

# The Link Between Primary Immunodeficiency Disorders and Skin Infections

By Bob Geng, MD



Understanding what types of immune system defects may be the cause of skin infections can help in the diagnosis of a primary immunodeficiency disorder.

**THE SKIN IS** the body's first line of immunity against infectious agents. During a breach of this immune system, infections of the skin affect a person's appearance, often leading to great anxiety and concern. Unfortunately, these invasive infections are all too common among individuals with primary immunodeficiency disorders (PIs). Patients with certain types of PI are known to be more prone to certain types of bacterial, fungal and viral skin infections. For this reason, recognition of various skin infections can help provide clues to potential defects in the immune system, which can lead to consideration of PIs in those undiagnosed.

## **Bacterial Infections**

Bacterial skin infections vary based on extent and depth of infection. They can range from mild folliculitis (inflammation/infection of skin follicles) to deep cutaneous abscesses. The most common types of bacteria that invade the skin include *Staphylococcus* and *Streptococcus* species. Critical first responders in the immune system that help to defend against bacteria that invade the skin are the phagocytes, including neutrophils and macrophages. No doubt, defects of the function of phagocytes often lead to bacterial skin infections.

One of the most well-known PI conditions related to phagocytic dysfunction is chronic granulomatous disease (CGD). CGD is characterized by a defect in the phagocyte's ability to generate reactive oxygen species to kill microorganisms that have been ingested by the phagocyte. CGD affects many organ systems and has both infectious and noninfectious (autoimmune) complications. However, skin infections are often the most noticeable and are frequently the complications that prompt patients to seek medical attention. The most common bacterial complications in CGD range from cellulitis (noncontagious spreading infection) and impetigo (contagious skin infection) to abscesses (tender, soft swellings filled with pus, often surrounded by an area of skin colored from pink to deep red). And, the most frequent culprit bacterial skin infection organism is generally *Staphylococcus aureus*.

In order for phagocytes to eliminate bacteria properly, they have to produce the reactive oxygen species, get to the location of the bacteria and then traffic the reactive oxygen species to the engulfed bacteria. Defects in either one of those processes can lead to susceptibility to bacterial infections. Chediak-Higashi syndrome (CHS) is a condition caused by a defect in lysosome fusion, which leads to the inability to move the reactive oxygen species in lysosomes to the engulfed bacteria. Patients with CHS develop pyogenic (pus-forming) skin infections that range from superficial to deep skin abscesses. The inciting organisms are often *Staphylococcus* or *Streptococcus*. Leukocyte adhesion disorder (LAD) is a condition in which the phagocytes cannot move out of the blood vessel to get to the site of infection. There are three subtypes of LAD, but they are generally all associated with bacterial skin infections without pus formation since the phagocytes cannot get to the actual location of the infections. Both CHS and LAD are extraordinarily rare disorders with many more severe clinical manifestations that extend beyond skin infections.

One of the key signals that activate the neutrophils and overall immunity in the mucosal and skin surfaces is interleukin-17 (IL-17). Defects in the activity or production of IL-17 will lead to susceptibility to bacterial skin infections, as well as fungal infections. The autosomal dominant hyper-IgE syndrome, otherwise known as Job's syndrome, is caused by a defect in one of the cell signaling proteins STAT3, which ultimately leads to a deficiency in production of IL-17. Job's syndrome, as the name suggests, is associated with skin abscesses, furuncles, cellulitis and lymph node infections caused by *Staphylococcus* organisms.

In addition to the specific disorders that have hallmark features of bacterial skin infections, PIs that lead to significant humoral/antibody deficiency, T-cell deficiency and combined

humoral and cellular immunodeficiency may also impair the body's ability to fight off bacteria that invade the skin and increase susceptibility to skin infections.

