REVIEW

Medical complications following splenectomy

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Summary Splenectomy is attended by medical complications, principally infectious and thromboembolic; the frequency of complications varies with the conditions that led to splenectomy (hematologic splenectomy, trauma, presence of portal hypertension). Most infectious complications are caused by encapsulated bacteria (*Meningococcus*, *Pneumococcus*, *Hemophilus*). These occur mainly in children and somewhat less commonly in adults within the first two years following splenectomy. Post-splenectomy infections are potentially severe with overwhelming post-splenectomy infection (OPSI) and this justifies preventive measures (prophylactic antibiotics, appropriate immunizations, patient education) and demands prompt antibiotic management with third-generation cephalosporins for any post-splenectomy fever. Thromboembolic complications can involve both the caval system (deep-vein thrombophlebitis, pulmonary embolism) and the portal system. Portal vein thrombosis occurs more commonly in patients with myeloproliferative disease and cirrhosis. No thromboembolic prophylaxis is recommended apart from perioperative low molecular weight heparin. However, some authors choose to prescribe a short course of anti-platelet medication if the post-splenectomy patient develops significant thrombocytosis. Thrombosis of the portal or caval venous system requires prolonged warfarin anticoagulation for 3 to 6 months. Finally, some studies have suggested an increase in the long-term incidence of cancer in splenectomized patients.
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Introduction

Although the indications for splenectomy have decreased in current trauma management and cancer surgery, splenectomy remains a frequently performed surgical procedure; the surgeon must be familiar with both surgical complications (hematoma, sub-phrenic

collection, pancreatic fistula due to pancreatic tail injury) as well as medical complications. Medical morbidity after splenectomy consists mainly of infectious complications and thromboembolic complications; their prevalence is sufficient to warrant the implementation of preventive measures. Other complications have been mentioned, particularly an increased risk of subsequent cancer [1—3]. This update aims to focus on the medical complications of splenectomy and on prophylactic measures that should be adopted for patients who undergo splenectomy.

Infectious complications

The most frequent complications of splenectomy are infectious. In addition to acute postoperative complications (in 40% of cases), severe infections such as overwhelming post-splenectomy infection (OPSI) may occur in from 3—5% of patients over the long-term [4—6]. Although the interval to infection following splenectomy is quite variable, most occur on average within two years. Because its prognosis can be extremely severe, the possible occurrence of OPSI should be considered when weighing the indications for splenectomy and warrants implementation of both short- and long-term preventive measures.

Pathophysiology

The spleen is a lymphoid organ that plays an important role in both innate and acquired immunity [7]. Its role is particularly crucial for the elimination of encapsulated bacteria, the clearance of intra-erythrocytic parasites, and for potentiating the immune response to vaccines against polysaccharide antigens.

The spleen is composed of three anatomical and functional structures:

- the red pulp is a network of capillary sinuses whose fenestrated epithelium allows contact between circulating blood elements and the extravascular environment. The red pulp's rich supply of macrophages, opsonins and properdines plays a crucial role in innate immunity. It also plays the role of a phagocytic filter, allowing the culling and destruction of senescent erythrocytes and platelets and the selective elimination of intra-cytoplasmic elements (pitting). This ''cleansing'' of red blood cells (RBC) also allows the clearance of intra-erythrocyte pathogens such as Plasmodium and Babesia. With the loss of this culling function, the post-splenectomy patient often develops transient thrombocytosis (600—800,000/mm^3). Elevated counts of polymorphonuclear leukocytes (PMN) also typical occur early after splenectomy and an elevated WBC count > 15,000/mm^3 may lead to the erroneous suspicion of an infectious complication [8]. The failure to remove intra-erythrocytic nuclear fragments (pitting) results in the typical finding of Howell—Jolly bodies on review of blood smear or by simple phase-contrasted microscopy (basophilic stippling of RBC's);
- the white pulp consists of a network of arterioles with peri-arteriolar distribution of lymphocytes forming an organized secondary lymphoid organ that is involved in the adaptive immune response. This involves the collaboration of phagocytic cells and T and B lymphocytes;
- the marginal zone is a region that contains a population of specific B lymphocytes called IgM memory B cells that play a major role in the opsonization and eradication of encapsulated bacteria. This specific population of lymphocytes

is present almost exclusively in the spleen, which largely explains why there is an excess risk of serious infection by encapsulated bacteria following splenectomy [9].

