

Prevention of sepsis in patients with impaired splenic function

Prevenção de sepse em pacientes com função esplênica prejudicada

Prevención de la sepsis en pacientes con función esplénica alterada

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Abstract

Asplenia refers to the complete loss of spleen function, while hyposplenism refers to the partial loss of splenic function, which may be of primary or secondary origin. The spleen is a secondary lymphoid organ, however, it is also connected with blood circulation. This organ houses a variety of cells, such as T and B lymphocytes, macrophages, dendritic cells, cytokines and antibodies essential for the development of immune responses. In this context, sepsis represents a risk for this group of patients and should be avoided with prophylactic measures, with the majority of infections being caused by encapsulated bacteria. To this end, a literature review was prepared with the main evidence on the prevention of sepsis in patients with asplenia/hyposplenism, using 17 materials from the SciELO, PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews (CDSR) databases, EBSCOhost, Virtual Health Library (VHL) and UpToDate. Prevention of sepsis in patients with asplenia or hyposplenism has been shown to involve a combination of vaccination, antibiotic prophylaxis, patient education, and appropriate medical monitoring. It is essential that patients follow medical advice and are aware of the risks and preventive measures necessary to protect their health. Due to the lifelong risk associated with infection in these patients, efforts are focused on improving the quality of care provided to children and adults with restricted splenic function, in addition to ongoing research aimed at alternatives for preventing and treating this condition.

Keywords: Asplenia; Hyposplenism; Sepsis; Prophylaxis.

Resumo

Asplenia refere-se à perda completa da função do baço, enquanto hipoesplenismo refere-se à perda parcial da função esplênica, que pode ser de origem primária ou secundária. O baço é um órgão linfóide secundário, porém também está relacionado à circulação sanguínea. Este órgão abriga uma variedade de células, como linfócitos T e B, macrófagos, células dendríticas, citocinas e anticorpos essenciais para o desenvolvimento de respostas imunes. Neste contexto, a sepse representa um risco para este grupo de pacientes e deve ser evitada com medidas profiláticas, sendo a maioria das infecções causadas por bactérias encapsuladas. Para tanto, foi elaborada uma revisão de literatura com as principais evidências sobre a prevenção da sepse em pacientes com asplenia/hiposplenism, utilizando 17 materiais das bases de dados SciELO, PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews (CDSR), EBSCOhost, Biblioteca Virtual em Saúde (BVS) e UpToDate. Foi demonstrado que a prevenção da sepse em pacientes com asplenia ou hiposplenism envolve uma combinação de vacinação, profilaxia antibiótica, educação do paciente e monitoramento médico apropriado. É essencial que os pacientes sigam as orientações médicas e estejam cientes dos riscos e das medidas preventivas necessárias para proteger a sua saúde. Devido ao risco vitalício associado à infecção nesses pacientes, os esforços estão focados na melhoria da qualidade do atendimento prestado a crianças e adultos com função esplênica restrita, além de pesquisas em andamento visando alternativas de prevenção e tratamento dessa condição.

Palavras-chave: Asplenia; Hiposplenism; Sepse; Profilaxia.

Resumen

La asplenia se refiere a la pérdida completa de la función del bazo, mientras que el hipoesplenismo se refiere a la pérdida parcial de la función esplénica, que puede ser de origen primario o secundario. El bazo es un órgano linfóide secundario, pero también está relacionado con la circulación sanguínea. Este órgano

alberga una variedad de células, como linfocitos T y B, macrófagos, células dendríticas, citoquinas y anticuerpos esenciales para el desarrollo de respuestas inmunes. En este contexto, la sepsis representa un riesgo para este grupo de pacientes y debe evitarse con medidas profilácticas, siendo la mayoría de las infecciones causadas por bacterias encapsuladas. Para ello, se elaboró una revisión de la literatura con las principales evidencias sobre la prevención de la sepsis en pacientes con asplenia/hipospenia, utilizando 17 materiales de las bases de datos SciELO, PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews (CDSR), EBSCOhost, Biblioteca Virtual en Salud (BVS) y UpToDate. Se ha demostrado que la prevención de la sepsis en pacientes con asplenia o hipospenia implica una combinación de vacunación, profilaxis antibiótica, educación del paciente y seguimiento médico adecuado. Es fundamental que los pacientes sigan los consejos médicos y sean conscientes de los riesgos y las medidas preventivas necesarias para proteger su salud. Debido al riesgo de por vida asociado con la infección en estos pacientes, los esfuerzos se centran en mejorar la calidad de la atención brindada a niños y adultos con función esplénica restringida, además de investigaciones en curso dirigidas a alternativas para prevenir y tratar esta condición.

