

Specific Antibody Deficiencies



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KEYWORDS

- Specific antibody deficiency • Pneumococcal polysaccharide vaccine
- Recurrent sinopulmonary infections • Vaccine failure • Immunoglobulin replacement

KEY POINTS

- Specific antibody deficiency (SAD) is characterized by failure of response to polysaccharide antigens, with otherwise intact immunity.
- Immunologic challenge with the 23-valent pneumococcal polysaccharide vaccine is currently used as the gold standard for diagnosis.
- SAD encompasses multiple phenotypes, including mild, moderate, severe, and poor immunologic memory.
- Without appropriate diagnosis and treatment, permanent sequelae such as bronchiectasis may occur. Appropriate management allows most patients to achieve a normal life.
- Management options include additional vaccinations, antibiotics, and immunoglobulin replacement.

INTRODUCTION

Specific antibody deficiency (SAD), also known as selective polysaccharide antibody deficiency, is a common primary immunodeficiency disease (PIDD) of the B-cell compartment. Defined as an insufficient antibody response to polysaccharide antigens, evaluation of response to the 23-valent pneumococcal polysaccharide vaccine (PPV23) is the current diagnostic gold standard. Using a pure polysaccharide challenge allows a true assessment of the B-cell compartment, whereas challenge with a protein or protein conjugate vaccine elicits a maximal helper T-cell response. PPV23 has the advantage that a high number of serotypes are included, disallowing a diagnosis based on a single antigen response. It is essential to recognize that

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patients with SAD typically have completely intact response to protein antigens, including the protein conjugated vaccines.

Failure of polysaccharide response may be observed as a component of a more global PIDD, as well as in the setting of multiple secondary immunodeficient states (Box 1). Such disorders are referred to by the more global diagnosis and are not labeled as SAD. This article focuses on SAD in the strictest definition, as the failure of response to polysaccharide antigens in the setting of recurrent infections with normal immunoglobulin isotypes and normal serologic response to protein antigens in patients 2 years old and older.¹⁻³

Clinical manifestations of SAD predominantly include recurrent sinopulmonary infections that are more frequent, severe, or prolonged than infections experienced by individuals with intact immunity. SAD may resolve over time, especially when diagnosed in childhood. However, in some patients the deficiency is lifelong. Four phenotypes exist based on the response to PPV23: mild, moderate, severe, and memory.³

The management of SAD, including prevention and treatment of recurrent infections, can be classified into the following broad categories: additional immunization, antibiotic prophylaxis and treatment, and immunoglobulin therapy. With appropriate treatment, most patients have an excellent prognosis.

PATHOPHYSIOLOGY

There is no single immunologic mechanism for SAD. Some patients represent delayed physiologic maturation of the immune system, considering that human infants respond in robust fashion to protein antigens, whereas response to polysaccharides may be suboptimal. Hence, the phenotype of young children who are diagnosed with SAD and subsequently experience resolution over time could be explained by a delay in the normal maturation process. The underlying cause for this delay remains unknown.

Abnormally low or deficient specific antibody responses are found in association with many well-defined PIDDs, some of which are presented in Box 1.⁴ Although these PIDDs with weak polysaccharide response are not classified as SAD per se, they do highlight that a wide spectrum of inborn immunologic defects may lead to a common functional defect manifested by impaired polysaccharide antigen response and susceptibility to sinopulmonary infections.

SAD has been associated with several other subtle immunologic findings. For example, association of SAD with immunoglobulin (Ig) G subclass deficiencies,

Box 1 Primary immunodeficiencies and secondary immunodeficient states that may be associated with impaired vaccine response	
Primary	Acquired
Wiskott-Aldrich syndrome	Splenectomy
DiGeorge syndrome	Immunosuppression
Asplenia	Malnutrition
Hyper-immunoglobulin E (Job) syndrome	Protein-losing enteropathy
Common variable immune deficiency	Nephrotic syndrome
Dock8 deficiency	Chylothorax
NEMO deficiency	Human immunodeficiency virus infection
Class switch recombination defects	—
Selective immunoglobulin A deficiency	—
Immunoglobulin G subclass deficiency	—

particularly IgG2 deficiency, has been described.⁵ Typically, IgG2 subclass-deficient patients develop protective antibody titers to a restricted number of serotypes in the pneumococcal polysaccharide vaccine. These patients often have poor immunologic memory, with titers decreasing to preimmunization levels several months following vaccination.⁶ Although such associations may offer important clues to the pathophysiologic mechanisms of SAD, details remain elusive despite years of research.

