Clinical Commentary Review

Specific Antibody Deficiencies in Clinical Practice

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Specific antibody deficiency (SAD) is defined as the inability to mount an antibody response to purified *Streptococcus pneumoniae* capsular polysaccharide antigens in the presence of normal immunoglobulin concentrations and normal antibody responses to protein antigens. In this review, we discuss the difficulties in using presently available testing methods to adequately define SAD. The fact that there are different forms of SADs to pneumococcal surface polysaccharides is detailed. The diagnostic and therapeutic implications of recognizing that, in addition to SAD, there are other forms of SAD in the response to *S. pneumoniae* polysaccharides are described in detail. The conclusion of this review is that assessment of immunity and therapeutic actions to deal with SADs need to be based on clinical evidence rather than solely on arbitrarily defined antibody responses. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:801-8)

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This review article offers another look at the testing and interpretation of the antibody responses to pneumococcal polysaccharide vaccines in the evaluation of patients for antibody deficiency. Specific antibody deficiency (SAD) has conventionally been described as the inability to mount an antibody response to purified *Streptococcus pneumoniae* capsular polysaccharide antigens in the presence of normal immunoglobulin concentrations and normal antibody responses to protein antigens.[1-3] This is a narrow definition that excludes antibody abnormalities that can involve unresponsiveness to antigens other than purified polysaccharides. While keeping the conventional definition of SAD, here we offer a broader view of deficiencies that may affect other antibodies and may require a different management.

Antibody deficiency is the most common form of primary and secondary immunodeficiencies.[4] Broadly defined, antibody deficiencies are present when an expected antibody fails to develop at an age or in a situation in which it would be expected to be present, for example, after immunization or an infection.

Antibody deficiencies may narrowly predispose to specific, single pathogen infections or they may signal a broader deficiency of antibody-mediated immunity, predisposing to infections with multiple pathogens and frequently to noninfectious clinical phenotypes associated with abnormalities in immune regulation.

SADs vary according to the type of antigen inducing the response, that is, to proteins, purified polysaccharides, or a combination of polysaccharides conjugated with proteins. Each of these broad groups of antigens defines general immunologic pathways of antibody production. Response to a specific antigen may also be due to an abnormality in a specific pathogen-associated molecular pathway. This explains why the ability to produce antibodies to one protein or polysaccharide antigen does not mean that a given individual will respond to all antigens of this type in the same way. SADs therefore are extremely variable and may affect different specific antibodies, even if total immunoglobulin concentrations and all other component of immunity are normal.

Assessment of antibodies against *S. pneumoniae* capsular polysaccharides offers many benefits if used as part of an immunological evaluation. These advantages include the availability and regular use of polyvalent vaccines that provide protection against common pneumococcal serotypes, and several kinds of tests that allow the measurement of antipolysaccharide antibodies.

EVALUATION OF ANTIBODY-MEDIATED IMMUNITY TO *S. PNEUMONIAE*

The evaluation of antipneumococcal polysaccharide antibodies is important in several ways: the evaluation of antibody-mediated immunity; assessment of specific immunity elicited by pneumococcal polysaccharide vaccines; and the measurement of antibodies in therapeutic IgG preparations.[5]

Several different methods have been used for these purposes. The most important antibodies that are measured by these assays are IgG antibodies. IgM and IgA antibodies can also be measured, but because they do not confer long-lasting systemic immunity, they are not commonly assessed.

The specific pneumococcal antigen against which antibodies are measured is an important variable. The antigens used most commonly are individual serotype-specific capsular

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Abbreviations used
ELISA- Enzyme-linked immunosorbent assay
OPA- Opsonophagocytosis
PCV- Pneumococcal conjugate vaccine
PPV-23- Pneumococcal polysaccharide vaccine
SAD- Specific antibody deficiency
WHO- World Health Organization

polysaccharides of pneumococci. The availability of purified serotype-specific polysaccharides and of multivalent vaccines presently containing between 10 and 23 serotype-specific polysaccharides allows the measurement of antibodies against different serotypes. The concentration of specific antibodies against different serotype polysaccharides can vary significantly from one individual to another.[6] An ideal pattern of response is a protective concentration of antibodies to all serotypes measured. In patients, high levels of antibodies to all or most serotype-specific polysaccharides are considered evidence of normal antibody-mediated immunity, especially if in response to a purified polysaccharide vaccine (unconjugated to proteins).

Attempts to identify a response to one or several selected serotypes as representative of the response to all or most serotypes included in the 23-valent polysaccharide vaccine have failed (R. U. Sorensen, unpublished data).

SEROTYPE-SPECIFIC ANTIBODY TESTS

Two main methods are used to measure IgG antibodies against individual polysaccharide serotypes: enzyme-linked immunosorbent assay (ELISA) and multiplex assays.

A standardized and reproducible method is the World Health Organization ELISA test (WHO ELISA).[7] This method defines a specific way to perform the ELISA test. It was developed under the auspices of the WHO to evaluate the response to newly developed conjugate polysaccharide vaccines.[8,9] Initially, it measured IgG antibodies against 7 serotypes and now measures up to 23 serotypes included in purified or conjugated pneumococcal vaccines (Table I). Before testing, sera must be absorbed with pneumococcal C-polysaccharide antigen that induces non-protective antibodies and with serotype 22 polysaccharide, to remove cross-reactive antibodies.[3,10] The WHO ELISA results were initially calibrated based on the Food and Drug Administration 89SF standard now replaced by 007sp and by laboratory standards prepared using 89SF. It is available to clinicians in few laboratories today.

Antibodies measured by ELISA are expressed as μg/mL. Serotype-specific titers as low as 0.35 μg/mL developed after pneumococcal conjugate vaccine (PCV) immunization are protective against invasive infections with the corresponding *S. pneumoniae* in infants and young children.[11-15] In the evaluation of immunity, titer of 1.3 μg/mL is generally considered protective against mucosal and systemic infections and is commonly used as the threshold of response.[6,7,16] Antibodies of 1.3 μg/mL or above are also considered evidence for the adequate production of antibodies against a pneumococcal polysaccharide if triggered by natural infection or vaccination.

