

Specific Antibody Deficiency:

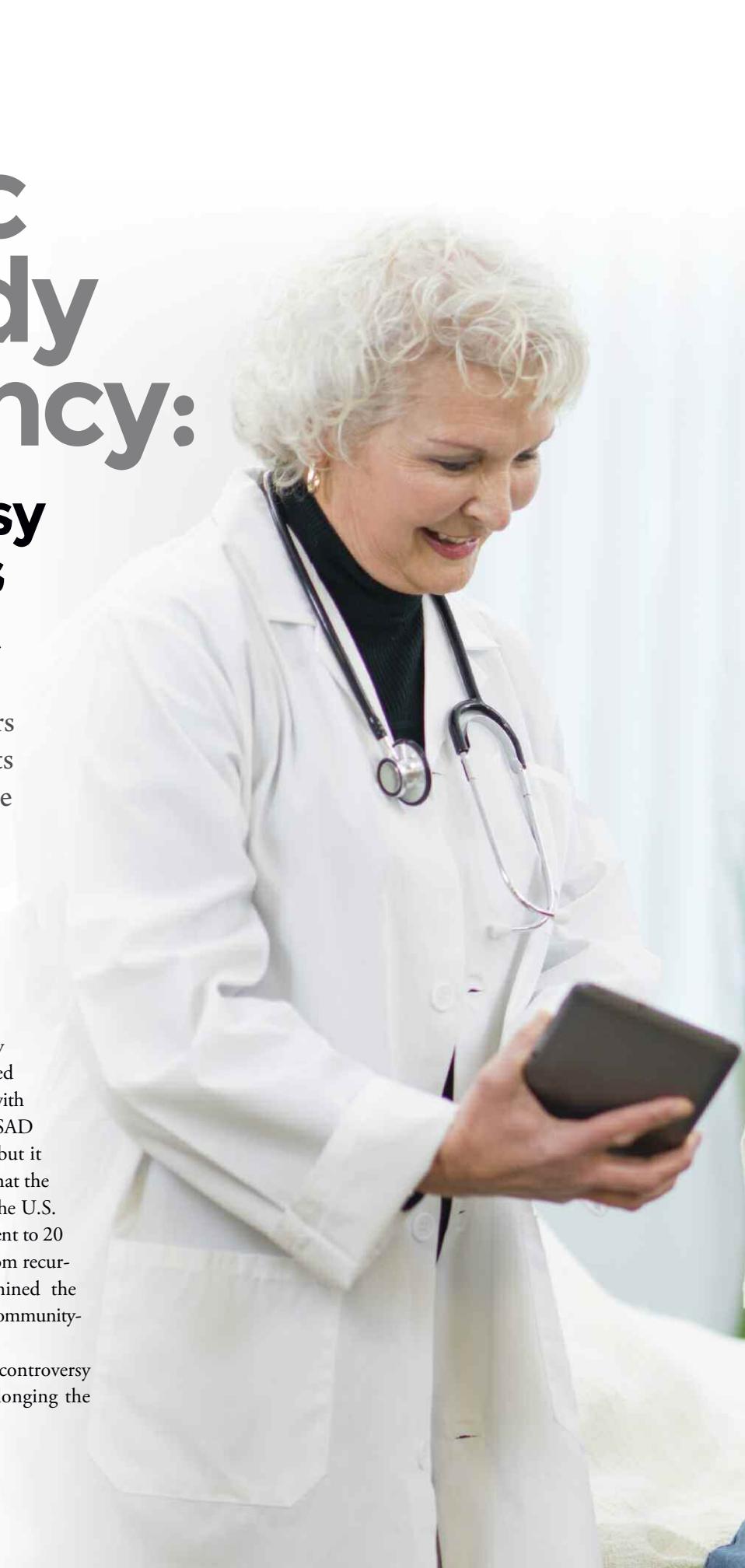
The Controversy Over Diagnosis and Treatment

Specific antibody deficiency occurs in both children and adults, but its diagnosis and treatment continue to be controversial.

