

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Selective Antibody Deficiency with Normal Immunoglobulins

Ricardo U. Sorensen, Tammy Harvey and Lily E. Leiva

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/51709>

1. Introduction

Specific antibody deficiency (SAD) is a common antibody immunodeficiency defined as a poor antibody response to unconjugated pneumococcal polysaccharides present in the 23-valent pneumococcal vaccine (PPV23). Clinical manifestations of specific antibody deficiency include recurrent sinopulmonary infections, such as sinusitis, otitis media, bronchitis, and pneumonia. All immunoglobulin concentrations, including IgG subclasses, are normal, and antibody response to protein antigens (eg, tetanus toxoid, diphtheria toxoid) and the conjugate H influenzae b vaccine are also normal in most patients. [11, 44, 56] In some patients with SAD, the response to the pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) is also normal.

SAD was first reported in a small group of patients in the early 1980s. [6, 46] The widespread use of pneumococcal immunization to assess antibody responses has revealed that specific unresponsiveness to polysaccharide antigens is not unusual. [21, 25]

The vast majority of SAD patients have a deficiency of specific antibodies to polysaccharides but normal antibodies to protein antigens, resembling the developing immunologic status of human newborns and infants. Infants readily produce antibodies against vaccine proteins but fail to respond to most vaccine polysaccharides until approximately two years of age. In some patient with early onset SAD, this condition may represent a delayed maturation of the immune response to polysaccharides.

SAD is also found in association with many primary and secondary immunodeficiencies. An association of SAD with IgG subclass deficiencies, particularly IgG2 deficiencies, has been described. [9] IgG2 subclass deficient patients have antibody responses to a restricted number of polysaccharides in the PPV vaccine. Frequently, these patients also have poor immunological memory, with IgG antibody titers decreasing to pre-immunization levels within 6 to 12 months. [51]

Other primary immunodeficiency disorders with an immunologic phenotype associated with specific antibody deficiency include Wiskott-Aldrich syndrome, partial DiGeorge syndrome, asplenia, hyper-IgE syndrome, and selective IgA deficiency (without IgG subclass deficiency).^[30] In addition, specific antibody deficiency can be identified in some patients with congenital dysmorphic syndromes or chromosomal abnormalities associated with recurrent sinopulmonary infections. Acquired or secondary immunodeficiencies associated with specific antibody deficiency include splenectomy, immunosuppression, chronic lung disease, protein-calorie malnutrition, and human immunodeficiency virus infection.

There is not a single pathogenic mechanism for specific anti-polysaccharide antibody deficiencies. The variable conditions in which an inability to respond to polysaccharides is found suggest that many different immunologic phenotypes may lead to the same clinical phenotypic antibody deficiency. Further defining different SAD phenotypes and relating these phenotypes to associated conditions may shed further insight into possible pathogenic mechanisms.

2. Assessment of specific antibodies

The assessment of specific antibodies always needs to take into account:

1. Evidence of exposure to vaccines or infections. In the case of vaccines, this includes an exact record of immunizations;
2. Time since last exposure or vaccination to the time of obtaining the blood sample to be tested ;
3. Method of antibody measurement, including the method, the antigen used, the standards used to normalize values and normal values for different age groups obtained with the same method used to test the patient sample.

All this information is essential to determine if the antibody response is normal or abnormal and also to determine if further immunization is likely to increase antibody titers and protection.

Pneumococcal vaccines are an ideal tool to evaluate the ability to produce specific antibodies in response to a known stimulus. All pneumococcal vaccines contain antigens from several serotypes so the immunologic evaluation is not based on a single antibody response. More recently, research has also revealed that these serotypes allow for clear differentiation between antibody responses to conjugate and pure polysaccharide vaccines, a difference that is clinically relevant.

Current recommendations for the use of pneumococcal vaccines are based on the age at which immunization began. Pneumococcal conjugate vaccines (PCV) are recommended for all infants at 2, 4, 6 and 12 months of age. PCV has also been used in children 24 to 59 months of age who are unimmunized, had incomplete vaccination prior to age 24 months, or are at high risk of acquired invasive pneumococcal disease^[2].

