



Specific Antibody Deficiency and/or Impaired Polysaccharide Responsiveness

Much is being learned from research and case studies about this very common primary immunodeficiency that is only rarely treated with immune globulin therapy.

By E. Richard Stiehm, MD

SAD IS a primary immunodeficiency (PI) characterized by recurrent infections, normal immunoglobulin levels and normal antibody responses to protein antigens, but impaired antibody responses to polysaccharide antigens.^{1,2} These antigens are typically those present in the PPSV23 Pneumovax vaccine.

SAD is probably the most common PI. However, because of its mild symptoms and cumbersome diagnostic procedure, the illness is often overlooked, and patients are not referred to an immunology center for detailed immunologic studies. They are also not entered into PI registries.

SAD was first described in 1983 by Ambrosino, et al., under the title impaired antibody response to polysaccharides.³ The patient was a 30-year-old man with a history of otitis, bronchitis and several bouts of pneumococcal pneumonia. His immunoglobulins were normal except for a slightly elevated IgM, and antibody responses to tetanus and diphtheria vaccines were normal, but he had no detectable antibody to H. influenzae,

meningococcal and pneumococcal polysaccharide vaccines.

The diagnosis of SAD should be reserved for patients with no other PI or secondary immunodeficiency (SI). Yet, its signature immune defect, impaired polysaccharide responsiveness (IPR), is common in many other PIs and SIs, which will be discussed later.

The cause of SAD is not established. It is maturational in infants and associated with waning immunity of the elderly. In a few cases, there may be a genetic defect of the BTK (Bruton's tyrosine kinase) gene associated with Bruton's agammaglobulinemia, subtle T-cell defects or a defect in generation of memory B cells.²

Incidence

A normal response to each serotype of the PPSV23 vaccine was defined as a protective titer of 1.3 ug/ml by an American Academy of Allergy, Asthma and Immunology (AAAAI) working group.¹ Immunized children should respond to at least 50 percent of the serotypes not present in the PCV13 vaccine, and



A SAD Vignette

Five-year-old Sadie has had several episodes of otitis (middle ear infection) with low-grade fever, runny nose and cough since she started day care at 3 years old. She has had multiple courses of antibiotics, but the respiratory complaints recur after a few weeks. Growth and development is normal, and a family history is unremarkable. Childhood vaccines are up to date, including the 13-valent pneumococcal conjugated vaccine (PCV13, Prevnar).

A physical exam disclosed a pale girl with circles under her eyes. She was in the 20th percentile for height and weight. There were moderately enlarged neck lymph nodes, dull and scarred tympanic membranes (ear drums), enlarged tonsils, posterior pharyngeal cobblestoning (lymphoid nodules) and an absent cough reflex. Her chest was clear, and the rest of the exam was unremarkable.

Hemoglobin was 10.5 gm/dl, and the white blood count was 5,400 cells/ul with a normal differential. The erythrocyte (red blood cell) sedimentation rate was slightly elevated at 18 mm/hr. A throat culture showed normal flora (bacteria). A Waters' view sinus X-ray showed opacification of the right maxillary sinus and mucosal thickening of the left maxillary sinus (a symptom of acute sinusitis). A lateral pharyngeal X-ray showed enlarged adenoids.

Immunoglobulin levels were 630 mg/dl for IgG, 85 mg/dl for IgA, 42 mg/dl for IgM and 55 IU/ml for IgE. Antibodies to tetanus, H. influenzae and nine of 23 pneumococcal serotypes were protective, all of which were in the protein-conjugated PCV13 vaccine. The 23 valent pneumococcal polysaccharide vaccine (PPSV23, Pneumovax) was given, and repeat antibody titers one month later showed protective titers (1.3 ug/ml or higher) to only three of the 10 serotypes present in the PPSV23 vaccine but absent in the PCV13 vaccine.

