of the immunologic and/or genetic defect underlying the CVID diagnosis.”

According to Kathleen Sullivan, MD, PhD, chief of allergy and immunology at Children’s Hospital of Philadelphia and co-author of the retrospective study: “Although I would not recommend a BMT for my patients with CVID in general, I think it does represent a feasible therapy for some carefully selected patients. When I look back on the trajectory of BMT historically, it is clear that the success rates improve for all diseases over time. BMT is not a single procedure. There are components of a BMT conceptually that occur in all transplants, but the details vary according to the donor, recipient, disease and concurrent medical problems. Ongoing research on those details is what moves a disease from having a low success rate to a high success rate, and the good news is that there are now efforts to optimize those details for CVID transplants. Right now, the success for BMT in CVID is fairly low, but it is likely to improve. I think that it will become a viable treatment for some subset of patients with CVID, likely those with autoimmune complications. In the meantime, I think only CVID patients who have been found to have a genetic composition with an unfavorable prognosis or those for whom current treatments are simply failing should be considered as candidates. Research holds great promise for optimizing treatments for all CVID patients and ensuring good outcomes for everyone.”

The Future of HSCT

The list of diseases for which HSCT is a treatment option has been growing over the last several years, and there is a good deal of discussion about HSCT for PIs. While historically HSCT has been limited to PIs for which there are no effective treatments and for those with an increased risk of mortality, in the future, it could offer a cure for many other forms of PIs, including CVID.

MICHICLE GREER, RN, is senior vice president of sales for NuFACTOR Specialty Pharmacy.

References

HYQVIA, the only once-a-month subQ Ig¹
For adults with primary immunodeficiency

Schedule an appointment with your physician to see if HYQVIA is right for you.

¹ subQ Ig, also known as subcutaneous immune globulin.

Reference

Please see the Detailed Important Risk Information on the adjacent pages and the Brief Summary of HYQVIA Prescribing Information, including Boxed Warning, on the reverse side.

To learn more about HYQVIA, visit www.HYQVIA.com
Hyaluronidase is a recombinant human enzyme that temporarily opens the sub-Q space, allowing a larger amount of Ig to reach the sub-Q tissue and be absorbed into the bloodstream to help fight infection. It’s the reason you can infuse your monthly dose of HYQVIA using 1 needle, 1 infusion site, 1 time a month.

**INDICATION AND USAGE**

HYQVIA (Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase) is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Limitation of Use: Safety and efficacy of chronic use of recombinant human hyaluronidase in HYQVIA have not been established in conditions other than PI.

**Detailed Important Risk Information**

HYQVIA can cause serious side effects. Call your healthcare professional or go to your emergency department right away if you get:

- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness. These could be signs of a serious allergic reaction.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of swelling in your brain.
- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s). These could be signs of a blood clot.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver or blood problem.
- Chest pain or trouble breathing, blue lips or extremities. These could be signs of a lung problem.

These are not all the possible side effects with HYQVIA. Talk to your healthcare professional about any side effects that bother you or that don’t go away.

**What is the most important information that I should know about HYQVIA?**

- HYQVIA can cause blood clots.
- Call your healthcare professional if you have pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s), unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.
- Your healthcare professional may perform blood tests regularly to check your IgG level.
- With your consent, your healthcare professional may provide blood samples to Baxter Healthcare Corporation to test for antibodies that may form against the hyaluronidase part of HYQVIA.
- Do not infuse HYQVIA into or around an infected or red swollen area because it can cause infection to spread.
- Talk to your healthcare professional if you become pregnant. Women who become pregnant during HYQVIA treatment are encouraged to enroll in the HYQVIA Pregnancy Registry by calling Medical Information at 1-866-424-6724.

**What are the possible or reasonably likely side effects of HYQVIA?**

After HYQVIA infusion a temporary, soft swelling may occur around the infusion site, which may last 1 to 3 days, due to the volume of fluid infused. Mild or moderate pain, redness, swelling, or itching may occur at the site of infusion and generally go away in a few hours.
You may be eligible to save up to $4,000 on HYQVIA

If you are starting or currently receiving treatment with HYQVIA (Immune Globulin Intravenous 10% (Human) with Recombinant Human Hyaluronidase) for PI, you may be eligible to save up to $4,000 on your deductible/co-payment/co-insurance costs over 12 months.

To enroll, call us.
We’ll take care of the rest.

Terms and Conditions

- To be eligible, patients must: 1) be starting or receiving treatment with (and have a current prescription for) HYQVIA with an IQR of IQR10, as applicable, for adult [≥16 years of age] Primary Immunodeficiency (PI); and 2) have commercial insurance that covers medication costs for HYQVIA treatment and allows for co-pay/coupon assistance.

- This manufacturer coupon program is not valid for prescriptions reimbursed, in whole or in part, by Medicaid, Medicare, Medicaid, VA, DoD, TRICARE, or any other federal or state healthcare programs, including state pharmaceutical assistance programs, and where prohibited by the health insurance provider or by law.

- The coupon program provides a maximum benefit of $4,000 for eligible out-of-pocket costs and expires 12 months from date of activation. Eligible costs include deductible, co-payment, and co-insurance costs for HYQVIA. Non-medication expenses, such as ancillary supplies or administration-related costs, are not eligible.

- Patients are eligible for a maximum benefit of $4,000 in total Baxter support in any 12-month period, including any amount received as part of the GAMMAFOCUS LIQUID SubQ CoPay Program.

- Acceptance of this offer must be consistent with the terms of benefits provided by the patient’s health insurance provider.

- Offer limited to one card per person and expires 12 months from date of activation and may not be combined with any other coupon, discount, prescription savings card, rebate, free trial or other offer.

- This program is only valid for residents of the United States, excluding Puerto Rico and other U.S. territories.

- Baxter reserves the right to change or discontinue this program at any time without notice.

- This is not health insurance.

Patient Instructions

By using this coupon, you are certifying that:

1. You meet the eligibility criteria and have read and agree to the terms and conditions of this program;

2. You will not, at any time, submit any costs for the product dispensed pursuant to this coupon to any other program for reimbursement;

3. You are permitting your personal information including name, address, phone number, email address, and information related to health insurance and treatment, to be shared with Baxter and companies working with Baxter for the purpose of administering this program.

4. You will notify your health insurance provider or other third-party payer of the use of this program if required to do so, at least 30 days prior to discontinuing use.

5. If your insurance situation changes, it is your responsibility to notify Baxter immediately by contacting the MygSource Patient Support Program.

For questions about this program, patients and caregivers can call the MygSource Patient Support Program at (855) 250-5111.

For pharmacy instructions please visit www.HYQVIA.com

Local reactions are less likely after the first few infusions. The most common side effects of HYQVIA are headache, fatigue, nausea, fever, and vomiting. Antibodies to the hyaluronidase component of HYQVIA were formed in some patients taking HYQVIA. It is not known if there is any long term effect. In theory, these antibodies could react with your body’s own PH20, PH20 is present in the male reproductive tract. So far, these antibodies have not been associated with increased or new side effects.

What is HYQVIA?

HYQVIA is a liquid medicine containing immune globulin and recombinant human hyaluronidase. HYQVIA contains IgG antibodies, collected from human plasma donated by healthy people. The antibodies help your body to fight off bacterial and viral infections. The hyaluronidase part of HYQVIA helps more of the immune globulin get absorbed into the body to fight infection.

Before starting HYQVIA, tell your healthcare professional if you have or had any kidney, liver, or heart problems, a history of blood clots, because HYQVIA can make these problems worse. Also tell your doctor if you have IgA deficiency or a history of severe allergic reactions to immune globulin (IgG) or other blood products, or are pregnant, trying to become pregnant or are breast feeding.

How should I take HYQVIA?

HYQVIA is infused under the skin (subcutaneously) up to once every 4 weeks. You can get HYQVIA at your healthcare professional’s office, clinic, or hospital. You can use HYQVIA at home. You and your healthcare professional will decide if home self-infusion is right for you. Do not use HYQVIA at home until you get instructions and training from your healthcare professional.

Who should not take HYQVIA?

Do not take HYQVIA if you are allergic to IgG, hyaluronidase, or other blood products, or have IgA deficiency with antibodies to IgA.

To report suspected side effects, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of HYQVIA Prescribing Information on following page, including Boxed Warning.
More free time
with HYQVIA¹

Infusing 1 time a month with HYQVIA doesn’t mean your infusions will take longer. Typically, infusions take less than 3 hours with HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]. Instead, you’ll have more free time.

Please see the Detailed Important Risk Information on the adjacent pages and the Brief Summary of HYQVIA Prescribing Information, including Boxed Warning, on the reverse side.

INDICATION AND USAGE
HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase] is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Limitation of Use:
Safety and efficacy of chronic use of recombinant human hyaluronidase in HYQVIA have not been established in conditions other than PI.

Selected Important Risk Information about HYQVIA
HYQVIA can cause blood clots. Call your healthcare professional or go to your emergency department right away if you have pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s), unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body. These could be signs of a blood clot.

Do not use HYQVIA if you are allergic to immune globulin (IgG), hyaluronidase, or other blood products, or have IgA deficiency.

These are not all the possible side effects with HYQVIA. Talk to your healthcare professional about any side effects that bother you or that don’t go away.
Brief Summary of Prescribing Information
HYQVIA [Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]

The following summarizes important information about HYQVIA (pronounced Hy-Q-via). Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare professional. If you have any questions after reading this, ask your healthcare professional.

What is the most important information that I should know about HYQVIA?

- HYQVIA can cause blood clots.
- Call your healthcare professional if you have pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s), unexplained shortness of breath, chest pain or discomfort that worsens on deep breathing, unexplained rapid pulse, numbness or weakness on one side of the body.
- Your healthcare professional may perform blood tests regularly to check your IgG level.
- With your consent, your healthcare professional may provide blood samples to Baxter Healthcare Corporation to test for antibodies that may form against the hyaluronidase part of HYQVIA.
- Do not infuse HYQVIA into or around an infected or red swollen area because it can cause infection to spread.
- Talk to your healthcare professional if you become pregnant. Women who become pregnant during HYQVIA treatment are encouraged to enroll in the HYQVIA Pregnancy Registry by calling Medical Information at 1-866-424-6724.

What should I tell my healthcare professional before I start using HYQVIA?

Before starting HYQVIA, tell your healthcare professional if you:
- Have or had any kidney, liver, or heart problems or history of blood clots because HYQVIA can make these problems worse.
- Have IgA deficiency or a history of severe allergic reactions to IgG or other blood products.
- Are pregnant, trying to become pregnant or are breast feeding.

What is HYQVIA?

HYQVIA is a liquid medicine containing immune globulin and recombinant human hyaluronidase. HYQVIA contains IgG antibodies, collected from human plasma donated by healthy people. The antibodies help your body to fight off bacterial and viral infections. The hyaluronidase part of HYQVIA helps more of the immune globulin get absorbed into the body to fight infection.

Who should not take HYQVIA?

- Do not take HYQVIA if you: Are allergic to IgG, hyaluronidase, or other blood products.
- Have IgA deficiency with antibodies to IgA.

How should I take HYQVIA?

- HYQVIA is infused under the skin (subcutaneously) up to once every 4 weeks.
- You can get HYQVIA at your healthcare professional’s office, clinic, or hospital.
- You can use HYQVIA at home. You and your healthcare professional will decide if home self-infusion is right for you.

What are the possible or reasonably likely side effects of HYQVIA?

After HYQVIA infusion a temporary, soft swelling may occur around the infusion site, which may last 1 to 3 days, due to the volume of fluid infused.

The following local reactions may occur at the site of infusion and generally go away in a few hours. Local reactions are less likely after the first few infusions: mild or moderate pain, redness, swelling, and itching.

The most common side effects of HYQVIA are headache, fatigue, nausea, fever, and vomiting.

Antibodies to the hyaluronidase component of HYQVIA were formed in some patients taking HYQVIA. It is not known if there is any long term effect. In theory, these antibodies could react with your body’s own PH20. PH20 is present in the male reproductive tract. So far, these antibodies have not been associated with increased or new side-effects.

Call your healthcare professional or go to your emergency department right away if you get:
- Hives, swelling in the mouth or throat, itching, trouble breathing, wheezing, fainting or dizziness. These could be signs of a serious allergic reaction.
- Bad headache with nausea, vomiting, stiff neck, fever, and sensitivity to light. These could be signs of swelling in your brain.
- Reduced urination, sudden weight gain, or swelling in your legs. These could be signs of a kidney problem.
- Pain, swelling, warmth, redness, or a lump in your legs or arms, other than at the infusion site(s). These could be signs of a blood clot.
- Brown or red urine, fast heart rate, yellow skin or eyes. These could be signs of a liver or blood problem.
- Chest pain or trouble breathing, blue lips or extremities. These could be signs of a lung problem.