Palabras clave: Asplenia; Hipospenia; Septicemia; Profilaxis.

1. Introduction

Asplenia refers to the complete loss of spleen function and can be anatomical or functional. Anatomical is secondary to surgical splenectomy, whether performed by trauma or therapeutically (e.g., for hemolytic anemias or immune thrombocytopenias) or to congenital absence conditions. Functional asplenia translates into complete loss of function caused by medical conditions and occurs more frequently in sickle cell anemia (Pasternack, 2022).

Hyposplenism refers to partial loss of splenic function and is commonly caused by medical disorders that lead to atrophy, infarction, engorgement, or infiltration of the spleen, such as thalassemias, chronic liver disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), immunological disorders or malignant diseases (Premawardena et al., 2018; Pasternack, 2022).

The functions attributed to the spleen were little known in the past. Therefore, total splenectomy was considered the only therapeutic option regardless of the type and extent of the splenic disease for many years (Rezende, 2007). The spleen is a secondary lymphoid organ, however, it is also connected with blood circulation. This organ houses a variety of cells, such as T and B lymphocytes, macrophages and dendritic cells. It is also important in the production of cytokines and antibodies essential for the development of immune responses (Kanhutu et al., 2017).

The risk of infection after splenectomy is well documented and a spectrum of microorganisms can cause serious infections. Most cases of serious infection are due to encapsulated bacteria, such as *Streptococcus pneumoniae* (pneumococcus), *Haemophilus influenzae* type b, and *Neisseria meningitidis* (meningococcus). Pneumococcal infection is more common and causes a mortality rate of up to 60%. Infection with *H. influenzae* type b is much less common, but no less significant, particularly in children. Meningococcus can also be associated with a serious infection. Other infections include *Escherichia coli*, malaria, babesiosis and *Capnocytophaga canimorsus* which is associated with dog bites (Kanhutu et al., 2017; Rezende, 2007).

Infections generally appear within the first two years after splenectomy, but up to a third may appear at least five years later. Cases of fulminant infection have been reported more than 20 years after splenectomy. The risk of dying from serious infection, although not quantifiable, is clinically significant throughout life. Patients should receive appropriate vaccination and counseling on antibiotic prophylaxis (Picoita et al., 2020). From this perspective, the objective of this study was to prepare a literature review with the main evidence on the prevention of sepsis in patients with asplenia/hyposplenia.

The present study is justified by the need to prepare a literature review on the prevention of sepsis in patients with asplenia/hyposplenia based on the main available evidence. Asplenic or hyposplenic patients are at risk for fulminant sepsis. This entity has a mortality rate of up to 50%. The spectrum of causative organisms is evolving, as are recommended preventive

strategies, which include education, prophylactic and backup antibiotics, preventive immunizations, optimal antimalarial counseling when visiting endemic countries, and early treatment of animal bites (Dendle et al., 2012).

2. Methodology

This is a descriptive study, based on a literature review on infection prevention strategies in the context of asplenia/hyposplenia. Data collection was carried out using the SciELO, PubMed, Web of Science, Scopus, Cochrane Database of Systematic Reviews (CDSR), EBSCOhost, Virtual Health Library (VHL) and UpToDate, as well as analyzing updated protocols and renowned literature on the topic, selecting studies in revision of theme of the last years, like this as books text classics, regardless of the date. The following descriptors were used: “spleen”, “hyposplenia”, “sepsis” and “prophylaxis”, between the years 2010 and 2023.