Functional asplenia

In addition to splenectomy, many other diseases can result in functional asplenia. Sickle cell disease in the most common, but celiac disease, inflammatory bowel disease, acquired immunodeficiency syndrome (AIDS), active autoimmune diseases, cirrhosis with Felty's syndrome, or chronic hematologic diseases (including stem cell bone marrow transplant with graft versus host reaction). In such cases or after splenectomy, evidence of splenic dysfunction may be manifested by RBC morphologic abnormalities; immunological dysfunction seems to be correlated to the number of pitted erythrocytes seen on electron microscopy and the presence of Howell—Jolly bodies on peripheral blood smear [7]. Other methods that may help to evaluate splenic function or dysfunction require specific tools that are uncommonly used in practice, such as phase-contrast microscopy to detect RBC pitting or scintigraphy to detect accessory spleens [7].

Infectious risk

Pathogens and risk factors

Due to decreased response to encapsulated bacteria, the principal bacteria involved in post-splenectomy sepsis are primarily *Streptococcus pneumoniae* (50% to 70%), and *Neisseria meningitidis* and *Haemophilus influenzae* B (15—25% each), although the epidemiology of post-splenectomy infection has not been reassessed since the advent of vaccines against *Pneumococcus*, *Meningococcus* and *Hemophilus*. There is also an increased risk of serious infection due to *Capnocytophaga canimorsus* after animal bites, *Bordetella holmesii*, *Ehrlichia* species and intra-erythrocytic parasites such as *Babesia* after tick bites, and *Plasmodium* species in malaria-endemic areas [10—12]. No excess risk of infection by other pathogens such as *Escherichia coli*, or *Staphylococcus aureus* has been established.

The infectious risk varies with associated co-morbidities and the time interval following splenectomy [10]. The risk of OPSI is higher in children, in patients beyond the age of 60, in patients who undergo splenectomy for hematological malignancies or thalassemia, for patients with associated immunosuppression, a previous history of serious post-splenectomy infection, or failure to respond to pneumococcal vaccination [13]. The incidence of infection is highest in the first two years after splenectomy, but the risk persists throughout life [14,15]. In longitudinal studies, 50—75% of post-splenectomy infections occurred within the first two years, at an average interval of 22.6 months [4]. The average interval to infection after splenectomy is shorter when splenectomy was performed for hematological disease vs. posttraumatic splenectomy (20 months vs. 50 months) [16].

The risk is possibly lower when partial splenectomy is performed, but no specific study encourages the same recommendations as after total splenectomy [7]. Furthermore, the risk of infection also seems to be just as high for functional asplenia as for splenectomy.

Early postoperative infectious complications

Emergency splenectomy is associated with an excess risk of acute infection during the early postoperative period compared to elective splenectomy or emergency abdominal surgery without splenectomy (incidence 30—45% for all types of infection) [17,18]. The diagnosis of early postoperative sepsis is often more difficult because of reactive post-splenectomy thrombocytosis and leukocytosis. Changes in platelet and WBC counts have mainly been studied in post-traumatic splenectomy, where the WBC count rises rapidly from day 1 (maximum 15,000/mm^3) and returns to normal within days, while thrombocytosis is noted from day 3, usually peaking between 600,000—800,000/mm^3 on day 8—10 [8]. In a retrospective series of 118 patients undergoing emergency splenectomy, Toutouzas et al. showed that a WBC count > 15,000/mm^3 in combination with a platelet/WBC ratio of < 20 on day 5 were associated with early postoperative sepsis. An ISS > 16 was also a risk factor for early sepsis [8]. These results were later confirmed in a prospective cohort of 96 patients [19]. The positive predictive value for early sepsis when all three risk factors were present was 96.4%, and the negative predictive value in the absence of the three factors was 97.5%.

Overwhelming post-splenectomy infection

Overwhelming post-splenectomy infection (OPSI) is the most formidable infectious complication in the splenectomized patient. OPSI is a rapidly progressive fulminant infection linked to spontaneous bacteremia, particularly involving *S. pneumoniae* in over 50% of cases [4,10,11,15]. The presentation is non-specific and there is often no obvious portal of infection. The initial clinical presentation typically involves fever, gastrointestinal symptoms, and diffuse pain; it can progress rapidly to septic shock with coagulation disorders or disseminated intravascular coagulation (DIC) and purpura fulminans [7,11] (Fig. 1). The mortality of OPSI is close to 50% [4,5], and is even higher in patients with hematologic disease.

It is difficult to estimate the incidence of OPSI, since most studies have been retrospective with variable monitoring periods, variable definitions [7], and were published before the advent of conjugate vaccines against *Pneumococcus*, *Hemophilus*, and *Neisseria* species [16]. A large 2001 literature review by Bisharat et al. that included 19,680 patients

Figure 1. Splenectomized patient presenting with purpura fulminans due to OPSI.

with an average follow-up of 6.9 years, found a 3.2% incidence of OPSI, and 1.4% mortality for all patients with OPSI in that period [4]. Other studies have reported an annual incidence of OPSI between 0.18% and 0.42%, and 5% over the long-term [5,6]. The risk of death from infection in splenectomized patients before the era of pneumococcal conjugate vaccines was 0.29/100 patient-years in children and 0.13/100 patient-years in adults [20].