The pneumococcal polysaccharide vaccine (PPV23) is not recommended for children under 24 months since the responses to polysaccharide antigens is considered absent or ineffective in the first 2 years of life. Pneumococcal polysaccharide vaccines (PPV23) are recommended for in high risk patients over age 5 and for individuals over age 65. ^[1]

Serotypes	Vaccines	7-PCV	13-PCV
	23-PPV		
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		

23-PPV: 23-valent polysaccharide vaccine; 7-PCV: heptavalent conjugate vaccine; 13-PCV: 13-valent conjugate vaccine
PCV: 13-valent conjugate vaccine. *Courtesy of RU Sorensen, MD.*

Table 1. Pneumococcal vaccines and antibody testing for conjugate and pure pneumococcal polysaccharides

	Vaccine	
	Conjugate (CV)*	Polysaccharide (PV)
Normal infants	2, 4, 6, 12-15 months	Not given to patients this age
7 to 11 months	3 doses •	Not given to patients this age
12 to 23 months	2 doses	Not given to patients this age Δ
2 to 5 years	1 dose ◇	1 dose
>5 years		1 dose §

The measurement of pre-immunization immunoglobulin and serotype-specific antibody concentrations, as well as 4 - to-6-week post immunization serotype-specific antibody concentrations are recommended.

* Recommendations for the use of CV are based upon the recommendations of the CDC Advisory Committee (press release 10/22/99), FDA (HHS News release 2/17/00) and of the American Council on Immunization Practices [4].

• Intervals between doses of any vaccine combination should be ≥ 2 months.

Δ One study showed excellent serological responses to 22 of the 23 serotypes in the PV vaccine in 56 12-month old children. [7] These results support personal observations (Sorensen RU) of good responses to PV in younger children. The use of PV in patients 12-24 months of age could be considered when CVs are not available.

◇ Patients with IgG2 deficiency may require 2 doses at any age [62].

§ If there is no antibody response to PV, give CV; repeating PV is not effective [55].

Adapted from: Sorensen RU, Moore C. *Peds Clin N A* 2000;42:1225.

Table 2. Pneumococcal immunization in patients with recurrent infections

Severity of deficiency	IgG anti-pneumococcal antibodies	
	Post-immunization	
	2-5 years of age	≥6 years of age
Severe	No protective antibody levels for any serotype	No protective antibody levels for any serotype
Moderate	Protective antibody levels for <50% of serotypes administered	Protective antibody levels for <70% of serotypes administered

A protective antibody concentration is defined as ≥1.3 micrograms/mL, based on response to polysaccharide vaccine serotypes in patients >2 years of age.

If a patient previously received the conjugate pneumococcal vaccine and had protective titers to those serotypes, then an adequate response would be expected to the age-appropriate percentage (50% or 70%) of those serotypes exclusive to the polysaccharide vaccine.

%; percent of polysaccharide vaccine serotypes administered and tested.

Adapted from Sorensen, RU, Moore, C. *Peds Clin N A* 2000;43:1225.

Table 3. Classification of deficient response to pneumococcal vaccination

3. Measurement of specific antibody responses

Various methods for the measurement of antigen-specific antibodies include nephelometry, turbidimetry, chemiluminescence and enzyme-linked assay (ELISA) .

Although infections and immunizations elicit IgM, IgA, and IgG antibody responses, only IgG titers are relevant to the assessment of vaccine responses. IgG antibodies confer long-term protection and are considered indicative of immunity. The specific IgG titer represents the total of all IgG subclass concentrations, since most antibody tests do not differentiate among Ig subclasses.

For IgG anti-pneumococcal antibody assessment, the standard method is the third generation WHO ELISA, which incorporates double absorption of samples with capsular polysaccharide (CPS) and serotype 22F and correlates closely with OPA measurements [Concepcion 2001]. Multiplex technologies allow simultaneous quantitation of multiple serotype-specific antibodies. There has been limited validation against the established gold standard ELISA and assay performance in the clinical setting has not been carefully examined.

Measurements of antibodies to all 23 pneumococcal serotypes in a single test, without differentiating specific antibodies to single serotypes, is not useful. The correlation of this test with the standard ELISA test is poor. For instance, the presence of a high concentration antibody to a single serotype may give a falsely high antibody concentration, though the antibody response to other serotypes may be deficient.

Ideally, evaluation of antibody-mediated immunity includes the measurement of immunoglobulin and pre-immunization anti-pneumococcal antibody concentrations, with follow-up assessment of post immunization antibodies four to six weeks later. In practice today, most patients needing evaluation for recurrent infections have already received one or more pneumococcal vaccines and pre-immunization antibody concentrations cannot be measured. So, an exact immunization history becomes essential for the adequate interpretation of results [43].