An easier method to measure all 23 serotypes included in the polysaccharide vaccine is also available. It is based on a multiplex fluorescent bead assay Luminex. Luminex technologies allow simultaneous quantitation of multiple serotype-specific antibodies. It is used by most reference laboratories in the USA. Although the Luminex assay is an attractive alternative to ELISA, its correlation with ELISA test results is not perfect. Based on reported experiences, it is apparent that this assay does not allow reliable evaluation of antibody responses to polysaccharide antigens for the assessment of humoral immune competence (see Table II).[17-21]

Different laboratories using Luminex technology operating in different regions of the world have established their own ranges of serotype-specific antibody concentrations. The use of serotype-specific threshold values could be applicable for some defined, uniform populations.[22] However, for values obtained by different commercial and private laboratories, this kind of definition of antibody responses is unrealistic, as it is influenced by prevalent infections and pneumococcal immunization practices.[23] Therefore, it is important to always use the same test and source when evaluating a patient repeatedly.

TABLE I. *Streptococcus pneumoniae* serotypes in pneumococcal polysaccharide vaccines

Serotypes	23-PPV	7-PCV	13-PCV	10-PCV
1	X		X	X
2	**X**			
3	X		X	
4	X	X	X	X
5	X		X	X
6A			X	
6B	X	X	X	X
7F	X		X	X
8	**X**			
9N	**X**			
9V	X	X	X	X
10A	**X**			
11A	**X**			
12F	**X**			
14	X	X	X	X
15B	**X**			
17F	**X**			
18C	X	X	X	X
19A	X		X	
19F	X	X	X	X
20	**X**			
22F	**X**			
23F	X	X	X	X
33F	**X**			

Currently available pneumococcal vaccines are the purified polysaccharide vaccine (PPV-23) and in 3 conjugate vaccines (PCV): Prevnar 7, Prevnar 13, and Sinflorix with 10 serotypes. To evaluate the TI response to purified polysaccharides in individuals who received 1 or more conjugate vaccines, only the response to serotypes underlined and marked in bold under PPV-23 can be considered. Thus, specific antibody deficiency may exist in patients who had an appropriate response to conjugate polysaccharides.

GLOBAL TESTS

Although most tests of antipneumococcal IgG antibodies measure specific antiserotype antibodies individually, in many places the global ELISA test measuring antibodies against all serotypes present in the 23-valent vaccine simultaneously is

TABLE II. Key features of tests used to measure anti–*Streptococcus pneumonia* polysaccharide antibodies

Test features	WHO ELISA	Luminex	Global test	OPA
Performance	Cumbersome	Easier and faster	Easy	Under improvement
Availability	Few mostly research laboratories	Widely used in commercial laboratories	Widely, worldwide	Limited to specialized laboratories
Serum sample	Larger	Smaller	Small	Variable
Type of test	Weight/volume	Weight/volume	Weight/volume	Functional killing
No. of serotypes	Limited, variable 12-16	Multiple, usually 23 in PPV-23	23 serotypes used as one antigen	Increasing in special laboratories
Laboratory to laboratory reproducibility	High worldwide	Low	Questionable	Under evaluation
Cost*	High	Relatively low	Low	Unknown
Main uses	Vaccine and clinical evaluation	Clinical evaluation of immunity	Clinical evaluation of immunity	Vaccine and human IgG preparations
Cutoff values	0.35 and 1.30 μg/mL			Under evaluation

ELISA, Enzyme-linked immunosorbent assay; *OPA*, opsonophagocytosis; *PPV*, pneumococcal polysaccharide vaccine; *WHO*, World Health Organization.
WHO ELISA and Luminex are pneumococcal serotype-specific antibody assays (PSSA) with results expressed as weight/volume. OPA is a test used to evaluate vaccine and human gamma globulin preparation effectiveness. It still has to find its way into clinical practice.
*Cost refers to reagent and performance cost, not commercial price.

preferred, because of its simplicity and low cost. The assay is performed using the 23-valent vaccine as antigen or a commercially available enzyme immunoassay kit.[24] Results in the normal range for this test can be due to antibodies to most or all included serotypes or by high antibodies to only one. We do not recommend results of global testing to be used to diagnose and make therapeutic decisions regarding SADs.

METHODS TO ASSESS FUNCTIONAL IMMUNITY: OPSONOPHAGOCYTOSIS

Opsonophagocytosis (OPA) measures the function of IgM, IgG, and IgA antibodies against polysaccharide and protein surface antigens. There is no strict relationship between the weight by volume antibody concentration results by ELISA and OPA. When the 2 tests are compared in sera from adult donors, their results correlate closely. However, when using sera from elderly donors, ELISA concentrations are relatively higher than the OPA results, suggesting a decrease in the opsonizing capability in the elderly population.[25] Booster immunization of this age group partially corrects this difference. In clinical practice, there are patients who have normal ELISA titers but who improve clinically when given therapeutic IgG, suggesting that the lower function observed in the elderly may also be present in other individuals at an earlier age (R. U. Sorensen, Unpublished observations).

The OPA assay has undergone significant developments that have improved its availability.[26-29] However, it tests whole patient sera that include the measurement of IgM and IgA antibodies in addition to IgG antibodies against surface antigens. These antigens include both polysaccharide and protein capsular antigens. Patients are likely to have circulating antibodies against both types of antigens. Therefore, this test is unlikely to offer specific information about a patient's ability to develop IgG antipneumococcal capsular polysaccharides.

A summary of the key features of the tests discussed above is offered in Table III.

