Post-Splenectomy Complications And Their Prevention

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Abstract
The spleen has several important functions in the human body, the leading of which is protective Therefore, its removal is often not safe, but is accompanied by various complications, primarily infectious and vascular, which can occur even 20 years after surgery. The most serious consequence of asplenia is the development of instant sepsis, which is accompanied by mortality of up to 70%. Therefore, it is important, first of all, to prevent infection in these patients. Using the literature from the MedLine database, modern ideas about the immunological function of the spleen, the pathogenesis of complications and the main ways of prevention, including the use of vaccines, antibiotics, are described. Particular attention is paid to the awareness of people with asplenia or hyposplenism.

Keywords: *spleen, splenectomy, complications, vaccination, antibiotics, education.*

Introduction

Asplenia is a complete loss of spleen function due to anatomical or functional reasons [1]. Anatomical asplenia occurs due to surgical removal of the spleen or its congenital absence in genetic variations, functional - most often (almost 100%) in sickle cell disease [1]. Conditions associated with the absence or decrease in spleen function are shown in Table 1 [2].

Table 1. Main causes of asplenia or hyposplenism [2]

Autoimmune	Systemic lupus erythematosus, rheumatoid arthritis, glomerulonephritis, granulomatosis with polyangiitis, anti-glomerular basement membrane disease, Sjogren's syndrome, nodular polyarteritis, thyroiditis, sarcoidosis, antiphospholipid syndrome, multiple sclerosis
Congenital	Congenital asplenia/hyposplenia, Ivemark syndrome, hypoparathyroidism syndrome, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome, Stomorken syndrome, congenital cyanotic heart disease
Gastro-intestinal	Celiac disease, inflammatory bowel disease, Whipple's disease, dermatitis herpetiform, intestinal lymphangiectasia, chronic ulcerative enteritis
Hematological/oncological diseases	Sickle cell disease (SS, SC, S/B-thalassemia, SE, etc.), bone marrow transplantation, graft versus host disease, acute leukemia, non-Hodgkin's lymphoma, chronic myeloproliferative disorders, advanced malignancies (breast), essential thrombocythemia, systemic mastocytosis, Sezary syndrome, pure red cell aplasia, Fanconi syndrome, malignant histiocytosis, splenic malignancy, selective IgA deficiency
Hepatic	Hepatitis, primary biliary cholangitis, cirrhosis, portal hypertension, alcoholic liver disease
Iatrogenic	Methyldopa, high doses of corticosteroids, general parenteral nutrition, splenic irradiation
Infectious	Human immunodeficiency virus, acquired immunodeficiency syndrome, pneumococcal infection/meningitis, malaria
Different	Amyloidosis, hypopituitarism, old age, surgical splenectomy
Vascular diseases of the spleen	Thrombosis of the splenic artery, thrombosis of the splenic veins, thrombosis of the celiac trunk

Splenectomy (SE) is oftenly performed as a rescue procedure for spleen injury with life-threatening hemodynamic instability, as therapeutic – in hematological conditions, to save lives - in patients with malignant tumors, tactical – to diagnose the disease [3]. The incidence of SE is approximately 6.4 – 7.1 per 100,000 population per year worldwide [4]. In the United States, for example, more than 22,000 SEs are held each year [5]. The spleen is an important organ in the modulation of immune response, thrombosis, and inflammation. In a patient with asplenia, these changes may cause systemic consequences in the form of severe sepsis or general microvascular dysfunction, as well as localized vascular processes in the form of thrombosis, myocardial infarction or pulmonary hypertension. It is unclear in which patients with asplenia these severe complications occur and why this cascade of events occurs. An understanding of the expected pathophysiological disorders is necessary for the appropriate prevention and treatment of critical conditions in patients with asplenia.

Immunological function of the spleen and the consequences of its loss

The spleen consists of cells involved in both innate and adaptive immunity. The cellular structure of the spleen is designed not only to effectively ensure immunity, but also to remove old or damaged erythrocytes from the circulation.