These are not all of the possible side effects for HYQVIA. For more information about HYQVIA, go to www.HYQVIA.com. For more information on patient resources and education, please visit www.immunedisease.com.
How to Diagnose an Antibody Deficiency,  
Summarization Part 4  
By Terry O. Harville, MD, PhD  

Conceptually, the steps to making a diagnosis of antibody deficiency are somewhat simple. A patient presents with recurrent/chronic infections of the respiratory system. Testing reveals decreased functional antibody responses. The patient is diagnosed with an antibody deficiency, is placed on immune globulin replacement therapy and shows great improvement in his or her clinical status. However, in the real world, putting this process into practice can be challenging.  

As we have discussed in previous issues of *IG Living*, just as people come in a number of varieties (tall and short, slim and not so slim), antibody deficiencies also come in many varieties. While they may be similar, no two patients have exactly the same issues and problems, and ultimately, therapeutic interventions have to be tailored to each patient to achieve optimal results. Because of this variability, absolute rigidity by a physician in contemplating the issues may result in missed diagnoses. On the other hand, considering the issues too broadly can lead to expensive and potentially unnecessary testing and treatment (as well as anxiety for a patient and his or her family fearing the worst). Thus, it is important for the evaluating physician to scrutinize the details of the presentation, history of illnesses and family history to establish a differential diagnosis, and follow this with a physical examination to further fine-tune the considerations, as well as order a sufficient number of relevant tests to confirm the diagnosis.  

While this diagnostic process is what physicians are taught, adhering to the process is becoming more difficult. These evaluations take time, which is at a premium in this modern age of medicine, and they can be expensive. As a result, important information may be missed along the way and incomplete testing may be performed, especially in an attempt to keep costs down. A physician does not want to be in a position of trying to convince third-party payers that further testing or treatment is necessary when test results may be normal, even though individually, or in aggregate, there may be an indication that something is amiss. A physician also does not want to create more alarm for the patient when the diagnosis cannot be fully confirmed or explained, or pieces of the clinical presentation, history or laboratory tests are not adding up to a reasonable conclusion — a situation that can result in frustration for both the patient and physician.  

Patients seek help because they want answers to what is happening and why, and they want therapies to make them better. But many physicians are not comfortable with testing for and diagnosing an immunodeficiency. So, these patients may be at a disadvantage from the start.  

Now, with the Internet, patients seek out their own information, which can have its downsides and upsides. These disadvantages include: 1) trying to get the physician to listen to the information the patient has found (remember, time is short); and 2) patients may be following a wrong trail of information and unreliable sources of information (good Internet searches require asking the right questions, and many patients may not know the correct terms to use).  

Many physicians are not comfortable with testing for and diagnosing an immunodeficiency.  

The advantages to patients seeking their own information on the Internet include: 1) helpful advice offered by others who have gone through similar situations; 2) valuable resources, such as *IG Living*, may be found; and 3) a physician better capable of performing the correct evaluations may be located to help make the diagnosis of an antibody deficiency more straightforward, or to at least provide a better understanding of the nuances of the patient’s clinical problems, which may lead to better help and outcomes.  

In conclusion, to expediently diagnose an antibody deficiency, the laboratory testing must clearly indicate the diagnosis, and the physician must have the right experience to appropriately put all the information together. When the diagnosis is not clearly established, patients must become their own advocates to find the best clinical help to establish a correct diagnosis, or to at least find a physician who is willing to work with them to improve their health.  

TERRY O. HARRVILLE, 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.
Abbie » According to the literature, certain conditions have a higher potential to affect the central nervous system, and unfortunately, primary immunodeficiency disease (PI) is one of them, which can result in meningitis. So, even though it’s rare, there is a slightly higher chance of aseptic meningitis in people with PI. The risk for aseptic meningitis also increases for people who have ongoing migraines. If this is something that applies to you, discuss adding migraine medication to your premedications with your physician. This may not prevent aseptic meningitis, but it can help with severe headaches. Other medications that can help with severe headaches are IV steroids and IV hydration.

If IG replacement therapy isn’t working for you because of side effects, you likely aren’t really giving it a fair chance, which is why your IgG levels are still low. If your IgG levels are low in spite of being on IG replacement therapy or if you have continued to battle infections despite long-term IG therapy, it’s possible that other medications and your past medical history may be affecting treatment.
Medicines

Gammaplex Approved for PI Patients 2 Years and Older

In August, the U.S. Food and Drug Administration (FDA) approved Bio Products Laboratory’s Gammaplex (immune globulin intravenous [human] 5% liquid) for pediatric patients 2 years of age and older who have primary immunodeficiency disease (PI). The approval was based on study data submitted as part of a post-marketing commitment following the approval of Gammaplex for adults in 2009. In the study, 25 children and adolescents with PI aged 3 years to 16 years were treated with Gammaplex for 12 months. During the study, two serious acute bacterial infections (SABIs) of pneumonia were reported, resulting in an annual SABI event rate of 0.09, well below the maximum SABI event rate of 0.5 per subject required for approval. Fourteen children had an adverse reaction at some point during the study that was considered product-related. Of those, two had adverse reactions that were considered definitely related to Gammaplex, including headache, fatigue and myalgia. The most common adverse reactions, occurring in less than 5 percent of children, were dyspnea, otitis media acute and tonsillar disorder (two). Two subjects reported a serious adverse event of lobar pneumonia. Neither serious adverse reaction was considered related to Gammaplex, and neither met FDA-defined SABI criteria.
Reimbursement

CMS Expands In-Home Coverage of HYQVIA for PI Patients

The Centers for Medicare and Medicaid Services (CMS) has expanded coverage to include in-home use of HYQVIA (immune globulin infusion 10 percent [human] with recombinant human hyaluronidase) to treat primary immunodeficiency patients. Following HYQVIA’s U.S. Food and Drug Administration approval in 2014, CMS covered both provider facility and in-office treatment with HYQVIA. The expansion includes durable medical equipment coverage of the infusion pump required to administer the drug. “Today’s decision from CMS reinforces the value of HYQVIA and will help expand access to even more people who can benefit from the flexibility of self-administering HYQVIA in their own homes,” said Jacopo Leonardi, executive vice president and president, immunology, for Baxalta. “This coverage is a critical step forward in meeting their needs and equipping them to better manage their disease.”

Medicines

Recombinant IVIG Granted Orphan Drug Designation for CIDP

Pfizer (a licensee if Gliknik Inc.) has been granted orphan drug designation by the U.S. Food and Drug Administration (FDA) for its recombinant intravenous immune globulin (IVIG)-mimetic drug GL-2045 to treat chronic inflammatory demyelinating polyneuropathy (CIDP). The FDA grants orphan drug designation to novel drugs or biologics that treat a disease or condition affecting fewer than 200,000 patient in the U.S. Several brands of the human blood product IVIG have previously received orphan drug designation for CIDP, but GL-2045 is a recombinant (not blood-derived) drug candidate under development. GL-2045 may eventually provides patients an alternative that is at least as effective as IVIG but potentially more convenient and safer without the risk of bloodborne pathogens. “This orphan drug designation is important in that it provides numerous incentives to develop GL-2045 to address an unmet need in CIDP, a rare neurological disorder,” said David Block, CEO of Gliknik.

Medicines

Baxter Files for European Approval of 20% SCIG Treatment for PI

Baxter’s BioScience business has submitted a marketing authorization application to 17 competent authorities in Europe following the decentralized procedure for approval of its investigational 20% concentration subcutaneous immune globulin (SCIG) treatment for primary immunodeficiencies (PI). The filing is based on the positive results of its Phase 2/3 study that evaluated the efficacy, safety, tolerability and pharmacokinetics of SCIG 20% in European patients at least 2 years old with PI. The study met its primary endpoint that measured the rate of validated acute serious bacterial infections (VASBI). Only one VASBI was reported during treatment with SCIG 20%, which equated to a low rate of 0.022 per patient-year compared with the specific threshold of one VASBI per patient-year. Nearly all infusions were completed without any interruption, slowing or stopping the infusion. The rate of local adverse events considered related to treatment was 0.052 per affected infusion (in 17 of 48 patients), and the majority of local adverse events were erythema, swelling, pruritis and pain/discomfort.

Results from a separate study of SCIG 20% among patients with PI in North America are expected to be available in the fall, and based on the outcomes, Baxter intends to file for U.S. approval of the product before the end of 2015.

People & Places

CSL Behring will spend $450 million over the next few years to expand its production facilities in the U.S. and Australia. It will invest $240 million into its Kankakee, Ill., facility that produces albumin and immunoglobulins (adding 190 jobs) and $210 million into its Broadmeadows plant in Melbourne, Australia.
Marcia Boyle, President of IDF, Recognized as “Champion of Change”

In July, Marcia Boyle, president and founder of the Immune Deficiency Foundation (IDF), was one of nine individuals recognized by President Obama as “Champions of Change” for precision medicine who are making a difference in transforming the way we improve health and treat disease. The chosen individuals embody the promise of the President’s Precision Medicine Initiative, which was launched in early 2015 to enable a new era of medicine through research and technology that empowers patients, researchers and providers to work together toward the development of individualized treatments.

Boyle has dedicated her life to being a champion for those living with primary immunodeficiency diseases (PI) through IDF’s ongoing advocacy, education and research initiatives. Under her leadership, IDF developed an electronic personal health record, IDF ePHR, for the PI community that allows patients to better track and manage their health. And, as a Patient-Centered Outcomes Research Institute grant recipient, IDF created PI CONNECT, the IDF Patient-Powered Research Network, which brings together patient data from the IDF ePHR with clinical data from the U.S. Immunodeficiency Network patient-consented registry, a program of IDF, to provide researchers further insights about the diagnosis and treatment of PI, ultimately helping to improve quality of life for patients.  

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- Pivotal trial showed that PI patients missed 2.3 days/year of work or school
- BIVIGAM is well tolerated
  - The rate of adverse reactions per infusion has been calculated at 0.091% with a rate of serious adverse reactions at 0.076%\(^1\)
  - The most common adverse reactions (≥5%) were headache, fatigue, infusion site reaction, nausea, sinusitis, increased blood pressure, diarrhea, dizziness, and lethargy\(^2\)

A Step Ahead in IVIG\(^*\)

- First newly approved IVIG\(^*\) with a validated thrombin generation assay
- All lots of a subset of BIVIGAM lots that have been tested for anti-A and anti-B were found to be ≤1:16\(^1\)
- Sugar-free, 10% liquid preparation, glycine stabilized
- pH of solution: 4.0 – 4.6

Delivering Safety That Matters

- Tamper-evident seals
- Integrated hanger label
- Latex-free packaging

BIVIGAM\(^\circledR\) [Immune Globulin Intravenous (Human), 10% Liquid] is indicated for the treatment of primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
BIVIGAM is manufactured in the USA from US plasma for US providers and patients.

Available in Two Vial Sizes

**NDC: 59730-6502-1**
A carton contains a 50 mL vial (5 g IgG) and a package insert

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- May be stored for up to 24 months (until expiration date on vial packaging) at 2°C to 8°C (36°F to 46°F)

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**Warning:** Thrombosis may occur with immune globulin intravenous (IGIV) products, including BIVIGAM. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, the use of estrogens, indwelling vascular catheters, hyperviscosity and cardiovascular risk factors. Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients. Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. BIVIGAM does not contain sucrose. For patients at risk of thrombosis, renal dysfunction, or renal failure, administer BIVIGAM at the minimum dose recommended and infusion rate practicable. Ensure adequate hydration in patients before administrations. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for viscosity. See full Prescribing Information for complete boxed warning.

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

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


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Thrombosis may occur with immune globulin (IGIV) products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, use of estrogens, including central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including cryoglobulins, fasting chylohydrolasma/markedly high triglycerolys (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, renal dysfunction, or acute renal failure, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Indication and Usage: BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI). Contraindications: BIVIGAM is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. BIVIGAM is contraindicated in IgA deficiency patients with antibodies to IgA and a history of hypersensitivity.