SPECIFIC ANTIBODY DEFICIENCY PHENOTYPES

SAD was first reported in a small group of patients in the early 1980s.[30,31] At that time, only the purified polysaccharide, 23-valent vaccine (PPV-23), was available for immunization and subsequent evaluation of immunity. Therefore, the original definition of SAD referred only to the antibody response to purified, unconjugated polysaccharides present in patients with normal immunoglobulin and IgG subclass concentrations.[32-35]

The widespread use of pneumococcal immunization to assess antibody responses revealed that specific unresponsiveness to polysaccharide antigens is not unusual (R. U. Sorensen,

TABLE III. The comparison of WHO ELISA and Luminex in laboratories A and B test results

S. pneumo vaccines	*S. pneumo* serotypes	Luminex A	Luminex B	WHO ELISA
PCV-7, -13	**4**	**0.5**	2.9	**0.68**
	6B	1.3	2	**0.53**
	9V	1.8	2.5	**0.44**
	14	**0.9**	11.5	6
	18C	**0.5**	4	**0.68**
	19F	2.8	4.6	1.76
	23F	10.7	18.2	**0.45**
PCV-13	**1**	**0.5**	15.6	1.76
	3	1.3	4.3	1.79
	7F	2.3	4.7	1.88
	19A	3	6.4	–
PPV-23 only	**9V**	1.8	2.5	**0.44**
	11A	**0.3**	2.5	**0.82**
	15B	1.5	26.8	3.19
	33F	3	2.3	2.82

ELISA, Enzyme-linked immunosorbent assay; *PCV*, pneumococcal conjugate vaccines; *PPV*, pneumococcal polysaccharide vaccine; *WHO*, World Health Organization.
Numbers in bold font are results below 1.3 μg/mL. Only 4 serotypes are available to evaluate the response to purified polysaccharides. ELISA results indicate that the patient failed to develop antibodies ≥1.3 μg/mL to 2 of 4 serotypes present only in PPV-23. However, this patient failed to respond to 5 of 13 serotypes present in PCV-13 vaccines given 3 times before. See text for further discussion. Results obtained with Luminex at lab A show similar proportion of normal and low responses, but to different serotypes. Laboratory B reports all values above 1.3 μg/mL, suggesting a completely normal response to the PPV-23 polysaccharide vaccine.

TABLE IV. Impaired responses to pneumococcal polysaccharide vaccination[16]

Phenotype	PPV-23 response, 6 y and older	PPV-23 response, younger than 5 y
Severe	≤2 protective titers (≥1.3 mcg/mL)	≤2 protective titers (≥1.3 mcg/mL)
Moderate	<70% of serotypes are protective (≥1.3 mcg/mL)	<50% of serotypes are protective (≥1.3 mcg/mL)
Memory	Loss of response within 6-12 mo	Loss of response within 6-12 mo

If antibodies in previously unimmunized individuals or in subjects who previously received conjugate vaccine(s) are below 1.3 mg/mL, response to the polysaccharide vaccine given subsequently can be evaluated based on the results of all tested serotypes. In patients who already have protective antibodies in response to conjugate vaccines, the response to 23-valent pneumococcal polysaccharide vaccine (PPV23) can only be evaluated based on antibodies to serotypes that are not in the conjugate vaccine. Responses to conjugate vaccines do not rule out unresponsiveness to pure polysaccharides.

Unpublished observations).[4,7-10] SAD was found in approximately 5% to 10% of children referred for evaluation of recurrent infections.[36,37] When routinely sought, this syndrome is the most frequently identified immunodeficiency in clinics that evaluate patients with recurrent and/or severe infections (approximately 20% in 1 study).[4]

Patients with SAD have normal antibodies to protein antigens. This pathologic syndrome thus resembles the developmental status of human newborns and infants who readily produce antibodies against vaccine proteins but fail to respond to most vaccine polysaccharides until approximately 2 years of age. Therefore, this syndrome can be diagnosed only in patients older than 2 years of age.

In most instances, SAD is defined based on the results obtained by the WHO ELISA or, most frequently now, by the Luminex assay. When vaccines are used to evaluate specific antibodies, interpretation of results is based on a combination of the following: (1) increase in specific antibody concentration over preimmunization levels, (2) the final concentration of antibodies after immunization, and (3) the percentage of serotypes to which the patient developed the antibody concentration considered protective.[6,13,14,38]

There are shortcomings with each of these criteria. The requirement for a minimum 2- and 4-fold increase does not consider that a high preimmunization antibody concentration may not or only minimally be increased with immunization. The desired concentration to prove effective antibody production is also subject to variable interpretations. If the value is set 1.0 instead of 1.3 μg/mL, or even 0.35 μg/mL,[5,39] the number of responses considered normal can differ significantly, without proof that any of these differences is clinically significant. Although in general children with recurrent infections have lower antibody concentrations after vaccination than children without infections,[8] normal children and adults may have antibody responses that would be diagnosed as mild or moderate forms of SAD.[10] The concentration of specific antibodies in different populations and different ages has been noted to differ significantly.[35] Finally, the relevance of the percentages of serotypes inducing a given antibody concentration is also subject to interpretation. Antibody concentrations to different serotypes tested simultaneously can vary significantly.

Thus, different combinations of high, medium, and low antibody concentrations can be seen in the same patient sample. The serotypes that may elicit these different antibody concentrations vary from patient to patient. It is therefore not surprising that attempts to identify a response to one or several selected serotypes as representative of the response to all or most serotypes included in the 23-valent polysaccharide vaccine have failed. The possibility of using serotype-specific threshold values could be applicable for some defined, uniform populations.[22] However, in a diverse clinical practice, this kind of definition of antibody responses is unrealistic.

Using the arbitrarily defined cutoff level of 1.3 μg/mL, a working group of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma, and Immunology proposed a widely accepted and used classification of the types and severity of SAD.[16,38] A slight adaptation of this classification that is still in generalized use is offered in Table IV.