Red pulp macrophages filter the blood, removing solid particles larger than 1 μm from the circulation [3], eliminate bacteria, damaged erythrocytes and their inclusion. Macrophages remove cell fragments in the marginal area and in the embryonic center of the follicle. The white pulp of the spleen is a B-cell dominant (follicles) with some T-cell zones. Spleen B-cells are required for the production of specific antibodies for immunity (affinity maturation) and enhance the cytotoxic activity of T-cells. Some bacteria, such as encapsulated, require opsonization to facilitate phagocytosis. In this case, B-(IgM)-memory cells produce IgM, which acts as an opsonin to facilitate the clearance of polysaccharide-encapsulated

bacteria. The spleen is the only place where non-opsonized bacteria are eliminated [3], and is the main area of elimination of Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Capnocytophaga canimorsus, Escherichia coli, and Pseudomonas aeruginosa [3].

Due to its role in facilitating phagocytosis of infected erythrocytes, red spleen pulp is involved in protection against intra-erythrocyte parasitic infections such as babesiosis and malaria [6]. In addition, the spleen, along with the liver, removes C3b-opsonized immune complexes associated with complement 1 receptor (CR1), without lysis and sequestration of erythrocytes [7].

At the same time, there are also dendritic cells, natural killer cells, and monocytes in the spleen, which are involved in inducing a T-cell response to pathogens [8].

The spleen also produces and maintains levels of taftsin, which is important in stimulating phagocytosis [9].

Another important function of the spleen is the modulation of the inflammatory cascade. Swirski F. et al. [10] found that the mouse spleen is the main reservoir of non-circulating undifferentiated monocytes. These stress-releasing monocytes migrate to target tissues, differentiate into macrophages, and perform a variety of functions in addition to fighting infection, including facilitating tissue healing and repair [3, 11]. The spleen is also a specific and critical target of the cholinergic anti-inflammatory pathway, which inhibits proinflammatory cytokine production by transmitting vagus nerve signals through the α7 subunit of the nicotinic acetylcholine receptor. In nicotine-treated splenectomized mice, the α7 agonist, which mimics vagus nerve stimulation, increased inflammatory cytokine production and mortality from polymicrobial sepsis, suggesting that the spleen is important for a protective anti-inflammatory response dependent on α7nAC. Contrary, in unsplenectomized mice, nicotine administration protects mice from lethality from polymicrobial sepsis by inhibiting the production of proinflammatory cytokines through the α7 nicotinic acetylcholine receptor. Depletion of splenic nicotinic acetylcholine receptors after SE increases the level of tumor necrosis factor and a pronounced inflammatory response [12]. The spleen thus coordinates innate and adaptive immunity, and its loss can lead to impaired phagocytic function, dysfunction of adaptive and innate immunity, as well as increased regulation of the inflammatory cascade.

After SE there are changes in the number of cells, their quality and immune response. Reactive thrombocytosis and leukocytosis often occur initially after SE. Reactive thrombocytosis usually disappears 6-12 months after SE, but may persist. Leukocytosis is mainly due to granulocytosis, as neutrophils often increase after SE and can persist for many years [13]. Howell – Jolly bodies (nuclear residue of erythrocyte precursor), characteristic of asplenia, appear approximately 30 days after SE [13], as well as an increase in erythrocyte fossae [14]. In addition to the altered quality of erythrocytes, the proportions of lymphocytes change. Although the total number of B lymphocytes remains largely intact, there is a significant decrease in B (IgM) memory cells. This occurs approximately 150 days after SE [13] and leads to a decrease in the immune response to polysaccharide vaccines [15].

Lack of efficient opsonizing filtering function of the spleen increases the infection of poorly opsonized bacteria. Impaired clearance of the pathogen, which is caused by delayed and altered immunoglobulin production [16], decreased phagocytic function (absence of splenic macrophages and decreased production of taftsin) [17], increases both the rate of infection and susceptibility to severe infection. The complement system in patients after SE is largely intact because the major complement proteins C3, C4 and transferrin remain normal [17].