Warnings and Precautions: Thrombosis: Thrombosis may occur following treatment with IGIV products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, including central vascular catheters, hyperviscosity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including cryoglobulins, fasting chylohydrolasma/markedly high triglycerolys (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. Hypersensitivity: Severe hypersensitivity reactions may occur with IGIV products, including BIVIGAM. In case of hypersensitivity, discontinue BIVIGAM infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reactions. BIVIGAM contains trace amounts of IgA (≤ 200 micrograms per milliliter). Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity reactions. For patients with antibodies against IgA and a history of hypersensitivity reaction. Acute Renal Dysfunction and Acute Renal Failure: Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IgG products. Ensure that patients are not volume depleted before beginning BIVIGAM. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overweight, use of concomitant nephrotoxic medicinal products or age of ≥ 65 years), administer BIVIGAM at the minimum dose and infusion rate practicable. Increased Serum Viscosity and Hypernatremia: Hypernatremia, increased serum viscosity, and hypernatremia may occur in patients receiving IGIV therapy, including BIVIGAM. It is critical to clinically distinguish hypernatremia from a pseudonephrotic syndrome that is associated with IGIV products related to hypernatremia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudonephrotic syndrome may lead to volume depletion, a further increase in serum viscosity, and possible predisposition to thrombotic events. Aseptic Meningitis Syndrome (AMS): AMS may occur infrequently with IGIV treatments including BIVIGAM. AMS usually begins within several hours to 2 days following IGIV treatment. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. AMS is characterized by the following signs and symptoms: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. Conduct a thorough neurological examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (≥ 2 g/kg) and/or rapid infusion of IGIV. Herpes simplex virus (HSV) infection of products used in the production of BIVIGAM may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to the onset due to enhanced B cell response with concomitant in vivo cross-reactivity, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If these are present after BIVIGAM infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolysis, hematologically compatible RBCs after receiving IGIV are recommended. There is no current evidence that prophylactic anemia with oral iron, with a possible cross-matching to avoid exacerbating on-going hemolysis. Transfusion-Related Acute Lung Injury (TRALI): Noncardiogenic pulmonary edema may occur in patients following IGIV treatment including BIVIGAM. TRALI is characterized by severe respiratory distress (e.g., rales, rhonchi, pulmonary edema), hypotension, and a normal left ventricular filling pressure. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient’s serum. TRALI may be managed using oxygen therapy with adequate ventilatory support. Transmissible Infectious Agents: Because BIVIGAM is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted from BIVIGAM are promptly reported to the manufacturer. No cases of transmission of viral diseases or CJD have been associated with the use of BIVIGAM. All infections suspected by a physician possibly to have been transmitted from BIVIGAM are promptly reported to the manufacturer. Drug Interactions Live Virus Vaccines: Immunglobulin administration may transiently impair the efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella because the continued presence of high levels of passively acquired antibodies to the vaccine virus might interfere with the induction of protective immunity. The ineffectiveness of BIVIGAM to so that appropriate measures may be taken.
Autoimmune Disorders Associated with High Rates of Depression

Two recent studies show that autoimmune conditions such as rheumatoid arthritis and psoriasis are associated with high rates of depression. The finding suggests the impact on mental health, as well as the chronic pain and fatigue association with the conditions, could be much larger than previously estimated.

In one observational study (published in the journal *Arthritis Care and Research*) of 322 patients with severe rheumatoid arthritis who were waiting to go on biologic therapy, researchers investigated the impact of psychological factors upon each of the different parts of the current measure of disease, the DAS28. The DAS28 score takes into account the number of tender and swollen joints and the level of inflammation in the body and also includes a subjective, patient-reported measure based on how well the patient is feeling. The researchers found that subjective measures of response were more likely to be influenced by psychological factors such as mood or beliefs about their illness and the therapies used.

“This may seem obvious, but it has not been reported before and is important because without treating the depression, the patient’s DAS28 score might not improve as much as it should on a biological drug, and doctors may assume the drug is ineffective,” explained Dr. Lis Cordingley, a health psychologist who was the lead author of the study. As a result of this study, researchers at the Arthritis Researcher UK Center for Genetics and Genomics at the University of Manchester in the United Kingdom say that patients with severe active disease who are waiting to go onto a biological therapy should be routinely screened for depression.

Research has also shown that those with psoriasis have a 39 percent increased risk of depression. In a study published in the *Journal of Dermatological Treatment*, researchers looked at how certain biological therapies may also have an impact on depression in psoriasis patients. They reviewed various studies correlating increased levels of cytokines to depression and concluded that TNF inhibitors, frequently used in the treatment of psoriasis, may be helpful in directly reducing depressive symptoms for patients with psoriasis and other chronic inflammatory conditions.

Individuals with psoriasis are now being asked to take part in a new study at St. Vincent’s University Hospital that is looking at the effects of psychological intervention known as mindfulness, which aims to develop awareness of the present moment through the practice of a form of meditation. Mindfulness has been found effective for improving mental health by reducing the symptoms of depression, anxiety and stress, as well as for improving health-related quality of life.

Tuberculosis Vaccine Effective as Treatment for MS

A recent study shows that a vaccine typically used to prevent tuberculosis in countries outside of the U.S. could also prevent multiple sclerosis (MS) in people who are in the beginning stages of the disease. In the study, researchers looked at 73 patients who showed early signs of MS, 33 of whom received one injection of the Bacille Calmette-Guerin (BCG) vaccine, while the others received a placebo. After six months of brain scans, all the participants received another MS drug called interferon beta-1a for one year, followed by whatever MS drug their neurologist prescribed. Immediately following the BCG vaccine, all patients were evaluated for definite MS for five years. Six months into the study, patients who received the vaccine had a lower-than-average number of brain lesions (three) that are indicative of MS compared with the placebo group who had seven lesions. No major differences in side effects were noticed between the two groups by the end of the study. All together, 58 percent of the vaccinated group hadn’t developed MS, which was almost twice that of the placebo group (30 percent). Typically, half of all patients in the early stage of MS, known as the clinically isolated syndrome, develop a clinically definite form of MS within two years of diagnosis, while 10 percent remain unchanged. The study was reported on in the Dec. 4 issue of *Neurology*.
For individuals with chronic illness who are treated with expensive medications, ensuring the marketplace plan they pick is the most affordable can be complicated.

By Ronale Tucker Rhodes, MS
For the chronically ill, the Affordable Care Act (ACA) represents guaranteed access to care, coverage for essential health benefits, caps on out-of-pocket expenses, elimination of lifetime caps, expanded access to Medicaid and standardization of the appeals process. But, the ACA’s title — indicating its main purpose: to ensure that all Americans have access to “affordable” healthcare — is a misnomer for many patients who rely on expensive medications such as immune globulin (IG) when purchasing insurance on the healthcare exchanges (aka marketplaces).

Figuring out which marketplace plan will result in the lowest cost for patients is no easy task due to price variables and individual needs. Furthermore, these plans use specialty tiers, and expensive biologic medications like IG are placed in the highest tier with the highest level of cost-sharing. Consequently, patients who rely on these lifesaving medications could find that high out-of-pocket expenses put their therapy out of reach. In essence, the ACA may have resulted in more chronically ill patients being insured, but many continue to be underinsured.

Fortunately, states are taking steps to make their exchanges more patient-friendly, and laws are being passed that may help to lower cost-sharing.

The Marketplace Plans

While healthcare exchanges have been in existence in the private sector for some time, with the passage of the ACA in 2010, the new federal- and state-run health exchanges “provide a set of government-regulated and standardized health care plans from which individuals may purchase health insurance policies eligible for federal subsidies.” Marketplaces are not insurers, but they do determine which insurance companies participate in them.¹ This year, 11.7 million people are estimated to have enrolled in the marketplaces during the open enrollment period from November 2014 to February 2015, which includes 4.5 million from 2014 who re-enrolled.²

Consumers can choose from four metal plans — bronze, silver, gold and platinum — that are available to all individuals, as well as a catastrophic plan that is available only to individuals under age 30 or to those who have a hardship exemption (situations that keep one from getting insurance). Each of these plans offers a variety of plan types (e.g., PPOs and HMOs). In addition, all plans have a set of minimum benefits that includes hospitalizations, prescription drugs and maternity care.

However, premiums (the amount a person pays per month, quarter or year for a plan) vary widely based on the cost of healthcare where a person lives (even in the same state), age, family size and tobacco use, and that difference in price for the same plan can range in the thousands of dollars. Importantly, though, prices cannot be based on medical history, and patients with a preexisting condition can’t be turned away.³

Catastrophic plans have the lowest premiums, followed by bronze, silver, gold and platinum. But, each plan differs in financial protection. Generally, the lower premiums mean higher out-of-pocket costs. For instance, catastrophic plans cover less than 60 percent of expected costs, bronze covers 60 percent, silver covers 70 percent, gold covers 80 percent and platinum covers 90 percent. It’s important to note that catastrophic plans are intended for worst-case scenarios, like serious accidents or diseases. They require individuals to pay all of their medical costs until the deductible is reached, usually several thousand dollars. Once the deductible is reached, costs for essential health benefits are generally paid.⁴
The ACA’s tax credits to help with premiums are keyed to a benchmark silver plan, the standard for most consumers, in each geographical area. Gold plans are the closest to employer-provided coverage. For those with chronic illness, gold and platinum plans are likely a better option because they reduce out-of-pocket expenses.5,6 Federal subsidies are available to those whose income is between 100 percent ($11,490 for an individual) and 400 percent ($45,960) of the federal poverty level. In addition, a family of four can get a subsidy, although just a small one, with income up to $94,200. To qualify for subsidies for deductibles and co-pays, income has to be less than 2.5 times the poverty level ($28,725 for an individual or $58,875 for a family of four). However, out-of-pocket subsidies are available only to people who have a silver plan. Subsidy amounts are calculated based on modified adjusted gross income.7

A NUMBER OF LAWS ARE BEING PROPOSED IN VARIOUS STATES TO CAP CO-PAYS, AND SOME HAVE ALREADY PASSED.

Out-of-Pocket Expenses

Out-of-pocket costs include annual deductibles, co-insurance, co-pays and out-of-pocket maximums. A deductible is the amount patients pay for covered services before the insurance starts to pay.8 More than 70 percent of marketplace plans have deductibles under $3,000.9 After the deductible is reached, some services might be covered at 100 percent, while others might require a co-insurance to be paid. Co-insurance is a share of the costs of a healthcare service, which is typically a fixed percentage. A co-pay is a fixed dollar amount that is paid for certain healthcare services such as doctor office or emergency room visits. In most cases, co-pays do not count toward the deductible. A plan’s out-of-pocket maximum is the most patients have to pay during a policy period (typically a year) before the plan starts to pay 100 percent of the allowed amount.8 Depending on the plan, deductibles, co-payments and/or co-insurance may apply toward the out-of-pocket maximum. But, premiums and non-covered healthcare (e.g., elective surgery) do not. The various healthcare plans have different out-of-pocket maximums. In 2015, under the ACA, the limits are $6,600 for an individual plan and $13,200 for a family plan. Once the deductibles, co-payments and co-insurance reach these limits, the insurance company pays 100 percent of the costs for covered care under all plans.5,10

Interestingly, an analysis by Avalere Health, a consulting firm, shows that out-of-pocket spending caps in 2015 for 71 percent of bronze, 74 percent of silver, 94 percent of gold and 98 percent of platinum plans are below the allowed limits. These include an average of $6,381 for bronze, $5,853 for silver, $4,458 for gold and $2,145 for platinum. However, the trade-off is higher deductibles, with the average deductible for a silver plan having increased 7 percent in 2015 to $2,658.11

Specialty Tiers

Understanding what out-of-pocket expenses are is one thing. Understanding what they will cost, especially when specialty medications are involved, is yet another. Most of the marketplace plans use a specialty tier structure that includes four tiers. Tier one includes low-cost generic drugs that require a modest co-pay such as $15, while the highest tier (tier four) includes the most expensive medications such as IG or other cell-derived biologic medications, cancer medicines and drugs for chronic or rare diseases that are disproportionately higher. Tier four also has the highest level of cost-sharing, a co-insurance rate that is a percent of the drug’s cost.12 According to a study by Avalere Health, these co-insurance rates are often 30 percent to 40 percent of the cost of the drug.13

What’s worse is that when choosing marketplace plans, Avalere Health reported that “HealthCare.gov may not accurately reflect these specialty tiers’ out-of-pocket obligations for some patients.”12 For instance, HealthCare.gov fails to report cost-sharing information for many of the specialty tier structures, which leaves patients in the dark about their cost-sharing requirements.13 And, the analysis by Avalere Health suggests a cost-sharing discrepancy for patients with chronic or serious illnesses. In seven of the drug classes it studied, one-fifth of silver plans had a patient co-insurance requirement of 40 percent or higher.14

The four-tier structure is being called discriminatory, with more than 300 patient groups having sent a letter to Health and Human Services Secretary Sylvia Mathews Burwell to complain.13 Specialty tiers apply a totally different benefit structure to certain medications, most of which are used by those living with specific conditions such as cancer, multiple sclerosis, hemophilia, primary immune deficiencies and certain neuropathies.

Fortunately, a number of laws are being proposed in various states to cap co-pays, and some have already passed. For instance,
in California, the Neuropathy Action Foundation and 30 other patient and provider groups asked the state’s insurance commissioner to investigate whether specialty tier structures violate federal and California law. In Oregon, two bills are pending that would cap co-pays at $100 per 30-day supply of standard drugs and $200 for specialty medications. In Maryland and Louisiana, bills that limit co-pays or co-insurance to $150 per specialty drug up to a 30-day supply were signed into law May 5, 2014, and June 14, 2014, respectively. And, in Virginia, a law passed that requires insurers to provide affected enrollees 30 days’ notice of a modification to a formulary that moves a prescription drug to a tier with higher cost-sharing requirements.

Calculating Costs

Few state exchange websites offer cost-calculating tools that allow consumers to figure out how much they would owe under various plan options. But, one is offered by the National Health Council, which has an initiative titled Putting Patients First that strives to ensure that the voices of individuals living with a chronic disease or disability and their family caregivers are heard. On its website (www.puttingpatientsfirst.net), a healthcare calculator titled Estimate My Costs allows individuals to enter personal information such as the state in which they reside, annual income, estimated doctor and hospital visits and medications they are prescribed. The site then calculates both the estimated premiums and out-of-pocket costs for the low and high of each metal plan.