Today many patients have received combinations of PPV-23 and conjugate vaccines, PCV-7, PCV-10, and PCV-13, and a classification should consider if the unresponsiveness is to purified, to conjugated, or to both types of polysaccharides (Table I):

A. Deficient response to purified polysaccharides, SAD (PPV SAD). Accepted antibody deficiency syndrome in patients above 2 years old.[40,41]
B. Deficient response to conjugate polysaccharides (PCV SAD). Frequently diagnosed in patients who have had all required conjugate vaccine doses.
C. Deficient response to PPV and PCV.
D. Natural infection nonresponders. Adolescents and adults without any protective antibody titers. It is not a deficiency unless unresponsiveness to immunization is proven.

These patterns of anti−*S. pneumoniae* polysaccharide antibody responses may be the only detectable immune abnormality without being part of a primary or secondary immunoglobulin or combined immunodeficiency.

For each of the 2 types of polysaccharide antigens, purified and conjugated, the antibody abnormality may be:

- Absent response to any serotype, concentration ≤0.35 μg/dL.
- Poor response to 50% to 80% of serotypes; ≥0.35, ≤1.3 μg/dL.
- Incomplete antibody repertoire. Protective titers to less than 50% to 80% of serotypes (maybe only to 1 serotype).
- Poor memory (antibody persistence) after initial adequate response to immunization.
- Deficient antibody function (OPA). Serological response may appear normal, but antibodies are not protective.

Eventually, it will be important to adapt definitions that include all forms of SADs that are relevant to define their management.

This list of alternatives refers to anti−*S. pneumoniae* capsular polysaccharides only. In reality, it is likely that there are clinically relevant SADs to many bacterial, viral, and fungal antigens. Such deficiencies may be concomitant with antipneumococcal antibody deficiencies or present without pneumococcal antibodies being affected. Patients with SAD and PCV SAD are rarely susceptible to *S. pneumoniae* infections only.

PATHOGENESIS

Given the multiplicity of immunological phenotypes and conditions in which a SAD can be observed, it is unlikely that there is a single pathogenic mechanism for selective anti-polysaccharide antibody deficiencies. Antibodies developed against purified or conjugate polysaccharides are known to develop through different cellular pathways that are likely to be affected by different mechanisms.[42,43]

Selective antibody deficiencies are also common in patients with known immunodeficiency syndromes that may have normal IgG concentrations, for example, patients with ataxia-telangiectasia, asplenia, hyper-IgE syndrome, or selective IgA deficiency (without IgG subclass deficiency). Frequently, however, unresponsiveness to pneumococcal polysaccharides is found in patients without any associated immunodeficiency.[8,44-50]

CD21^{low} B cells and IgM and class-switched memory B cells can be low in patients with SAD, but they are also low in patients with recurrent infections without SAD. Memory B cells can also be low in patients with unresponsiveness to conjugate polysaccharides. The prognostic implications of these differences in patients with SAD have not been determined.[50,51]

Congenital molecular abnormalities may also be the cause of SADs.[52] Unique associations between molecular abnormalities and deficient specific antibody responses are increasingly identified as evaluation of anti–*S. pneumoniae* antibodies that have become part of the evaluation of patients with different forms of immunodeficiencies.[53]

EVALUATION INDICATIONS

There are many indications for adding an evaluation of specific anti–*S. pneumoniae* polysaccharide antibodies to the evaluation of antibody-mediated immunity (Table V). It should be performed to assess antibody-mediated immunity in patients with severe or recurrent infections suggestive of an antibody deficiency. In many other conditions, the assessment of specific antibodies helps to define the severity of a concomitant cellular or antibody deficiency.[50] Knowing the status of specific antibodies against *S. pneumoniae* polysaccharides helps to decide on the need for additional immunization, intensified antibiotic treatment, or IgG replacement therapy. A correct assessment of a patient's specific antibody-mediated immunity requires consideration of the patient's age and *S. pneumoniae* immunization status before evaluation.

When an IgG subclass deficiency is identified and confirmed by a second testing,[54] a concomitant specific antibody or antibodies may help to define the severity, especially when the subclass deficiency is not very pronounced.[55]

The relationship of IgA and specific antibodies is interesting because lower than normal IgA concentrations that are not low enough to be accepted as a specific IgA deficiency differentiate patients with SAD with recurrent infections from those who have SAD but no clinical manifestations of recurrent infections.[56]

Mannose binding lectin deficiency has been identified as associated with more severe clinical manifestations of SAD.[57]

TABLE V. Indications for evaluation to specific antibody-mediated immunity

A. Infections: Patients with infections suggestive of a predominant antibody or a combined immunodeficiency in the absence of any known pathology. IgE-mediated respiratory allergies predisposing to respiratory infections need to be ruled out.[59]
B. Immunoglobulin abnormalities
1. Hypogammaglobulinemia
2. IgG subclass deficiencies
3. IgA deficiency
4. Common variable immunodeficiency
5. Transient hypogammaglobulinemia of infancy
6. Note: not necessary in agammaglobulinemias and hyper-IgM syndromes
C. Combined immunodeficiencies, without and with other syndromes
1. Di George syndrome
2. Wiskott-Aldrich
3. Hyper-IgE syndromes
4. Ataxia telangiectasia
5. Asplenia
D. Complement deficiencies
1. Mannose binding deficiency
E. Syndromes with infections suggestive of an antibody deficiency
1. Down syndrome
2. Cystic fibrosis
3. Muscular dystrophy
4. Many neurological diseases
5. Multiple genetic syndromes
F. Complications of upper and lower respiratory infections (even if infection history is not clear)
1. Recurrent otitis media
2. Recurrent sinus infection or surgeries
3. Bronchiectasis
G. Secondary immunodeficiencies
1. HIV
2. Hematologic malignancies
3. Protein loss
4. Increased metabolic catabolism
5. Malnutrition
6. Organ transplantation
7. Therapeutic immunosuppression (multiple autoimmune and inflammatory conditions)

When patients without known immunodeficiencies develop recurrent severe infections, an additional immune problem needs to be considered and ruled out by investigation. Cystic fibrosis figures prominently among diseases predisposing to SAD.[9]

The evaluation of patients with respiratory symptoms and bronchiectasis of unknown origin should include the assessment of specific antipneumococcal polysaccharide antibodies, because in some of these patients, the detection of an SAD offers further therapeutic options.[56] There is increasing awareness of secondary immunodeficiencies, many of which include specific antibody deficiencies.[67,68] Some of these conditions, such as HIV and protein calorie malnutrition, may have elevated total IgG concentrations and an SAD.