A diagnosis of sinusitis, chronic otitis and specific antibody deficiency (SAD) was made. She was given a three-week course of cefdinir, followed by four months of 5 mg/kg of azithromycin prophylaxis three times a week. Repeat sinus films and respiratory symptoms were improved significantly. Prophylaxis was stopped since it was summer, and she will be reevaluated before entering school.

adults should respond to at least 70 percent of the serotypes not present in the PCV13 vaccine. For simplicity's sake, the rise in titer or prevaccine titers is not used in the calculation. These arbitrary levels have been questioned, some using 1.0 ug/ml or 1.5 ug/ml as a protective titer,⁴ and at least one group using 50 percent of the titers as a normal response in adults.⁵

A diminished response to the PPSV23 vaccine may occur in up to 10 percent of the population that is not clinically ill.^{6,7} Vaccine responsiveness increases with age in children and young adults, and wanes after age 60. Accordingly, children younger than 24 months and adults older than 60 should get the PCV13 vaccine for protection against pneumococcal disease.

Among children older than 2 years with recurrent respiratory infections, SAD is exceedingly common. In five studies, the pooled frequency of SAD was 221 of 825 children or 27 percent,⁸⁻¹² compared to 3 percent to 10 percent of well age-matched controls with the same immune profile.

Among adults with chronic rhinosinusitis (CRS), two large studies showed 200 of 834 (19 percent) had SAD,^{5,13} which is in agreement with a meta-analysis of 13 studies in which 8 percent to 35 percent of adults had SAD.¹⁴ Among adults older than age 60, SAD may be even more frequent as surmised by their weakened responses to the PPSV23 vaccine¹⁵ and by one small study that showed SAD in 12 of 15 (70 percent) older adults with CRS.¹⁶

The high frequency of CRS, estimated to be present in 31 million persons in the U.S.,¹⁷ and the high frequency of SAD in these adults lends credence to the Immune Deficiency Foundation's estimate that PI may affect one in 1,200 people.¹⁸

Clinical Features

As in the highlighted vignette, children with SAD characteristically have recurrent episodes of runny nose, cough, sore throat, otitis and low-grade fever. Many have allergic rhinitis, asthma and eczema. Nasal obstruction leads to mouth breathing and nighttime snoring. Physical examination may disclose the

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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

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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.

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

*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.



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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 st	2 nd to 4 th	5 th	6 th 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.

-----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.

Table 1. Summary of PPSV23-Deficient Response Phenotypes in SAD

Phenotype*	PPV23 response, age >6 y	PPV23 response, age <6 y	Notes
Severe	≤2 protective titers (≥1.3 µg/mL)	≤2 protective titers (≥1.3 µg/mL)	Protective titers present are low
Moderate	<70% of serotypes are protective (≥1.3 µg/mL)	<50% of serotypes are protective (≥1.3 µg/mL)	Protective titers present to ≥3 serotypes
Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes	2-Fold increases assume a prevaccination titer of less than cutoff values in Summary Statement 26
Memory	Loss of response within 6 mo	Loss of response within 6 mo	Adequate initial response to ≥50% of serotypes in children <6 y of age and ≥70% in those >6 y of age

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allergic facies (pallor, circles under the eyes, open mouth), enlarged tonsils, postnasal drip, pharyngeal cobblestoning (lymphoid nodules) and a diminished gag reflex. Cervical lymphadenopathy may be present. Pectus excavatum (a congenital disorder that causes the chest to have a sunken appearance), rales (rattling noises), wheezing or a Harrison’s groove (a dip or crevice in the chest where the ribcage meets the diaphragm) suggest chronic asthma or other chronic lung disease.

Adults with SAD typically have CRS, as characterized by at least 12 weeks of symptoms, including purulent nasal discharge, nasal congestion, headache, anosmia (loss of smell) and fever, with objective findings of sinusitis by nasal endoscopy or a CAT scan.¹⁷ There is a high frequency of tobacco use, asthma and other chronic lung disease. Physical examination may reveal turbinate (inverted cone) swelling, nasal discharge, polyps, postnasal drip, wheezing, rales, increased anti-posterior diameter and digital clubbing, the latter suggesting chronic lung disease.