In addition to these immunological changes, a person after SE has a change in the course of systemic inflammation. After SE, the cholinergic anti-inflammatory pathway is completely inhibited [18].

Infectious complications after SE

Given the loss of important functions of the spleen, asplenia has an increased risk of infection and vascular complications [4]. Removal of the spleen leaves the body vulnerable to many infections because the ability to eliminate bacteria is weakened. The individual becomes susceptible to various respiratory, urinary, and meningeal infections with the development of irresistible post-splenectomy infection (OPSI - overwhelming post-splenectomy infection).

After SE, people have an increased risk of infection, mainly with encapsulated gram-negative pathogens [19, 20], and intra-erythrocyte parasites [21, 22]. In the late 1990s and early 2000s, pneumococcus was considered a major cause of post-SE infection (57-87%). However, recent studies suggest that Neisseria meningitidis and Haemophilus influenzae (type b) are also common etiological agents [23]. Gram-negative bacteria such as Pseudomonas aeruginosa, Capnocytophaga canimorsus, Bartonella spp. and Babesia spp. are less common [24]. Pneumococcal infection is by far the most common, with a mortality rate of up to 60% [3].

The risk of infection, sepsis, and mortality from infection in patients with asplenia is 2-3 times higher than in the general population [25]. This risk is greatest in patients younger than 5 years and older than 65 years [25]. After infection, patients have a higher risk of re-infection up to 3 years, which is almost 6 times higher than those who did not have a history of infection [26]. A 27-year study of 8,000 patients showed a relative risk of 1.98 for nonspecific pneumonia, 2.06 for pneumococcal pneumonia, 2.44 for meningitis, 3.38 for sepsis, and 3.02 for death from sepsis [4]. The risk of infectious processes in the urinary tract, as well as in atypical areas (eg, septic arthritis, epidural abscess, endocarditis) is increased [27], there is a higher risk of adrenal hemorrhage [28].

Irresistible post-splenectomy infection

People after SE have a high risk of developing OPSI, which is often caused by encapsulated bacteria such as Streptococcus pneumoniae, Neisseria meningitidis and Haemophilus influenzae type B or gram-negative bacteria such as Escherichia coli and Pseudomonas (spp.). The prevalence of OPSI after splenectomy is 0.1-0.5%, with mortality up to 70% [29]. OPSI, although defined differently [26], is usually characterized as a syndrome of fulminant sepsis, which may initially be manifested by generalized nonspecific viral symptoms, but very quickly, within 24-48 hours, turns into sepsis. OPSI usually

begins with fever, chills, rigidity, myalgia, vomiting, and diarrhea [25]. After 2 days, a rash may develop, accompanied by severe decompensation within a few hours, which may be manifested by hypotension, septic shock, disseminated intravascular coagulation, acute respiratory distress syndrome, and multiple organ failure. [29]. OPSI is an urgent situation in the clinic, as shock and death can occur within 12-24 hours after the onset of symptoms [30].

The period of the highest risk of OPSI - the first 3 years after SE; however, the risk remains high throughout human life, as evidenced by reports of fulminant infections 20 years after SE [29]. Children under 2 to 5 years of age, those who have had SE after an injury, with a haematological or other malignancy, and people with immunosuppressive or immunodeficient states are at greater risk for OPSI [31].