Regarding susceptibility to infection among patients with SAD, pathogens are not restricted to *Streptococcus pneumoniae*. Other encapsulated bacterial pathogens, such as *Haemophilus influenzae* and *Moraxella catarrhalis*, are common. *Staphylococcus aureus* and respiratory viruses also cause significant infections in patients with SAD.⁷ This observation emphasizes that the presence of SAD represents a more general dysfunction of antibody-mediated immunity, rather than susceptibility to a specific pathogen.

EPIDEMIOLOGY

Although prevalence in the general population is not well established, up to 15% of children undergoing evaluation for recurrent infections are diagnosed with SAD.⁸ Among all PIDDs treated in the immunology clinic, SAD accounted for at least 23% of all diagnoses in a review of a referral center in the United States.⁹ A recent study from the United Kingdom reported diagnosis of SAD in 58% of children who underwent evaluation for chronic wet cough with duration of greater than 8 weeks.¹⁰

SAD may also be diagnosed in adolescents and adults. In a recent study, 12% of adults with refractory chronic rhinosinusitis met diagnostic criteria for SAD.¹¹

NATURAL HISTORY

Among children with SAD, symptoms and immunologic findings may improve with age. Roughly half of children show resolution of SAD within 3 years. Treatment is often required, but may be temporary (1–2 years).¹² Permanent sequelae or organ damage secondary to infections is rare among such children if treatment is instituted appropriately.

A new diagnosis of SAD outside of childhood could either represent a previously missed diagnosis or progression of a previously mild immunologic phenotype. Adolescent and adult patients require close attention, because they may have already developed bronchiectasis and SAD is less likely to resolve over time in this age group. A subset of adults and adolescents with SAD may experience progression to more severe forms of PIDD, including hypogammaglobulinemia and common variable immunodeficiency.⁷

SYMPTOMS

The signs and symptoms of SAD are similar to those of other antibody deficiency syndromes. Common manifestations include chronic and recurrent otitis media, sinusitis, bronchitis, and pneumonia. Infections are more frequent, severe, or prolonged than those experienced by normal individuals. A common pattern is partial or temporary improvement with antibiotic therapy, followed by a rapid return of infections on discontinuation of antibiotics. In the United States, less than 5% of patients with SAD experience invasive infections.¹² This relative absence of life-threatening infections is not surprising because antibiotics are prescribed commonly in the general population, early in the course of infection. Nonetheless, patients who have not been appropriately identified and treated may present with bronchiectasis or severe refractory sinusitis.^{11,13}

For a common childhood infection such as otitis media, characteristics frequently found in patients with SAD include:

- Early onset of infections, as early as 3 to 4 months of age
- Recurrence of infection after antibiotic treatment
- Recurrence after tympanostomy tube placement
- Need for replacement of tympanostomy tubes multiple times

It is common for patients with SAD to also present with symptoms resembling atopic diseases, including rhinitis and asthma. One study reported asthma in 58% and rhinitis in 55% of children with SAD.¹² Only some of these patients have a well-documented IgE-mediated allergic sensitization. It is important to consider that patients with allergic symptoms experience inflammation of the nasopharynx leading to impaired sinus cavity drainage and eustachian tube dysfunction, which can lead to sinopulmonary infections. Patients with SAD who fit this clinical description are among the most challenging to identify because sinopulmonary infections may be blamed solely on allergic symptoms of rhinitis and asthma. Astute clinicians may use several clues, listed in **Box 2**, to determine when an evaluation for antibody deficiency is appropriate among such patients.

DIAGNOSTIC EVALUATION

Initial Approach to the Patient

The initial evaluation of a patient with an abnormal pattern of sinopulmonary infections must include a detailed history and physical examination focused on the pattern of infections, documentation of any pathogens previously isolated, and consideration of any permanent sequelae. At a minimum, a complete blood cell count with differential, immunoglobulin isotypes (IgG, IgA, IgM, and IgE), and baseline pneumococcal serotype-specific IgG antibody titers should be obtained. Immunization with PPV23 during the first clinic visit is optional in patients who have a highly convincing clinical history, as long as baseline titers are ordered the same day. A local vaccine reaction (Arthus reaction) is possible in patients who already have high antipneumococcal antibodies. For this reason, many clinicians opt to administer PPV23 at the second clinic visit, after the baseline pneumococcal titer results are available. Following PPV23 administration, titers should be repeated by the same laboratory in 4 to 8 weeks.