When there is a good initial clinical and serological response to vaccination but clinical infections recur after a period of time, usually 6 to 12 months, the antibody evaluation is repeated to rule out a rapid loss of antibody concentration down to non-protective concentrations.

In most cases, evaluation of specific antibody deficiency is based on the response to pneumococcal polysaccharides. In some circumstances, it is also important to consider the response to other vaccines or infections. In patients with hypogammaglobulinemia in the first year of life, the response to protein antigens such as tetanus and diphtheria toxoids may help to predict whether the patient has transient hypogammaglobulinemia of infancy, and whether the low IgG concentrations will spontaneously increase into the normal range. The present role of the response to the conjugate *Hemophilus influenzae* type b vaccine has not been well defined.

The measurement of anti-A and B isoagglutinins is not useful in the diagnosis of specific antibody deficiency. Blood groups A and B are galactosamines on red blood cells that cross-react with galactosamines on the capsule of gut E coli bacteria. The method currently in use

does not differentiate between IgM and IgG responses so is not clinically useful except for in rare instances, such as suspected Wiskott-Aldrich syndrome that needs evaluation in the first year of life. A normal child should have detectable isoglobulin titers after age 6 months.

In patients with persistent or recurrent infections with a single pathogen, such as varicella, shingles, or a specific hepatitis, assessing the specific antibody response to a causative pathogen may be clinically relevant. However, such evaluations are usually not part of the evaluation for SAD.

4. Diagnostic criteria

The interpretation of anti-pneumococcal antibody concentration results is based on increased post-immunization antibody concentrations over pre-immunization concentrations (immune response) and on the final post-immunization antibody concentrations, regardless of increase from pre-immunization concentrations (antibody concentration). Patients who already have high baseline antibody concentrations of specific antibodies to a pneumococcal serotype are less likely to have a significant increase in antibody concentrations after immunization.

The definition of adequate response to individual pneumococcal polysaccharides is not well defined. Protection against invasive disease, as assessed in clinical vaccine trials, may require lower antibody concentrations than protection against mucosal diseases like sinusitis and otitis ^[10]. Immunocompetence, as a reflection of the ability of producing a response for clinical protection against mucosal infections and pneumonia, has been arbitrarily defined as a post-immunization antibody concentration ≥ 1.3 mcg/mL. This antibody concentration can be used as a marker of immunocompetence, regardless of degree of response over pre-immunization baseline antibody concentrations ^[56]. For instance, a patient with a pre-immunization titer of 0.15 mcg/mL may have a 4-fold increase to 0.6 mcg/mL, still significantly below the level needed to show immunocompetence.

The number of individual polysaccharide responses required in the immunologic evaluation for a reliable assessment of the antibody response to polysaccharides has not been established. Response to a single serotype-specific polysaccharide does not predict the ability or inability to respond to most or all other serotypes. Therefore, measuring response of at least **six** different antibodies to vaccine serotypes is recommended to obtain a reliable estimate of the spectrum of responses of a given patient. For patients who received one or more doses of the conjugate pneumococcal vaccine, at least six or more non-conjugate vaccine serotypes (present only in polysaccharide vaccine) need to be measured. A patient that responds to the conjugate vaccine may still be unresponsive to pure polysaccharides, which is an immunologic abnormality that may be clinically relevant.

The age of the patient significantly affects the intensity of the antibody response to individual serotypes and the number of serotypes inducing an adequate response ^[56].

Normal children between two and five years of age are expected to have an adequate response to >50 percent of serotypes evaluated. Older patients are expected to respond to >70 percent of serotypes evaluated. These criteria have not been tested critically; however, they have allowed us to predict a clinical course and decide upon treatment options in over 1000 patients of all ages tested since 1995 (Sorensen et al, unpublished observations).

Other factors that affect pneumococcal antibody concentrations in the evaluation of SAD include treatment with intravenous or subcutaneous gammaglobulin within the previous 6 months and underlying diseases and/or treatments possibly affecting immune response. Examples include long-term steroid therapy, malignancy, and chemotherapy.

In addition to immunization, responses to natural, often subclinical, infection influence the antibody concentrations in patients. In fact, absent protective antibodies in unimmunized patients above 2 years of age are unusual. However, upon vaccination, older patients who never developed protective antibodies to pneumococcal serotypes often have adequate response to most serotypes. Low antibody concentrations in an unimmunized individual do not define an immunodeficiency syndrome unless there is inadequate response to immunization.