By Ronale Tucker Rhodes, MS

FIRST REPORTED IN a small group of patients in the early 1980s, specific antibody deficiency (SAD) is one of the most commonly identified immune abnormalities among patients presenting with recurrent and/or severe sinopulmonary infections.¹ SAD affects both males and females and all age groups, but it is more often diagnosed in adults. It is unknown what the prevalence of SAD is in the general population in the U.S. Some studies show that SAD is recognized in 5 percent to 20 percent of children older than 2 years who suffer from recurrent or severe infections, and one study determined the prevalence of SAD among adults with recurrent community-acquired pneumonia to be approximately 8 percent.²

Why, then, despite the prevalence of SAD, does controversy about its diagnosis and treatment exist, thus prolonging the diagnosis and treatment options for many?



What Is SAD?

According to Terry Harville, MD, PhD, medical director of the Special Immunology Laboratory at the University of Arkansas for Medical Sciences, some immunologists disagree that SAD is an immunodeficiency. Yet, in 2014, the International Union of Immunological Societies (IUIS) Expert Committee for Primary Immunodeficiency lists SAD in its table of primary B lymphocyte/immunoglobulin deficiencies. According to IUIS, SAD is characterized by normal, and in some instances, somewhat low-normal B lymphocyte numbers with a deficiency to specific antigens.³

Sometimes termed “partial antibody deficiency” or “impaired polysaccharide responsiveness,” SAD describes a deficient-specific response to pneumococcal polysaccharide antigens in individuals who have normal responses to protein antigens, normal serum levels of immunoglobulins and normal IgG subclass concentrations.¹ It is a common antibody

immunodeficiency defined as a poor antibody response to unconjugated pneumococcal polysaccharides present in the 23-valent pneumococcal vaccine.⁴ In essence, in SAD patients, the total quantity of antibodies that fight infection are normal, but the quality of those antibodies, or the ability for them to fight infection, is not.

“Typically, the immunoglobulin classes IgG, IgA and IgM are all in the normal ranges for age,” explains Dr. Harville. “Yet, the pneumococcal titers are low.” Immunoglobulins are antibodies produced by plasma cells that are used by the immune system to identify and neutralize foreign objects such as bacteria and viruses. But, there are also specific antibodies that the immune system produces in response to specific vaccines. The pneumococcal vaccine is used to test for the response to polysaccharide antigens that are found on the surfaces of most bacteria and other pathogens that cause infections. Measuring the pneumococcal titers reveals how well the body is able to make those specific antibodies to eradicate bacteria and infections.⁵



Symptoms of SAD

Most frequently, the symptoms of SAD are the same as other primary immunodeficiency disease symptoms. They can be as severe or in some cases moreso than some patients with a greater extent of antibody deficiency. These include recurrent ear infections, sinusitis, bronchitis and pneumonia. When symptoms begin differs. Some people present with infections with increased frequency during the first years of life, while the onset of infections for others may occur later in life.⁶

What Causes SAD?

The precise underlying mechanisms resulting in SAD remain unknown. Ongoing research is trying to elucidate the cause of SAD and how it may be inherited.^{6,7}

Diagnosing SAD

Presentation with a history of recurrent infections is typically indicative that an antibody deficiency may be present. However, SAD can be a diagnostic challenge because total IgG levels are normal, whereas antibody deficiencies typically present with either absent or deficient total IgG levels.

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Diagnostic criteria for SAD include measuring the levels of the three main classes of immunoglobulin (IgG, IgA and IgM); using tetanus, pneumococcus and haemophilus influenza type b indicators to check whether specific immunoglobulins are present that can fight infection; testing the immune system's response to vaccination if specific immunoglobulins are low; and counting the numbers of different immune cells in the blood (which should be normal in SAD).⁷

The problem, says Dr. Harville, is that the proper testing isn't always performed. "A patient shows up to a clinic with recurrent infections, sinus problems, upper-respiratory problems, fatigue,

headaches, and they just don't feel good — a nonspecific set of symptoms that suggests a problem with infections. Because there is a lack of a cure with antibiotics, the decision is made to measure the serum IgG levels, and they're normal," he explains. And, frequently, that's where the testing stops. But, what should be done, he says, is to have that patient tested for pneumococcal titers as well. If that person's pneumococcal titers are low, then the diagnosis of SAD should be considered.⁸