An out-of-pocket cost estimator is currently under development for the federally facilitated marketplace for the 2016 enrollment period, and at the end of June, 103 patient, provider and consumer organizations sent a letter to the Center for Consumer Information and Insurance Oversight to encourage the Centers for Medicare and Medicaid to include accurate drug-specific tier placement information, 2) allow patients to enter their medications and 3) use approximate negotiated prices of these drugs.12

Access Today, Affordability Tomorrow

According to a National Health Council report, all 50 states, plus the District of Columbia, have taken steps to enhance their health insurance exchanges to make them more patient-friendly. But, it adds that much more needs to be done to ensure the marketplaces meet the needs of people with chronic diseases and disabilities. The report identified five key principles of concern to the patient community: non-discrimination, transparency, state oversight, uniformity and continuity of care.13

While passage of the ACA has greatly improved access to care, there are many aspects of the law that still need improvement to make the marketplaces more navigable and affordable for patients with chronic illness. Fortunately, many organizations are “putting patients first,” and it is likely only a matter of time before cost-sharing under specialty tiers becomes more equitable. “If the question is, will some people find that coverage and care remain unaffordable, the answer is yes,” said Ron Pollack, executive director of Families USA. “There will be some people who feel that way. [But,] the overwhelming majority will be far better off, even if what they have is not perfect.”

Ronale Tucker Rhodes, MS, is the editor of IG Living magazine.

References
Transitioning IG Coverage to Medicare

Options in Medicare coverage can be more complicated than IG therapy, but these guidelines for individuals turning 65 can help to ensure a smooth transition.

By Michelle Greer, RN, and Leslie Vaughan, RPh

**IMMUNE GLOBULIN (IG)** is a complex therapy, both clinically and financially, that is used to treat rare and difficult-to-diagnose diseases. For some, IG is a lifetime therapy. And, while at one time this therapy was typically approved and reimbursed without question, today there are extensive medical policies in place that require a diagnosis to be proved and the medical need for IG justified. Compared with all other insurance plans, Medicare probably varies most in its coverage policies for IG therapy. Therefore, patients who continue to receive IG therapy when they turn 65 or otherwise become eligible for Medicare need to know how to successfully transition to Medicare, which may require changes in site of care and route of administration to ensure therapy is continued without disruption and financial strain.
**Applying for Medicare**

To be eligible for Medicare coverage, patients must be age 65 or older and eligible for retirement benefits under Social Security, or a federal, state or local employee. To be eligible for Social Security, individuals must have 40-plus quarters of Social Security-covered employment, receive benefits under a spouse’s work record and be currently married, or have received benefits under a former spouse to whom they were married for at least 10 years.

Individuals also may be eligible for Medicare if they are receiving disability benefits under Social Security Disability Insurance; have received railroad retirement benefits for 24 or more months; have end stage renal disease; or have amyotrophic lateral sclerosis, also known as Lou Gehrig’s disease.

Some individuals will be automatically enrolled in Medicare when they turn 65, whereas others will need to apply. Those who are already receiving Social Security benefits and have enough work quarters will automatically be enrolled for Medicare Parts A and B when they turn 65 or on the 25th month of disability. All others will need to apply for Medicare. An individual who needs to apply for Medicare has a seven-month initial enrollment period to sign up for Part A and/or Part B. This initial enrollment period begins three months prior to the individual’s 65th birthday month, includes the birthday month and concludes three months after the birthday month. Starting the application process as early as possible can minimize any problems getting enrolled.

One of the most important things to consider when turning 65 is if the insurance through an employer will continue. If patients or their spouses are still working and the employer has 20 or more employees, Medicare becomes the secondary insurance until they retire. If patients or their spouses plan to retire, and their employer’s insurance will continue, Medicare will become the primary insurance and will cover all approved charges at 80 percent, with the employer’s insurance generally covering the remaining 20 percent of approved charges. If the employer’s insurance will terminate, patients may consider obtaining a Medicare supplemental plan, since 20 percent of the cost of monthly IG therapy can be financially taxing.

For detailed information on this, Medicare has a free booklet titled *Medicare and Other Health Benefits: Your Guide to Who Pays First* that explains all of the options. Another excellent free resource for learning about Medicare is a booklet titled *Medicare and You*. These booklets, as well as more detailed information on basic Medicare coverage, including eligibility, coverage criteria and plan options, can be found on the Medicare website at www.Medicare.gov.

**Choosing Medicare Benefits**

The original Medicare plans include Medicare Parts A and B. There also is Medicare Part D (the Medicare prescription drug plan) for which patients can sign up. An alternative option to Parts A and B is Medicare Part C (the Medicare Advantage Plan), which is similar to an HMO and usually includes prescription drug coverage.

Coverage for IG varies based on the patients’ diagnosis, where they currently receive therapy and whether or not they receive therapy via the intravenous (IVIG) or subcutaneous (SCIG) route.

**Drug coverage for an immune deficiency diagnosis.** IG therapy for an immune deficiency is 80 percent covered under Medicare Part B. This is the case whether patients receive IVIG or SCIG. However, any coverage changes should be confirmed for the site of therapy, including the hospital, physician’s office or home. There is broader coverage in the hospital and physician’s office than there is in the home. In the homecare setting, coverage is limited to five specific diagnosis codes:

- 279.04: congenital hypogammaglobulinemia (aka Bruton’s agammaglobulinemia)
- 279.05: immune deficiency with increased IgM
- 279.06: common variable immune deficiency
- 279.12: Wiskott-Aldrich syndrome
- 279.2: severe combined immune deficiency

Unfortunately, IVIG is not reimbursed very well under Medicare Part B. For some providers, Medicare reimbursement is below their cost to purchase IVIG, and this may cause them to ask patients to change their site of care or route of administration. This is mostly true for patients who receive IVIG in the physician’s office and at home.

Patients who receive IVIG in a physician’s office may be asked to change their site of care to a hospital outpatient setting if continuing to receive IVIG, or to change to a home setting to

**Compared with all other insurance plans, Medicare probably varies most in its coverage policies for IG therapy.**
begin receiving SCIG. There are five SCIG products: Gammagard Liquid (Baxalta), Gamunex-C (Grifols), Gammaked (Kedrion Biopharma), Hizentra (CSL Behring) and HYQVIA (Baxalta). HYQVIA is the most recent addition to SCIG products, and it differs from the others because it is a combination product using IG and hyaluronidase. The hyaluronidase component makes it possible for patients to infuse monthly rather than the more frequent dosing that may be required when using traditional SCIG products. Medicare originally did not allow coverage for HYQVIA in the home setting under the Part B benefit; however, more recently, that decision has been partially reversed. The manufacturer of HYQVIA, Baxalta, recommends a dose ramp up, which means patients start with a partial dose and increase the dose with each subsequent treatment until they reach a maintenance dose. Currently, coverage under Medicare Part B will not pay for the ramp-up phase in the home. Payment for the ramp-up phase is available only in the hospital outpatient and physician office settings. Once the patient is stabilized with the maintenance dose, Part B will cover ongoing doses in the home setting.

Many Medicare beneficiaries in this position have successfully changed to SCIG and have learned to self-administer in their home setting. SCIG offers many benefits, including a lower incidence of side effects, no need to start IV lines, and the ability to choose when and where to administer therapy. Most home infusion providers will teach patients how to self-administer SCIG. And, there are many patient education materials, including DVDs, that demonstrate SCIG self-administration. Those interested in learning more should ask their physician to obtain the materials for them, or they can go to the website of the manufacturers of SCIG products: www.gammagard.com, www.gamunex-c.com, www.gammaked.com, www.hizentra.com, www.hyqvia.com.

Patients receiving IVIG at home may be asked to switch to SCIG. If this is not an option for patients, they may be asked to transfer their services to a hospital outpatient infusion center. Patients’ homecare providers should be discussing this and reviewing these options with them well before transitioning to Medicare so there is time to facilitate a smooth transfer. If a provider hasn’t started discussing this with them prior to transitioning to Medicare, patients should contact their homecare provider to discuss services and options.

Patients who self-administer SCIG will not likely be asked to make a change because SCIG is not reimbursed at the low IVIG rate. Patients who receive IVIG in the hospital also will not likely be asked to make a change. However, they should speak with someone in their infusion center who can explain Medicare coverage to them and confirm there will be no change.

Drug coverage for other diagnoses. IG therapy for many other diagnoses is usually covered under Medicare Part B in the hospital outpatient setting or in a physician’s office. For those currently receiving IVIG in these sites of care, the same rules apply for transitioning to Medicare as they do for patients diagnosed with an immune deficiency.

If receiving IVIG at home, the rules become more complicated. If patients will keep their employer’s insurance, it’s possible that no changes will be necessary. Medicare will be billed; however, reimbursement will be denied, and then the secondary insurance will be billed. All deductibles and co-payments apply as they did when the employer’s insurance was in the primary payment position. This includes government insurance such as Tricare and Champus.

If patients who receive IVIG at home will not keep their employer’s insurance, one option that will allow them to continue IG therapy is to purchase Medicare Part D insurance, which is a government program for prescription drugs administered by commercial entities. Medicare Part D consists of many plans, so it can be complicated to choose one. All medications that are prescribed, including IG, should be considered when selecting a plan.

Patients can choose a standard benefit program that may have a lower premium but may not offer assistance through the different phases of coverage. Or, they can choose a plan that may have a slightly higher monthly premium but may have better assistance through the coverage phases. The four coverage phases for a standard plan in 2015 are:

1. Deductible: This is paid 100 percent by the member up to a total of $320.
2. Co-insurance/co-payment: For the standard benefit, the patient pays 25 percent and the plan pays 75 percent up to a total out-of-pocket cost of $2,960. This means the patient pays a total of $651.25 in this phase.
3. Coverage gap: In this phase, also known as the doughnut hole, the patient is responsible for most of the charges; however, the drug manufacturer may provide payment assistance. For brand-name drugs, the patient’s responsibility is 45 percent, and for generics, the patient’s responsibility is 65 percent. In 2015, the total doughnut hole amount is $3,713.75, of which the patient may be responsible for all or as little as $1,738.
4. Catastrophic phase: Once a patient (with the assistance of the drug manufacturer) has spent a total of $4,700, the patient becomes responsible for a smaller portion of the ongoing cost of the drugs, usually 5 percent of the total cost.

Again, there are options. Patients may qualify for Extra Help, a Medicare program to help people with limited income and resources pay Medicare prescription drug plan costs. When
applying for Medicare, it is important for patients to find out if they might qualify for this program. If they don’t qualify when first obtaining Medicare, patients should periodically recheck as their finances change to see if they qualify. In addition, some homecare providers may offer financial assistance programs. If the patients are eligible, their financial responsibility can be reduced or waived. And, last, patient advocacy groups also may offer some assistance.

Guidance on selecting the right Medicare Part D coverage can be found at www.medicare.gov, or Medicare assistance can be obtained by calling (800) MEDICARE (633-2273).

The last option for patients who receive IVIG at home is to transition to a hospital outpatient setting where IVIG will be covered at 100 percent under Medicare Part B and a supplemental insurance plan. If patients choose to enroll in a Medicare HMO (Medicare Part C or Medicare Advantage Plan), they will automatically be enrolled in a Medicare Part D prescription plan in most cases, and the same rules apply as previously stated. It’s important for patients to understand this before choosing a Medicare HMO so they can make the best choice and have the least interruption in therapy.

If patients also have Medicaid, also known as being dual eligible, they typically have the most options. Medicare is the primary insurance, Medicaid is the secondary insurance, and they will automatically be enrolled in Medicare Part D. Co-pays for dual-eligible patients are very low, usually in the $3 to $4 range. And, coverage may be 100 percent for infusions in the hospital or at home. However, if patients are infused in a physician’s office, they should check on their options. Nursing and supply coverage for all diagnoses. In the physician’s office and hospital outpatient setting, nursing and supplies are covered under Medicare Part B. In the home, nursing for both IVIG and SCIG is covered under Medicare Part A if the patient meets homebound criteria. If the patient does not meet homebound criteria, nursing is not covered for the vast majority of patients. Nursing may be covered at home under a Medicare Advantage Plan. Also in the home, supplies for IVIG are not covered, whereas they are covered for SCIG.

However, on January 10, 2013, President Obama signed into law HR 1845, the Medicare IVIG Access Act. The Act provides for a demonstration project, known as the Medicare IVIG Demonstration Project, to examine the benefits of providing coverage and payment for items and services necessary to administer IVIG in the home for patients with primary immune deficiency disease. The three-year project will enroll up to 4,000 Medicare beneficiaries for whom it will allow some payment for nursing services and supplies. The project only applies to situations in which the beneficiary requires IVIG for the treatment of one of the five qualifying immune deficiency diagnosis codes. Patients receiving SCIG are not eligible for the project unless they wish to switch to IVIG.

Medicare beneficiaries can apply for the project by visiting the NHIC Corp. website at www.medicarenhic.com. However, there is one cautionary note: Approval for the project does not guarantee coverage. The application and approval process do not specifically list the five covered home diagnosis codes; rather, there is a blanket statement of: “I attest that I am treating this patient, that the patient has primary immune deficiency disease, and is a candidate for home IVIG.” This has led to approval for some patients under the project, but they don’t have a diagnosis that qualifies for drug coverage at home.