5. Clinical manifestations

The clinical manifestations of patients with selective anti-polysaccharide antibody deficiency are similar to those of all antibody deficiency syndromes. The majority of patients have recurrent upper and/or lower respiratory infections such as sinusitis, otitis, bronchitis or pneumonia due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Branhamella catarrhalis*, or *Staphylococcus aureus*.

The sinopulmonary infections must be more frequent or severe than normally expected for the age group of the patient. Most of these infections require antibiotic treatment for clinical improvement, and an evaluation is warranted when multiple antibiotic treatments are needed, even when antibiotics effectively resolve each infection.

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

- Early onset of infections, as early as 3-4 months of age
- Recurrence of infection after antibiotic treatment
- Infectious complications such as mastoiditis
- Association with invasive infections
- Recurrence after ear tubes
- Repeated ear tube placement
- Clinical change to sinusitis after ear tubes

Very few patients with specific antibody deficiency also present with atopic diseases, including atopic dermatitis and asthma, complicated by recurrent infections

requiring frequent antibiotic treatments for improvement. Patients with asthma and selective antibody deficiency may also have chronic sinusitis or other recurrent sinopulmonary infections.

6. Sad phenotypes

There are many different forms of SAD based on the immunologic and clinical phenotypes, the transient or permanent nature of the defect, and the maintenance or loss of antibody concentrations after an initial normal response.

The classic SAD with absent or poor responses to pneumococcal polysaccharides is well defined and is based on the response to polysaccharides from serotypes present in PPV23. When patients have received one or more conjugate pneumococcal vaccines, differentiating antibody responses to serotypes present in the conjugate vaccines from responses to serotypes present only in the polysaccharide vaccines is important. In specific antibody deficiency, antibody response to the conjugate serotypes may be normal with poor responses to polysaccharide serotypes.

The intensity of antibody responses to polysaccharides and the number of polysaccharides eliciting antibody responses vary considerably from one individual to another, even in the same age group. This variability makes it difficult to clearly define immunologic phenotypes of polysaccharide antibody unresponsiveness.

The severe immunologic phenotype of SAD is the easiest phenotype to define. These patients have little or no antibody response and no protective antibody concentrations to any pneumococcal serotype evaluated. Some patients with a severe immunologic phenotype have protective titers to one serotype, and the titer tends to be low (1.3 to 2.0 ug/ml) [45, 51].

A moderate immunologic SAD phenotype is characterized by partial antibody responses, with less than the expected arbitrarily defined adequate response to serotypes for their age group. Some of these patients can have a severe clinical phenotype despite their relatively mild or moderate immunological abnormality.

Since the introduction of conjugate pneumococcal vaccines in the USA in 2000, patients with recurrent respiratory infections who are fully immunized with 4 doses of PCV may be clearly unresponsive to conjugate polysaccharides. These patients usually are able to develop protective antibody concentrations against protein antigens such as diphtheria and tetanus toxoids and to the single antigen conjugate *Haemophilus influenza* vaccine. The immunologic and clinical severity of these patients is similar to the phenotypes of patients unresponsive to PPV. There is a large subgroup of PCV-SAD patients that respond only to serotype 14, revealing that the immunologic properties of the polysaccharide in serotype 14 is different from other pneumococcal polysaccharides.

A different clinical phenotype of SAD occurs in patients who have an initial adequate response to a pneumococcal vaccine, followed by a rapid loss of antibody concentrations

over time. This form of SAD, based on poor persistence of IgG antibodies against pneumococci, is usually suspected when a patient who had a significant improvement with decreased infections after immunization begins again to have recurrent infections, typically six or more months post-immunization.

Some unimmunized patients in all age groups fail to develop protective antibody concentrations to any pneumococcal serotype tested. This lack of antibody response is unusual in individuals above two years of age who typically develop antibodies in response to natural infections. Most unimmunized adults have protective antibodies to at least 80 percent of serotypes tested. The lack of pre-immunization protective antibodies does not define an immunodeficiency, and most of these patients have a normal response to immunization. Those patients that completely fail to respond to natural infection and immunization have a severe form of selective antibody deficiency. Responders to immunization cannot be differentiated from non-responders without evaluation with immunization and retesting after immunization.

7. Management of SAD

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 immune serum globulin therapy.

