

Immunization for Patients with Asplenia: Importance and Recommendations

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Abstract

The spleen is an important component of the lympho-hematopoietic complex system, playing a relevant role in the defense against infections. Patients with functional or anatomic asplenia have an increased susceptibility to infections related to the absence or reduction of splenic function. This group of patients is particularly vulnerable to encapsulated bacteria. Therefore, the infectious complications associated with these pathogens are the most threatening in the scenario of spleen function impairment.

Streptococcus pneumoniae, *Neisseria meningitidis* and *Haemophilus influenzae* type b are encapsulated bacteria and are considered to be the main factors responsible for infections with high morbidity and mortality in asplenic patients. Thus, immunization against these microorganisms is an indispensable strategy in order to ensure the survival of these individuals.

Keywords: Spleen; Encapsulated; Infections; Asplenic; Immunization

Introduction

The spleen is an important component of the complex lympho-hematopoietic system, playing a relevant role in the defense against infections. It acts by removing non-opsonized bacteria, antigen-antibody complexes and other antigens in the bloodstream. The spleen is also responsible for presenting antigens to T cells, for the differentiation of memory B cell and for the stimulation of the production of IgM antibodies and peptides that facilitate phagocytosis [1-5].

Therefore, the spleen is of great importance in the destruction and elimination via opsonization of extracellular encapsulated bacteria. These encapsulated pathogens containing polysaccharides in the cell wall induce a predominantly humoral immune response by means of T cell-independent mechanisms. The antibodies produced by marginal zone B cells without the involvement of T cells are generally of low affinity, consisting mainly of IgM with isotype changes limited to some IgG and IgA subtypes, which act on the opsonization and neutralization of microorganisms and activate the classical complement pathway [6]. On the other hand, macrophages present in the marginal zone have high-affinity receptors for capsular polysaccharide antigens and, when activated, they express C-type lectin (SIGN-R 1), capable of recognizing polysaccharides and activating the complement system, culminating in the destruction of these pathogens by lysis of the cell membrane [7-9]. Therefore, the removal of encapsulated bacteria is related to SIGN-R1 macrophages, complement activation and differentiation of B cells of the marginal zone [6].

Thus, asplenic patients (anatomic or functional) have increased susceptibility to infections caused by encapsulated bacteria, especially fulminant sepsis. The main pathogen responsible is *Streptococcus pneumoniae*, although *Haemophilus influenzae* type b and *Neisseria meningitidis* are also frequent etiological agents [1-5,10,11].

In this respect, vaccines against these microorganisms are formally indicated for all patients. In the case of elective splenectomy, they should be preferably administered at least 14 days before surgery (from 2 to 6 weeks). Regarding the impossibility of previous administration, the vaccine should be administered on the 14th postoperative day [1-5,10,12].

The indications of each vaccine for asplenic patients are addressed below.

Vaccination against *Streptococcus pneumoniae*

The risk of serious invasive infections by encapsulated bacteria in splenectomized patients is more than 50 times higher than in the general population; however, 50-90% of the cases are caused by *Streptococcus pneumoniae* [13].

Currently post-splenectomy fulminant sepsis has a mortality rate of 30-70% [14-16]. When routine immunization is adopted for patients with anatomic or functional asplenia, there is a reduction of sepsis rate by pneumococcus [17].

However, infection by serotypes that are not present in the vaccine is still a problem for these patients [18-20].

The 23-valent pneumococcal polysaccharide vaccine

This vaccine consists of unconjugated polysaccharides of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A,

19F, 20, 22F, 23F and 33F, accounting for 85% to 90% of the strains responsible for invasive disease in the USA and just over 80% in Brazil [4,10,11].

It is indicated for all asplenic patients over 2 years of age. Before this age, there is no recommendation, because the T-independent immune response triggered by polysaccharide antigens is unsatisfactory [21].

Whenever possible, the vaccine should be given within 2 weeks before elective splenectomy to obtain a more effective immune response [2,10-12]. Booster doses are recommended. If the first dose was administered before 7 years of age, the booster dose should be supplied at an interval of three years [10,12].

On the other hand, if the first dose of the vaccine was administered after 7 years of age, the booster dose should be administered at a 5-year minimum interval [1,3-5,10-12,22].

Due to the fact that antibody titers fall over the years in response to the vaccine, some European countries recommend revaccination every 5 years indefinitely [1].

Asplenic infants who were given complete schemes with conjugate vaccines should receive a dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) after completing 2 years of age, besides a booster dose after 5 years [1-3,10,12].

Adults aged ≥ 65 years who received an anti-pneumococcal vaccine in childhood/youth including the 23-valent polysaccharide pneumococcal vaccine (PPSV23), or before 60 years of age, should receive another dose of 23-valent polysaccharide vaccine [1,2,4].

Recent studies have shown that repeated exposure to the polysaccharide vaccine can induce immune tolerance or hyporesponsiveness. Accordingly, some guidelines recommend re-immunization with a single booster dose in immunocompromised patients [21].