To develop the research question for this review, the following steps were used: identification of the topic and selection of the research question; establishment of inclusion and exclusion criteria; identification and selection of studies; categorization of selected studies; analysis and interpretation of results and presentation of the review/synthesis of knowledge. 19 materials were selected for the construction of the literature review. A literature review was prepared addressing indications, contraindications and other relevant aspects for the management of patients with asplenia and hyposplenia in the context of avoiding sepsis and other infections.

3. Results and Discussion

Although the role of the spleen is not essential for survival, removing this organ is not without consequences. Before the 20th century, the spleen was widely considered an obsolete organ. However, it is now clear that splenectomy, as well as hyposplenia, are associated with an increased risk of infections and thromboembolic events (Chonget al., 2017).

Globally, the occurrence rate of splenectomies is approximately 6.4-7.1 cases per 100,000 individuals each year, with trauma (25%) and hematological disorders (25%) appearing as the most frequent causes. Abdominal injuries that result in rupture of the spleen, causing internal bleeding and hemodynamic instability, often lead to the need for splenectomy. However, due to the emergence of alternative approaches, the frequency of splenectomies in trauma cases is declining. Hematological conditions that may require splenectomy include idiopathic thrombocytopenic purpura (ITP), sickle cell disease, thalassemia and hereditary spherocytosis (Tahir; Ahmed; Malik, 2020).

Thus, splenectomy, although often necessary in healthy patients after severe trauma, has found its primary indication for patients with underlying malignant or non-malignant hematological diseases. Rarely, spleen rupture can occur spontaneously, more frequently in a pathological spleen for infectious and/or hematological diseases and in patients taking anticoagulation. Considering splenic function and vulnerability to infections, the specific role in removing encapsulated bacteria is related to marginal zone macrophages, which can detect and capture such organisms (Leone & Pizzigallo, 2015).

Sepsis in patients with impaired or absent splenic function requires immediate and forceful intervention to prevent fulminant disease progression. To optimize initial management, sepsis treatment protocols are available. In this context, it is essential to collect two sets of blood cultures before starting the administration of antibiotics, as this is crucial to identify the pathogen responsible. Urgently performing a blood smear for leukocyte analysis or Gram staining can accelerate the identification of the pathogen, allowing for more specific and appropriate antibiotic treatment (Rubin & Schaffner, 2014; Davies et al., 2011).

- **Vaccination**

All hyposplenic patients should be immunized in accordance with national immunization programs unless specific individual contraindications exist, such as anaphylaxis to any component of the vaccine. The live attenuated intranasal influenza vaccine (LAIV) is the only vaccine not recommended in hyposplenic patients due to lack of data, so far. Furthermore, additional vaccines targeting infections associated with splenic dysfunction are recommended in this group of patients (Rubin & Schaffner, 2014; Duarte et al., 2014).

According to updated Australian protocols and guidelines (Kanhutu et al., 2017), individuals undergoing splenectomy have compromised immunological memory due to the absence of IgM memory B cells and the reduced capacity to opsonize and eliminate encapsulated bacteria. Vaccination against *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib) can help prevent sepsis by establishing effective immunological memory (Leone & Pizzigallo, 2015). Vaccines should initially be administered 14 days before planned splenectomy or 14 days after emergency splenectomy to ensure an adequate immune response (Wanget al., 2014).

To target pneumococcus, it is possible to use a combined regimen of the 13-valent conjugate vaccine (PCV13) and the 23-valent polysaccharide vaccine (PPV23). The objective is to ensure effective and broad coverage of pneumococcal serotypes. Broad-coverage conjugate vaccines currently in development and testing will provide superior immune responses to a broader range of pneumococcal serotypes (Lee, 2020). Conjugate vaccines are also recommended for the prevention of meningococcal meningitis, including a quadrivalent vaccine (serotypes A, C, W and Y) and a recently available serotype B vaccine (Hernandez et al., 2019; Nascimeno et al., 2015).

Additionally, Hib vaccination is often performed in combination with other vaccines, such as diphtheria, and can be safely administered to splenectomized individuals. Annual vaccination against seasonal flu is also recommended, as flu increases the risk of secondary bacterial infections (Davies et al., 2011).