Laboratory Investigations

The presence of a chronic infection of the upper airway should be documented by cultures, rhinoscopy or sinus imaging. In children, a Waters view sinus X-ray and a lateral pharyngeal X-ray for adenoidal enlargement are convenient and rapid. Respiratory cultures may disclose *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis* or *Streptococcus pyogenes*. A complete blood count may disclose eosinophilia or leukocytosis (both of which are a higher than normal level of a certain type of white blood cells), or lymphopenia (a lower than normal level of white blood cells). An elevated erythrocyte sedimentation rate or C-reactive protein suggests chronic inflammation.

Immune system evaluation includes IgG, IgM, IgA, IgE and sometimes IgG subclass levels, all characteristically normal in SAD. Antibody tests to previously administered protein vaccines (tetanus, H. influenzae and PCV13 vaccines) are also normal. Other tests for immune deficiencies, including B and T cell subsets, lymphoproliferative studies to antigens and mitogens, rhodamine dye study for chronic granulomatous disease, complement activity and component assays, and mannose binding lectin, are used to identify other PIs.

The hallmark of SAD is the presence of impaired polysaccharide responsiveness. This requires the administration of the PPSV23 vaccine, which contains 10 serotypes not present in the PCV13 vaccine. After four to six weeks, a blood sample is taken and the antibody levels to 23 pneumococcal serotypes are obtained. These are available in many reference laboratories using ELISA (enzyme-linked immunosorbent assay) or multiplex bead assays. A protective level of pneumococcal antibody is 1.3 µg/ml.¹ The number of serotypes unique to the PPSV23 vaccine that are protective establishes a diagnosis. Normal children should develop a protective response to 50 percent of these serotypes, and normal adults should develop a protective response to 70 percent of them. (If a prevaccine antibody test was performed, the rise in titer to individual serotypes or the prevaccine titers are not used to estimate the response. Thus, a titer that increases from 0.4 to 1.0 µg/ml is considered nonprotective, a titer of 1.6 falling to 1.4 µg/ml is protective, and a titer that falls from 1.4 to 0.8 µg/ml is nonprotective).

The response to the PPSV23 pneumococcal vaccine is also used to determine the severity of SAD. An AAAAI working group has designated these as mild, moderate, severe and memory phenotypes as summarized in Table 1. The mild phenotype

includes patients who respond to some but less than 50 percent of the serotypes, the moderate phenotype responds to two to three serotypes, and the severe phenotype responds to none or one serotype. The memory phenotype includes patients who initially have a protective phenotype but revert to a nonprotective phenotype after six months. Many of these latter patients continue with recurrent infections. Repeating the PPSV23 vaccine immediately after a poor response is not useful or recommended since polysaccharide vaccines do not elicit a T-cell memory cell response.

Other polysaccharide vaccines are available for use in identifying SAD. These include the meningococcal (Menactra) and Typhoid Vi polysaccharide vaccines.¹⁹ The latter vaccine's advantage is that nearly all patients have no antibodies to it nor are these antibodies present in immune globulin (IG) preparations. Thus, it is of special value in identifying SAD in a patient while on IG replacement therapy.

Management

The first step in managing SAD is to treat the infectious illnesses that brought the patient to the doctor. This screening includes blood tests, cultures, imaging studies and antimicrobial therapy. Then, the immune evaluation outlined above is initiated, including a blood test for antibodies to protein antigens and 23 pneumococcal serotypes. Then, the PPSV23 vaccine is given, and its response is rechecked in four to six weeks.

At that time, a diagnosis of SAD is made, and the plan for continued therapy is established. If chronic infection persists, antibiotics must be continued or changed. Long-term prophylactic antibodies may be necessary. Other measures may include environmental control of allergies, inhaled steroids for asthma, surgical removal of tonsils and adenoids, and sinus washes.

SAD is probably the most common PI.

If the antibody test shows waning immunity to PCV13 serotypes, this vaccine may be repeated. As noted above, an immediate booster of the PPSV23 is not recommended or useful since polysaccharide vaccines do not provide T-cell memory responses.