## Fungal Infections

As previously discussed, IL-17 plays an integral role in mucosal and cutaneous (skin) immunity. Because Job's syndrome can increase susceptibility to bacterial skin infections, the risk of candidal (yeast) infections on the skin is also increased. Other PI syndromes that are associated with IL-17 defects include the AIRE (autoimmune regulator) mutation and the IL-17 receptor mutations. These conditions lead to a condition called chronic mucocutaneous candidiasis (CMC), which is a chronic fungal infection of the skin, nails and mucosa (oral and urogenital). CMC, in general, is limited to the skin and mucosa, and most cases do not tend to lead to systemic fungal infections, although in a minority of cases systemic infection has been reported. The AIRE mutation leads to neutralizing autoantibodies that inhibit the function of IL-17. The IL-17 receptor mutations lead to impaired binding of IL-17 to its target, diminishing its function. Another relatively recently discovered defect of the IL-17 pathway is the STAT-1 gain-of-function (GOF) mutation. While STAT-1 GOF can lead to an overactivation of the intracellular signaling protein STAT-1, the end result is an impairment in the production of IL-17 pathway signaling molecules.

## THE MOST COMMON TYPES OF BACTERIA THAT INVADE THE SKIN INCLUDE STAPHYLOCOCCUS AND STREPTOCOCCUS SPECIES.

The body recognizes general patterns of fungal organisms using pattern recognition receptors. These receptors, which can bind to common components of fungal cell wall, work together with another receptor called dectin-1 to enhance the recognition of fungal organisms, leading to adequate immunity against these infections. Therefore, mutations that affect the function of dectin-1 leading to deficiency would reduce antifungal immunity. Interestingly, dectin-1 deficiency has only been described to be associated with CMC, and not invasive systemic fungal infections.

**Hizentra**<sup>®</sup>  
Immune Globulin Subcutaneous  
(Human) 20% Liquid

Hizentra is the only subcutaneous Ig treatment with over **70,000 patient-years** of experience<sup>1</sup>

#1 Ig

Prescribed for PI<sup>1</sup>



### Important Safety Information

Hizentra treats various forms of primary immunodeficiency (PI) in patients age 2 and over.

**WARNING: Thrombosis (blood clotting) can occur with immune globulin products, including Hizentra. Risk factors can include: advanced age, prolonged immobilization, a history of blood clotting or hyperviscosity (blood thickness), use of estrogens, installed vascular catheters, and cardiovascular risk factors.**

**If you are at high risk of thrombosis, your doctor will prescribe Hizentra at the minimum dose and infusion rate practicable and will monitor you for signs of thrombosis and hyperviscosity. Always drink sufficient fluids before administration.**

Tell your doctor if you have had a serious reaction to other immune globulin medicines or have been told you also have a deficiency of the immunoglobulin called IgA, as you might not be able to take Hizentra.

You should not take Hizentra if you know you have hyperprolinemia (too much proline in your blood).

**Infuse Hizentra under your skin *only*; do not inject into a blood vessel.**

Allergic reactions can occur with Hizentra. If your doctor suspects you are having a bad allergic reaction or are going into shock, treatment will be discontinued. Immediately tell your doctor or go to the emergency room if you have signs of such a reaction, including hives, trouble breathing, wheezing, dizziness, or fainting.

Tell your doctor about any side effects that concern you. Immediately report symptoms that could indicate a blood clot, including pain and/or swelling of an arm or leg, with warmth over affected area; discoloration in arm or leg; unexplained shortness of breath; chest pain or discomfort that worsens with deep breathing; unexplained rapid pulse; and numbness or weakness on one side of the body. Your doctor will also monitor

**Are you a person with PI who takes Hizentra?  
Do you care for someone who does?**

**Voice2Voice®**

Voice2Voice gives you an opportunity to connect with others who have been in your shoes. Dealing with PI can be a challenge, and knowing someone who truly understands what you're going through can mean a lot.\*

**It's good to know you're not alone.**

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You may also call 1-877-355-IGIQ (4447)  
Monday–Friday, 8 AM to 8 PM ET

symptoms that could indicate hemolysis (destruction of red blood cells), and other potentially serious reactions that have been seen with Ig treatment, including aseptic meningitis syndrome (brain swelling); kidney problems; and transfusion-related acute lung injury.

The most common drug-related adverse reactions in the clinical trial for Hizentra were swelling, pain, redness, heat or itching at the site of injection; headache; back pain; diarrhea; tiredness; cough; rash; itching; nausea and vomiting.

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

Before being treated with Hizentra, inform your doctor if you are pregnant, nursing or plan to become pregnant. Vaccines (such as measles, mumps and rubella) might not work well if you are using Hizentra. Before receiving any vaccine, tell the healthcare professional you are being treated with Hizentra.