Management of fever in a splenectomized patient

Because of the fulminance and severity of OPSI, this complication must be feared whenever any asplenic patient presents with fever. Urgent antibiotic treatment is the only way to prevent progression to OPSI and should be started without delay. Antibiotic therapy should target encapsulated bacteria, primarily *S. pneumoniae*. A third-generation cephalosporin such as ceftriaxone is therefore recommended as first-line therapy, by either intravenous route (or by intramuscular route in a non-hospital setting). For penicillin or cephalosporin allergic patients, levofloxacin is an alternative. Combined therapy with vancomycin is sometimes recommended for cases of severe sepsis although no studies document the benefit of dual antibiotic therapy.

Management is the same for patients with suspected or proven functional asplenia as for splenectomized patients. The management strategy is summarized in Fig. 2 [10].

Prevention of infectious risk in the splenectomized patient

Prevention is based on three axes: vaccination against the most common causative pathogens, antibiotic prophylaxis, and patient education. El-Alfy and El-Sayed reported a decrease in the incidence of OPSI with the use of pneumococcal immunization, good knowledge of preventive measures and proper observance of antibiotic prophylaxis [14]. Patient education measures may require consultation with an infectious disease specialist.

Immunizations

Since encapsulated bacteria are the most common causative agents of OPSI, immunization against *S. pneumoniae*, *N. meningitidis* and *H. influenzae* B are recommended. Because seasonal influenza is often associated with the risk of pneumococcal superinfection, influenza vaccine should be given every year. Management of the splenectomized patient is also an opportunity to update the overall immunization schedule, which may require a specialized infectious disease consultation [7,10,21]. In a French cohort study reported by Coignard-Biehler et al., vaccine coverage among 92 adults and 62 children post-splenectomy was 75% and 65% respectively for *S. pneumoniae* vaccination, 10% and 40% for *N. meningitidis*, 37% and 89% for *H. influenzae* B. Only 4% of adults and 40% of children had received all three vaccinations [22].

When elective splenectomy is planned, it is preferable to administer the vaccine at least two weeks before surgery to ensure better immunogenicity. For emergency splenectomy or when vaccines were not administered beforehand, it is recommended that the immunization be administered at least two weeks after surgery because the vaccine response is lower in the first two weeks after splenectomy. However, when patients are discharged early from the hospital, the
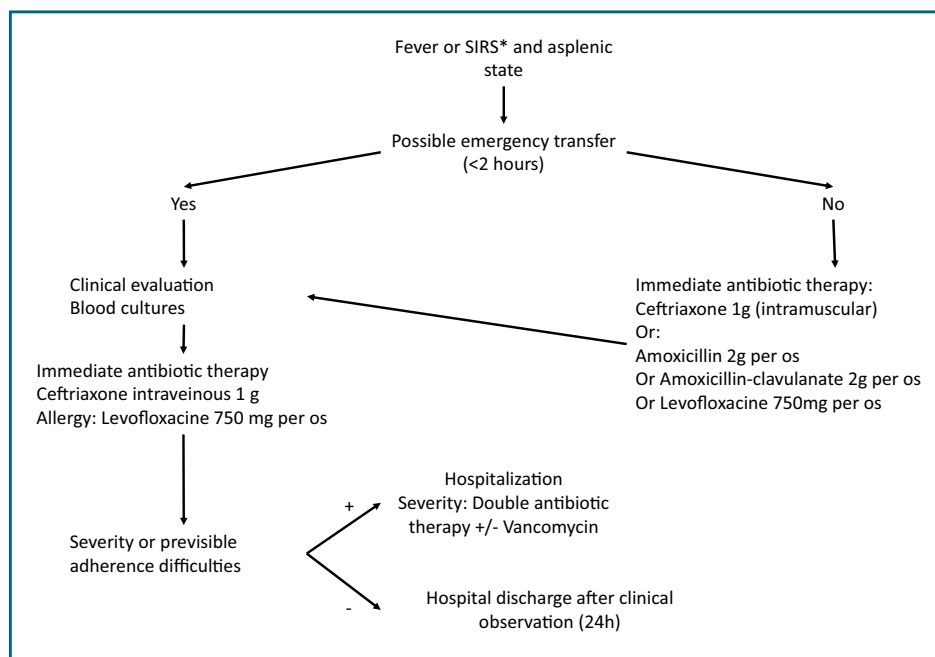
Figure 2.   Antibiotic management for an asplenic patient with fever [10]. SIRS: systemic inflammatory response syndrome.

risk of non-vaccination or loss to follow-up after splenectomy may encourage the administration of immunizations before that time [10,21].