The response to the pneumococcal vaccine, according to the Immune Deficiency Foundation (IDF), is why the criteria for the diagnosis of SAD have been somewhat controversial. Now, however, IDF says most immunologists agree that several patterns of responses after receiving the vaccine can be used to diagnose SAD. "Patients may fail to respond to any of the serotypes included in the vaccine and have a more severe form of SAD," writes IDF. "Responses in which children respond to less than 50 percent of serotypes and adults respond to less than 70 percent have a moderate form of SAD with an increased risk of upper- and lower-respiratory infections that may warrant treatment. An additional subset of patients appears to respond normally initially [and] then lose protective levels within months."⁶

Treating SAD

As mentioned previously, treatment for SAD can be controversial. Many patients' infections can be controlled with the aggressive use of antibiotics, which has been the conventional treatment for SAD. But this is not true for many other patients who continue to have more frequent and severe infections. For these latter patients, many immunologists recommend intravenous immune globulin (IVIG) replacement therapy. If there is a clinical response (infections stop), it is still recommended that treatment be stopped after a period of time (typically in the spring) to determine if a deficiency still exists. This is especially true for children because many outgrow SAD as they get older.⁶ The patients' immune response would then be re-evaluated at least five months after discontinuation of IVIG.⁹ If a deficiency still exists, IVIG would be restarted.

IVIG, however, is not a U.S. Food and Drug Administration-approved therapy for SAD.⁹ Therefore, there is disagreement over whether someone diagnosed with SAD should receive IVIG therapy. "There are those who suspect that SAD is not a 'true' disease category, especially one deserving IVIG treatment," explains Dr. Harville. Indeed, because of the doubt over the validity of the diagnosis, "there is resistance by third-party payers to cover IVIG treatment," he says. One insurance company's policy states that SAD "generally does not require

Jennifer Wang's Story

For well over a decade, Jennifer Wang was sick with allergies, asthma, respiratory infections, sinus infections and the list goes on. Her symptoms started in her early teens. Even with back-to-back rounds of antibiotics and two sinus surgeries, she was always sick. "It's disheartening to be sick and not know what's wrong with you," explains Jennifer. "You feel angry and confused, and it definitely has an impact on your psyche." Jennifer had been seeing the same allergist/immunologist since 2004 when in mid-2013, "he finally figured it out." Diagnosis: specific antibody deficiency (SAD). "That's the problem with SAD; we have to get sick enough to finally figure it out," says Jennifer.

Because Jennifer had been on different rounds of antibiotics for several months and she had had sinus surgery, neither of which stopped the recurrent infections, when she was diagnosed, she was prescribed intravenous immune globulin (IVIG). "After the insurance approved it, I was treated with IVIG," says Jennifer. "I've never been denied, just delayed." Jennifer was treated with IVIG for seven months, and she then switched to subcutaneous IG (SCIG) infusions. "I was doing SCIG weekly at first, but I was feeling down on days, like a roller coaster. So, my doctor switched me to every six days," she explains. "That little tweak was exactly what I needed." Jennifer is still on daily antibiotics, but she has switched from high dose to low dose, and she is hoping she eventually won't need them.

The challenges Jennifer, now 28, has faced are many. When she was sick and didn't know what was wrong with her, she said she always faked that she was fine. "You don't tell people you're sick. It's this big thing looming over you that you hide," explains Jennifer. But, since her diagnosis, she's open to talking about it: "The shame and guilt sort of went away

with the diagnosis." Fortunately for Jennifer, she doesn't have to work full time, and she has a flexible schedule. "It would be very hard to have to deal with an employer, especially with my every-six-day infusion schedule," she says. "I've had the time to concentrate on my health." But the one thing she'd really like to do she can't: travel to China to see her husband's family. "I went to China once and I was so sick. I thought maybe it was because they all smoke," she explains. "I wish I could go again, but I don't know if I am able with my disease."