Some diseases have a specific susceptibility to *S. pneumoniae* infections. For these patients, pneumococcal immunization is recommended. However, evaluation of antipneumococcal antibodies is not necessary unless severe or recurrent infections occur. Diseases considered high risk for pneumococcal infections include: (1) sickle cell disease, (2) asplenia, (3) asthma, (4) diabetes mellitus, (5) cochlear implant, (6) cerebrospinal fluid (CSF) leaks, (7) nephrotic syndrome, (8) heart disease, and (9) community-based pneumonia.[58]

MANAGEMENT OF SPECIFIC ANTIBODY ABNORMALITIES

Treatment options for patients with an SAD include the following:

1. Aggressive management of other conditions predisposing to recurrent sinopulmonary infections (eg, asthma, allergic rhinitis, chronic rhinosinusitis).
2. Increased vigilance and appropriate antibiotic therapy for infections or prophylactic antibiotics.
3. Immunization with *S. pneumoniae* vaccines.
4. Intravenous or subcutaneous immunoglobulin replacement.

The mainstay of treatment of patients with SADs is adequate antibiotic treatment of acute infections and, in some situations, the use of preventive antibiotics. Because low immunity to *S. pneumonia* polysaccharides frequently is a marker for impaired antibody-mediated immunity to a variety of bacterial and viral pathogens, the management of SADs requires an adequate identification of infections and its complications. Nasopharyngeal cultures may reveal the presence of pathogens with antibiotic resistance, suggesting the importance of treating conditions that favor colonization. Inflammation of mucosal surfaces favors bacterial colonization and should be addressed when present. Topical nasal treatment with mupirocin is often an effective complementary treatment to systemic antibiotic use when it becomes necessary to treat recurrent or severe infections.

Treatment of sinopulmonary bacterial infections usually requires antibiotics, because these infections rarely clear spontaneously in patients with antibody defects. When appropriate, cultures should be performed, selective use should be made of imaging (being mindful of cumulative radiation exposure), and complete blood counts, measurement of C-reactive protein levels, and evaluation of the erythrocyte sedimentation rate should also be performed. This should allow the administration of antibiotics only when there are clinical or laboratory signs of active infection and to ensure that the infection is fully resolved before discontinuation of treatment. Prolonged courses of antibiotic treatment (eg, 1-3 months for chronic sinusitis) are sometimes needed to clear infections completely in these patients.

For patients who continue to have sinopulmonary infections despite the measures outlined above, prophylactic antibiotics should be considered. Prophylactic antibiotics are particularly useful in younger patients, who are more likely to outgrow their selective antibody deficiency.[59] In these situations, prophylaxis may be required for only a limited time, such as during the winter months.

Immunization with *S. pneumonia* vaccines, either to update incomplete immunization schedules or to provide additional immunization to overcome some forms of poor response to pneumococcal capsular polysaccharides, is a very effective form of management. The immunization used depends on a detailed record of pneumococcal vaccines received and on the type of SAD that has been identified.

Unimmunized children or adult patients who have not developed protective antibodies in response to natural infection should be immunized with PCV followed by PPV. In situations where PCV is not available or affordable, PPV alone is frequently very effective. Although the PPV-23 vaccine is recommended only after the second year of life, Tang et al[60] observed strong responses in unimmunized 12-month-old patients.

The following additional immunizations of patients are recommended in patients with an identified abnormal antibody response to pneumococcal polysaccharides who have been previously immunized:

(1) *SAD (PPV nonresponders).* As expected from the fact that conjugated vaccines can induce an antibody response in young children below 1 or 2 years of age who do not respond to the PPV, conjugate vaccines, PCV-7 and PCV-13, produce a normal response in the majority of patients with SAD.[34,61] Immunization with PCV should be a first step in the treatment of SAD. Administering repeated doses of PPV-23 to PPV nonresponders (severe forms of SAD) is ineffective.[10]

(2) *PCV nonresponders.* Many children who failed to respond to 3 or 4 doses of PCV respond clinically and serologically to 1 dose of PPV-23. Estrada et al[62] observed that the PPV-23 vaccine serologically and clinically improved children who had failed to develop strong antibody responses and had recurrent infections despite a full complement of PCV vaccines. Notably, it did not matter if the infections were caused by pneumococci, other bacterial pathogens, or respiratory viruses. A general stimulating effect of immunity was also reported by Leiva et al.[63] The authors' personal observations confirmed strong antibody responses to the PPV-23 in a high percentage of patients between 1 and 2 years of age. Although not recommending this course of action, considering the significant cost saving of 1 dose of PPV-23, in economically strapped situations, an earlier use of PPV-23 may be admissible on cost benefit grounds.

The recommended response assessment of immunization in patients can be summarized as follows: measure antibodies 4 to 6 weeks after last immunization and monitor infections, antibiotic treatment, and quality of life regardless of antibody concentrations. If there is no serological and clinical response, a more detailed investigation of the patient's immunity is indicated.