Since asplenia causes an impaired immune response to polysaccharide antigens, conjugate vaccines must be used. Conjugate vaccines consist of polysaccharide antigens covalently bonded to bacterial protein antigens resulting in improved antigenicity and a more-prolonged immune response. (Pneumococcal-conjugate-13V, Meningococcal-conjugate-4V or Meningo-conjugate anti-C for meningococcal vaccination) in order to obtain a thymus-dependent immune response, with development of a long-term memory response.

The different immunization schedules are detailed in Table 1 according to patient age, while their chronology is shown in Fig. 3.

For pneumococcal vaccination, initial vaccination with a Pneumo-13V-conjugate vaccine provides better response and amplification effect than use of a non-conjugate vaccine administered two months later (Pneumo-Polysaccharide-23V). In contrast, prior vaccination with Pneumo-Polysaccharide-23V within two years may cause a hypo-response to vaccination with conjugate vaccine Pneumo-conjugate-13V; in this case, administration of a conjugate vaccine should be delayed for a period of three years after the last immunization with Pneumo-Polysaccharide-23V before resuming the indicated vaccination schedule. Since conjugate pneumococcal vaccines became available, they have allowed a significant reduction in invasive pneumococcal infections in children with sickle cell disease [23,24], making it difficult to estimate the current incidence of these infections in asplenic patients.

For immunization against *H. influenzae* B, a specific immunization schedule should be followed. In unvaccinated adults or children > 5 yrs or when in doubt, immunization should be performed.

Anti-meningococcal immunization is based on a quadrivalent conjugate vaccine against the A, C, Y and W135 serotypes —Meningo-conjugate-4V (MCV-4), (Nimenrix®,

Menveo®) or use of two monovalent vaccines against serotype C (Meningo-conjugate-C; [Men-C]), and B, (Bexsero® conjugate vaccine). The recommended regimen for Meningo-conjugate-4V in adults and children older than one year includes two vaccinations at an interval of six months. For patients who have received prior vaccination with non-conjugate polysaccharide vaccine, an interval of three years must be observed before revaccination with conjugate vaccine because of the hypo-response phenomenon. Vaccination with Bexsero® comprises two injections at a one-month interval.

Finally, the immunization schedule should be reviewed and regularly updated. Note that in the splenectomized patient, there are no contraindications to the administration of live attenuated vaccines against such viral diseases as measles or yellow fever, as long as there are no other associated immunosuppression factors.

All immunizations must be recorded in a vaccination record given to the patient, which should be updated thereafter for each new vaccination.

Prophylactic antibiotics

Early postoperative antibiotic prophylaxis must be distinguished from long-term antibiotic prophylaxis.

Perioperative antibiotic prophylaxis should follow the recommendations of the SFAR (French Society of Anesthesia and Resuscitation) [25]. In the early postoperative period, if there is no evidence of sepsis, intravenous antibiotic prophylaxis with low-dose Amoxicillin (1 g to 2 g per day in two injections) should be continued until oral diet resumes, and then switched to long-term oral antibiotic prophylaxis.

If sepsis requires antibiotic therapy against encapsulated bacteria, the need for Amoxicillin prophylaxis may be suspended temporarily.

Evidence regarding long-term antibiotic prophylaxis comes from studies that focused primarily on children with sickle cell disease in the era before conjugate pneumococcal vaccines were available and when *S. pneumoniae* was far more sensitive to penicillin [26]. These studies were then

Table 1 Recommended immunizations in France for the asplenic patient at various ages (HCSP recommendations).