**Please see brief summary of full prescribing information for Hizentra on adjacent page. For full prescribing information, including boxed warning and patient product information, please visit [Hizentra.com](http://Hizentra.com).**

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

\*Voice2Voice advocates are not healthcare professionals or medical experts. For medical questions, please contact your physician. Voice2Voice advocates are compensated by CSL Behring LLC for their time and/or expenses.

Reference: 1. Data on File. Available from CSL Behring as DOF HIZ-003.



**Can IgIQ® help you?**  
**If you answer YES to any of these questions,**  
**call 1-877-355-IGIQ (4447) Monday–Friday, 8 AM to 8 PM ET.**

- Have you had a lapse in your insurance coverage?
- Are you unable to afford Hizentra®?
- Would you like to connect with other Hizentra patients?
- Do you need help paying for Hizentra?
- Are you unable to afford Hizentra infusion supplies?

**Hizentra®**, Immune Globulin Subcutaneous (Human), 20% Liquid  
 Initial U.S. Approval: 2010

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

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

**WARNING: THROMBOSIS**

*See full prescribing information for complete boxed warning.*

- **Thrombosis may occur with immune globulin products, including Hizentra. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.**
- **For patients at risk of thrombosis, administer Hizentra 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.**

-----INDICATIONS AND USAGE-----  
 Hizentra is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Liquid indicated for the treatment of primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older.

-----DOSAGE AND ADMINISTRATION-----  
**For subcutaneous infusion only.**  
 Administer at regular intervals from daily up to every two weeks (biweekly).

- Dosage (2.2)**  
 Before switching to Hizentra, obtain the patient’s serum IgG trough level to guide subsequent dose adjustments.
- **Weekly:** Start Hizentra 1 week after last IGIV infusion  
 Initial weekly dose =  $\frac{\text{Previous IGIV dose (in grams)}}{\text{No. of weeks between IGIV doses}} \times 1.37$
  - **Biweekly:** Start Hizentra 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly Hizentra/IGSC infusion. Administer twice the calculated weekly dose.
  - **Frequent dosing (2 to 7 times per week):** Start Hizentra 1 week after the last IGIV or Hizentra/IGSC infusion. Divide the calculated weekly dose by the desired number of times per week.
  - **Adjust the dose** based on clinical response and serum IgG trough levels.

**Administration**

- Infusion sites – 1 to 4 injection sites simultaneously, with at least 2 inches between sites.

Infusion Parameters*	Infusion Number			
	1 <sup>st</sup>	2 <sup>nd</sup> to 4 <sup>th</sup>	5 <sup>th</sup>	6 <sup>th</sup> and above
Volume (mL/site)	≤ 15		≤ 20	≤ 25
Rate (mL/hr/site)	15	≤ 25		

\* As tolerated

-----DOSAGE FORMS AND STRENGTHS-----  
 0.2 g per mL (20%) protein solution for subcutaneous injection

- CONTRAINDICATIONS-----
- Anaphylactic or severe systemic reaction to human immune globulin or components of Hizentra, such as polysorbate 80
  - Hyperprolinemia (type I or II) (Hizentra contains the stabilizer L-proline)
  - IgA-deficient patients with antibodies against IgA and a history of hypersensitivity

- WARNINGS AND PRECAUTIONS-----
- IgA-deficient patients with anti-IgA antibodies are at greater risk of severe hypersensitivity and anaphylactic reactions.
  - Thrombosis may occur following treatment with immune globulin products, including Hizentra.
  - Aseptic meningitis syndrome has been reported with IGIV or IGSC treatment.
  - Monitor renal function, including blood urea nitrogen, serum creatinine, and urine output in patients at risk of acute renal failure.
  - Monitor for clinical signs and symptoms of hemolysis.
  - Monitor for pulmonary adverse reactions (transfusion-related acute lung injury [TRALI])
  - Hizentra is made from human plasma and may contain infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

-----ADVERSE REACTIONS-----  
 The most common adverse reactions observed in ≥5% of study subjects were local reactions (i.e., swelling, redness, heat, pain, and itching at the injection site), headache, diarrhea, fatigue, back pain, nausea, pain in extremity, cough, rash, pruritus, vomiting, abdominal pain (upper), migraine, and pain.

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

-----DRUG INTERACTIONS-----  
 The passive transfer of antibodies may interfere with the response to live virus vaccines, and lead to misinterpretation of the results of serological testing.