IG therapy has made all the difference for Jennifer. In college and graduate school, she was a professional belly dancer. Now, she does samba dancing. "I'm in a dance group called sambacolorado.com, and I dance 10 to 15 hours a week," says Jennifer. "I wouldn't be able to do that without IG therapy. I went through feeling like I only

have the energy to do a load of laundry to being able to go to samba five days a week."

"I know there's no cure," says Jennifer. "So, right now, the expectation is a lifelong treatment, which at first was a hard thing to wrap my mind around. Everyone wants to just be normal." One of the things that helps Jennifer is keeping educated about her disease. "I'm still in discovery mode, and the more I find out, the clearer the picture becomes. I'd give up everything I have for a cure; I'm just glad with IG therapy, I can live a somewhat normal life."

Jennifer's passion now is spreading awareness about the disease. "I'm trying to figure out where my role is going to be in the advocate world now," she says. "My heart feels like I need to do something, because it would almost be a crime to have this illness and not spread awareness."

Jennifer's advice: "If you feel like there's something wrong with you beyond allergies and asthma, speak up. And, don't feel ashamed of having the disease. You can still have a life. You may not be able to climb Mount Everest, or in my case travel the world, but you can still do a lot of things. I can dance for hours in high heels. Don't let [SAD] suck the life out of you. Find what makes you happy. Life is not over."



Coryn Barks' Story

Laura Harland's daughter, Coryn, was sick right after she was born. "She always had something. We were at the doctor every week," explains Laura. "As soon as she got off an antibiotic, she was on another for something else. She had the typical childhood infections: ear infections, strep, sinus, pneumonia, colds, etc."

But getting a diagnosis for Coryn wasn't easy. "It was beyond frustrating," says Laura. "I honestly don't know how people who have gone longer without a diagnosis handled it. [Coryn] wasn't growing or thriving because she was sick all the time. The ER doctors and nurses knew us because she was there all the time. I knew there was something wrong. It's heartbreaking to see your child go through that and to be told she is normal when you know she is not." Coryn was originally diagnosed with an IgG subclass deficiency at age 2. But, after additional testing for pneumococcal titers, she was diagnosed with SAD.

Coryn was treated with prophylactic antibiotics for about two years, which kept her from getting pneumonia. However, she did continue to have upper-respiratory and sinus infections. "So, at one of our immunology checkups, the doctor asked how she was doing. I was thrilled to tell him she hadn't had pneumonia. He asked about other infections, since she had continued to have many, and that's when he decided it was time to try immune globulin," says Laura. Coryn was 4 years old when she started intravenous immune globulin (IVIG) therapy, and she was treated with it for 13 months, when she had a strep infection and the doctor decided to check her levels. "It turned out that her B cells were normal when they hadn't been before, so he decided to take her off of IVIG to see if her immune system would start working," explains Laura. "She did well for a couple of months, and then she started getting sinus infections again. She then had her adenoids removed, and she did well for a few months, but then she started getting sick again, and we couldn't get her better. As soon as an infection was gone, a week later it was back. So, after 19 months, the infusions were started again." Coryn is now 8 years old and is still being treated with IVIG every four weeks.

Trying to make others understand that Coryn's infections represent a serious illness has been difficult. When Coryn gets sick, she doesn't get fevers. "A fever for her would be 99.5," says Laura. "It's almost like her body doesn't realize she's trying to fight something — even when she has the flu. So when she goes to the nurse and says she doesn't feel good and she doesn't have a fever, she isn't believed. That's terrible for her self-esteem." Coryn, then, tries to portray being fine because she doesn't want people to know what's going on. "Coryn has told me that she can act perfectly fine even when she's miserable," says Laura.

It's tough for Laura, too. There are people she knows who don't remember seeing Coryn when she was 2 or 4, when she was sick all the time. "People think strep throat or a cold isn't that bad, but if it's constant, it's different, and people don't understand," explains Laura. "They don't understand why I'm so passionate about vaccines and herd immunity because her body doesn't accept vaccinations. I feel terrible as a parent for pulling her out of school for doctor appointments, treatments or illnesses and being looked at or judged when I have to pull her out of school because she's too tired to stay."