It is now recommended that, in addition to PCV, children at high risk for severe pneumococcal infection should receive PPV-23 starting at 24 months of age. This immunization should be given at least 8 weeks after the last PCV. A second dose of PPV-23 is recommended 5 years after the first dose. In patients older than 65 years, 1 dose of PCV-13 should be followed by PPV-23 6-12 months later. If PPV-23 was given first, PCV-13 is recommended to be given at least 12 months later.[64] The possibility that the sequential use of PPV-23 and PCV could cause hyporesponsiveness has been postulated, but this issue has not been resolved conclusively.[11]

IgG replacement for a period of time in young children and probably for life in adolescents and adults is an option for patients with proven recurrent infections that persist after adequate treatment and additional immunization.[38,65] Based on the clinical severity of infections, a requirement for IgG replacement therapy may arise in patients with different levels of unresponsiveness.

The recommended IgG dose of 400 mg/kg is given intravenously every 3 to 4 weeks, or the equivalent IgG dose is given subcutaneously on a weekly basis. Occasionally, patients require either higher doses (500-600 mg/kg every 4 weeks) or shorter intervals between infusions to prevent infections in the period before the next IgG dose.

In patients with SAD, the decision to adjust the IgG dose should be based on clinical response to treatment, rather than through IgG levels. By definition, patients with SAD have normal IgG concentrations already at the beginning of therapy.

The use of immune globulin replacement therapy in patients with SAD has not been evaluated in randomized, placebo-controlled trials, although its efficacy in hypogammaglobulinemia is well established. In case reports and retrospective series of adult and pediatric patients with SAD, significant decreases in the number of infections were consistently reported.[46,66,67] Of note is that in patients without a clear immunoglobulin-deficiency syndrome, a large group of immunologists in the United Kingdom and Ireland reported that they prescribe IgG replacement based on a complete assessment of the patient's condition and not only on the presence or absence of anti-pneumococcal antibodies.[5]

In young children, when the severity of infections warrants the use of IgG replacement treatment, it is wise to tell patients that the treatment will be stopped after a period of 1 to 2 years and that the immune response will have to be reevaluated 4 to 6 months after discontinuation of IgG replacement. Whenever possible, the discontinuation of IgG replacement should be scheduled for spring or summer, when the incidence of infections decreases.

The differences in prognosis of SADs in different age groups may reflect distinct pathogenic mechanisms. Further insights into the various forms of SAD and the different pathogenic mechanisms involved may eventually result in a more reliable assessment of the risk for persistent immune abnormalities and recurrent infections in these patients.

REFERENCES

1. Inostroza J, Illesca V, Reydet P, Vinet A, Ossa G, Muñoz S, et al. Ten-year surveillance of pneumococcal infections in Temuco, Chile. Implications for vaccination strategies. Clin Vaccine Immunol 2007;14:660-4.
2. Inostroza J, Vinet A, Retamal G, Lorca P, Ossa G, Facklam R, et al. Influence of patient age on *Streptococcus pneumoniae* serotypes causing invasive disease. Clin Diagn Lab Immunol 2001;8:556-9.
3. Concepcion NF, Frasch CE. Pneumococcal type 22f polysaccharide absorption improves the specificity of a pneumococcal-polysaccharide enzyme-linked immunosorbent assay. Clin Diagn Lab Immunol 2001;8:266-72.
4. Javier FC, Moore CM, Sorensen RU. Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. Ann Allergy Asthma Immunol 2000;84:25-30.
5. Edgar J, Richter A, Huissoon A, Kumararatne D, Baxendale H, Bethune C, et al. Prescribing immunoglobulin replacement therapy for patients with non-classical and secondary antibody deficiency: an analysis of the practice of clinical immunologists in the UK and Republic of Ireland. J Clin Immunol 2018;38:204-13.
6. Perez E, Bonilla FA, Orange JS, Ballow M. Specific antibody deficiency: controversies in diagnosis and management. Front Immunol 2017;8:586.
7. WHO. Training. Manual for Enzyme Linked Immunosorbent Assay for the Quantitation of Streptococcus Pneumoniae Serotype Specific IgG (Pn PS ELISA). A Guide to Procedures for Qualification of Materials and Analysis of Assay Performance. Geneva, Switzerland: WHO; 2003.