PPV23 is typically not administered to patients who have high titers to most serotypes at baseline. This approach applies to patients who have high titers despite being

Box 2
Helpful hints: when to suspect an antibody defect among patients with presumed allergic rhinosinusitis and/or asthma

Frequent purulent nasal discharge
Failure to identify allergic triggers (negative allergy testing)
Little improvement with allergy treatment and allergen avoidance
Chest symptoms do not improve with inhaled bronchodilators
Frequent wet cough (as opposed to classic dry cough of asthma)
Absence of itchy, watery eyes
Infrequent sneezing and itching of the nose
Transient improvement with antibiotic treatment

pneumococcal conjugate vaccine (PCV) naive, as well as those who have received PCV and have protective titers to PCV and non-PCV serotypes. Such patients who have developed high titers in response to natural infection, but maintain an abnormal pattern of infections, should be considered for other forms of PID as well as other causes for recurrent infections such as mucociliary or anatomic defects.

Laboratory Considerations Regarding Antipneumococcal Antibody Titers

Although a variety of panels are available commercially with varying numbers of serotypes, most immunologists include at least 14 serotype-specific IgG antipneumococcal antibody titers. It is optimal for the panel to include at least 7 PPV23-exclusive serotypes, present only in the PPV23 and absent in the conjugated vaccine that was previously administered (**Table 1**). Completion of the 13-valent conjugate vaccine (PCV13) series is recommended in young children before challenge with PPV23. Therefore, measurement of PPV23-exclusive serotypes is necessary in evaluating the PPV23 response.^{14,15}

Serotypes	Vaccines		
	PPV23	PCV7	PCV13
1	X	—	X
2	X	—	—
3	X	—	X
4	X	X	X
5	X	—	X
6A	—	—	X
6B	X	X	X
7F	X	—	X
8	X	—	—
9N	X	—	—
9V	X	X	X
10A	X	—	—
11A	X	—	—
12F	X	—	—
14	X	X	X
15B	X	—	—
17F	X	—	—
18C	X	X	X
19A	X	—	X
19F	X	X	X
20	X	—	—
22F	X	—	—
23F	X	X	X
33F	X	—	—

Abbreviations: PCV7, heptavalent conjugate vaccine; PCV13, 13-valent conjugate vaccine.
 Courtesy of R.U. Sorensen, MD, New Orleans, LA.

For IgG serotype-specific antipneumococcal antibody assessment, the standard method is the third-generation World Health Organization enzyme-linked immunosorbent assay (ELISA), which incorporates double absorption of samples with capsular polysaccharide and serotype 22F. This technique increases specificity by removing nonspecific antibodies.^{16–18} Commercial laboratories have now adopted measurement of specific antibodies using Luminex. Results with this test vary from those obtained by ELISA. Clinical validation of the usefulness of Luminex is still in progress.^{18,19}

PPV23 has the advantage that a high number of serotypes are included, disallowing a diagnosis based on a single antigen response. Measurement of total antipneumococcal IgG in a single test that produces 1 numeric value without differentiating specific antibodies to individual serotypes is not useful. It is common for patients with SAD to develop an increased titer to a limited number of serotypes, whereas most serotypes remain nonprotective. Such a pattern cannot be elucidated by a test that does not distinguish between serotypes.

Although serotype-specific titers as low as 0.35 $\mu\text{g/mL}$ have been considered to be protective against invasive infections, a titer of 1.3 $\mu\text{g/mL}$ is generally considered protective against mucosal infections and is used as the threshold of response to PPV23.^{3,20,21}

Interpretation of the Pneumococcal Polysaccharide Response

By 2 years of age, most individuals have developed protective titers to at least some serotypes in response to natural infection. Hence, the absence of protective antibodies to all serotypes tested at baseline is unusual, even in nonimmunized patients. By current definitions, low antibody concentrations following natural infection, or following PCV administration, do not specifically define a SAD phenotype unless there is a subsequent inadequate response to PPV23.