Age	Anti-pneumococcal vaccination	Anti-meningococcus vaccination	Anti-meningococcus B (Bexsero®) vaccination	Anti-haemophilus influenzae b vaccination
< 2 yrs	PCV-13 at 2 months, 3 months, 4 months and 11 months Then PPV-23 between 2 and 5 years	< 1 yr: MCV or Hib-Men-CY-TT at 2 months, 4 months, Booster at 12 months with MCV-4 (Nimenrix®) > 1 yr: 2 doses of MCV-4 with a 6 months interval (Nimenrix® < 2 yrs, Nimenrix® or Menveo® > 2 yrs)	2—5 months: Men-B —1 dose at 2 months, 4 months, 6 months Booster between 12 and 24 months 6—11 months: Men-B — 2 doses with a 2 months interval; Booster between 12 and 24 months 12—24 months: Men-B — 2 doses with an interval of 2 months Booster: 12 to 24 months later	< 1 yr: immunization schedule Hib-5 or Hib-6 (Penta- or hexa-valent vaccine including the vaccine against serotype B) at 2 months, 4 months, and 11 months > 1 yr: if not yet vaccinated, 1 dose of anti-H1b vaccine (combined vaccine or not)
2—5 yrs	If no prior PCV-13 vaccination: PCV-13, 2 injections at an interval of 3 months, then PPV-23 2 months later If PCV-13 vaccination has already started: continue with the vaccination schedule for < 2 yrs If patient has already received PPV-23: wait 3 yrs before resuming immunization with PCV-13 injection, then PPV-23 2 months later	2 doses of MCV-4 with a 6 months interval (Nimenrix® or Menveo®)	2 doses with an interval of 2 months	If non-vaccinated or no information is available, 1 dose of Hib-5 or Hib-6
> 5 yrs and adults	PCV-13 1 injection, PPV-23 1 injection 2 months later If the patient has already received PPV-23: wait 3 years before resuming PCV-131 injection PPV-23 2 months later	2 doses of MCV-4 with a 6 months interval (Nimenrix® or Menveo®)	< 10 yrs: 2 doses with an interval of 2 months > 10 yrs: 2 doses with at interval of 1 month	If non-vaccinated or no information is available, 1 dose of Hib-5 or Hib-6
Booster	Booster: PPV-23 every 5 years	No specific recommendations	No specific recommendations	None

PCV-13: Pneumococcal conjugate vaccine, 13 valent; PPV-23: Pneumococcal polysaccharide vaccine-23 valent; MCV: monovalent meningococcal conjugate vaccine against serotype C; Hib-Men-CY-TT: conjugate vaccine against *H. influenzae* B, *Meningococcus* C & Y serotypes, and tetanus toxoid; MCV-4: Meningococcal conjugate vaccine, quadrivalent against serotypes A, C, W, Y (Nimenrix®, Menveo®); Men-B: monovalent meningococcal vaccine against serotype B; Hib-5 or Hib-6: Hemophilus influenzae conjugate vaccine against *H. influenzae* B, penta- or hexa-valent; HCSP: French High Council on Public Health.

extrapolated to all asplenic patients. Since the advent of conjugate vaccines, the benefit of antibiotic prophylaxis is less certain, particularly since long-term antibiotic prophylaxis has been shown to result in the carriage of pneumococci with decreased penicillin-sensitivity [27]. Thus, oral antibiotic prophylaxis is currently proposed for patients at the most risk, i.e., in the first two years post-splenectomy, or for children up to the age of five years, and should continue for at least two years, or for long-term use if there are other factors of immunosuppression, a prior history of OPSI,
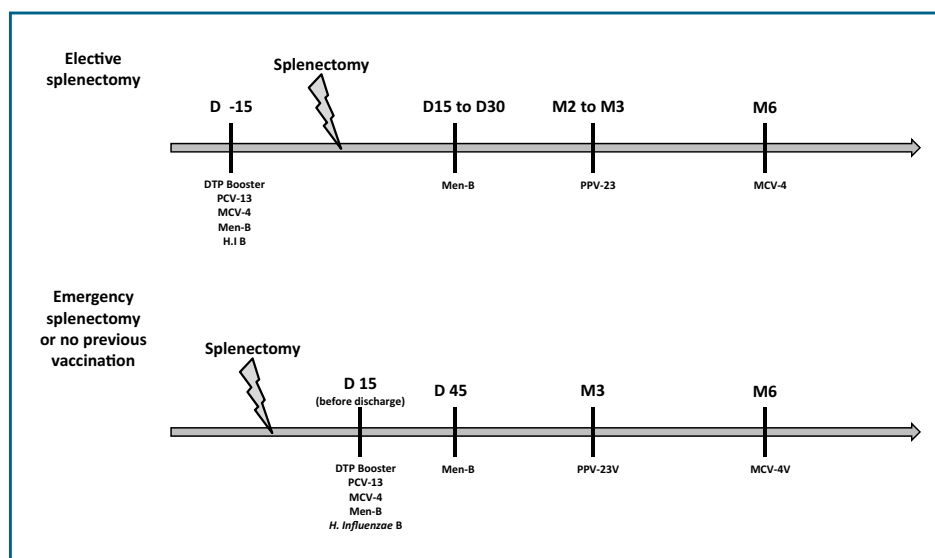
Figure 3. Immunization schedule for elective or emergency splenectomy.

or sickle cell disease. In addition, compliance with antibiotic prophylaxis regimens seems to decrease with time. Studies concerning the prescription and compliance with antibiotic prophylaxis have shown that, in France, 90% of children and 64% of adults were receiving antibiotic prophylaxis, while an Australian study showed that compliance with antibiotic prophylaxis decreased over time (83% within 2 years, 62% after 2 years and 32% after 10 years) [22,27]. In principle, ideal antibiotic prophylaxis should consist of an inexpensive, well-tolerated narrow spectrum antibiotic with good efficacy against encapsulated bacteria. Thus, penicillin V (Pen-Vee K®: 1 million units BID) remains the antibiotic of choice. If there is penicillin allergy, no specific antibiotic is recommended. Pristinamycin (500 mg BID), a macrolide effective against MRSA, may be proposed off-label, but gastrointestinal tolerance is often sub-optimal.