Sepsis in a patient after SE should be treated quickly and aggressively to prevent a fulminant course of the disease. In this case, before the introduction of antibiotics, it is necessary to make two blood cultures to detect the pathogen. Gram staining can speed up the identification of the pathogen and target a more specific and appropriate course of antibiotics. Aggressive fluid resuscitation and intensive care are necessary for these people. The use of extracorporeal blood purification treatment should also be considered to reduce inflammatory mediators concentration and improve hemodynamic stability [32, 33]. Despite the severity and mortality of sepsis in patients after SE, there are no prospective clinical studies that determine the optimal therapy. Cefepime and vancomycin are recommended for adult patients with asplenia in acute infection [27]. Alternative empirical schemes include vancomycin plus ceftriaxone, levofloxacin or ciprofloxacin. These schemes provide coverage against S. pneumoniae, S. aureus, H. influenzae, Neisseria meningitidis and susceptible Enterobacteriaceae. If there is a concern for resistant gram-negative pathogens, these schemes should be changed to include targeted antimicrobial coverage of these organisms. Cephalosporins should be a priority in cases of proven or suspected central nervous system infection. The pleiotropic anti-inflammatory effect of the macrolide in combination with the β-lactam antibiotic may be useful in the empirical treatment of critically ill patients with asplenia and S. pneumoniae infection, although this issue has not been studied specifically in the SE population.

Vascular complications

Patients with asplenia have a higher risk of arterial and venous thrombosis [34]. The risk of these vascular complications is associated with ongoing intravascular hemolysis, thrombocytosis and platelet activation, the presence of nuclei-containing erythrocytes, and mistakes in transfusion therapy [35], and may be due to chronic inflammation and endothelial dysfunction. Erythrocyte membrane disorders, circulating microparticles, and cell-free hemoglobin from hemolysis have been shown to alter vascular endothelium, disrupting nitric oxide metabolism and function [36]. These changes contribute to vasoconstriction, smooth muscle proliferation, and activation of endothelium and platelets, especially in the pulmonary circulation [37].

Deep vein thrombosis (DVT), pulmonary embolism (PE), splenic and portal vein thrombosis are associated with SE [38]. PE is the leading cause of death in patients after SE with the death of upper 30% [39]. The frequency of VTE is from 10% to 37.2%, even with appropriate prophylaxis [38], and 6.7% of patients developed DVT within 3 months after SE [40].

The risk of VTE is particularly high (93-100%) in patients with asplenia due to haematological diseases such as stomatocytosis [41], thalassemia [42]. Changes in the phospholipid composition of the erythrocyte cell membrane provide a procoagulant surface for increased thrombin formation and hypercoagulation in thalassemia [43]. In addition, patients with thalassemia have changes in endothelial adhesion molecules, which may further promote hemostasis and vascular occlusion; after SE, these patients have elevated levels of P-selectin, indicating ongoing platelet activation [44]. These changes may be combined with post-splenectomy leukocytosis, thrombocytosis, and increased hemoglobin, cholesterol, and C-reactive protein levels. Atichartakarn V. et al. [45] found that patients with hemoglobin E/beta-thalassemia after SE had hyperactive platelets (determined by hyperaggregation in response to adenosine diphosphate, thrombin, and ristocetin) compared with normal and patients with hemoglobin E/beta thalassemia without SE. Elevated plasma thrombin levels were also observed, suggesting that long-term intravascular coagulation was observed in these patients. Crary S. and Buchanan G. [46] reported an increased risk of VTE in SE patients with hemolytic processes other than beta-thalassemia.

Splenectomy is a risk factor for pulmonary hypertension (PH) due to complex mechanisms, including the above-mentioned inflammation and thrombosis. The frequency of PH in patients after SE from 8% to 11.5% has been reported [47]. In addition, the prevalence of PH in patients with asplenia with hemoglobinopathies, such as thalassemia and sickle cell disease, maybe even higher, and reported cases consistently exceed 30% [48]. Many studies have also shown an association between SE and chronic thromboembolic PH [49, 50]. The pathophysiology of PH in patients with asplenia is complex and not fully understood. Potential mechanisms include nitric oxide deficiency, hemolysis, endothelial dysfunction and damage, development and circulation of microparticles [34], such as components of erythrocytes, leukocytes, platelets, and endothelial cells. These components play a significant role in immunity, inflammation, cell adhesion, endothelial cells function, smooth muscle function, blood clotting, and angiogenesis [34].