When gauging a sufficient PPV23 response for an individual patient, one approach in the past has been to compare postimmunization serotype-specific antibody concentrations with preimmunization concentrations, considering normal to be a 4-fold increase in the concentration. Other sources accept a 2-fold increase. This approach is no longer favored, because it involves at least 2 major pitfalls. First, if the baseline titer is greater than 4 $\mu\text{g/mL}$, individuals with intact immunity may not produce a significant increase in titer on vaccine challenge²²; the higher the baseline titer to an individual serotype, the less likely a significant increase is in the setting of a normal immune response.^{2,3} The second downfall to this approach is that, if a baseline titer to an individual serotype is exceedingly low, even with an increase of several fold, the post-PPV23 titer may remain less than the protective range. Such low post-PPV23 titers indicate a failed response.

Most experts now agree that the most reliable and straightforward approach in gauging response to PPV23 is to consider the percentage of serotype-specific titers measured (titers to serotypes included in PPV23) that are within the protective range post-PPV23. Note that with this approach to interpretation the final enumeration of serotypes to which protective titers have developed may include a combination of titers that are achieved through natural infection, as well as those achieved following PPV23 administration. An acceptable percentage of protective serotypes is greater than or equal to 50% of serotypes for patients less than 6 years of age, and greater than or equal to 70% of serotypes of patients aged greater than or equal to 6 years. This approach assumes that an individual serotype is considered protective at a value of greater than or equal to 1.3 $\mu\text{g/mL}$. This straightforward recommendation adds a much-needed simplicity to the evaluation process. When assessing patients who have previously received PCV, the most consistent and straightforward approach is

to focus solely on the PPV23-exclusive serotypes, which were not included in the PCV that was previously administered.²³ Considering all of the aforementioned factors, the approach to the interpretation of response to PPV23 is summarized as follows:

- Patients who are PCV naive:
 - Among all PPV23 serotype titers measured, the percentage of these serotypes that are in the protective range post-PPV23 is considered the percentage response.
- Patients who have previously received PCV:
 - At least 7 PPV23-exclusive serotypes should be measured.
 - The evaluation may be based solely on the PPV23-exclusive serotypes.
 - Among all PPV23-exclusive serotypes measured, the percentage of these that are in the protective range post-PPV23 is considered the percentage response.

Diagnosis of Specific Antibody Deficiency Phenotypes

Four defined phenotypes of SAD are currently accepted based on the antibody response to individual PPV23 serotypes: mild, moderate, severe, and memory (Table 2). All phenotypes assume an abnormal pattern of infection.³ It is essential to recognize that these phenotypes refer exclusively to characteristics of the serologic diagnosis, and may or may not correlate with the clinical severity or degree of susceptibility to infections for an individual patient.

- Severe phenotype, defined as nearly absent response to pneumococcal polysaccharides, is the most straightforward to diagnose. These patients have protective titers to less than or equal to 2 serotypes following PPV23.^{3,6} The clinical susceptibility to infections is typically severe as well.
- Moderate phenotype is defined based on age at the time of PPV23 administration:
 - Age less than 6 years: less than 50% of serotypes protective
 - Age greater than or equal to 6 years: less than 70% of serotypes protective
- Mild phenotype is less well defined. However, many patients with significant infections are in this category. Considering that most normal individuals have a robust response to most PPV23 serotypes, mild SAD can be defined in the broadest sense as failure of response to multiple serotypes.

Table 2
Summary of SAD phenotypes based on PPV23 response

Phenotype	Age ≥6 y	Age <6 y	Notes
Severe	≤2 protective titers	≤2 protective titers	Protective titers present are low
Moderate	<70% of serotypes protective	<50% of serotypes protective	Protective titers present to ≥3 serotypes
Mild	Failure to generate protective titers to multiple serotypes	Failure to generate protective titers to multiple serotypes	—
Memory	Loss of response within 6 mo	Loss of response within 6 mo	Adequate initial response

Note that all phenotypes assume a history of infections.

Protective level refers to greater than or equal to 1.3 µg/mL.

Adapted from Orange J, Ballou M, Stiehm ER, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2012;130(3 Suppl):S14; with permission.

- Memory phenotype is defined by an adequate initial response (based on age) with subsequent loss of titers within 6 months.

