

# PIDD ANTIBODY AND SUBCLASS DEFICIENCIES

It is often a long road to diagnose these two less severe forms of PIDD, and while treatment is available, it is sometimes controversial and has its share of insurance issues.

By Kris McFalls and Amy Scanlin, MS

The World Health Organization recognizes more than 150 diseases classified as a primary immune deficiency disease (PIDD), affecting as many as one in 500 individuals. While some disease states require immediate hospitalization and even bone marrow transplants, others can cause minor illnesses and even go undiagnosed. Two of the less severe forms of PIDD that may require immune globulin (IG) treatment are selective antibody deficiency (SAD) and IgG subclass deficiency. Unfortunately, these two forms are difficult to diagnose, but once they are detected, with the proper treatment, patients can lead relatively normal lives.



## Diagnosing SAD and IgG Subclass Deficiency

Typically, when a primary care provider (PCP) has a patient that presents with sinus or respiratory infections, the PCP will likely treat each infection with appropriate antibiotics. However, if the patient returns time and again with chronic infections that won't heal, don't respond well to antibiotics or increase in frequency, the PCP will suspect something more. At this point, the PCP will likely take a complete blood panel (CBC) to screen for infections, anemia and other possible diseases.

In many cases, a CBC for a mild PIDD patient generally will not sound alarm bells. So, if infections persist, increase in frequency and respond poorly to antibiotics, the PCP may suspect allergies, environmental factors such as smoke, mold or even gastrointestinal reflux, and again try to treat the patient symptomatically. For PIDD patients, these measures may help, but they will not stop the onslaught of infections. Finally, after years of failing to get infections under control, the PCP may refer the patient for further evaluation.

The hope is that the patient will be referred to an immunologist for testing. But, the reality is that the patient will likely see an otolaryngologist, allergist or infectious disease specialist. The Jeffery Modell Foundation (JMF) and the Immune Deficiency Foundation (IDF) have taken very active roles to try to educate PCPs and medical students to think outside the box, notice the warning signs and seek an immunology consult before long-term damage from infections occur. Unfortunately, according to one IDF study, it takes, on average, more than nine years for a PIDD patient to be diagnosed. Perhaps further education and heightened awareness can help decrease considerably the average time to achieve diagnosis.

Once a patient is referred to an immunologist, patient history, labs and other testing will be reviewed. In addition, further blood testing will likely be ordered to look at immunoglobulin G (IgG) subclass levels named IgG1, IgG2, IgG3 and IgG4, as well as antibody function. A deficiency in any of these typically may be found in association with frequent respiratory infections, including ear, sinus, bronchitis and pneumonia, as well as excessive viral infections. The sooner an immunologist can order the correct tests, the sooner a diagnosis can be made and treatment can begin.

## IgG Subclass Deficiencies

There are four subclasses of the IgG antibody, named in order of their concentration in the blood serum. In most people, IgG1 constitutes 60 percent to 65 percent of total

IgG, followed by IgG2 at 20 percent to 25 percent, IgG3 at 5 percent to 10 percent and IgG4 at 3 percent to 6 percent. However, these ranges vary. It's possible for a person to be deficient in one or more subclasses but have a normal serum IgG level due to compensation from the other IgG subclasses.

Because IgG1 levels are so high, a person who is low in this subclass will typically have a low overall IgG level.<sup>1</sup> IgG1 and IgG3 are the primary protectors against tetanus and diphtheria, and a deficiency in one often coincides with a deficiency in the other.

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A deficiency of IgG2, which is most common in children, is often associated with respiratory infections and asthma. IgG2 is responsible for making antibodies to the polysaccharide in cell walls of bacteria. It protects against bacteria and is the primary protector against pneumococcus, which can cause bacterial meningitis, pneumonia and infections in the bloodstream and sinuses. Often, an IgG2 and either an IgA or IgG4 deficiency will be found alongside each other. A person with an IgG2 deficiency may be asymptomatic. Yet, for those who do present with infections, encapsulated bacteria are often the cause due to the antibody response to polysaccharides.<sup>2</sup>

IgG3 deficiencies are most common in adults and are commonly associated with upper and lower respiratory tract infections. IgG3 is a primary response to viral respiratory agents. A significant fraction of the IgG antibodies against pneumococcal polysaccharides may be of the IgG3 subclass.