- USE IN SPECIFIC POPULATIONS-----
- **Pediatric:** No specific dose requirements are necessary to achieve the desired serum IgG levels.

Cellular immunity is crucial in antifungal immunity. Deficiencies in cellular immunity lead to an increased susceptibility to fungal infections. Classical severe combined immunodeficiency (SCID) and hypomorphic (leaky) SCID patients will have a greater predisposition to developing fungal skin infections. Other forms of combined cellular/humoral immunodeficiency disorders and predominately cellular immunodeficiency disorders can also lead to CMC. A few examples of these conditions include Wiskott-Aldrich syndrome, dedicator-of-cytokinesis 8 deficiency (DOCK8), DiGeorge syndrome, etc.

## Viral Infections

Viral infections of the skin can be broadly categorized into those caused by herpes viruses, poxviruses and papillomaviruses. Key parts of the immune system that help control viral infections are T cells (both T-helper as well as T-cytotoxic) and natural killer (NK) cells. PIs that decrease the number of these cells or disrupt/impair their function will increase susceptibility to developing viral skin infections.

The most common herpes viruses are herpes simplex virus (HSV) 1 and 2 and herpes zoster. Following primary infection, herpes viruses generally reside in a dormant state in the cell bodies of neurons. Both herpes simplex and zoster can reactivate depending on degree of stress or immunodeficiency. While there are systemic symptoms associated with primary infection, reactivation is generally limited to skin symptoms such as the development of a burning, painful red rash with vesicles (fluid- or air-filled sacs). Generally, reactivation of herpes simplex is in the same area or a nearby area to the primary infection. Herpes zoster reactivation generally is isolated to a particular dermatome nerve distribution (an area of the skin that is supplied by a single spinal nerve) on one side of the body. Herpes zoster reactivation can occur in immunocompetent individuals under periods of high stress, but immunodeficiency will increase the risk and rate of reactivation. Defects in cellular immunity will lead to more frequent and greater severity and possibility of systemic complications of both HSV and zoster.

The most common poxvirus-induced skin disease is molluscum contagiosum, which is characterized by flesh-colored dome-shaped papules with a central dimple. Molluscum is a common skin infection in childhood, but can also be seen in adults. It is spread by skin-to-skin contact, so sexual contact and contact sports are often risk factors in immunocompetent patients. Immunodeficiency can increase the risk of developing molluscum, particularly conditions that are associated with defects in T-cell function. Examples of PIs that are associated

with increased risk of molluscum are Wiskott-Aldrich syndrome and DOCK8 deficiency.

The most common skin condition caused by herpes papillomaviruses (HPVs) are warts. T cells and NK cells help to control HPV infections, and PIs that lead to defects in their function will often predispose individuals to develop more significant and extensive HPV infections. Primary NK cell deficiency and DOCK8 deficiency have been associated with refractory and, often, extensive warts all over the body. One syndrome called warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) is particularly associated with increased susceptibility to HPV infections. In WHIM, the defect is in a chemokine (signaling protein) called CXCR4. This syndrome affects cellular and humoral immunity (antibody production) and can lead to retention of mature neutrophils in the bone marrow, leading to low levels of neutrophils in the peripheral blood.

Another distinct condition associated with increased uncontrolled HPV infection is epidermodysplasia verruciformis (EV). EV can have a variety of presentations, including flat skin lesions to reddish-brownish plaques to warts. The primary defect in EV does not appear to be a cellular immunodeficiency, but rather a defect in restricting HPV's access to zinc. The defect in EV is related to mutations in either the EVER1 or EVER2 gene. The normal function of these genes leads to encoding of proteins that would restrict the ability of HPV to access cellular zinc stores, which are necessary for function of various viral proteins. EV patients are at an increased risk to develop squamous cell cancers of the skin.

## The Diagnostic Link

The skin is the most visible organ in the body and also serves as the first line of defense in our immune system. There are many key skin infections seen in a variety of PI disorders. By considering the mechanism in which a normal functioning immune system defends against various microorganisms, it's possible that specific skin infections may offer diagnostic clues to the type of PI a patient may have. Therefore, prompt recognition of severe, unusual or recurrent skin infection/disease will alert us to the possibility of systemic illness and underlying immunodeficiency disorders. ■

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