Patient education

It is of primordial importance that the patient be informed and educated about infectious risks associated with history of splenectomy, and understand the steps that must be taken should situations of risk arise. Studies have reported these measures to have benefit on the patient's ability to promptly access appropriate care [28]. A benefit was also reported with decreased incidence of OPSI (1.4% versus 16.5% depending on the level of patient knowledge) [14]. Similarly, in a series of 77 patients who developed OPSI, only one patient had been properly informed of the appropriate preventive measures [15]. Finally, knowledge concerning the risks of post-splenectomy infection seems to decrease over time in the absence of co-morbid episodes; therefore, long-term medical follow-up is necessary with periodic knowledge reinforcement, as well as provision of information to the various caregivers, particularly the primary care physician (PCP) [29].

The patient must be fully aware of at least three risk situations related to splenectomy that require special attention:

- fever: the patient should be informed that OPSI can manifest initially as a trivial infection, which should never be underestimated or overlooked. The patient should recognize and react to fever as a life-threatening emergency, resorting, if necessary, to pre-emptive antibiotic therapy at home before seeking medical care if the anticipated delay exceeds two hours. The patient should therefore have a supply of antibiotics at home for emergency use, typically an oral antibiotic such as Amoxicillin-clavulanate 2 g (or Levofloxacin 750 mg for penicillin-allergic patients);
- animal bites: asplenic patients have a higher risk of sepsis complicating bites, classically from *C. canimorsus* but also from other commonplace bacteria (*Streptococcus pyogenes*, *S. aureus*). Emergency medical care after animal bites is always required for local wound care and debridement as well as for a short course of pre-emptive antibiotic therapy (Amoxicillin-clavulanate, for 3—5 days);
- if traveling: when traveling, especially in the tropics, a specialized consultation is necessary to inform the post-splenectomy patient of what to do in case of fever, and of the increased risk of severe malaria. Anti-malarial prophylaxis and protection from insect vectors should be optimized for the asplenic patient living in malaria-endemic areas. This consultation is also an opportunity to update vaccinations, and to provide a written document in English confirming the history of splenectomy. Splenectomy by itself is not a contraindication to vaccination against yellow fever or to the use of live vaccines in general.

Preventive measures

Educational measures, optimal vaccination, and, to a lesser extent, antibiotic prophylaxis are essential in protecting against the increased risk of infection in the asplenic patient. Similarly, the communication of information and preventive measures to the patient's family and to his PCP or any other medical attendant is also important. An explanatory document outlining what to do in case of risk situations should be provided to the patient, and a standardized specific notification should be sent to medical caregivers, particularly the PCP. The patient should be provided with a

wallet card, documenting the history of splenectomy as well as a summary of steps to take in case of fever for any caregiver who may be called upon to manage the patient. The delivery of an up-to-date vaccination record is also important.

Conclusions on the management of infectious risk

The increased risk of infection starts immediately in the postoperative period, is highest in the first two years after splenectomy, but persists throughout life. The potential gravity of infections in splenectomized patient (historically dominated by *S. pneumoniae*, *N. meningitidis* and *H. influenzae*) becomes maximal with the extreme gravity OPSI, and justifies rigorous management of immunizations (Anti-*pneumococcal*, *Meningococcal*, and *H. influenzae* in particular), as well as antibiotic prophylaxis started in the immediate postoperative period, and patient education. Prompt reaction by the splenectomized patient and attending physician when fever or signs suggest the possibility of OPSI is essential to avoid rapid deterioration, and stresses the importance of these preventive and educational measures.

Thromboembolic complications

Thrombotic complications following splenectomy include thrombosis of the porto-mesenteric system, thrombosis of the caval system and pulmonary embolism. Their origin is probably multifactorial. The patient's underlying condition and the indications for splenectomy are elements that must be considered in assessing the patient's thrombotic risk, including the existence of cirrhosis or a myeloproliferative disorder.

Pathophysiology

Multiple factors probably contribute to the occurrence of post-splenectomy thrombotic complications involving hypercoagulability, platelet activation, endothelial alteration and altered lipid profiles as well as hemodynamic alterations of portal flow [30].