IgG4 deficiencies occur with surprising frequency. Fifteen percent of children and 10 percent of adults have completely undetectable IgG4. Since its role in infection susceptibility is unknown, its absence is not considered clinically significant by itself when looking for a cause of a patient's symptoms.<sup>3</sup>

According to Dr. Francisco Bonilla, immunologist at Boston Children's Hospital, "Doctors are more likely to look more closely at patients who have more than one

deficiency. For instance, treating a patient with IG who only has an IgG3 or an IgG4 deficiency may be controversial. However, if a patient has an IgG2 and an IgG4 deficiency, plus an IgA deficiency, doctors may be willing to give it more consideration.”

Also, it’s important to note that because the levels of circulating IgG subclasses vary throughout people’s lives, age must be taken into account when analyzing the results of subclass testing.

### Selective Antibody Deficiency (SAD)

SAD is just as it sounds: The body produces too little of a certain antibody and normal amounts of others, which causes a patient to be more susceptible to encapsulated bacteria and enteroviruses, and conditions such as respiratory infections with bacteria and viruses.

While there are five main classes of antibodies, the IgG class has the highest concentration in the blood and fluids that surround the tissues and cells. Interestingly, IgG is the only immunoglobulin that can cross from the mother to the placenta and fight infection in utero.



### Testing

Approximately 60 percent of PIDDs can be diagnosed with simple blood tests, yet 70 percent to 90 percent of patients remain undiagnosed.<sup>4</sup> To simplify the explanation of testing, JMF has classified the tests into four stages, yet because they can overlap, there is no set sequence.<sup>5</sup> “The stages are not necessarily sequential and may occur simultaneously, but should be based on the initial information obtained from the history, physical examination and previous

laboratory testing,” explains Dr. Terry O. Harville, medical director of immunology at the Departments of Pathology and Laboratory Services and Pediatrics at the University of Arkansas for Medical Sciences. “These stages are more or less possibilities, but have no particular time scale.”

A typical immune evaluation likely would include a vaccine challenge, which helps assess the immune system’s ability to function as expected. The most common is a pneumococcal vaccine challenge. In this test, several (usually 12 to 14 depending on the lab) antibodies against 23 pneumococcal serotypes are measured before the pneumococcal vaccine is given. Three to four weeks following, the patient’s blood is again tested and antibodies are remeasured. A level of 1.3 micrograms/milliliter or higher is considered protective. However, immunologists also like to see an increase in antibody levels of two to four times the starting level for at least half of the serotypes.

If more information is needed, the specialist will look further at the four subclasses, IgG1 through IgG4. However, some specialists feel that the subclass information is not particularly helpful because it doesn’t provide any information about the patient’s ability to produce antibodies to protein, polysaccharides or viral antigens.

Assessment of antibody responses to polysaccharide antigens also must be considered, because responses may be deficient in some who otherwise respond normally to protein antigens. Antibodies measured after a pneumococcal capsular polysaccharide vaccine are useful in children over 2 years of age and can provide information about a patient’s immunocompetence.<sup>6</sup>

A patient’s symptoms will guide which tests a doctor chooses. “[If] the patient presents with recurrent boils, furuncles, poor wound healing, etc., the evaluation would not necessarily require measurement of IgG levels or lymphocyte enumeration, but does require neutrophil counts and oxidative burst assay,” explains Dr. Harville. “The most common evaluation would be for recurrent sinopulmonary disease/infections. This implies humoral immunodeficiency. Therefore, the evaluation would consist of IG levels (IgG, IgA, IgM, and IgE), CBC with differential to determine the lymphocyte count, pre-immunization diphtheria, tetanus and pneumococcal titers, and CH50. Most also will assess lymphocyte enumeration to determine the extent of B lymphocyte lack and the alterations in B lymphocyte subpopulations.”

### Treatments

Intravenous IG (IVIG) therapy can be a controversial topic for patients who have antibody and subclass

deficiencies. Some clinical immunologists believe that patients with only SAD or a subclass deficiency should not be treated with IG. When deciding whether to treat with IG, doctors should consider a patient's quality of life and infection history. According to Dr. Bonilla, the SAD and subclass deficiencies are still considered to be at the mild end of the immune deficiency spectrum. As a result, many patients are managed with antibiotics.

"Some patients can be managed with extra immunizations and/or antibiotics alone," says Dr. Melvin Berger, MD, PhD, division chief, allergy and immunology at University Hospitals Case Medical Center. "It depends on the pattern of infections the patient has experienced, the exposure of the patient to infectious agents, and the response and tolerance to antibiotics." Also, some patients have good success using a prophylactic antibiotic to prevent infections, and once they get an infection, they can then be moved to another antibiotic.