Still, Laura strives to make Coryn's life as normal as possible. Coryn's infusion days are made better because there is a little boy her age who also has an immune deficiency. "They sit in bed together and get their IV poles tangled up and go to the game room and play games," says Laura. "Sometimes we go to the zoo after their infusions. It's made a big difference for her to know that other kids have the same struggles as her and have to get poked as often as she does. She's 8, and knowing someone else who is going through something similar makes it easier on her."

Laura's advice to other parents of kids with SAD: "Find someone who is going through the same thing. Meet another parent at an infusion clinic. Get on Facebook. No one truly is going to understand except someone who is going through it themselves. And having that person makes all the difference in the world."



IVIG replacement for control of recurrent bacterial infections.” Yet, IVIG treatment is recommended for SAD by many of the major medical organizations, including the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology, which states that IVIG is “probably beneficial” for the treatment of “primary immune defects with normogammaglobulinemia and impaired specific antibody production.”¹⁰

The logistics and cost of IVIG therapy also lend themselves to controversy considering the high expense and potential shortages of this plasma product. “This is not an inconsequential issue,” says Dr. Harville. “Some people are trying to think of things in a global context of keeping the cost of medicine down.”

SAD Prognosis

The long-term prognosis for SAD can be different for children than for adults. For instance, it’s possible that some kids will simply outgrow it over time. But, it’s also possible that a diagnosis of SAD may progress into a more serious immune deficiency such as common variable immunodeficiency (CVID). The only way to monitor for progression is to periodically re-evaluate serum IgG, IgA and IgM levels, as well as specific antibody titer responses to the pneumococcal vaccine. IgA and IgM are not influenced by IG replacement and, if falling, can indicate the evolution toward CVID. When treated with IVIG, a fall in the serum level IgG trough values can also indicate a progression in disease. Unfortunately, when treated with subcutaneous IG, measurement of serum IgG levels may not be as useful, but a fall could be indicative of disease progression and/or lack of adequate replacement. If the serum levels of IgA or IgM are falling, there may not be a need to stop therapy for retesting.⁶ “Is it a transitional point toward normalcy or toward a full-blown CVID illness, or is it a prolonged state that doesn’t progress further?” asks Dr. Harville. “That’s a difficult question to answer. In most kids, it changes, and they will either outgrow it or it will turn into a full-blown CVID.”

According to Dr. Harville, the patients who are more likely to be evolving to CVID are those whose IgG levels become lower as they are retested over a period of seven to 10 years. On the other hand, it is more difficult to tell if patients are evolving to CVID if their IgG, IgA and IgM levels continue to remain normal at the same time that their pneumococcal responses are poor. “For an adult, the normal IgG level is 800 to 1,200 mg/dL,” explains Dr. Harville. “If someone has an IgA or IgG that is borderline and the pneumococcal titers are poor, that is an ominous sign that there is going to be more of an evolution of things occurring. Even though someone is in the ‘normal’ range, if they are below the mean, I think they may be on the cusp of having problems.”

There is also the possibility that patients if not treated early or properly will suffer recurrent or chronic infections of the ears, sinuses, bronchi and lungs, which can, possibly, result in permanent damage such as hearing loss or chronic lung disease and scarring. But with proper treatment to prevent infections and the development of impaired lung function, hearing loss or other organ systems, the outlook for SAD is good.⁶

IVIG IS NOT A U.S. FOOD AND DRUG ADMINISTRATION-APPROVED THERAPY FOR SAD.

A Real Disease

SAD patients produce an adequate quantity of immunoglobulins, but those immunoglobulins are deficient in quality to fight infection. This, according to Dr. Harville, is where the controversy over this disease lies: “Some do not believe that if the serum immunoglobulin levels are normal that an immunodeficiency exists.” Yet, despite the controversy, it is a real disease. Without successful treatment with antibiotics or IG, these patients will continue to suffer with recurrent, serious infections that could lead to permanent disability. The good news is that there is greater awareness about SAD, and more patients are being properly diagnosed and treated. ■

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