In post-splenectomy patients in general, there is a hypercoagulable state [31] with increased postoperative levels of platelets (starting on day 3), fibrinogen, tissue plasminogen activator inhibitor-type 1, plasminogen activators and activated partial thromboplastin time. Thrombocytosis and hyperfibrinogenemia persist during late follow-up after splenectomy. Thromboelastography measurements confirm that hypercoagulability is evident by the second day post-splenectomy [32] and persists for at least three months [31]. Patients with cirrhosis also have a hypercoagulable state [33] with reduced production of the anti-clotting factors (protein C, protein S, antithrombin III) and increased production of procoagulative factors (factor VIII, VonWillebrand factor). The hemodynamic effect of splenic vein ligation is a decrease in portal blood flow, whether or not the patient has portal hypertension and cirrhosis [34,35]. Danno et al. have shown that the risk of portal vein thrombosis after splenectomy rises in proportionate to the diameter of the splenic vein, $\geq 8\,mm$ as measured on preoperative CT scan [34].

Thrombotic risk

We must distinguish the well-documented risk of thrombosis in the portal system from the risk of thrombosis in the caval system.

Postoperative abdominal pain or fever should lead to suspicion of postoperative portal vein thrombosis; diagnosis can be made by Doppler ultrasonography or contrast-enhanced CT [36,37]. In series that reported more than 100 post-splenectomy patients, the incidence of portal vein thrombosis varied from 1.6% [36] to 15% [38], with a median time to onset of thrombosis between 8 and 12 days [39]. The thrombotic risk, particularly for the portal system, is related to the indications for splenectomy and the patient's underlying condition: splenectomy in the polytrauma patient is less likely to result in thrombosis, while the risk is higher in patients with cirrhosis, myeloproliferative disease, splenomegaly [37], hemolytic anemia [36,39], autoimmune thrombocytopenia, or congenital thrombophilia [40].

The risk of post-splenectomy portal thrombosis is significantly higher for cirrhotic patients, ranging from 17% to 36% [41—43]. In cirrhotic patients without underlying neoplasia [43], the risk factors for spleno-portal thrombosis are preoperative portal vein diameter, postoperative thrombocytosis and gastroesophageal devascularisation. Splenic enlargement is predictive of the risk of portal thrombosis [44].

With regard to the surgical approach, Ikeda et al. [45] observed a higher incidence of portal vein thrombosis after laparoscopy than after laparotomy; possible causes that have been proposed include the effects of pneumoperitoneum and the laparoscopic stapling technique for vessels. However, in this study population, there were very few cirrhotic patients and none had abnormal pro-coagulant laboratory findings. Splenomegaly was a risk factor for portal thrombosis. The increased risk associated with laparoscopy was not confirmed in two other studies [46,47].

The occurrence of pulmonary embolic events arising from thrombosis in the caval system has been less studied. In patients with multiple trauma (and without portal hypertension or hematologic disease), the risk of thrombotic events in the caval system is between 7% [31] and 18% [32]. If trauma includes splenic injury, the risk of deep-vein thrombosis and pulmonary embolism is higher after splenectomy than after non-operative treatment [31,32].

Management of post-splenectomy thrombosis

In the meta-analysis by Krauth et al. [39], treatment of spleno-portal thrombosis by effective therapeutic anticoagulation using heparin initially followed by warfarin for 3 to 6 months resulted in complete resolution of thrombosis in 67% of patients and partial resolution in 13% cases. However, persistent portal obstruction with portal hypertension and cavernous transformation occurred in 20% of patients. Other treatments of portal vein thrombosis (interventional radiology with thrombolysis, surgical thrombectomy) have not been studied in this context [48,49].

Prevention of thrombotic risk after splenectomy

No benefit of routine preoperative screening for thrombophilia has been demonstrated [50]. The value of routine thromboprophylaxis is debatable.

In their meta-analysis, Qi et al. [51] examined the role of thromboprophylaxis for post-splenectomy portal thrombosis using prophylaxis with anticoagulants, thrombolytics, or prostaglandins; this appeared to reduce the incidence of post-splenectomy portal thrombosis in cirrhotic patients without increasing the risk of bleeding, but the beneficial effect was not found in the subgroup of patients who underwent splenectomy for hematologic disease. Some authors have proposed prophylaxis for portal thrombosis in cirrhotic patients using antithrombin III concentrates and the Factor Xa inhibitor, fondaparinux, based on thrombosis risk factors (activity of antithrombin III, splenic vein diameter) [52]. This protocol has not been evaluated in other studies.

With regard to thrombo-prevention of the caval system after splenectomy, the French Society of Anesthesia Resuscitation (SFAR) has not issued specific recommendations [53].