Robinette C. and Fraumeni J. [51] published an important series of cases in 1977, which described a long-term increase in the risk of death in 740 World War II soldiers who suffered from SE due to injury. In addition to pneumonia, the authors also noted an increased risk of death from heart diseases.

Prevention of complications after splenectomy

There are currently three main aspects of long-term management of patients who have suffered from SE to prevent adverse effects, especially OPSI, as mortality rates remain high. Patient education, vaccination, and antibiotic prophylaxis are important [23].

Patient education

Patient education is considered an integral, if not the most important, factor in preventing OPSI. Individuals should be aware of their post-SE condition, increased risk of infection, how to prevent the risk of infection, and what to do if they become ill [52]. In addition, SE individuals should consult a physician before any trip, especially if they are traveling to a country that is endemic for malaria. Studies showed that a large proportion of patients after SE had limited knowledge of asplenia and related potential complications [53, 54]. This emphasizes the importance of health professionals in educating patients with asplenia.

The vast majority (85%) of patients after SE are unaware of their increased susceptibility to infectious diseases and the need to take appropriate safety measures [55]. Insufficient information and lack of training are the main reasons of this lack of awareness [56]. Patients and their families should be informed of their asplenic status in written and electronic form.

Information to be provided to people with asplenia [3, 57, 58]:

- Splenectomy carries an increased risk of infection throughout life;
- Initial symptoms of OPSI include fever (> 38° C), chills, myalgia, headache, vomiting, and abdominal pain;
- Patients should not be concerned about minor viral infections (eg, chills without fever or other common symptoms);
- Contact a doctor immediately for animal bites and scratches;
- Dental procedures usually do not require the additional use of antibiotics, unless indicated for a medical condition;
- Pregnancy or breastfeeding does not increase the risk of infection, but the timing of the recommended vaccinations for asplenia should be discussed with the doctor;
- Think about the need to see a doctor before traveling, especially before visiting a malaria-endemic area;
- Always carry antibiotics (may be helpful in case of sudden illness);
- Patients should be informed of the risks and types of infection, the importance of vaccinations and when to seek further medical care;
- Instructions for asplenia are best displayed on a bracelet or special card;
- Patients should inform all healthcare professionals about their immune status;
- If available, you should consider registering in a special register.

Vaccination

Patients after SE have impaired immune memory due to lack of B-(IgM)-memory cells and defects in opsonization and purification of encapsulated bacteria. Vaccination against S. pneumoniae, N. meningitidis and H. influenzae type b (Hib) can help in preventing OPSI by establishing immunological memory. Vaccination with conjugated vaccines or combined regimens with polysaccharide vaccines are aimed at ensuring proper immunological memory and broad coverage of serotypes. Conjugate vaccines provide better immune responses in people with asplenia than polysaccharide vaccines. Immunological memory initiated by polysaccharide vaccine is based on the thymus-independent (T-cell-independent) pathway, which is significantly impaired after SE. Conjugated vaccines, however, use the thymus-dependent (T-cell-dependent) pathway to establish immunological memory that remains intact [59]. While mucosal vaccines are currently being studied to induce immunity against S. pneumoniae and N. meningitidis serotype B, their role in individuals with asplenia has yet to be assessed [60].

Pneumococcus may be a target when using a combined 13-valent conjugate vaccine (PCV13) with a 23-valent polysaccharide (PPV23) [52]. This is aimed to ensure both efficient and widespread coverage of pneumococcal serotypes. Conjugated meningococcal vaccines are recommended for people with asplenia as a tetravalent vaccine (serotypes A, C, W, and Y), as well as a recently available vaccine against serotype B. Hib vaccines are often conjugated to diphtheria or other proteins and can be safely administered to people with asplenia. Although flu itself does not pose a significant risk to a patient after SE, there is an increased risk associated with secondary bacterial infection. Thus, seasonal (annual) flu vaccination is also recommended. There is little variability in the recommendations for vaccination of people with asplenia. Recent guidelines [3, 61, 62] recommend the introduction of PCV13 before the introduction of PPV23. The same guidelines also recommend starting and booster doses of tetravalent meningococcal conjugate vaccine (MenACWY) and recombinant meningococcal B vaccine (MenBV) in SE adult patients. In addition to the pneumococcal and meningococcal vaccine recommendations, all recommendations support the administration of a single dose of Hib vaccine and a seasonal annual flu vaccine.