The 7-valent conjugated vaccine

The 7-valent vaccine contains capsular polysaccharides of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F covalently bound to a protein. This combination aims to elicit a T-dependent immune response characterized by excellent immunogenicity in infants, high antibody concentration, induction of cellular memory and amplification of the immune response to subsequent exposure to the antigen [13].

It can be given to asplenic children under 2 years of age according to the routine immunization schedule depending on age (from 2 months) [12]. After completing two years, these children should receive the first dose of PPSV23 and its booster dose after 5 years due to the high risk of infection.

However, the 7-valent conjugate vaccine was replaced by the 13-valent vaccine. Patients with asplenia who had previously been vaccinated with a complete or incomplete schedule with the 7-valent vaccine must complete the schedule with the 13-valent vaccine and still receive an additional dose of the latter, besides two doses of the PPSV23 [2,3,22].

The 13-valent conjugate vaccine

This vaccine contains conjugate polysaccharides of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F. It is recommended for asplenic patients under 2 years of age, according to the vaccination schedules appropriate for early ages (from 2 months) [2,4,22].

Asplenic patients vaccinated with the 13-valent vaccine should receive an extra dose of the PPSV23 after completing 2 years of age, at least 8 weeks apart and a booster dose after 5 years [2,22].

The current recommendation for children and adults with asplenia (anatomic or functional) and who have never been vaccinated against pneumococcus is that they receive both the 13-valent pneumococcal conjugate vaccine (for which there are no age restrictions) and the PPSV23 vaccine, with a minimum interval of 8 weeks, and a booster dose of the latter vaccine [2,4,22].

Patients receiving an incomplete previous schedule of the 7-valent pneumococcal conjugate vaccines or the 10-valent pneumococcal conjugate vaccine or receive an extra dose of the same vaccine, besides the PPSV23 [2,22].

The 10-valent pneumococcal conjugate vaccine

This vaccine contains conjugated polysaccharides of serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F.

Children under 2 years of age who received an incomplete schedule with the 7-valent pneumococcal conjugate vaccine can complement it with the 10-valent conjugate vaccine [23].

Nevertheless, patients who are susceptible to invasive pneumococcal disease (asplenic patients and other conditions), even if they have been vaccinated with a complete schedule of the 10-valent conjugate vaccine, should receive an extra dose of 13-valent pneumococcal conjugate vaccine, which is the current pneumococcal conjugate vaccine recommended for children and adults with asplenia according to UK and US guidelines [2,4,22-24].

The 10-valent conjugate vaccine is routinely used in Brazil for children under 1 year of age, according to Ministry of Health.

Vaccination against *Haemophilus influenzae* type b (Hib)

Haemophilus influenzae type b is the most virulent of all serotypes. The conjugate vaccine against Hib is recommended for all asplenic patients not previously vaccinated [2,4,5,11,12,25].

For individuals over five years of age, even those not previously vaccinated, a single dose is sufficient because from that age almost all of them already have titers of anti-Hib antibodies acquired by passive or natural immunization [1,4,12].

However, for patients under 5 years of age, a booster dose is recommended, even if they had been previously vaccinated [1]. UK guidelines recommend one booster dose of Hib vaccine irrespective of immunization history in individuals aged 2 years and over [26].

In US, according to recommendations from the CDC/ACIP, hyposplenic children under 5 years of age should follow the same routine Hib schedule as in healthy children. For completely immunized children who are going to be splenectomized, an additional dose may be considered.

Previously unvaccinated or incompletely immunized children over 12 years of age with a defective spleen should be given one or two doses of Hib vaccine. The number of doses depends on their age at the time of the first dose and their vaccination history as presented in Table 1 [27].

Age, time of the first dose and vaccination history	Recommended Schedule
Patients aged <12 months	Follow routine Hib vaccination recommendations
Patients aged 12–59 months	If unimmunized or received 0 or 1 dose before age 12 months: 2 doses, 8 wks apart If received ≥2 doses before age 12 months: 1 dose 8 weeks after last dose. If completed a dose at age ≥12 months: no additional doses primary series and received a booster
Patients aged ≥15 months undergoing elective splenectomy	If unimmunized: 1 dose at least 14 days before procedure

Table 1: ACIP guidance for *Haemophilus influenzae* type b (Hib) vaccination in asplenic children under 5 years of age.

Vaccination against *Neisseria meningitidis*

The conjugate vaccine against *meningococcus* is recommended for all patients with asplenia according to recommendations from each country (there are epidemiological differences in prevalence of serogroups) [1,4,28,29]

Meningococcal C conjugate vaccine

The meningococcal C conjugate vaccine is recommended for all asplenic patients, with the indication of receiving a booster dose every five years [1,4,11].