8. Immunization

Immunization beyond the suggested regular immunization schedule should be the first step in a newly diagnosed SAD patient. Patients who fail to respond to a complete series of PCV vaccinations, PCV-SAD patients, should be immunized with one dose of PPV. This vaccine should increase the patient's protection against bacterial polysaccharide infections, and this immunization allows for assessment of the patient's immunologic response to polysaccharides. Clinical experience shows that these patients typically have good immunologic response to most or all 23 PPV serotypes (Sorensen, unpublished observations).

Patients with recurrent infections despite good response to PCV may benefit from immunization with PPV. PPV contains serotypes common to PCV and serotypes not present in PCV, so this vaccine may increase antibody response to PCV and nonPCV serotypes. For less severe mucosal infections not requiring multiple antibiotic treatments, it may be possible to immunize the patient first, with a subsequent complete immunological evaluation only if infections persist.

After immunizing with one dose of PPV initially, repeated immunization with PPV should not be considered a routine therapeutic option in patients with recurrent infections that fail to respond to PPV. If patients do not respond to one dose of PPV-23, our experience suggests that these patients likely do not have an appropriate immunologic response to polysaccharide antigens. So, a second dose of PPV-23 generally has little benefit. An

exception may be re-immunization of otherwise immunologically normal patients who partially responded to PPV initially, with resulting titers slightly below protective levels.. Reimmunization of partial responders to PPV may result in protective antibody levels.

In contrast to the ineffectiveness of repeated PPV immunization, 80 to 90 percent of patients with classic PPV-SAD do have a serological response to the serotypes present in the conjugate vaccine that can be used to overcome the unresponsiveness to pure polysaccharides [56]. Conjugate vaccines were developed to immunize children younger than 2 years of age, as children below age 2 years typically demonstrate poor responses to polysaccharide antigens alone. Conjugation helps direct the immune response toward the immunogenic protein complexed to the polysaccharide antigen, thereby stimulating protective immune responses in those individuals. Therefore, it is not surprising that PPV-nonresponders typically have a good serological response to PCV serotypes.

Although most patients benefit from immunization with the conjugate vaccine by improving protection against common pneumococcal serotypes, none of the conjugate vaccines has all 23 serotypes present in the polysaccharide vaccine. This clinical improvement after a PCV immunization is notable because recurrent respiratory infections are caused by a much larger variety of pathogens than just the vaccine pneumococcal serotypes.

If there is a serological response to the conjugate vaccine without clinical improvement, then the PPV-SAD persists and further treatment options need to be considered. In PPV-SAD patients who are clinically unresponsive to immunization with additional PCV, reimmunizing with PPV is generally ineffective if repeated within one year of the initial PPV vaccine. After a period of IgG therapy, many patients respond to an additional PPV dose with or without clinical improvement, so a second PPV dose should be given after completion of 1-2 years of IgG replacement therapy.

For patients with poor immunological memory (loss of antibody concentrations after an adequate initial response), immunization with a second dose of polysaccharide vaccine generally triggers a vigorous IgG antibody response. Further study is needed since this phenotype may not be attributable only to poor immunological memory.

9. Antibiotics

If the frequency and severity of infections persists after additional immunization, antibiotic prophylaxis should be considered, especially in younger patients who will likely outgrow their selective antibody deficiency. When an oral antibiotic is considered for prophylaxis, treatment doses of trimethoprim-sulfa can be very effective. Prolonged daily use of topical mupirocin intranasally, for several months to a year, is a safe alternative treatment plan.

Appropriate antibiotic selection and duration for any febrile and/or purulent respiratory infection is important. Treatment with high doses of antibiotics for periods of at least 2 to 3 weeks is necessary. When antibiotic use alone improves the patient's quality of life and prevents infectious complications, no additional treatment is needed.

10. IgG replacement therapy

IgG replacement by the intravenous or the subcutaneous route is appropriate when the infection history is well documented, when immunizations have been utilized, and most of all, when proper antibiotic prophylaxis and treatment has been optimized. Patients with any form of SAD need decreased infections to improve quality of life and to prevent complications such hearing loss, sinus damage or bronchiectasis.

The recommended IgG dose is 400 to 600 mg/kg calculated on a monthly basis. ItgG can be given intravenously every four weeks or subcutaneously in divided doses one or twice weekly. Occasional patients require either higher doses if they have breakthrough infections or complications such as bronchiectasis.