The more general recommendations for digestive surgery therefore apply, with low molecular weight heparin prophylaxis for a period of one month, similar to that proposed for oncological abdominal surgery. For patients who develop marked thrombocytosis ($> 1-1.5$ million/mm^3), there are no specific recommendations concerning the prescription of anti-platelet medications or hydroxyurea although some authors have advocated this attitude [54]. The HAS (French High Health Authority) has published no recommendation on this subject for post-splenectomy patients [55], except for essential thrombocythemia or polycythemia vera where low-dose aspirin is recommended.

Conclusions on the management of thrombotic risk

Porto-mesenteric thrombosis should always be sought when abdominal pain develops after splenectomy, especially in patients with cirrhosis or myeloproliferative disease. After emergency splenectomy for trauma, thrombosis of the caval system is more frequent. For prophylaxis, isocoagulant therapy with low molecular weight heparin is recommended; there is no French recommendation for anti-platelet or other anticoagulant medications. For anti-thrombotic therapy, anticoagulation with therapeutic doses of heparin is recommended, followed by 3—6 months of an anti-Vitamin K medication such as coumadin.

Does splenectomy increase the risk of cancer?

A 1995 study suggested the possibility of an excess risk of cancer after splenectomy performed for non-traumatic indications [1]. More recently, a 2014 study revived the debate by comparing the long-term follow-up of 8149 American veterans who underwent splenectomy for benign disease and were followed for an average of 12.6 years (maximum 27 years) [2]; this study confirmed an excess risk of hospitalization for infectious complications (pneumonia, meningitis and sepsis [relative risks between 1.9 and 3.4]), for deep-vein thrombosis and pulmonary embolism (relative risk: 2.2), and also for solid tumors (upper aerodigestive tract, lungs, colon, pancreas, liver and prostate with a relative risk between 1.3 and 1.9), and for malignant hematological diseases (mainly lymphomas and leukemias of various types, with a relative risk between 1.8 and 6.0). In this study, there was also increased mortality risk from infection,

pulmonary embolism, coronary artery disease, and cancer, regardless of its type (solid tumors, lymphoma or leukemia). This excess risk persisted more than ten years after splenectomy and was also observed in the subgroup of patients who underwent splenectomy for trauma. However, this registry study probably did not consider other co-morbid habits in this population, such as tobacco, alcohol, or toxic exposures to carcinogenic agents and provided no results in terms of overall survival.

This study suggests that secondary immune defects post-splenectomy may also extend to anti-tumor immunity. This hypothesis is consistent with the results of certain series of oncologic gastrectomy [3] or pancreatectomy [56], in which the adjunction of splenectomy to improve the completeness of lymphadenectomy in gastric cancer and often routinely performed with distal pancreatectomy was associated with poorer late survival in multivariable analysis.

Conclusion

Because splenectomy may be attended by infectious and thrombotic complications, the splenectomized patient requires careful monitoring in the early postoperative period as well as in medium and long-term follow-up. Patient education, antibiotic prophylaxis and regular updating of vaccinations are key elements of management. There are no specific recommendations for the prevention of thrombotic complications but special attention should be paid to the detection of thrombosis of the porto-mesenteric and caval venous systems, where the risk is increased, especially in cases of myeloproliferative disease or cirrhosis.

Key points

- Infectious risk following splenectomy is well documented and linked to a decreased immune response to encapsulated bacteria, principally *S. pneumoniae*, *N. meningitidis* and *H. influenzae* B.
- The incidence of infection is highest in the first two years following splenectomy, but persists throughout life.
- ''Overwhelming post-splenectomy infection'' (OPSI), the most feared complication, is a rapidly progressive fulminant infection, linked to spontaneous bacteremia, principally by *S. pneumoniae* in over 50% of cases. Its mortality is about 50%.
- The prevention of post-splenectomy infection relies on immunization against the most commonly-involved pathogens, prophylactic antibiotics (as a rule, Penicillin V for two years), and patient education.
- If infection develops in a splenectomized patient, first-line treatment with a 3rd generation cephalosporin (ceftriaxone) or levofloxacin for penicillin-allergic patients is recommended.
- Splenectomy increases the risk of thromboembolic complications in the immediate postoperative period but also in the long-term. The thrombotic risk of the porto-mesenteric system is higher when splenectomy is performed for hematological indications or in a cirrhotic patient.

- Preventive measures for thromboembolic complications are not well codified. There are currently no recommendations other than for postoperative prophylaxis with low molecular weight heparin.
- Curative therapy of porto-mesenteric and caval venous systems in post-splenectomy patients requires therapeutic anticoagulation for 3—6 months.
- Splenectomy may increase the risk of subsequent cancers (solid and hematologic tumors).

Disclosure of interest

AS: Eumédica, Novartis.
BF: Eumédica, Novartis, Astra-Zeneca.
LB and RB declare that they have no competing interest.

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