**Patients may qualify for Extra Help, a Medicare program to help people with limited income and resources pay Medicare prescription drug plan costs.**

**Know the Options!**

Understanding coverage and the options for site of care and route of administration is crucial as patients transition to Medicare. When Medicare becomes the primary insurance, patients need to know whether they will be asked to make changes in their care. Medicare coverage can be more complex than IG therapy! But by discussing the coverages and options with someone knowledgeable in Medicare guidelines and IG therapy coverage, patients can make the best choices for uninterrupted care.

LESLIE J. VAUGHAN, RPh, is senior vice president of clinical services and MICHELLE GREER, RN, is the senior vice president of sales at NuFACTOR Specialty Pharmacy.

**Editor’s note:** This is an update of the original article that appeared in the February-March 2013 issue of IG Living.
WISKOTT-ALDRICH SYNDROME (WAS) is a rare hereditary disorder of the immune system. It is classified as a primary immunodeficiency and is present at birth, but it may be mild and go undiagnosed until childhood. It is characterized with a pattern of clinical problems that usually includes abnormal bleeding due to small size and low number of blood platelets (microthrombocytopenia), eczema of the skin, recurrent infections, a high incidence of autoimmune symptoms and cancers, particularly lymphoma.

The disorder was first described in 1937 by a German pediatrician, Dr. Alfred Wiskott. He reported a family with three brothers who all presented in infancy with symptoms of eczema, bloody diarrhea and thrombocytopenia with small platelets. The sisters of these boys had none of these conditions. Seventeen years later, an American pediatrician, Dr. Robert Aldrich, studied six generations of a family in which 16 out of 40 males all died in infancy of the symptoms described by Wiskott.¹

Clinical Features
Eczema, recurrent infections, bleeding tendency, autoimmunity and malignancy are the most common symptoms of WAS. Most individuals with WAS have recurrent ear, sinus and lung infections, as well as an increase in viral infections such as molluscum and warts. The WAS protein is important in the structure and function of white blood cells and their immune responses to infection. The two main types of white blood cells that are affected in WAS are T and B lymphocyte cells. T cells help defend against yeast and viral infections and some bacterial infections. T cells arise in the bone marrow and are “educated” in the thymus gland. B cells are formed in the bone marrow and work to fight infections caused by other viruses and bacteria. T cells help B cells make antibodies specific for infections. How severely the immune system is affected is variable as some boys have many more infections than others.
Individuals with WAS have frequent small purple spots on the skin (see Figure 1) from small bleeding sites under the skin called petechiae. They may also have nosebleeds, bloody bowel movements, bleeding gums and prolonged bleeding from cuts or at the time of circumcision. This occurs in WAS because the platelets are small and low in number. Platelets are blood cells that function to prevent and stop bleeding. A normal platelet count typically ranges from 150,000 to 300,000. In WAS, the platelet count is frequently much lower, around 15,000 to 50,000. The low platelet count may be the only feature or may be the dominant feature of WAS. The platelets are also extremely small in size. In a newborn or child with a low platelet count, examining the size of the platelets is important in making a diagnosis. Since aspirin may interfere with the ability of platelets to clump together in blood clotting, aspirin should be avoided in boys with severe thrombocytopenia. Serious hemorrhage into the brain is a very real danger in WAS boys and has caused deaths in boys with this syndrome. Therefore, “roughhousing” play should be restricted. To avoid being accused of child abuse, some parents always carry a letter from the doctor that identifies the child as having a bleeding disorder that causes bruises to last longer than in other children.

Typically, the skin is affected with eczema in WAS (see Figure 2). In infants, this can be seen as a “cradle cap” that is prolonged beyond infancy or as severe diaper rash. The folds of the neck, the front of the elbow and behind the knees are also areas that are frequently affected. It can also be generalized over the skin in an itchy rash. Sometimes, the itching is so intense and miserable that the boys will scratch until their skin bleeds, even when asleep. This rash can then become infected with bacteria such as Staphylococcus aureus (staph infection). As a preventative, dermatologists recommend heavy moisturizing after bathing. Steroid creams used sparingly on the skin can help inflammation, as can baths containing household bleach as an antiseptic measure. These “swimming pool” baths can be created by mixing in one-half cup of ordinary liquid bleach in a full bathtub of water, in which the patient can soak for 10 to 15 minutes followed by patting the skin dry and applying prescribed medications or moisturizers.

With advances in treatment, WAS-affected boys are living longer into adulthood, and later, onset manifestations — such as autoimmunity — are being recognized. Autoimmune disorders are conditions that result from the immune system reacting against part of the patient’s own body. A variety of symptoms can result such as joint swelling, new rashes, lower blood counts and kidney and bowel disease. Joint pains are mostly in the ankles, knees or hip, and sometimes are associated with swelling and/or fever. New skin rashes unrelated to eczema may appear, often associated with painful joints that can be severe enough to prevent walking. Sometimes the platelet count can decrease further because of autoimmune platelet disorder. Kidney involvement can cause nephropathy of varying severity, including renal failure, and inflammatory bowel disease can cause colitis and bloody diarrhea. Occasionally, inflammation of the arteries (vasculitis) can occur in the skin, heart, brain or elsewhere. Non-steroidal anti-inflammatory medications can help with the inflammation. These painful episodes, which may require

**Figure 1.** Petechiae, small purple spots on the skin from small bleeding sites under the skin, is a symptom of WAS.

**Figure 2.** Eczema, an itchy rash, can be localized in certain areas, or it can be generalized over the skin.
hospitalization and treatment with high doses of steroids and several days of intravenous immune globulin (IVIG), can occur at any age and may last only a few days or come in waves that recur over many years.

A cancer that usually affects cells of the immune system (lymphoma) has also been seen at an increased incidence in boys and men with WAS. It has been shown that lymphoma is more likely to occur in those WAS patients who also have significant autoimmunity and less likely in those who do not have this complication.

There is a range of severity in WAS, from very mild to severe. The term for the milder presentations is “XLT,” or X-linked thrombocytopenia, which is the major issue in these boys. Patients on the more severe end of the scale have extremely low platelet counts, high incidence and frequency of infection, more complications of autoimmunity and more extensive skin involvement.3

**Inheritance and Diagnosis**

The WAS gene, identified in the early 1990s,4 carries the information to make the protein WASp (Wiskott-Aldrich syndrome protein). Pinpointing the precise gene now allows genetic testing to look for a mutation in the WAS gene. Genetic testing, which can be done at special laboratories, should be conducted in children who have recurrent infections and small and/or low platelets. The platelet size (extremely small) is one of the best tests to confirm the diagnosis of WAS.

**Gene therapy for WAS has also been used since 2006 for those severely affected by WAS, although results of these trials have been mixed.**

WAS affects males almost exclusively and follows an X-linked inheritance pattern. X-linked disorders are caused by mutations (defects) in genes on the X chromosome. Families with an X-linked recessive disorder often have affected males, but rarely affected females, in each generation. A characteristic of X-linked inheritance is that affected fathers cannot pass X-linked traits to their sons (no male-to-male transmission), but their daughters will be obligate carriers. There is a one-in-four chance of a pregnancy of a carrier female resulting in a boy affected with WAS. It is possible to have two or more pregnancies in a row that result in affected boys, or for entire generations to be skipped even though the gene is present.5 WAS is most easily diagnosed with a known family history. Frequently, there are brothers or maternal uncles or grandfathers with the family bleeding disorder.

WAS has similarities to other diseases that manifest with low platelets or recurrent infections. For example, idiopathic thrombocytopenic purpura (ITP) can be mistaken for WAS. However, the size of the platelets in ITP is normal, while WAS platelets are very small, and ITP is not associated with increased infections. Likewise, hyper IgE syndromes such as DOCK8 deficiency and Job’s syndrome manifest with the similar clinical features of eczema and recurrent infections, but the platelet size and count are normal for these primary immunodeficiencies.

The presence of WAS within a family can be challenging, but many advancements in treatment have been made over the last several decades, and boys are living well into adulthood, marrying and having families of their own. There is no right or wrong decision about having children in a family affected with WAS. Parents should seek genetic counseling so they are fully aware of their options, including the possibility of pre-implantation genetic testing. The decisions about having children are highly personal and dependent upon many factors, including the basic philosophy and religious beliefs of the parents, their concept of the impact of a child’s illness on their lives and the lives of the other family members, and other issues that are different for each family.

**Treatment Options**

For all individuals with WAS, supportive and preventive treatment includes avoiding aggressive physical activity and sports, attention to infection prevention and skin care, and monitoring for bleeding. Bone marrow transplantation using a human leukocyte antigen (HLA)-identical matched sibling donor provides a definite cure. If no matched sibling is available, finding HLA-matched unrelated donors identified through the National Marrow Donor Program is a possibility.

Gene therapy for WAS has also been used since 2006 for those severely affected by WAS, although results of these trials have been mixed. Developments and improvements in the field of
gene therapy, including improvements in the vectors (molecular vehicles) to carry the corrected gene into the cells to correct genetic mutation, have led to more success for more boys. The main benefit of gene therapy compared with bone marrow transplantation is that the treatment uses the boys’ own cells and no rejection occurs. However, previous trials did have the serious complication of developing leukemia in some boys, who later had to undergo bone marrow transplantation.

For those with less serious symptoms from WAS, preventive strategies are used to keep these children and adults as healthy as possible. Primary care doctors should establish a low threshold when looking for infections in individuals with WAS. In addition, for those with recurrent trouble with infections, prophylactic (preventive) antibiotics may be used long-term, including the use of IVIG or subcutaneous IG on a monthly or weekly basis, depending on the frequency of infections and antibody responses. Special precautions should be taken in boys with WAS to avoid receiving routine immunizations with live vaccines such as measles, mumps, rubella, chickenpox and flu nasal spray vaccine. The killed vaccine in an annual flu shot is safe to receive and should be given to family members with WAS, as well as the other household members. Similarly, healthy members of a WAS family household should receive all the standard immunizations to help prevent sharing a potentially dangerous infection to the WAS patient in the home.

Splenectomy was a treatment option used more frequently in the past to control bleeding and hemorrhage. Splenectomy results in immediate correction of thrombocytopenia, as the spleen acts as a filter of the bloodstream. The small size of platelets allows them to be trapped in the spleen during normal circulation, reducing the circulating platelets available for blood clotting. Splenectomy can also allow for a more normal active life because it reduces the risk of hemorrhage. The disadvantage of removing the spleen is that it greatly increases risk for infection and, therefore, requires lifelong prophylaxis with antibiotics and IVIG or SCIG. Splenectomy may also affect the success of subsequent bone marrow transplantation.

Playing individual and team sports is a fun part of life, but individuals with WAS need to take special precautions to prevent injury. Some sports that are safe for everyone, with or without a bleeding disorder, are walking, swimming, biking, golf, fishing, frisbee and tennis. Some sports that are particularly dangerous for those with a bleeding disorder are tackle football, skiing, wrestling, soccer, hockey, basketball and baseball. WAS families should check with their hematologists for parameters of a safe range of platelet counts before joining a sport, and the WAS patient should always use protective equipment (helmet, padding, elbow and wrist guards) to lessen the chance of injury. Babies and young boys can benefit from wearing soft helmets to protect their heads from trauma. Some sources for this protective helmet are www.softtop4toddlers.com, www.danmarproducts.com and www.thudguard.com.

A Unique Disease

As with other primary immunodeficiencies, WAS patients are at risk of infection, but the disease is distinct because it presents with low platelet count and small platelets. For the best treatment, it is important to have a multidisciplinary team that is aware of all the issues those with WAS may face. It is also essential to assemble a medical team that is aware of the latest advances in the immunology field as lifesaving therapies such as gene therapy and bone marrow transplantation are improved.

ELIZABETH GARABEDIAN, RN, MLS, is a research nurse, and ALEXANDRA F. FREEMAN, MD, is a pediatric infectious diseases physician at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, Bethesda, Md.

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IN THE FIELD of clinical immunology, laboratory studies as well as symptom presentation are often the keys to accurate diagnosis. There are a myriad of laboratory studies that evaluate the various aspects and functions of the immune system, and it is often confusing for the patient to navigate or understand the legion of labs that are performed and how they are relevant to the care of their condition. Therefore, this article explains the significance of some of the most frequently drawn labs in the area of primary immunodeficiency (PI) evaluation. The following is not an exhaustive list of all the labs that exist in the field of clinical immunology. Rather, they are the labs that almost any patient who is being evaluated for the potential of PI would receive at some point during their care. Understanding these labs will help patients become more knowledgeable members of their own healthcare team.