When the severity of infections warrants the use of IgG replacement treatment, patients should be advised that treatment will be discontinued after a period of one to two years and the immune response will be reevaluated four to six months after discontinuation of IgG replacement. Whenever possible, the discontinuation of IVIG should be scheduled for during the spring or summer time when the incidence of infections typically decreases.

Four to six months after the IgG dose, a complete immunological evaluation of antibody mediated immunity should be performed. This evaluation includes an additional dose of PPV and measurement of antibodies 3 to 6 weeks after immunizations. Many children do not require further IgG replacement therapy, but some continue to have persistent infections and need continue replacement IgG therapy. These patients are likely to have additional immunological abnormalities that presently under evaluation. Patient management, IgG replacement therapy, and post treatment evaluation is best done by experts in the management of patients with all forms of primary immunodeficiency diseases.

11. Prognosis

The immunologic phenotypes of specific antibody deficiency may be transient or permanent. Transient forms are common in children two to five years of age. Even in permanent phenotypes, the natural history of specific antibody deficiency is usually benign with proper management of these patients.

Reassessment of antibody-mediated immunity should always be performed after discontinuation of IVIG therapy and in patients with recurrent infections. In particular, older patients with selective antibody deficiencies with normal immunoglobulin concentrations should be monitored closely, as they may eventually develop common variable immunodeficiency.

Further insights into the pathogenesis of this immunodeficiency by studying larger numbers of patients will allow further understanding of the correlation between immunologic and clinical phenotypes of specific antibody deficiency. Further study will result in a more reliable assessment of the risk for persistent immune abnormalities and recurrent sinopulmonary infections in subgroups of these patients.

Author details

Ricardo U. Sorensen, and

Department of Pediatrics, New Orleans, Louisiana, USA

Tammy Harvey

Jeffrey Modell Center for Immunodeficiencies, New Orleans, Louisiana, USA

Lily E. Leiva

Louisiana State University Health Science Center, New Orleans, Louisiana, USA

12. References

- [1] Centers of Disease Control and Prevention. Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1997;46:1-24.
- [2] American Academy of Pediatrics: Pneumococcal infections. In: In: Pickering LK BC, Long SS, Kimberlin DW, Long SS, editor. Red Book: 2009 Report of the Committee on Infectious Diseases. 28 ed. Elk Grove Village, IL; 2009. p. 524-535.
- [3] Recommendations for the prevention of Streptococcus pneumoniae infections in infants and children: use of 13-valent pneumococcal conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23). Pediatrics 2010;126(1):186-90.
- [4] Recommended childhood immunization schedule--United States. MMWR Morb Mortal Wkly Rep 2002;51:31.
- [5] 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.
- [6] Ambrosino DM, Siber GR, Chilmonczyk BA, Jernberg JB, Finberg RW. An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med 1987;316(13):790-3.
- [7] Balloch A, Licciardi P, Russell F, et al. Infants aged 12 months can mount adequate serotype-specific IgG responses to pneumococcal polysaccharide vaccine. J Allergy Clin Immunol 2010;126:395.
- [8] Barrett D, Ayoub E. IgG2 subclass restriction of antibody to pneumococcal polysaccharides. Clin Exp Immunol 1986;63:127.
- [9] Bernatowska-Matuszkiewicz E, Pac M, Pum M, Liszka K, Leibl H, Eibl MM. IgG subclasses and antibody response to pneumococcal capsular polysaccharides in children with severe sinopulmonary infections and asthma. Immunol Invest 1991;20(2):173-85.
- [10] Black S, Eskola J, Whitney C, Shinefield H. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Plotkin SA OW, Offit, PA,, editor. Vaccines. 5 ed. Philadelphia: Elsevier; 2006. p. 521-567.