8. Wernette CM, Frasch CE, Madore D, Carlone G, Goldblatt D, Plikaytis B, et al. Enzyme-linked immunosorbent assay for quantitation of human antibodies to pneumococcal polysaccharides. Clin Diagn Lab Immunol 2003;10:514-9.
9. Carvalho B, Carneiro-Sampaio M, Solé D, Naspitz C, Leiva LE, Sorensen RU. Transplacental transmission of serotype-specific pneumococcal antibodies in a Brazilian population. Clin Diagn Lab Immunol 1999;6:50-4.
10. Inostroza J, Villanueva S, Mason K, Leiva L, Sorensen R. Effects of absorption with pneumococcal type 22F polysaccharide on maternal, cord blood, and infant immunoglobulin G antipneumococcal polysaccharide antibodies. Clin Diagn Lab Immunol 2005;12:722-6.
11. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. Pediatr Infect Dis J 2000;19:187-95.
12. Shinefield HR, Black S. Efficacy of pneumococcal conjugate vaccines in large scale field trials. Pediatr Infect Dis J 2000;19:394-7.
13. Huebner RE, Mbelle N, Forrest B, Madore DV, Klugman KP. Immunogenicity after one, two or three doses and impact on the antibody response to coadministered antigens of a nonavalent pneumococcal conjugate vaccine in infants of Soweto, South Africa. Pediatr Infect Dis J 2002;21:1004-7.
14. Black S, Eskola J, Whitney C, Shinefield H. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. Philadelphia, PA: Elsevier; 2006. p. 521-67.
15. Siber G, Chang I, Baker S, Fernsten P, O'Brien K, Santosham M, et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. Vaccine 2007;25:3816-26.
16. Orange J, Ballow M, Stiehm E, Ballas ZK, Chinen J, De La Morena M, 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(Suppl 1):S1-24.
17. Whaley MJ, Rose C, Martinez J, Laher G, Sammons DL, Smith JP, et al. Interlaboratory comparison of three multiplexed bead-based immunoassays for measuring serum antibodies to pneumococcal polysaccharides. Clin Vaccine Immunol 2010;17:862-9.
18. Zhang X, Simmerman K, Yen-Lieberman B, Daly TM. Impact of analytical variability on clinical interpretation of multiplex pneumococcal serology assays. Clin Vaccine Immunol 2013;20:957-61.
19. Daly TM, Pickering JW, Zhang X, Prince HE, Hill HR. Multilaboratory assessment of threshold versus fold-change algorithms for minimizing analytical variability in multiplexed pneumococcal IgG measurements. Clin Vaccine Immunol 2014;21:982-8.
20. Daly TM, Hill HR. Use and clinical interpretation of pneumococcal antibody measurements in the evaluation of humoral immune function. Clin Vaccine Immunol 2015;22:148-52.
21. Hajjar J, Al-Kaabi A, Kutac C, Dunn J, Shearer WT, Orange JS. Questioning the accuracy of currently available pneumococcal antibody testing. J Allergy Clin Immunol 2018;142:1358-60.
22. Schaballie H, Bosch B, Schrijvers R, Proesmans M, de Boeck K, Boon M, et al. Fifth percentile cutoff values for antipneumococcal polysaccharide and anti-salmonella typhi vi IgG describe a normal polysaccharide response. Front Immunol 2017;8:546.
23. Balloch A, Licciardi PV, Tang ML. Serotype-specific anti-pneumococcal IgG and immune competence: critical differences in interpretation criteria when different methods are used. J Clin Immunol 2013;33:335-41.
24. Lopez B, Bahuaud M, Fieschi C, Mehlal S, Jeljeli M, Rogeau S, et al. Value of the overall pneumococcal polysaccharide response in the diagnosis of primary humoral immunodeficiencies. Front Immunol 2017;8:1862.
25. Romero-Steiner S, Musher D, Cetron M, Pais L, Groover J, Fiore A, et al. Reduction in functional antibody activity against *Streptococcus pneumoniae* in vaccinated elderly individuals highly correlates with decreased IgG antibody avidity. Clin Infect Dis 1999;29:281-8.
26. Burton RL, Kim HW, Lee S, Kim H, Seok JH, Lee SH, et al. Creation, characterization, and assignment of opsonic values for a new pneumococcal OPA calibration serum panel (Ewha QC sera panel A) for 13 serotypes. Medicine (Baltimore) 2018;97:e0567.
27. Burton RL, Nahm MH. Development of a fourfold multiplexed opsonophagocytosis assay for pneumococcal antibodies against additional serotypes and discovery of serological subtypes in *Streptococcus pneumoniae* serotype 20. Clin Vaccine Immunol 2012;19:835-41.
28. Martinez JE, Clutterbuck EA, Li H, Romero-Steiner S, Carlone GM. Evaluation of multiplex flow cytometric opsonophagocytic assays for determination of functional anticapsular antibodies to *Streptococcus pneumoniae*. Clin Vaccine Immunol 2006;13:459-66.
29. Simell B, Nurkka A, Ekstrom N, Givon-Lavi N, Kayhty H, Dagan R. Serum IgM antibodies contribute to high levels of opsonophagocytic activities in