By Bob Geng, MD, MA
Overview of the Immune System

In humans, the immune system is divided between the innate and adaptive systems. Almost all multicellular organisms have evolved to possess some form of innate immunity. It is called innate immunity because it exists in the body without the initial recognition or interaction with any foreign elements. The key to innate immunity is that it works quickly to neutralize any invading foreign elements such as bacteria or viruses. The agents involved in innate immunity include both cells such as neutrophils, macrophages and natural killer cells, as well as molecules in the blood such as complement proteins. These agents are programmed from birth to recognize key patterns that are common in foreign invaders and danger signals to the body, and will act to neutralize those elements upon recognition.

The limitation of the innate immune system is that it does not acquire memory of the interactions with foreign invaders, and the response is not specific. Therefore, in humans, it cannot exist in isolation and must work in conjunction with the adaptive immune system to provide the body with optimal protection. The adaptive immune system is so named because it adapts to the interactions it has with the specific encounters with foreign invaders. It possesses immunologic memory so that while the initial response may be slow to develop, subsequent responses will be accelerated and augmented. The responses are specifically tailored to the particular foreign invader that is threatening the host at a particular time. Another key element of the adaptive immune system is that it has the capability of generating an innumerably diverse array of specific responses to the foreign invaders, and it constantly evolves to produce more targeted and stronger responses to those foreign elements. Unlike the innate immune system that recognizes only a limited number of key patterns on foreign elements, the adaptive immune system can learn and evolve to recognize specific patterns unique to each foreign invader.

The most common laboratory evaluations for the diagnosis of PI are the studies that examine the function of humoral immunity.

The adaptive immune system is comprised of both cellular components and humoral elements. The main cells that are involved are the B and T cells, which are collectively referred to as lymphocytes. The T cells are then subdivided into helper T cells and killer T cells. The helper T cells assist members of the innate immune system and B cells to fight off infections. The killer T cells directly destroy cells in our body that have been infected with viruses. B cells produce molecules called antibodies that help neutralize foreign invaders or toxins, and these antibodies can mediate direct destruction of foreign invaders, as well as increase the efficiency of the innate immune system to clear infections. These antibodies are divided into several classes: IgG (most abundant), IgA (involved in mucosal immunity), IgM (the initial antibody response) and IgE (involved in allergic disease).

Humoral Immunodeficiency Labs

The most common laboratory evaluations for the diagnosis of PI are the studies that examine the function of humoral immunity. Humoral immunity encompasses the arm of the immune system that is primarily composed of antibodies, or immunoglobulins (for the purpose of this article these two terms will be used interchangeably). Humoral immunodeficiencies are also the most common form of PI. They can present at birth such as Bruton’s agammaglobulinemia or in adulthood such as common variable immunodeficiency (CVID).
The most common humoral immunodeficiency lab is the quantitative immunoglobulin panel that includes an evaluation of IgG, IgM and IgA (see Table 1). The reference ranges for these immunoglobulins are age-specific before age 6 years, when adult levels are generally reached. In order to not overcomplicate the discussion, we will focus on the reference ranges for ages 6 and above.

For IgG, the normal range can vary between 700 and 1,500 mg/dL. For IgM, the normal range can vary between 40 and 270 mg/dL. For IgA, the normal range can vary between 80 and 420 mg/dL. For complete agammaglobulinemia (absence of immunoglobulins) due to Bruton’s agammaglobulinemia or autosomal recessive agammaglobulinemia, the levels are nearly absent for all types. For CVID, there have to be two types of immunoglobulins that are deficient by at least two standard deviations below the lower limit of normal, and IgG has to be one of those two types (i.e., low IgG and IgA or low IgG and IgM). There can be many other reasons for low quantitative levels of immunoglobulin including hyper-IgM syndrome, IgA deficiency, selective IgM deficiency, combined immunodeficiency syndromes, protein-losing enteropathy, kidney disease (nephrotic syndrome) or medication-induced (i.e., chronic use of immunosuppression drugs).

**PI labs are often difficult to interpret for both patients and providers.**

In some cases, the quantity of immunoglobulin may appear normal, but the quality of the immunoglobulin may not be normal. The quality of immunoglobulins is assessed by looking at specific antibody titers. The body may be producing immunoglobulins, but it may not be producing the functional type that helps fight off infections effectively. The most common specific antibody titer that is checked is the pneumococcal titer. Streptococcal pneumonia is one of the most common organisms that leads to upper and lower respiratory infections in adults and children. The most thorough assays assess the levels of antibody made to 23 of the most common virulent subtypes of Streptococcal pneumonia bacteria. The absolute cutoff used for the protective level is 1.3 micrograms/mL for any of the subtypes. Generally, the pneumococcal titers are either checked as part of the routine evaluation for CVID or as part of the evaluation for specific antibody deficiency, which is a condition in which the quantitative immunoglobulin level is normal, but the patient is still suffering from recurrent infections due to lack of production of specific antibodies. The criterion for an abnormal assay is different depending on the age group assessed. For 2- to 5-year-olds, greater than 50 percent of the 23 subtypes should exhibit protective levels (>1.3 micrograms/mL). For patients older than 6 years, greater than 70 percent of the 23 subtypes should be protective.

Prior exposure is necessary in order to have protective levels of antibody against a certain subtype of pneumococcal bacteria. If someone has never been infected by a strain of pneumococcus, then there may not be a baseline protective level. Therefore, if the baseline level is not adequate, it does not necessarily mean that the patient has a specific antibody deficiency, but that there was no prior exposure. In that situation, the unconjugated polysaccharide vaccine (Pneumovax) will be administered, and the patient will be retested in four to six weeks to determine whether there would be adequate response. If the repeat pneumococcal titers are still inadequate (i.e., less than 50 percent for 2- to 5-year-olds or less than 70 percent for those older than 6 years), then a diagnosis of selective antibody deficiency can be made. However, there is a group of individuals who have a particular deficiency due to inadequate response to polysaccharide antigens (non-protein-based components of the bacteria). To evaluate for that condition, the protein-conjugated pneumococcal vaccine (Prevnar) can be administered for repeat testing in four to six weeks to determine whether the subtypes covered by Prevnar show protective titers.

Some providers occasionally evaluate the quantitative levels of IgG subclasses to determine whether there is a selective subclass deficiency. There are four subclasses of IgG: IgG1, IgG2, IgG3 and IgG4. IgG1 is the most abundant, making up over 60 percent to 70 percent of the total IgG, and IgG4 is the least abundant and sometimes even undetectable in some normal individuals. Therefore, in the setting of a normal total IgG level, selective subclass deficiency is generally due to a low IgG2 or IgG3 level. These subclasses perform slightly different functions.

<table>
<thead>
<tr>
<th>Immunoglobulin Class</th>
<th>Concentration in mg/dL</th>
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<tr>
<td>IgG</td>
<td>700–1,500</td>
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<tr>
<td>IgM</td>
<td>40–270</td>
</tr>
<tr>
<td>IgA</td>
<td>80–420</td>
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Table 1. Normal Reference Range for Immunoglobulins in Adults
Table 2. Normal Reference Range for Flow Cytometry Lymphocyte Counts

<table>
<thead>
<tr>
<th>Lymphocyte Subset</th>
<th>Concentration: Cells/Microliter</th>
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<tbody>
<tr>
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<td>1,000–2,200</td>
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<tr>
<td>CD4</td>
<td>530–1,300</td>
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<tr>
<td>CD8</td>
<td>330–920</td>
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<tr>
<td>CD19</td>
<td>110–570</td>
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It is believed that IgG1 and IgG3 are antibodies that focus on recognizing protein and toxin elements of foreign infectious agents. A significant amount of IgG2 antibodies are thought to recognize polysaccharide components of bacteria. The value of checking for subclass deficiency is questionable, and the clinical relevance of a subclass deficiency in isolation is very controversial. Oftentimes, patients with isolated subclass deficiency in the setting of normal total immunoglobulin levels and normal protective antibody titers are asymptomatic, and should not be labeled as being immunodeficient.

Assessment of Cellular Immune Function

To assess cellular immunity, the most common lab aside from a complete blood count is the basic B and T cell flow cytometry panel (see Table 2). This is a technique that analyzes the number of cells in distinct groups based on their size, presence of specific cell surface markers and degree of granularity inside the cells. The immune cells are often distinguished based on the presence or absence of specific cell surface proteins. The key components of this study are the counts for the CD3, CD4, CD8, CD19 and CD16/CD56 cells (CD stands for cluster of differentiation, and all these components are specific cell surface markers). CD3 is the hallmark of all T cells, including both helper and killer T cells ranging between 1,000 and 2,200 cells/microliter in adults. The reference normal levels are much higher in infants and young children. The ranges are approximated and can differ between institutions and processing laboratories. CD4 is the marker for T helper cells and can range between 530 and 1,300 cells/microliter in adults. CD8 is the marker for T killer cells and can range between 330 and 920 cells/microliter in adults. In normal individuals, the number of CD4 cells always outnumbers the absolute CD8 cells. CD19 is one of the key markers of B cells and can range between 110 and 570 cells/microliter in adults. Lastly, CD16/CD56 are the markers for natural killer cells (actually part of the innate rather than the adaptive immune system) and can range between 70 and 480 cells/microliter.

For PI, different types of isolated cellular immunodeficiency conditions, as well as combined humoral and cellular immunodeficiency syndromes, can present with decreased levels of various immune cell types. In addition, various secondary immunodeficiency conditions can present with low levels of immune cells such as infectious causes, medication-induced causes (i.e., being on immunosuppressive medications), increased loss due to enteropathy (chronic loss from the gastrointestinal tract) or decreased production due to bone marrow abnormalities.

In addition to assessing the quantity of adaptive immune cells, there are assays that will evaluate the quality and function of these cells. These are called the lymphocyte proliferation assays. These tests are not widely available (generally only offered in major academic tertiary referral centers). Both the B and T cells are extracted from the patient and are then exposed to different types of stimulants to determine whether the cells would grow and multiply normally. These tests are not easy to perform and rely on the comparison to the response of normal cells from healthy volunteers. The stimulants that are used can be non-specific, assessing whether the overall machinery of the B and T cells is functional, or they can be specific and examine whether the B and T cells can adequately respond to a particular foreign infectious agent. Reference ranges will depend on the method employed for the assays and can differ between laboratories. Furthermore, the ranges are also set by comparison to normal healthy volunteers. The importance of these assays is that they help the physician understand whether the cells of the adaptive immune system are functionally adequate regardless of the total quantity present.

Demystifying the Diagnostic Process

There are many other laboratory tests in the field of clinical immunology assessing the potential of PI. The labs discussed in this article are most commonly performed for the evaluation of the most common types of PI. Like all laboratory evaluations, the results must not be interpreted in a vacuum and should always be coupled with the clinical presentation to arrive at the right diagnosis. PI labs are often difficult to interpret for both patients and providers. Hopefully, this article can help shed some light on the understanding of these tests and demystify the complexity of the diagnostic process.

BOB GENG, MD, MA, studied medicine at Washington University School of Medicine in St. Louis, where he also completed his residency training in internal medicine. He is currently an assistant professor in allergy and immunology at the University of California, San Diego. Dr. Geng received his bachelor and master of arts degrees in Georgetown University’s School of Foreign Service.
LET’S TALK

DEBBIE KONRAD is a cancer survivor and common variable immunodeficiency (CVID) patient who refuses to allow chronic conditions to limit or define her. This interior decorator and blogger found her strength and her voice through adversity, and encourages others to do the same.

Trudie: When were you diagnosed with CVID?
Debbie: I was diagnosed in 2012 after a year of recurrent sinus infections that eventually did not respond to even the strongest antibiotics. My CVID is acquired, a complication of lymphoma and the drug Rituxan that was used to treat it.

Trudie: What was your life like before your diagnosis?
Debbie: I was actually very healthy and active for the first 50 years of my life. I did all the right things: ate well, hardly ever drank, didn’t smoke and exercised every day, typically running or race walking five to seven miles each morning, along with strength training. I also enjoyed ballet dancing. I have my own decorating/drapery business and was enjoying the prospect of expanding it. I enjoyed traveling with my husband and our two sons. I was also researching my family genealogy, planning some trips related to the research, trying new recipes, gardening. My life was full, and I felt so blessed.

Trudie: What is your current treatment plan?
Debbie: I receive intravenous immune globulin every three weeks.

Trudie: You have other health conditions; tell us about that.
Debbie: In addition to CVID, I have a rare, incurable and recurring form of lymphoma that is currently in remission. Along with the lymphoma, I was diagnosed with a very rare complication called paraneoplastic syndrome. I received Rituxan for two years to treat it. As a result of the high steroid treatment that was initially tried and failed, I was diagnosed with severe osteoporosis in 2010. I was 53, but my bones were that of a 70-year-old. I am happy to report with three yearly infusions of Reclast, my bone loss has stabilized and even appears to be regaining strength. Recently, I was diagnosed with an undifferentiated autoinflammatory disorder that is causing lots of pain and fevers. I am currently working with my rheumatologist to find a medication that will help treat it.