- [11] Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. *Ann Allergy Asthma Immunol* 2005;94(5 Suppl 1):S1-63.
- [12] Bossuyt X, Borgers H, Moens L, et al. Age- and serotype-dependent antibody response to pneumococcal polysaccharides. *J Allergy Clin Immunol* 2011;127:1079.
- [13] Boyle R, Le C, Balloch A, et al. The clinical syndrome of specific antibody deficiency in children. *Clin Exper Immunol* 2006;146:486-92.
- [14] Burton R, Nahm M. Development and validation of a fourfold multiplexed opsonization assay (MOPA4) for pneumococcal antibodies. *Clin Vaccine Immunol* 2006;13:1004-9.
- [15] Concepcion N, Frasch C. Pneumococcal type 22f polysaccharide absorption improves the specificity of a pneumococcal-polysaccharide enzyme-linked immunosorbent assay. *Clin Diagn Lab Immunol* 2001;8:266-72.
- [16] Epstein M, Gruskay F. Selective deficiency in pneumococcal antibody response in children with recurrent infections. *Ann Allergy Asthma Immunol* 1995;75:125.
- [17] Eskola J. Polysaccharide-based pneumococcal vaccines in the prevention of acute otitis media. *Vaccine* 2001;19:S78-S82.
- [18] Fong S, Qaqundah B, Taylor W. Developmental patterns of ABO isoagglutinins in normal children correlated with the effects of age, sex, and maternal isoagglutinins. *Transfusion* 1974;14(14):551.
- [19] French M, Harrison G. Systemic antibody deficiency in patients without serum immunoglobulin deficiency or with selective IgA deficiency. *Clin Exp Immunol* 1984;56:18.
- [20] Go E, Ballas Z. Anti-pneumococcal antibody response in normal subjects: A meta-analysis. *J Allergy Clin Immunol* 1996;98:205-15.
- [21] Gross S, Blaiss M, Herrod H. Role of immunoglobulin subclasses and specific antibody determinations in the evaluation of recurrent infection in children. *J Pediatr* 1992;121:516.
- [22] Hare N, Smith B, Ballas Z. Antibody response to pneumococcal vaccination as a function of preimmunization titer. *J Allergy Clin Immunol* 2009;123:195.
- [23] Herer B, Labrousse F, Mordelet-Dambrine M, et al. Selective IgG subclass deficiencies and antibody responses to pneumococcal polysaccharide antigen in adult community-acquired pneumonia. *Am Rev Respir Dis* 1990;142:854.
- [24] Hidalgo H, Inostroza J, Leiva L, Sorensen RU. [immunization and immune response to pneumococcal vaccination]. *Rev Med Chil* 1996;124(3):287-92.
- [25] 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(4):341-6.
- [26] Jackson L, Neuzil K. Pneumococcal vaccines. In: Plotkin S, Orenstein W, Offit P, editors. *Vaccines*. 5 ed. Philadelphia, PA: Elsevier; 2006. p. 569-604.
- [27] Jackson LA, Baxter R, Naleway AL, Belongia EA, Baggs J. Patterns of pneumococcal vaccination and revaccination in elderly and non-elderly adults: a Vaccine Safety Datalink study. *BMC Infect Dis* 2009;9:37.

- [28] Javier F, Moore C, Sorensen R. Distribution of primary immunodeficiency diseases diagnosed in a pediatric tertiary hospital. *Ann Allergy Asthma Immunol* 2000;84:25.
- [29] Kamchaisatian W, Wamwatsuntikul W, Sleasman J, et al. Validation of current joint AAAAI and ACAAI guidelines for antibody response to the 23-valent pneumococcal vaccine using a population of HIV-infected children. *J Allergy Clin Immunol* 2006;118:1336-41.
- [30] 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.
- [31] Landesman S, Schiffman G. Assessment of the antibody response to pneumococcal vaccine in high-risk populations. *Rev Infect Dis* 1981;3 Suppl:S184.
- [32] Lawrence E, Edwards K, Schiffmann G, et al. Pneumococcal vaccine in normal children. *Am J Dis Child* 1983;137:846.
- [33] Lim P, Lau Y. Occurrence of IgG subclass antibodies to ovalbumin, avidin, and pneumococcal polysaccharide in children. *Int Arch Allergy Immunol* 1994;104:137.
- [34] Lortan J, Kaniuk A, Monteil M. Relationship of in vitro phagocytosis of serotype 14 *Streptococcus pneumoniae* to specific class and IgG subclass antibody levels in healthy adults. *Clin Exp Immunol* 1993;91:54.
- [35] Makela P, Herva E, Sibakov M, et al. Pneumococcal vaccine and otitis media. *Lancet* 1980;2:547-51.
- [36] McQuillan G, Kruszon-Moran D, Deforest A, et al. Serologic immunity to diphtheria and tetanus in the United States. *Ann Intern Med* 2002;136:660.
- [37] Ochs H, Buckley R, Kobayashi R, et al. Antibody responses to bacteriophage phi X174 in patients with adenosine deaminase deficiency. *Blood* 1992;80:1163.
- [38] Ortigas A, Leiva L, Moore C, et al. Natural history of specific antibody deficiency after IgG replacement therapy. *Ann Allergy Asthma Immunol* 1999;82:71.
- [39] Paris K, Sorensen R. Assessment and clinical interpretation of polysaccharide antibody responses. *Ann Allergy Asthma Immunol* 2007;99:462-4.
- [40] Ridda I, Macintyre C, Lindley R, et al. Immunological responses to pneumococcal vaccine in frail older people. *Vaccine* 2009;27:1628.
- [41] Rijkers G, Sanders L, Zegers B. Anti-Capsular polysaccharide antibody deficiency states. *Immunodeficiency* 1993;5:1.
- [42] Romero-Steiner S, Frasch C, Carlone G, Fleck R, Goldblatt D, Nahm M. Use of opsonophagocytosis for the serologic evaluation of pneumococcal vaccines. *Clin Vaccine Immunol* 2006;13:165-9.
- [43] Rose MA, 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(10):1216-22.
- [44] 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(1 Pt 1):110-9.
- [45] Sanders LA, Rijkers GT, Tenbergen-Meekes AM, Voorhorst-Ogink MM, Zegers BJ. Immunoglobulin isotype-specific antibody responses to pneumococcal polysaccharide