MANAGEMENT

Management must always be tailored based on the clinical severity of infections. Overall, the management of patients who have failed to respond serologically to PPV23 can be grouped into the following broad categories: additional immunization, antibiotic prophylaxis and treatment, and immunoglobulin therapy.

Immunization

In patients with poor immunologic memory, once antipneumococcal titers wane, reimmunization with PPV23 may result in reestablishing protective antibody levels and increased clinical protection. There is a counterargument against repeated administration of polysaccharide vaccines based on limited, controversial reports that repeated immunization may produce hyporesponsiveness.²⁴ Most clinicians recommend waiting at least 1 year before administration of a second dose of PPV23, and only consider administration in patients who showed a transient initial response. Multiple, repeat PPV23 administration is not likely to be effective and is not recommended. For patients who showed complete absence of response to an initial dose, there is no indication to administer the vaccine again.

Patients who fail to respond to the initial challenge with PPV23 may respond to the conjugated vaccine. Between 80% and 90% of patients with SAD have a strong serologic response to PCV.² Therefore, the pneumococcal conjugate vaccine containing the largest number of serotypes currently available (PCV13) should be considered in patients who have failed PPV23 and may produce clinical benefit. However, even if the serologic PCV response is robust, such patients must be approached with caution because they have previously shown polysaccharide response failure and may not respond normally to natural infections with encapsulated organisms.

There is also evidence that PCV may prime the response to a subsequent dose of PPV23. Therefore, if patients have failed to respond to PPV23 at the initial evaluation and subsequently receive a PCV dose based on the aforementioned approach, but maintain an abnormal pattern of infection, reimmunization with PPV23 after 1 year may produce a better response by taking advantage of the priming effect of the conjugate vaccine.^{14,25} This approach may be more practical in patients who were truly naïve to pneumococcal vaccines at the time of their initial evaluation.

Antibiotics

Antibiotic prophylaxis should be considered, especially in young patients who are likely to outgrow SAD. When an oral antibiotic is considered for prophylaxis, trimethoprim-sulfamethoxazole or amoxicillin can be effective. Use of intranasal mupirocin ointment, applied daily for several months to a year, is a safe adjunct prophylactic measure.

Appropriate antibiotic treatment of any bacterial respiratory infection is important. Treatment with high doses of antibiotics for a period of at least 2 weeks is necessary. When antibiotic use alone improves the patient's quality of life and prevents infectious complications, no additional treatment is needed. Note that patients with SAD who are excessively and/or chronically infected may have been previously treated with many antibiotics. Such patients may warrant imaging for complicated chronic sinusitis or bronchiectasis, based on the clinical manifestations, and treatment of any identified chronic infection. For such patients, prophylaxis may be futile because of infection and colonization with multiple antibiotic-resistant organisms. Implementation of

immunoglobulin replacement, without a trial of antibiotic prophylaxis, may be appropriate in such clinically severe patients.

Immunoglobulin Replacement Therapy

Immunoglobulin replacement is indicated for patients with mild, moderate, or memory phenotypes who experience persistent infections despite appropriate management. Furthermore, patients with the severe phenotype may be placed directly on immunoglobulin replacement. Immunoglobulin replacement may prevent complications such as hearing loss, sinus damage, and bronchiectasis while significantly affecting quality of life and reducing the need for excessive medical visits and missed work/school. Patients with any form of SAD who have already developed permanent organ damage, such as bronchiectasis, should be placed directly on immunoglobulin replacement, because other treatment options are likely to fail.

The recommended immunoglobulin starting dose is at least 400 to 600 mg/kg/month. Immunoglobulin can be given intravenously once monthly. In addition, several subcutaneous immunoglobulin options are available with various techniques and intervals. Patients who experience repeated breakthrough infections or have bronchiectasis require higher doses and/or shorter intervals between doses.

When immunoglobulin replacement is initiated, patients should be advised that treatment will be discontinued after a period of 1 to 2 years and the immune response will be reevaluated 4 to 6 months after discontinuation of immunoglobulin replacement. The discontinuation of immunoglobulin should be scheduled during the spring or summer seasons, when the incidence of infections typically decreases. As an exception to this approach, adults and adolescents with the severe phenotype and patients with permanent organ damage should continue to receive immunoglobulin infusion indefinitely, without the need for such reevaluation.