Trudie: How do you find the positive in difficult situations?
Debbie: I find that I have two choices when it comes to dealing with the blips on my radar, as I like to call them: Either I let myself get sucked into that black hole of despair, or I find a way to rise above it. I focus on something good in each day, and there is always something good, no matter how small. Sure, I have my “pity party” moments, and it took me a while to get back to the place where I now feel I have found my “center” once again. Before these health challenges appeared in my life, I was always the cup-half-full person. But the first three or four years after my cancer diagnosis, I was a mess emotionally. It is hard to focus on living when it seems that every day brings a new set of health issues. Finally, with help of a wonderful therapist and a year of antidepressant therapy, I started to make my way back to where I am now.

Trudie: How has having a pet helped you cope and keep a positive outlook?

Debbie: My dog, Charlie, makes me laugh; he is such a goofball, very loving and very sensitive to when I am not feeling well. He was 2 when I was first diagnosed with cancer, and he seemed to emotionally take in what I was going through. I wasn’t able to take him on the walks we enjoyed, and he developed a nervous habit of chewing his feet, like humans do when chewing their nails. He is still very aware of the days that I am not my best. He has always been my constant companion. Unconditional love at its best.

Trudie: What are your goals for the future?

Debbie: Once we get the autoinflammatory issues controlled by the correct medication, I want to travel with a cousin who is researching our family tree to some of the places where our ancestors lived, particularly Philadelphia. I want to expand my business. I want to travel more often with my husband. My eldest son is getting married in October, so we are planning showers, etc. I am looking forward to becoming a grandmother at some point and just living life to the fullest here, there and everywhere!

Trudie: Tell us about your blog.

Debbie: It is a private blog on Facebook titled “Musings from a Cancer and Chronic Illness Warrior.” I wanted it to be a place where people who are dealing with chronic conditions and cancer could express themselves without being chastised for their feelings. It is a very simple concept; I pick a subject each week that pertains to living with cancer and other chronic health conditions, and I blog about it. I ask for input from the members of the page. No one is allowed to put anyone else down for what they feel. If you disagree with a person’s point of view, you may say so; we are all entitled to our own opinions. I just don’t allow any nastiness. Respect must be shown for each other at all times. It is also not the type of page where you go to “one-up” someone else with a litany of all of your symptoms, etc. Frankly, I hate those types of so-called “support groups” because I don’t find them helpful or uplifting, just depressing.

Trudie: What advice do you offer others with chronic conditions?

Debbie: First of all, if you find yourself sinking into that black hole, get help! Even though I resisted big time at first, therapy and antidepressants worked wonders. Consider therapy if for no other reason than to give yourself an unbiased, unattached source to talk to. If you find a support group situation helpful, then go for it, but don’t feel that you have to; they are not for everyone. Do something every day that you enjoy, even if it is as simple as a bubble bath, a yummy treat or a favorite TV show. I also advise staying off the Internet when it comes to health issues. Only go to sources recommended by your doctors. And when seeking medical advice, don’t post your questions on a support group page; ask your doctor! Have you been thinking of trying to develop a new hobby? Go for it! Make it a goal every day to find that silver lining, the good thing in each day. Even on our worst days, there is always something good to be found, no matter how small. Focus on that light at the end of the tunnel; it may be faint, but keep pushing forward toward it, and it will grow larger and larger until once again you find yourself in the sunshine. Live!

Trudie: What has having chronic conditions taught you about yourself?

Debbie: That I am indeed a much stronger person than I ever thought I was. You must advocate for yourself!

TRUDIE MITSCHANG is a contributing writer for IG Living magazine.
I STILL HAVE memories that flash through my mind of when my body moved effortlessly — almost like it was yesterday. When I was a young girl, I’d slide down into the splits and do cartwheels across the lawn. When I was a teenager, I never worried about spinning around on razor-sharp blades while ice skating. Even in my 20s when I was performing improv and acting in theater shows, I’d throw my body around the stage in character. I found it exhilarating to find ways to express myself artistically through my body’s movement, with a special focus on what my hands might be conveying. When I used to belly dance, there were various hand motions that showcased my fingers and added to the fluidity of the dance. These kinds of muscle memories come rushing back to me now as I very carefully walk down a flight of stairs or struggle to button my blouse.

My current world of movement consists of yoga for senior citizens that involves using a chair to help with positions. I can no longer stretch into downward dog; I don’t have the strength, balance or agility. I exercise at my own pace and find ways to accommodate the activity. The neuropathy in my ankles, wrists and hands won’t give me the support I need. So, for example, I do push-ups against a wall and not on the floor.

The funny part is that, in my head, I can still do it all. Recently, I was asked to do jumping jacks. I hadn’t done them in ages. I thought: “How fun; it will be like when we were kids in school.” But, when I went to do them, I literally couldn’t move. My body couldn’t figure out how to jump, move my arms and feet and clap. I was looking around the room thinking: This is a dream, right? No, I’m awake. Let me try this again. A few disjointed movements. Nope. Not even close to being a jumping jack. If anyone had been videotaping my face and all the expressions it went through, they would have seen confidence, then bewilderment, concentration, panic, timidity, acceptance and, finally, silliness.

Yes, silliness! Because if you can’t laugh at yourself, who can you laugh at? I’m the gal whose nickname now is “Crazy Hands.” I can drop, throw and fumble anything in my hands without even trying. It’s impressive. When I say I’m a two-handed drinker, I mean I literally hold my glass with two hands so I don’t spill on myself or, more importantly, slosh it all over someone else. Then there are my award-winning falling skills due to foot drop. I have been known to be walking along perfectly fine and, bam, I’m down! Thank goodness my dog has very good reflexes and has managed to not get squashed by my impromptu falls.

But crazy hands and foot drop do not stop me from getting out and about. My main goal is to stay active. I have enough down time due to not feeling well and the demands of my immune globulin infusions. The rest of the time, I need to enjoy my life. If I know I’ll be out for a long day walking, I now use a cane. If my hands aren’t working well, I ask for help. I may have put my high heels in the back of the closet, but that doesn’t mean I still won’t strut my stuff and kick up my very low heels on the dance floor. I may have to think before I walk, but it’s a no-brainer that I’m moving in the direction of happiness. ✨

STACY OLIVER was diagnosed in 2008 with multifocal motor neuropathy (MMN). She is the assistant director of the Center for the Writing Arts at Northwestern University, and she is working on her supersecret identity as Neuropathy Girl, who will one day save the world after her infusion and a nap.
SO MANY HOLIDAYS, so little tolerance for relatives. Nothing says warmth and comfort quite like coming home to a group of people who remember more details about all the times you were hospitalized than, say, your recent graduation, promotion or new boyfriend.

Handling the big holiday dinners laced with stress and cold-induced symptoms isn’t just a skill, it’s an art form.

Whether you’re trying to survive the conversation, the actual food, the cousin who is liberally spreading his bronchitis while passing the mashed potatoes, or even finding a suitable excuse to just leave already, here’s what you’re going to need:

• Hand sanitizer (just as much as you use at any other event during the winter months to stop the spread of germs in their tracks)
• A turkey thermometer (Do you really need food poisoning on top of the flare you’re already having?)
• And a few simple rules when it comes to staying off topic

If your family is asking uncomfortable questions, or if you just don’t feel like sharing the hardships of your condition on this happy holiday night, you can avoid it by distracting, redirecting, involving and turning. Let’s break these down.

Let’s say Aunt Muriel is commiserating about both of your recent hospital stays and wants to go over all the gruesome post-surgical pains and aches in detail. Instead of just nodding, try to catch on to any sort of distraction. This could be the food coming to the table and asking if she made anything, or catching a topic and redirecting it: “Speaking of recovery, did you hear about your brother’s latest blind date anyway. You can make this transition swiftly by stopping her in the middle of her question and saying: “Oh, I have to ask . . .” And then turn to someone else. Worried about being rude? What are you, the table babysitter? You’re not responsible for their entertainment, especially when it’s the result of bringing up painful and uncomfortable moments from your medical file.

Another strategy is drawing one of your other table guests into your conversation. If you’ve gotten out of comfortable territory, you can always ask for the opinions of others. Broaden the topic from your personal experiences to general topics. Things like politics, religion and international tragedy tend to bring out the long-winded, highly distracting opinions of every utterly empowered or grimly repressed uncle, cousin and grandmother.

You can also try elevating the mood. If you’ve gone completely into disaster mode and now have the whole table staring at you and waiting to hear about how you’re feeling better and you’re not up for giving them a song and dance, say you are doing well. Maybe you finished all your Christmas shopping two weeks early. Maybe you just passed all your exams with flying colors. You can also talk about your plans for feeling better.

Launch into a talk about your New Year’s resolutions and what sort of things you hope to change this year. Then, swiftly turn it around and ask the table what their resolutions are (Maybe to be less nosy?). Remember that you aren’t alone and that it isn’t only people with chronic illness who have to face the complexities of family gatherings. Divorce, bankruptcy and addiction — you could play a bingo game of rotten experiences being drudged up under the scrutiny of relatives.

But it’s OK. All hope is not lost. I mean, there’s going to be stuffing, right?

ILANA JACQUELINE is a 24-year-old dysautonomia and primary immune deficiency disease patient from South Florida. She’s been writing professionally since 2004 on everything from health and wellness to celebrities and beauty. Her blog www.letsfeelbetter.com is both a personal collection of anecdotes about life with chronic illness, as well as a resource for patients of all ages.
THOSE OF US with a chronic illness value our animal companions in a unique way. Some guide us, some protect us, but ultimately, they all brighten our painful, emotional and medically fragile days. Allow me to share a few nuggets of wisdom our family has learned from some canine friends that have graced the halls of our home.

George: Tidiness Prevents Middle Class Crisis

From the get-go, George liked to collect things: socks, dirty underwear, rocks and teddy bears. Being a four-legged stomach, he was always looking for something to fill the big empty in his middle parts. If it was left on the floor, in the garage or in the garden or creek that runs through our backyard, it would somehow find its way into George’s innards. So the rule of the house: Don’t leave anything anywhere, anytime, anyplace that George could put his snout on. Hard thing to do when your kids are ages 3 years, 2 years and 18 months.

During one holiday, the kids were on home healthcare for their intravenous immune globulin (IVIG) infusions. Our specialty pharmacy sent us a festive holiday basket full of toothsome treats and tiny collectibles for the kids. Our daughter, Molly, immediately attached herself to a teddy bear that Calvin named Shirley. Shirley the bear went just about everywhere Molly went. But, after two weeks, Shirley suddenly disappeared. We couldn’t find her anywhere, which was truly a big bummer as we had just returned home from the hospital with Molly, who was fighting rotavirus. The first thing Molly did when we stepped into the house was cry: “I wan Earleeee! Where’s Earleeee?” Twenty-eight very long hours later, George had his own version of rotavirus.

“Great, that’s all I need is another sick person in the house,” I complained while making sugar cookies with three little ones. Between Molly whining for Shirley and making sure George got outside in time to take care of whatever it was that had him going, I was secretly wishing we were sprinkling Xanax on the sugar cookies.

Later that evening, while my husband Mark and I were indulging in our favorite cable show that didn’t teach us the alphabet or how to count, we both saw George acting a bit strange and made him go outside.

“Are you OK?” I asked Mark. He covered his mouth and pointed outside where George stood. There, in the frost-bitten grass, lay a mangled mound that resembled Shirley.

We made our way toward the mass that George had produced and, sure enough, Molly’s Shirley lay helpless, bow intact and ready to be loved — just not by our kid.

We prayed for and received a holiday miracle (which cost $5.99 plus overnight shipping) that resembled Shirley so much, we decided to keep her trip through George a long-lost secret. Not to mention we’ve been able to adhere to the house rule of keeping things as tidy as
possible; retainers from the orthodontist are much more expensive than Shirley bears!

**Emmy: The Tongue Is a Two-Edged Sword**

We considered ourselves the luckiest people on the planet when our neighbor Connie asked us if we could care for their uber-cute basset hound, Emmy, for the day.

“Why, of course we will!” I agreed with gusto while scratching Emmy’s long ears and fiddling with her fake diamond-encrusted collar. “We’ll take really good care of her, and keep her safe,” I assured Connie.

“And clean. Her tongue can get her into some impressive situations,” Connie added.

Of course I immediately thought: What in the world could a dog’s tongue get into?

Famous last thought as I realized that our day with Emmy was the same day as the kids’ infusion day. I was fully confident, though, that both Emmy and the kids were going to get my full attention and love.

“Well, who do we have here?” Nurse Nancy asked as she rubbed Emmy’s floppy ears.

“Nurse Nancy, this is Emmy; Emmy, meet Nurse Nancy,” I said with proper girlie tone.

“Well, aren’t you the cutest thing on the planet!” Nurse Nancy cooed. I was too busy applying Caleb’s EMLA cream to pay attention to Emmy and Nurse Nancy.

Thirty minutes later, Nurse Nancy had Caleb and Molly’s IVIG ready to infuse. As tradition dictated, Caleb went first, but Emmy demanded to be the center of Nurse Nancy’s attention. She wrapped herself into a puppy pillow in the corner of the couch, refusing to let Caleb lie down where he usually did. So, in his best puppy speak, Caleb asked Emmy: “Stay put, and I’ll use you as my pillow! But ya’ gotta stay nice and still so the needle goes in me and not you, OK?”