Meningococcal ACWY conjugated vaccine

The meningococcal ACWY conjugated vaccine contemplates the polysaccharides of *Neisseria meningitidis* serogroups A, C, W-135 and Y. Two quadrivalent meningococcal vaccines are currently licensed by Anvisa in Brazil for use starting at 12 months of age (Nimenrix®) and at 24 months of age (Menveo®) [30,31]. In the US, the meningococcal ACYW conjugated vaccine is recommended by CDC/ACIP for all hyposplenic individuals. The schedule recommended for infants aged 2 months to 2 years consists of 3 doses administered at 12 week intervals (Menveo®), with a booster 3 years after the last dose and every 5 years thereafter [32]. For individuals older than 2 years, two doses separated by a 12 week interval are recommended (Menveo® or Menactra®); if the last dose is administered before seven years of age, the first booster should be administered after three years, with subsequent boosters at 5 year intervals thereafter [33,34].

Recombinant meningococcal B vaccine

The polysaccharide capsule of *Neisseria meningitidis* serogroup B is poorly immunogenic, probably for being structurally similar to the molecules found in human neural tissue [35-38]. Thus, the strategies for the development of a vaccine against *meningococcus B* have focused on non-capsular antigens [38-40].

The recombinant vaccine (Bexsero®) has four antigenic components which are subcapsular proteins able to promote coverage against several strains of serogroup B [41,42].

In Brazil, for infants between 2 and 12 months of age with functional or anatomic asplenia, the recommendation is 3 doses with an interval of two months and a booster hamerdose between 12 and 15

months. In unvaccinated children between 12 months and 10 years of age, two doses at a 2-month interval are recommended. Two doses separated by a one-month interval are recommended for adolescents and adults [42].

In Europe, the recombinant vaccine is licensed for use from two months of age. The schedule recommended by the UK Department of Health varies depending on the age at which the diagnosis of asplenia was made, as shown in Table 2 [25,43].

Age of diagnosis	Recommended schedule
< 6 months of age	1 dose at 2,3 and 4 months of age, with one month interval between doses. First booster dose will be given two months after completing 12 months of age and the second one after completing 24 months.
6 and 11 months of age	2 doses with an interval of two months. First booster dose at 12 months of age and the second one after 24 months of age
Between 12 and 24 months of age	2 doses with a 2 month interval. Booster dose with an interval of 12 to 23 months after completion of the initial schedule.
Over two years of age	1 dose of recombinant meningococcal B vaccine. 1 booster dose two months after the last booster dose of the combined vaccine against meningococcus C/Hb

Table 2: Recombinant meningococcal B vaccine schedule recommended by the UK Department of Health.

Diagnosis performed in children under 6 months of age: 1 dose at 2, 3 and 4 months of age, with one-month interval between doses. The first booster dose will be given two months after completing 12 months of age and the second one after completing 24 months of age.

Diagnosis performed between 6 and 11 months of age: 2 doses with an interval of two months, with the first booster dose at 12 months of age and the second one after 24 months of age.

Diagnosis performed between 12 and 24 months of age: 2 doses with a 2-month interval and the booster dose with an interval of 12 to 23 months after completion of the initial schedule.

Diagnosis performed over two years of age: 1 dose of recombinant meningococcal B vaccine and then 1 booster dose two months after the last booster dose of the combined vaccine against meningococcus C/Hib.

In the US, the FDA only licenses this vaccine for individuals over 10 years of age. Older patients with asplenia or hypoasplenia should receive 2 doses of Bexsero® vaccine or 3 doses of Trumenba® vaccine [44].

Vaccine against Influenza

The available vaccine contains surface antigens (hemagglutinin and neuraminidase) in their inactivated form from strains recommended by the World Health Organization, according to each season.

The influenza virus is a risk factor for secondary bacterial infections, especially pneumococcal pneumonia. Thus, vaccination against

influenza is recommended annually for asplenic patients over 6 months of age [1-4]. In patients under eight years of age, if there were no previous influenza vaccination, 2 doses with a 4-week interval would be recommended. Otherwise, one dose is recommended. From 9 years of age, the recommendation is one annual dose [45,46].

General Contraindications of Vaccination in Patients with Asplenia

There are no contraindications of vaccination in patients with anatomic or functional asplenia [47]. However, the Infectious Diseases Society of America (IDSA) does not recommend the Live Attenuated Influenza Vaccine (LAIV) for asplenic patients [35]. This recommendation has a low level of evidence, being based only on unsystematic clinical studies and case reports.

Furthermore, it is recommended that these individuals receive all vaccines of the basic schedule, which are appropriate for each age.

Final Considerations

Active immunization strategies against encapsulated organisms sharply decrease the sepsis rates caused by encapsulated germs in patients with anatomic or functional asplenia. Thus, vaccines against *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b are formally indicated for all patients.

Influenza vaccine is also recommended for all asplenic patients aged over 6 months because the influenza virus is an important risk factor for secondary bacterial infections, particularly pneumococcal pneumonia.

In cases of elective splenectomy, the vaccines should be administered preferably at least 14 days prior to surgery (from 2 to 6 weeks). Due to the impossibility of previous administration, the vaccines should be given on the 14th postoperative day, or as soon as the patient achieves clinical stability.

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