Based on the Adult Immunization Schedule recommended by the Centers for Disease Control and Prevention (CDC), in Table 2 are shown details and timings of vaccination of SE patients [63].

Table 2. CDC (Centers for Disease Control and Prevention) recommendations for adult immunization after splenectomy [67]

Recommended vaccine	Dose	Route of administration	Terms
Hospital protocol			
Pneumococcal 13-valent conjugate (PCV13: Prevnar 13)	0,5 ml	intramuscularly	On the day of discharge or on the 14th day, if it occurs earlier
Haemophilus influenza type b Vaccine (Hib: ActHIB)	0,5 ml	intramuscularly	On the day of discharge or on the 14th day, if it occurs earlier
Meningococcal vaccine (Menactra)	0,5 ml	intramuscularly	On the day of discharge or on the 14th day, if it occurs earlier
Meningococcal serogroup B (Bexsero)	0,5 ml	intramuscularly	On the day of discharge or on the 14th day, if it occurs earlier
Short-term follow-up			
Pneumococcal polysaccharide (PPSV23: Pneumovax 23)	0,5 ml	intramuscularly	Two months after the initial vaccination
Meningococcal vaccine	0,5 ml	intramuscularly	Two months after the initial vaccination
Meningococcal serogroup B	0,5 ml	intramuscularly	Two months after the initial vaccination
Long-term follow-up			
Pneumococcal polysaccharide	0,5 ml	intramuscularly	5 years after the first dose

Meningococcal vaccine	0,5 ml	intramuscu-larly	Every 5 years
Seasonal flu vaccine			Annually

Of particular note are the current vaccination guidelines from Spleen Australia, which is considered the best in the world for monitoring people with asplenia and hyposplenism [58] (figure 1, 2). These guidelines take into account the availability of new vaccines and are introduced from October 2021. To date, almost 12,000 people are listed in the Spleen Australia registry.

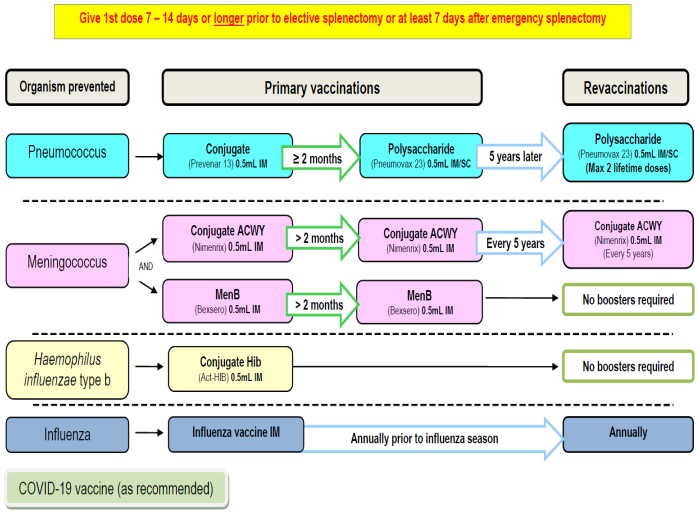

Figure 1. Spleen Australia – Medical Recommendations Vaccines for adults (>18 years) with asplenia/hyposplenism who have not previously been vaccinated