With Nurse Nancy’s approval and me standing near just in case Emmy decided to make any wrong move, Nurse Nancy and Caleb began their routine. Everything started off smoothly until Emmy got a whiff of Caleb’s EMLA. Then, her massively long tongue came to attention, and one impressive slurp later, Caleb’s EMLA was licked perfectly from his chest: no sponges needed, but a good bath for both dog and patient was in order.

Nurse Nancy and I chased Emmy around the living room until we finally nabbed her. Of course, we were worried the EMLA might be toxic to dogs, which it thankfully isn’t, according to my veterinarian. However, we were now in the presence of a very numbed doggie tongue that was perfect for stamp-licking. Emmy created so much drool that we went through six washcloths.

When Connie came to pick up Emmy, we were so grateful that Emmy’s drooling had subsided to a steady stream from the original tsunami. Of course, my dilemma was how to tell Connie the truth without saying a word.

“Well, you must have had a wonderful time, Ms. Emmy, cause you’re soppin’ in sweat from playing hard!” Connie said in her deep Southern drawl.

“Oh, yes! Emmy and the kids had a great time,” I said, telling nothing but the truth so help me dog.

“Well, one thing I did forget to mention,” Connie began, “Emmy does get drooly when she plays hard, so she must have had a lot of fun with y’all.”

I just nodded my head, avoiding the use of my own tongue. Emmy’d be so proud of me!

**Jackson: An Unconditional Friend and Family**

Our current dog, Jackson (aka Jax), has been our family’s best friend and my right-hand man for the past seven-and-a-half years. Sadly, he suffers with a recent diagnosis of bone cancer. Jax understands physical pain better than any dog we’ve ever had; he’ll follow the kids around if they are sick, risking being coughed, sneezed or even barfed upon. Now the roles have reversed. Jax constantly needs to be around one of us to be comforted, and we happily oblige. We are almost at the time when we must say goodbye. Until then, we’re blessing Jax with the greatest gift he has given us: unconditional “familyhood.” In the past weeks, we’ve enjoyed more family walks, albeit shorter distances, more family mealtimes that give him more opportunities to sop up table tidbits, and more hugs and kisses rather than disagreements. Cancer may have slowed our lovin’ Jax, but it has certainly turned up the volume on our family’s ability to love each other unconditionally.

So whether it’s a parrot, ferret, cat or snake, a tank full of guppies, lop-eared bunnies or a daily visit from a hummingbird, I am so glad those of us with chronic illness have the opportunity to share our burdens with four-legged, winged, slithering, hopping, swimming friends. Our pets tend to be the first ones to say “welcome home from the hospital,” and they encourage us to do things we didn’t think we were capable of — like walking that extra step, cleaning up that annoying mess or motivating us to just get out of bed.

That said, I’ll end with this quote: I may have chosen a rescue dog, but it is my dog that rescued me.

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**CHERYL L. HAGGARD** is a stay-at-home mom and has three children with PI, two of whom have CVID.
THE DEFINITION OF a well-balanced diet is forever changing. When I was a child, parents were encouraged to offer something from each of the four basic food groups in every meal. In the early ’90s, the Food Pyramid was introduced. Now, as a mom, I’m told I must refer to something called MyPlate to ensure that my children are eating a healthy, nutritious diet. But three of my four children suffer from primary immunodeficiency disease (PI). Does that mean I must look above and beyond what is typically considered “well-balanced” for a diet that will keep them healthy? What, exactly, should PI kids eat?

According to the Immune Deficiency Foundation, “unless the individual with primary immunodeficiency disease has another condition, like diabetes, gluten sensitivity or congestive heart failure, there is usually no need for a special diet.” Even so, eating healthy is important for all children, not just those who suffer from a chronic health condition like PI. The right diet provides nutrients that aid in growth and development and the proper maintenance of bodily functions.

A Well-Balanced Diet Is Still the Best Choice

While diet fads come and go, the age-old advice of our parents and grandparents still rings true. Consuming a variety of healthy foods is the best way to keep the body running smoothly. Eating too much of a good thing can be bad, while not getting enough of the nutrients the body needs can also be detrimental. As Grandpa always said, the key lies in balance and moderation.

What to Avoid

Parents should use common sense when feeding their PI kids, and that means limiting junk food. Seriously. This advice may sound trite, but it bears repeating. Any food that is dense in calories and poor in nutrition can be classified as “junk” food. These foods are often high in sodium and sugar, and the processing of junk foods removes many important vitamins, minerals and fiber that the body needs. Children who consume these processed foods may develop nutritional deficiencies that could lead to depression, low energy levels, sleep disturbances and poor academic performance.

Most fast food would fall under this category as well. Children for whom fast food is a major part of their diet consume more fat, carbohydrates, sugar and less...
fiber than those who do not eat fast food on a regular basis.  

Avoid giving children too much refined sugar except on rare or special occasions such as parties or when celebrating that first Little League victory. Although many kids love soda and Kool-Aid, overindulging in sugary drinks can lead to obesity. Even fruit juices, which contain acid, can cause diarrhea in small children and can irritate the bladder, leading to frequent urination.

Can Certain Foods Boost the Immune System?

According to the experts at Harvard Medical School, there have been few studies done on the effects of nutrition on the immune system of humans, but several studies have been conducted on animals. These studies seem to point to a correlation between diet and immune system function. For example, researchers studying nutrition’s effects on mice found that diets lacking in protein “reduce both the numbers and function of T cells and macrophages and also reduce the production of immunoglobulin A (IgA) antibody.” Does this evidence prove that all children with PI should adopt a high-protein diet like the Atkins diet? Not at all. Further studies, especially on humans, need to be conducted. If children are eating foods such as meat, fish, beans, eggs or dairy (or vegetables like spinach, kale, broccoli and sprouts) every day, they’re probably getting adequate protein.

What about vitamin supplements? Kids can be picky eaters. Telling a child he needs to get enough vitamin C and dietary fiber may not be enough to convince him to eat his broccoli if he just doesn’t like it. It makes sense that supplementing the child’s diet with vitamins and minerals he is lacking from the foods he refuses to eat would help to round out his diet. But does taking a supplement really make a difference, scientifically speaking?

It’s an established fact that vitamin C helps to repair and regenerate body tissues, and may prevent certain types of cancer by fighting off free radicals. Similarly, vitamin A plays a role in the body’s ability to fight infection while aiding in the protection of mucosal surfaces by influencing certain sub-categories of T cells and B cells. A lack of vitamin A can lead to an increased risk of infection and impaired immunity. While the best way to get these vitamins into the body is by eating the foods that contain them, that isn’t always possible. Taking a daily multivitamin can be a beneficial option. On the other hand, taking a megadose of a certain vitamin (for example: three times the amount of vitamin A for three times the immunity) does not help. The excess cannot be utilized or absorbed by the body and is instead removed as a waste product.

Be skeptical of gimmicks. There seem to be new products introduced every day that promise to be the newest, most potent “super food” or herbal remedy, providing support to the body’s natural immunity. Since the immune system is just that — a system made of many different, yet interconnected, cells that respond to disease-causing microorganisms in so many complex ways — it would be impossible for a single magic food to increase the effectiveness of the entire system, especially when a genetic defect is causing it not to function properly. If something seems too good to be true, it probably is.

Make the Healthy Choice

Whether it’s avoiding sick people like the plague, taking off work once a month for infusion day or driving three hours for an appointment with a medical specialist, parents of PI kids often go above and beyond the call of duty in an attempt to keep their kids healthy. They make choices every day to try to make living with the condition just a little bit easier for their children. One simple choice that will give PI kids the best possible start in life is to provide a healthy, well-balanced diet.

JESSICA LEIGH JOHNSON is a stay-at-home mom and mother of four kids, three of whom have X-linked agammaglobulinemia. She is a member of American Christian Fiction Writers and has written one book about the loss of her son to a primary immunodeficiency.

References
Gut Reactions

GI Problems are common maladies for PI patients. While a cure is not available, symptom relief is possible.

**THE EVENING WAS** magical:

A superb meal and engaging conversation, followed by the opening-weekend screening of the latest blockbuster. As you settle into your seat and the lights dim, you sense a telltale rumbling. With rising dread, you know what comes next: nausea, cramping, bloating and gas. Mortified, you excuse yourself and race to the restroom, hoping you make it in time. This embarrassing scenario is an all-too-common one for patients who suffer from chronic gastrointestinal (GI) problems such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). And, for many immune-compromised patients, it’s an everyday reality.

GI disorders present in up to 50 percent of patients with primary immunodeficiencies (PIs), particularly those with common variable immune deficiency (CVID). Because the GI tract is the largest lymphoid organ in the body, intestinal diseases are common among immunodeficient patients. CVID, in particular, is characterized by a low level of specific antibodies (immunoglobulins) in the fluid portion of the blood, which compromises the body’s ability to fight invading microorganisms, toxins or other foreign substances. In addition to painful and embarrassing GI distress, some CVID patients may also have an impaired ability to absorb vitamins, minerals, fat and certain sugars from the digestive tract, leaving their health in even more jeopardy.

**The Medication Connection**

PI patients are used to having a medicine cabinet full of prescription medications. Unfortunately, many medications for immune disorders and related infections can also have negative side effects, often directly affecting the GI system. Antibiotics, for example, are frequently prescribed to treat recurring respiratory infections and sinusitis, but when used long-term, they can wipe out the good bacteria required for maintaining a healthy intestinal tract. The resulting imbalance can contribute to troublesome GI symptoms, and even make them worse.

One of the reasons so many patients suffer in silence when dealing with IBS and IBD problems is that the symptoms themselves can often be embarrassing and difficult to talk about. Unfortunately, these issues are unlikely to resolve on their own, and while there is no cure for either IBS or IBD, effective treatments do exist. In addition to speaking with your doctor about your specific symptoms, you may also want to keep a food diary to determine if certain foods act as triggers for intestinal distress. While every case is different, common dietary triggers that are best avoided include:

- Insoluble fiber like that found in the skin of fruits and vegetables
- Food and drinks containing chocolate, caffeine, fructose or the sugar substitute sorbitol
- Carbonated beverages
- Fried and fatty foods
- Food and drinks containing dairy, especially for those who are lactose-intolerant

**Keeping Relief Close at Hand**

IBS affects between 25 million and 45 million people in the United States. If you are one of the unfortunate ones, there are a number of over-the-counter medications that can help relieve symptoms. Of course, symptoms and their severity vary, so you may want to experiment with different products to see what works best for you. Since IBS and IBD symptoms can often strike unexpectedly, a medicine cabinet filled with an arsenal of aids, including anti-diarrheal medications, fiber supplements, gas-relief formulas, constipation aids, probiotics and even natural remedies like peppermint oil can provide symptom relief and peace of mind. While not a cure, products like these can go a long way toward lessening the symptoms and stress associated with chronic GI discomfort. Just be sure to check with your doctor before beginning a new medication.

**TRUDIE MITSCANG** is a contributing writer for *IG Living* magazine.
**PRODUCT GUIDE**

**Symptoms:** Abdominal cramping, diarrhea  
**Solution:** Bismuth subsalicylate

Bismuth subsalicylate is the active ingredient in over-the-counter products like Kaopectate. It works by balancing the way fluid moves through your intestines. It also reduces inflammation and keeps certain bacteria and viruses that cause diarrhea from growing in the stomach and intestines.

*Kaopectate Vanilla, 12 ounces, $7.79 at CVS and other retailers*

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**Symptoms:** Gas, bloating  
**Solution:** Simethicone

Simethicone is used to relieve the painful symptoms of too much gas in the stomach and intestines, and is the active ingredient in most over-the-counter anti-gas medications. It acts in the stomach and intestines to change the surface tension of gas bubbles, enabling their breakdown and the formation of larger bubbles so that gas can be more easily eliminated.

Simethicone was approved by the U.S. Food and Drug Administration in 1952.

*DulcoGas Wild Berry Tablets, 125 mg, $5.99 at Walgreens.com and other retailers*

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**Symptoms:** Diarrhea, gut flora imbalance  
**Solution:** Saccharomyces Boulardii

Those with IBS and frequent bouts of diarrhea can consider the probiotic Saccharomyces Boulardii, which has been shown to ease symptoms in clinical trials. This probiotic microorganism is a tropical strain of yeast first isolated from lychee and mangosteen fruit in 1923 by French scientist Henri Boulard. It has also been shown in clinical trials to be helpful for diarrhea-associated IBD and long-term antibiotic use.

*Jarrow Saccharomyces Boulardii +MOS, 90 capsules, $18.99 at Drugstore.com*

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**Symptoms:** Flatulence, abdominal pain  
**Solution:** Peppermint oil

The peppermint plant is thought to relieve some GI problems by blocking the flow of calcium into muscle cells in the intestines, which in turn reduces muscle contractions. In a report financed by the American College of Gastroenterology in 2008, findings showed only 26 percent of patients treated with peppermint oil administered twice daily in capsule form for a period of one to three months continued to show symptoms of IBS after treatment, compared with 65 percent of those who were given placebo.

*NOW Peppermint Oil Gel Caps, $8.99 at drugstores*
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