More recent guidelines recommend the administration of PCV13 before PPV23, in addition to initial and booster doses of quadrivalent meningococcal conjugate vaccines (MenACWY) and recombinant meningococcal B vaccines (MenBV) in adult patients undergoing splenectomy (Leone & Pizzigallo, 2015). However, the administration of PCV13, booster doses of MenACWY or MenBV in splenectomized individuals is still controversial. Despite variations in recommendations for pneumococcal and meningococcal vaccines, all guidelines are consistent in recommending a single dose of the Hib vaccine and the annual seasonal flu vaccine (Hernandez et al., 2019).

Nationally, according to the guidelines of the Manual of Reference Centers for Special Immunobiologicals, of the Ministry of Health (2019), vaccination for patients who have undergone splenectomy should be conducted as follows: For immunizations such as measles, rubella, mumps (MMR), BCG, anti-polio and DTP, the schedule is the same as for individuals without splenectomy. For the Hib vaccine, 3 doses are required for those 2 to 6 months of age at 60-day intervals, 2 doses for children 7 to 11 months of age (4 to 8 weeks apart), and a single dose for people from 1 to 19 years old.

In the case of the pneumococcal vaccine, PPV-23 is administered in a single dose for those over 5 years of age, with a booster every 5 years, while PPV-7 requires 2 or 3 doses at 60-day intervals for children under 5 years of age. Chickenpox is administered from 1 year of age, with one dose for children under 13 years of age and two doses spaced 4-8 weeks apart for those over 13 years of age. Influenza vaccination must be carried out annually before winter, with a single dose for those over 8 years of age and two doses spaced 4-6 weeks apart for children aged 6 months to 8 years (Brasil, 2019).

The meningococcal conjugate vaccine (MncC) starts at 2 months of age, with 2 to 3 doses for children under 1 year of age, depending on the manufacturer, and a single dose for those over 1 year of age. Vaccination against hepatitis B is indicated for unvaccinated people, following the standard 3-dose schedule with intervals of 1 month between the first and second dose and 6 months between the first and third dose. Vaccination against hepatitis A consists of 2 doses 6 months apart, with the

choice of adult or pediatric dose depending on the manufacturer. It is important to note that, in cases of elective splenectomy, the vaccine must be administered at least 2 weeks before surgery (Brasil, 2019).

- **Antibioticotherapy**

Because the risk of infection is highest in the first few years after splenectomy, it is recommended that all patients undergoing splenectomy take daily antibiotic prophylaxis during this initial period. The Australian Antibiotic Guidelines and Spleen Australia recommend 3 years of daily antibiotic prophylaxis after splenectomy. Guidelines elsewhere may vary in their recommendations for the duration of daily antibiotic use after splenectomy. Individuals at high risk of infections due to other comorbidities may need daily antibiotics throughout their lives (Kanhutu et al., 2017).

Antibiotic prophylaxis is advised for several groups, including children under 16 years of age, adults over 50 years of age, patients who have had previous episodes of severe pneumococcal infections, people with compromised immune systems - individuals splenectomized for hematological malignancies, malignant neoplasms and thalassemia, individuals in the first year post-splenectomy, regardless of the cause (Tahir; Ahmed; Malik, 2020).

Australian guidelines suggest that patients with this condition should have a supply of antibiotics available for use when they suddenly experience symptoms and signs of infection and cannot be readily assessed by a doctor. Recommended antibiotic options include Amoxicillin (An initial dose of 3 g, followed by 1 g every 8 hours), Amoxicillin in combination with clavulanic acid (500/125 mg, every 8 hours), Cefuroxime (250 mg, every 12 hours) and Moxifloxacin (for patients allergic to penicillin) (Lee, 2020).