toddlers immunized with a single dose of the 9-valent pneumococcal conjugate vaccine. Clin Vaccine Immunol 2012;19:1618-23.
30. Saxon A, Kobayashi RH, Stevens RH, Singer AD, Stiehm ER, Siegel SC. *In vitro* analysis of humoral immunity in antibody deficiency with normal immunoglobulins. Clin Immunol Immunopathol 1980;17:235-44.
31. French M, Harrison G. Systemic antibody deficiency in patients without serum immunoglobulin deficiency or with selective IgA deficiency. Clin Exp Immunol 1984;56:18-22.
32. Ambrosino D, Siber G, Chilmonczyk B, Jernberg J, Finberg R. An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med 1987;316:790-3.
33. Ambrosino D, Umetsu D, Siber G, Howie G, Goularte T, Michaels R, et al. Selective defect in the antibody response to *Haemophilus influenzae* type b in children with recurrent infections and normal serum IgG subclass levels. J Allergy Clin Immunol 1988;81:1175-9.
34. Sorensen RU, Leiva LE, Giangrosso PA, Butler B, Javier FC III, Sacerdote DM, et al. Response to a heptavalent conjugate *Streptococcus pneumoniae* vaccine in children with recurrent infections who are unresponsive to the polysaccharide vaccine. Pediatr Infect Dis J 1998;17:685-91.
35. Sorensen RU, Leiva LE, Javier FC III, Sacerdote DM, Bradford N, Butler B, et al. Influence of age on the response to *Streptococcus pneumoniae* vaccine in patients with recurrent infections and normal immunoglobulin concentrations. J Allergy Clin Immunol 1998;102:215-21.
36. Hidalgo H, Moore C, Leiva LE, Sorensen RU. Preimmunization and postimmunization pneumococcal antibody titers in children with recurrent infections. Ann Allergy Asthma Immunol 1996;76:341-6.
37. Epstein MM, Gruskay F. Selective deficiency in pneumococcal antibody response in children with recurrent infections. Ann Allergy Asthma Immunol 1995;75:125-31.
38. Perez E, Orange J, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: a review of evidence. J Allergy Clin Immunol 2017;139(S1):S1-46.
39. Hoffman T, van Kessel D, Rijkers G. Impact of using different response criteria for pneumococcal polysaccharide vaccination for assessment of humoral immune status. J Clin Immunol 2018;38:149-52.
40. Bonilla F, Barlan I, Chapel H, Costa-Carvalho B, Cunningham-Rundles C, de la Morena M, et al. International Consensus Document (ICON): common variable immunodeficiency disorders. J Allergy Clin Immunol Pract 2016;4:38-59.
41. Bonilla F, Khan D, Ballas Z, Chinen J, Frank M, Hsu J, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136:1186-205.
42. Siber GR. Pneumococcal disease: prospects for a new generation of vaccines. Science 1994;265:1385-7.
43. Pletz MW, Maus U, Krug N, Welte T, Lode H. Pneumococcal vaccines: mechanism of action, impact on epidemiology and adaption of the species. Int J Antimicrob Agents 2008;32:199-206.
44. Gross S, Blaiss MS, Herrod HG. Role of immunoglobulin subclasses and specific antibody determinations in the evaluation of recurrent infection in children. J Pediatr 1992;121:516-22.
45. Sanders LA, Rijkers GT, Kuis W, Tenbergen-Meekes AJ, de Graeff-Meeder BR, Hiemstra I, et al. Defective antipneumococcal polysaccharide antibody response in children with recurrent respiratory tract infections. J Allergy Clin Immunol 1993;91(Pt 1):110-9.
46. Zora J, Silk H, Tinkelman D. Evaluation of postimmunization pneumococcal titers in children with recurrent infections and normal levels of immunoglobulin. Ann Allergy 1993;70:283-8.
47. Knutsen A. Patients with IgG subclass and/or selective antibody deficiency to polysaccharide antigens: initiation of a controlled clinical trial of intravenous immune globulin. J Allergy Clin Immunol 1989;84:640-7.
48. Herer B, Labrousse F, Mordelet-Dambrine M, Durandy A, Offredo-Hemmer C, Ekindjian O, et al. Selective IgG subclass deficiencies and antibody responses to pneumococcal capsular polysaccharide antigen in adult community-acquired pneumonia. Am Rev Respir Dis 1990;142:854-7.
49. Bernatowska-Matuszkiewicz E, Pac M, Pum M, Liszka K, Leibl H, Eibl M. IgG subclasses and antibody response to pneumococcal capsular polysaccharides in children with severe sinopulmonary infections and asthma. Immunol Invest 1991;20:173-85.
50. Leiva LEHT, Lefevre S, Monjure H, Sorensen RU, editors. Circulating CD21 low B cells are decreased in children with recurrent respiratory infections with or without Specific Antibody Deficiency (SAD). Florence, Italy: Proceedings of the 15th Meeting of the European Society for Immunodeficiencies (ESID); 2013.
51. Leiva LE, Monjure H, Sorensen RU. Recurrent respiratory infections, specific antibody deficiencies, and memory B cells. J Clin Immunol 2013;33(Suppl 1): S57-61.
52. Wall LA, Dimitriades VR, Sorensen RU. Specific antibody deficiencies. Immunol Allergy Clin North Am 2015;35:659-70.
53. Zhao Y, Pan-Hammarström Q, Zhao Z, Wen S, Hammarström L. Selective IgG2 deficiency due to a point mutation causing abnormal splicing of the Cgamma2 gene. Int Immunol 2005;17:95-101.
54. Wasserman R, Sorensen R. Evaluating children with respiratory tract infections: the role of immunization with bacterial polysaccharide vaccine. Pediatr Infect Dis J 1999;18:157-63.
55. Schatorje EJ, de Jong E, van Hout RW, Garcia Vivas Y, de Vries E. The challenge of immunoglobulin-G subclass deficiency and specific polysaccharide antibody deficiency—a Dutch pediatric cohort study. J Clin Immunol 2016;36: 141-8.
56. van de Vosse E, van Ostaijen-Ten Dam MM, Vermaire R, Verhard EM, Waaijer JL, Bakker JA, et al. Recurrent respiratory tract infections (RRTI) in the elderly: a late onset mild immunodeficiency? Clin Immunol 2017;180:111-9.
57. Lotz DR, Knutsen AP. Concomitant selective antibody deficiency in pediatric patients with mannose-binding lectin deficiency. Pediatr Allergy Immunol Pulmonol 2010;23:265-71.
58. Centers for Disease Control and Prevention ACoIPA. Pneumococcal ACIP Vaccine Recommendations 2015. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. Accessed September 8, 2015.
59. Ortigas A, Leiva L, Moore C, Bradford N, Sorensen RU. Natural history of specific antibody deficiency after IgG replacement therapy. Ann Allergy Asthma Immunol 1999;82:271.
60. Balloch A, Licciardi P, Russell F, Mulholland EK, Tang ML. Infants aged 12 months can mount adequate serotype-specific IgG responses to pneumococcal polysaccharide vaccine. J Allergy Clin Immunol 2010;126:395.
61. Rose M, Schubert R, Strnad N, Zielen S. Priming of immunological memory by pneumococcal conjugate vaccine in children unresponsive to 23-valent polysaccharide pneumococcal vaccine. Clin Diagn Lab Immunol 2005;12:1216-22.
62. Estrada J, Najera M, Pounds N, Catano G, Infante A. Clinical and serologic response to the 23-valent polysaccharide pneumococcal vaccine in children and teens with recurrent upper respiratory tract infections and selective antibody deficiency. Pediatr Infect Dis J 2016;35:205-8.
63. Leiva L, Butler B, Hempe J, Ortigas A, Sorensen R. Up-regulation of CD40L and induction of a Th2 response in children immunized with pneumococcal polysaccharide vaccines. Clin Diagn Lab Immunol 2001;8:233-40.
64. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morbidity and Mortality Weekly Report 1997;46: 1-24.
65. Jolles S, Chapel H, Litzman J. When to initiate immunoglobulin replacement therapy (IGRT) in antibody deficiency: a practical approach. Clin Exp Immunol 2017;188:333-41.
66. Wolpert J, Knutsen A. Natural history of selective antibody deficiency to bacterial polysaccharide antigens in children. Pediatr Asthma Allergy Immunol 1998;12:183.
67. Cohn JA, Skorpinski E, Cohn JR. Prevention of pneumococcal infection in a patient with normal immunoglobulin levels but impaired polysaccharide antibody production. Ann Allergy Asthma Immunol 2006;97:603-5.