- vaccine in patients with recurrent bacterial respiratory tract infections. *Pediatr Res* 1995;37(6):812-9.
- [46] 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(2):235-44.
 - [47] Schenkein J, Park S, Nahm M. Pneumococcal vaccination in older adults induces antibodies with low opsonic capacity and reduced antibody potency. *Vaccine* 2008;26:5521.
 - [48] Shrimpton A, Duddridge M, Ziegler-Heitbrock L. Vaccination with polysaccharide-conjugate-vaccines in adult patients with specific antibody deficiency. *Vaccine* 2006;24:3574.
 - [49] Siber G, Schur P, Aisenberg A, et al. Correlation between serum IgG-2 concentrations and the antibody response to bacterial polysaccharide antigens. *N Engl J Med* 1980;303:178.
 - [50] Simell B, Kilpi T, Kayhry H. Pneumococcal carriage and otitis media induce salivary antibodies to pneumococcal capsular polysaccharides in children. *J Infect Dis* 2002;186:1106-14.
 - [51] Sorensen R, Hidalgo H, Moore C, Leiva L. Anti-pneumococcal antibody titers and IgG subclasses in children with recurrent respiratory infections. *Pediatr Pulmonol* 1996;22:167.
 - [52] Sorensen R, Moore C. Immunology in the pediatrician's office. *Pediatr Clin North Am* 1994;41:691.
 - [53] Sorensen R, Moore C. Antibody deficiency syndromes. *Pediatr Clin North Am* 2000;47:1225.
 - [54] Sorensen RU, Hidalgo H, Moore C, Leiva LE. Post-immunization pneumococcal antibody titers and IgG subclasses. *Pediatr Pulmonol* 1996;22(3):167-73.
 - [55] Sorensen RU, Leiva LE, Giangrosso PA, Butler B, Javier FC, 3rd, 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(8):685-91.
 - [56] Sorensen RU, Leiva LE, Javier FC, 3rd, 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(2):215-21.
 - [57] Straetemans M, Sanders E, Veenhoven R, et al. Review of randomized controlled trials on pneumococcal vaccination for prevention of otitis media. *Pediatr Infect Dis J* 2003;22:515-24.
 - [58] Uddin S, Borrow R, Haeneuy M, et al. Total and serotype specific pneumococcal antibody titres in children with normal and abnormal humoral immunity. *Vaccine* 2006;24:5637-44.
 - [59] 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.

- [60] Wood P, Mayne A, Joyce H, et al. A mutation in Bruton's tyrosine kinase as a cause of selective anti-polysaccharide antibody deficiency. *J Pediatr* 2001;139:148.
- [61] Zhang Q, Finn A. Mucosal immunology of vaccines against pathogenic nasopharyngeal bacteria. *J Clin Pathol* 2004;57:1015-21.
- [62] Zielen S, Buhning I, Strnad N, et al. Immunogenicity and tolerance of a 7-valent pneumococcal conjugate vaccine in nonresponders to the 23-valent pneumococcal vaccine. *Infect Immun* 2000;68:1435.
- [63] 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.