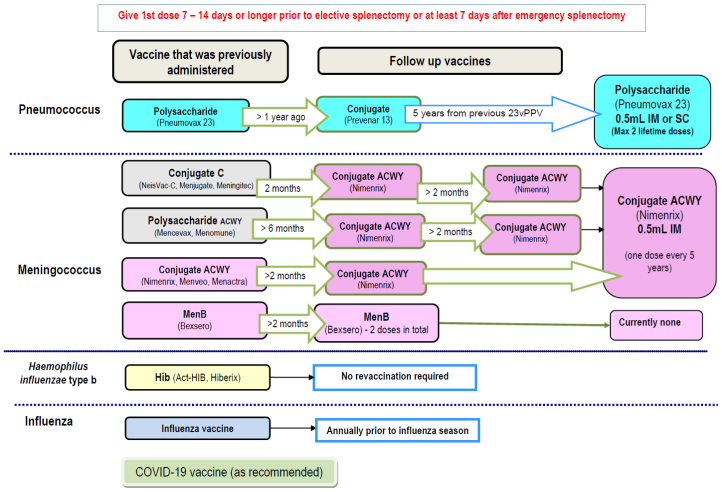

Figure 2. Spleen Australia – Medical Recommendations Vaccines for adults (>18 years) with asplenia/hyposplenism who have had one or more previous "spleen vaccines"

Antibiotic prophylaxis

Because the risk of infection is highest in the first years after SE, daily antibacterial prophylaxis is recommended for all individuals during the first few years after SE. These antibiotic recommendations are based on two studies in children with hyposplenism secondary to sickle cell disease [64, 65], in which antibiotic prophylaxis reduced S. pneumoniae infection. No studies have been performed to evaluate the effect of daily antibiotic use on any other indications before SE in adults. In addition, there are many questions about long-term use of antibiotics, including microbial resistance [66]. It remains unclear whether the benefits of antibacterial prophylaxis are appropriate for other SE groups and/or adults. Initially, after SE, most guidelines recommend a daily regimen of antibiotic therapy, whereas the need for lifelong consumption can be decided after assessing the risk of infection [57]. According to the British recommendations [23], to risk groups are included:

- Children under 16 years;
- Adults over 50 years;
- Individuals with a history of invasive pneumococcal infection in the past;
- SE in patients with hematological or other malignancies and thalassemia;
- Individuals in the first year after SE, regardless of the cause;
- Patients with sickle cell anemia;
- Individuals with a weak response to PPV-23 (pneumococcal polysaccharide vaccine).

Australian guidelines recommend three years of daily antibiotic prophylaxis after SE [58]: amoxicillin 250 mg once daily or phenoxymethylpenicillin (penicillin V) 250 mg twice daily. Immunocompromised patients are recommended to take lifelong antibiotics [58]. Guidelines in other countries differ in their recommendations for the duration of daily use of antibiotics after SE [3].

In addition to the daily use of antibiotics, SE individuals are encouraged to have their own reserve of antibiotics in the case of an emergency. These guidelines suggest that in the case of OPSI-related illness or symptoms, patients should self-administer high doses of antibiotics and seek medical care immediately. Amoxicillin clavulanate or cefdinir are the best options [3]. Levofloxacin or moxifloxacin are recommended for patients with severe allergies or intolerances.

Conclusion

The body's immune defenses are reduced with the removal of the spleen, providing a gateway for infection by poorly opsonized bacteria. Sepsis in SE individuals is often severe and is accompanied by significant morbidity and mortality. The physician should be aware to both infectious and vascular complications after SE: thrombosis/VTE, PH, and possibly cardiovascular disease. Shock in critically ill patients after SE may be due to the vasodilatory effect of fulminant sepsis, left ventricular dysfunction from pre-existing coronary heart disease or right ventricular failure resulting from previous PH or PE. A systematic strategy that takes all of these conditions into account is important when choosing appropriate resuscitation support. Prevention by vaccination, antibiotics and patient education are necessary to reduce the risk of infection. Early identification and prompt treatment in case of infection give a patient the best chance of survival. Further research is needed to optimize existing prevention strategies and improve therapy to reduce the impact of OPSI in humans after SE.

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