Six months after the final immunoglobulin dose, a complete evaluation of antibody-mediated immunity should be repeated. If the pneumococcal titers are again low, an additional dose of PPV23 should be administered followed by measurement of post-PPV23 titers 4 weeks after immunization. Many children do not require further immunoglobulin replacement therapy, but some continue to have persistent infections and need to resume the infusions. These patients are likely to have additional immunologic abnormalities that are presently under evaluation.

Some patients experience a significant recurrence of infections soon after discontinuation of immunoglobulin therapy. Such patients have proved, based on clinical grounds alone, that their diagnosis of SAD has not resolved. Immunoglobulin therapy should be reinstituted for such patients based on a significant recurrence of infections, without waiting 6 months for the repeat laboratory evaluation. Patient management, immunoglobulin replacement therapy, and posttreatment evaluation can be complex and are best served by experts in the management of patients with PIDD.

PROGNOSIS

The immunologic phenotypes of SAD may be transient or permanent. Transient forms are more common in children 2 to 5 years of age. Even in permanent phenotypes, the prognosis of patients with SAD is good with proper management. Undiagnosed or improperly treated patients may develop permanent sequelae.

Patients who outgrow SAD should continue to be monitored, because it has not been determined whether such patients will face immunologic problems later in life. These patients should be seen in clinic at least annually and educated to contact the immunologist if an abnormal pattern of infection returns.

In particular, older patients with selective antibody deficiencies should be monitored closely, because they may eventually develop common variable immunodeficiency.

FUTURE CONSIDERATIONS

The current era of research regarding the specific antibody deficiencies is promising. Immunologic markers, including IgM memory and class-switched memory B cells, are providing additional depth to the understanding of SAD.²⁶ It is expected that such markers in combination with large-scale DNA studies, correlated with detailed clinical patterns, will soon produce clinically relevant information that will aid in determining the diagnosis, treatment, and prognosis for individual patients with SAD.

There is a need for clinical correlation of laboratory tests that can determine the functional capacity of antibodies. Opsonophagocytic assays are cumbersome and have not been widely validated clinically. Avidity testing to individual pneumococcal serotypes is now available commercially. This test could be helpful in unique situations, such as when a patient manifests a severe pattern of sinopulmonary infections but challenge with PPV23 produces high antipneumococcal antibody titers. Such titers could be of robust levels, but they might not be functioning optimally. Much remains to be learned regarding such tests and their clinical application.

Additional phenotypes, which are already observed clinically, will undoubtedly come into acceptance as they are described in immunologic and clinical detail. For example, we have observed several children who manifest abnormal immunologic memory but do not strictly fit within the current diagnostic criteria. These patients show a robust response to PPV23, maintain titers at 6 months, but go on to experience complete loss of titers for essentially all serotypes with recurrence of infections by 12 to 18 months following PPV23. A cohort of such patients with the most impressive pattern of infections has been treated at our center with immunoglobulin replacement, which has produced drastic improvement. This group of patients is not currently well described in the literature. Perhaps these patients represent a second immunologic memory phenotype, in which memory wanes much faster than in the average population, but not as rapidly as 6 months.

Another group that deserves closer attention is the cohort of patients who completely fail to mount a serologic response to the 4-dose PCV series in childhood, which is not currently considered pathologic. Some clinicians argue that failure to develop antipneumococcal antibodies to all serotypes contained in PCV should be considered pathologic in a child with recurrent infections, regardless of subsequent response to PPV23. This entity has been proposed as PCV-SAD. More studies are needed in this group of patients with impaired antibody response.²⁶

Little is known about the long-term outcome of patients who are diagnosed with SAD at a young age and subsequently improve over time. Long-term studies are needed in this group of patients to determine the risk for immunologic derangements later in life.

SUMMARY

SAD is a group of antibody defects characterized by failure of immunologic response to polysaccharide antigens in the setting of recurrent sinopulmonary infections with otherwise intact immunity. SAD represents a group of disorders with a wide spectrum of clinical and immunologic phenotypes. Although permanent organ damage such as bronchiectasis is possible, most patients do well with appropriate treatment. Caution is strongly advised regarding the approach to patients who may fit a mild phenotype, or have a borderline diagnosis, but manifest a significant pattern of infections.

Because immunologic severity does not correlate with clinical severity in many patients, treatment should be tailored based on the clinical manifestations of the patient.

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