Depending on the infectious severity, a prolonged course of

Table 2. Primary Immunodeficiencies with Impaired Polysaccharide Responsiveness

Severe antibody deficiencies

- Agammaglobulinemias
- Common variable immunodeficiencies
- Hyper-IgM syndromes
- Immunodeficiency with thymoma

Less-severe antibody deficiencies

- Selective IgA deficiency
- Selective IgM deficiency
- IgG subclass deficiencies
- Transient hypogammaglobulinemia of infancy

Severe combined immunodeficiencies (many genetic types)

Well-recognized combined immunodeficiencies

- DiGeorge syndrome
- Wiskott-Aldrich syndrome
- Ataxia-telangiectasia
- Mucocutaneous candidiasis
- Hyper-IgM syndromes
- Cartilage hair hypoplasia
- Bloom syndrome
- Other syndromic immunodeficiencies

antibiotics may be necessary. Other children with less severe infections may do well on prophylactic antibiotics given three times a week. Some patients may require tonsillectomy and adenoidectomy. Others may require inhaled steroids, bronchodilators, antihistamines and sinus washes. Repeat titers and imaging are performed after several months if the patient does not do well.

IG therapy is reserved for patients with severe and refractory infections and persistent nonprotective antibody levels.

IPR in Other Conditions

IPR is present at the extremes of life. In infants younger than 2 years of age, this defect led to the development of protein conjugated vaccines for *D. pneumoniae* and *H. influenzae*, both serious bacterial infections in infants. IPR may persist beyond age 2 as part of transient hypogammaglobulinemia of infancy.

IPR is also common in the elderly, rendering the recommended PPSV23 vaccines unreliably protective and, thus, the PCV13 vaccine is now also recommended.

IPR has been identified in many other conditions (Table 2 and Table 3). All PIs with global antibody defects, including

agammaglobulinemias, common variable immunodeficiency and severe combined immunodeficiencies, will have IPR. Less-severe antibody deficiencies (e.g., selective IgA deficiency, selective IgM deficiency, IgG subclass deficiencies and transient hypogammaglobulinemia of infancy) have a high incidence of chronic respiratory infections and IPR.²⁰ Several less-severe combined immunodeficiencies (e.g., Wiskott-Aldrich syndrome, ataxia-telangiectasia, DiGeorge syndrome and the hyper-IgM syndromes) often have IPR and frequent respiratory infections.

Many other SIs will have IPR and resultant susceptibility to respiratory infections despite normal or near normal IgG levels. IPR may be associated with several chronic illnesses, medications, trauma, malnutrition and surgery. If an immune workup is deemed necessary, assays for polysaccharide responsiveness should be included. Such information is of use in determining whether vaccines should be given, whether postexposure prophylaxis is needed, whether antibiotics should be used and whether IG therapy is indicated.

The take-home message is that if an immune deficiency is suspected, an IPR must always be considered.

Summary

SAD is a PI characterized by normal immunoglobulin levels and normal antibody responses to protein antigens, but impaired antibody responses to polysaccharide antigens in the absence of

Table 3. Secondary Immunodeficiencies at Risk for Impaired Polysaccharide Responsiveness

- Infants under 24 months
- Adults over age 60
- Major trauma or surgery
- Splenectomy and asplenia
- Severe burns
- Postorgan transplant with immunosuppression
- Uremia and renal dialysis
- Diabetes
- Cirrhosis
- Malnutrition
- Radiation
- Lymphoma and leukemia
- High-dose corticosteroids
- Immunosuppressive drugs
- Monoclonal antibodies (rituximab, etc.)
- Protein-losing illnesses (nephrosis, intestinal lymphangiectasia, etc.)

any other PIs or SIs. It is probably the most common PI, occurring in 15 percent of children with recurrent respiratory infections and 25 percent of adults with CRS. Diagnosis is established by a

Among children older
than 2 years with recurrent
respiratory infections, SAD is
exceedingly common.

deficient response to the PPSV23 vaccine. Management requires antibiotics, occasional sinus or adenoid surgery and, rarely, IG therapy. ■

E. RICHARD STIEHM, MD, is professor of pediatrics at the David Geffen School of Medicine at the University of California, Los Angeles.

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