In some cases, such as chronic sinusitis, IV treatment may be warranted because antibiotics will not be effective due to a hampered humoral immune response.<sup>7</sup> In addition, some patients develop resistance and sensitivities to entire

classes of antibiotics. For those patients in particular, IG may be the best option to prevent infections.

Before a patient with a subclass deficiency will be considered for IVIG therapy, antibody responses to polysaccharides and proteins will be tested for clinical significance. If the subclass deficiency is considered to be clinically significant, the patient will have both recurrent infections and impaired functional antibody responses.<sup>8</sup> According to Dr. Bonilla, "When a patient gets to the point where they are always on antibiotics and are still getting sick and they are missing work or school, then it may be appropriate to start IG therapy."

The controversy over treating patients with IG can be very confusing. Dr. Bonilla encourages patients to talk with other patients and find a doctor that will work with them. The IDF is a good place to start the search. Patients can go to [www.primaryimmune.org](http://www.primaryimmune.org) and click on Patients and Families to find information about joining the foundation's free peer support network. The IDF will determine the patient's needs, then work closely to find a peer support. Trained volunteers are partnered with patients and family members who share similar situations to provide information and support. And, all correspondence is confidential.

IG Living ([www.IGLiving.com](http://www.IGLiving.com)) also has a fan page on Facebook where patients are able to participate in discussions. On the site's homepage, there is a Facebook link at the bottom left.

### Precautions

Because patients with antibody deficiencies do not produce a good antibody immune response, they should speak with their doctor about their particular risks of receiving live vaccines while undergoing IVIG treatment. For most, the risk is low. According to Dr. Bonilla, patients with SAD generally do not have a problem with live vaccines: "In my 15 years of practice, I cannot think of one patient with SAD who suffered serious complications from a live vaccine."

Dr. Berger adds, "In general, the precaution of avoiding live vaccines is recommended for patients with T-cell defects (an exception being live nasal influenza vaccine in IgA-deficient patients). Therefore, these vaccines may be given to specific antibody deficiency patients who may still produce antibodies to protein antigens and whose T cells may be stimulated by the vaccine antigens. Individual patients should discuss immunization plans with a doctor who is familiar with their exact immunologic defects."

Patients with SAD or subclass deficiency need to take



reasonable precautions to avoid interaction with people they know to be sick, and they need to have good hygiene, a healthy diet and get plenty of exercise and rest.

### Insurance Issues

Dealing with insurance companies can be as confusing as testing and treatment. It can be a challenge to get IVIG approved because, as Dr. Bonilla explains, although there are quality-of-life issues, SAD or subclass deficiencies still are considered to be at the mild end of the immunodeficiency disease spectrum. However, copious notes, lab reports, culture results, radiological confirmation of infection and persistence in determining what documentation and verification a patient's insurance company needs will help.

In addition, doctors must show that they have tried reasonable alternatives to IG before it will be approved. It is not uncommon to see patients develop allergies or intolerance to certain classes of antibiotics, leaving few treatment options should a severe infection develop. In addition, patients may require IV antibiotics to clear a recurrent infection. But, in order to show that infections are recurrent and a switch to IG is necessary, specific documentation will need to be provided to the insurer. In fact, some insurers specifically state in their policy that "calling in a prescription is not proof enough of infection."

Children with SAD and/or subclass deficiency may be required by some insurers to go through a trial period during which they go off of IG after one year for re-evaluation. This is because it is possible that children's immune systems could further mature and, therefore, they could "grow out" of their immune deficiency. "Particularly when specific antibody deficiency is diagnosed in young children, it may be a delay in development of the full repertoire of antibody responses, and the patient may well grow out of the problem as their immune system matures," explains Dr. Berger.

While growing out of an immune deficiency may be possible for a child, Dr. Bonilla says, "I can count on one hand the number of adults who have had apparent spontaneous remission of PIDD."

### Research

New research could shed additional light on SAD and subclass deficiencies. At the 2009 Immune Deficiency National Patient Conference, Dr. Bonilla reported that some patients may produce antibodies, but those antibodies may not be of sufficient quality. He and his colleagues have been studying this theory and were scheduled to

present an abstract regarding this topic at the First Clinical Immunology Society's North American Primary Immune Deficiency National Conference, which took place May 20-23 in Philadelphia, Pa.

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### Patience Helps Patients

Because of the often misunderstood symptoms of SAD and subclass deficiency, finding the cause and appropriate treatment is rarely easy. Patients and doctors most often spend countless hours working together to find the appropriate tests and protocols for treating the disorder. But, with proper management, patients can enjoy work and play, and avoid future complications despite their reduced immune capacity. ■

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