Streptococcus pneumoniae infections prolonged use of antibiotics presents challenges, such as microbial resistance and issues related to medication adherence. It is still unclear whether the benefits of antibiotic prophylaxis are appropriate for other groups of patients undergoing splenectomy or for adults (Rubin & Schaffner, 2014; Di Sabatino et al., 2011). Some guidelines do not recommend an initial period and suggest lifelong antibiotics for all individuals undergoing splenectomy. Most guidelines recommend an initial period of daily antibiotic use after splenectomy and then consideration of continued use based on the risk of infection (Kanhutu et al., 2017).

In addition to daily antibiotic use, it is recommended that individuals undergoing splenectomy carry their own supply of high-dose antibiotics for use in an emergency. These recommendations suggest that, in case of illness or symptoms related to post-splenectomy sepsis, patients should self-administer a high dose of antibiotics and seek emergency medical care (Davies et al., 2011; Taniguchi, 2014).

- **Clinical registration and health education**

Studies conducted by Montes (2021) suggested that the use of clinical records can improve acceptance and adherence to recommended interventions, as well as patient education. Previously, several registries existed for individuals with asplenia, including formal registries and informal registries. These records served several purposes, such as review of immunization at registration over a 2-year period, adherence and acceptance of preventive interventions, and ongoing clinical management.

According to Kanhutu et al. (2017), the UK Department of Health provides education and treatment for individuals with asplenia. Unlike the UK, Spleen Australia, a clinical service based at The Alfred Hospital in Melbourne, provides education and ongoing management recommendations for patients and their doctors. Studies have shown that the local clinical registry, the Spleen Australia clinical registry, improves patient adherence to booster vaccines, is associated with a reduction in invasive pneumococcal disease, and is cost-effective in its activities. Improving vaccination uptake through participation in a registration program has also been demonstrated in other settings. The Spleen Australia registry is aimed at individuals with

asplenia and hyposplenism in Australia and has been shown to be effective in improving the long-term care of these patients (Edgren et al., 2014).

Awareness of the impact and severity of sepsis during stages of asplenia or hyposplenism among healthcare professionals, patients and the wider community is essential. Individuals who have had total splenectomy should be registered in a splenectomy registry, if available. Furthermore, as explained above, they must receive adequate prophylaxis (Davies et al., 2011; Kanhutu et al., 2017). Patients must have a complete understanding of the risk of infection without a functioning spleen and know what to do if they become ill. Prevention of infections and immediate treatment are imperative to ensure the best chance of surviving the condition without complications. Additionally, further research into the effectiveness of recommended interventions will allow clinicians to optimize treatment for these patients (Rubin & Schaffner, 2014).

It is extremely important to provide health education to all patients after surgery so that they are aware of their postoperative clinical condition. They should be informed about the increased risk of sepsis, the associated symptoms, and the rapid progression of the disease. Furthermore, it is crucial to instruct patients to seek medical attention immediately if they experience signs or symptoms of infection, such as fever (Duarte et al., 2014).

It is also important to advise them about traveling to endemic areas, especially tropical regions with a high incidence of malaria. In these cases, prophylactic measures must be implemented to prevent infectious complications. Furthermore, patients should be instructed to seek medical assistance in the event of an animal bite, as studies have revealed that many patients undergoing splenectomy have limited knowledge about their condition and its potential complications (Luu et al., 2019).

Educating patients, along with vaccination and antibiotic prophylaxis, plays a key role in preventing infections in individuals with reduced splenic function. There is room to optimize these strategies through the development of new vaccines and research into new pharmacological agents that can combat the impairment of immune function after this process. The use of clinical records has been shown to be effective in preventing adverse outcomes mainly related to splenectomy (Chong et al., 2017).

4. Final Considerations

Therefore, prevention of sepsis in patients with asplenia or hyposplenism is seen to involve a combination of vaccination, antibiotic prophylaxis, patient education, and appropriate medical monitoring. It is essential that patients follow medical advice and are aware of the risks and preventive measures necessary to protect their health. Adherence to best practices can be challenging in the absence of targeted efforts to provide care to this population and track key process measures, such as vaccination rates. Given the lifelong risk associated with infection in these patients, future efforts should focus on improving the quality of care provided to children and adults with restricted splenic function. Additionally, ongoing research in the field of immunology and medicine helps improve understanding and treatment of this condition.

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