

W Post-splenectomy and hyposplenic states

Antonio Di Sabatino, Rita Carsetti, Gino Roberto Corazza

Lancet 2011; 378: 86–97

Published Online

April 6, 2011

DOI:10.1016/S0140-6736(10)61493-6

First Department of Medicine, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico S Matteo, University of Pavia, Pavia, Italy (A Di Sabatino MD, Prof G R Corazza MD); and B-cell Development Laboratory, Bambino Gesù Children Hospital, Rome, Italy (R Carsetti MD)

Correspondence to: Prof Gino Roberto Corazza, Clinica Medical, Fondazione IRCCS Policlinico S Matteo, Università di Pavia, Piazzale Golgi 5, 27100 Pavia, Italy
gr.corazza@smatteo.pv.it

The spleen is crucial in regulating immune homeostasis through its ability to link innate and adaptive immunity and in protecting against infections. The impairment of splenic function is defined as hyposplenism, an acquired disorder caused by several haematological and immunological diseases. The term asplenia refers to the absence of the spleen, a condition that is rarely congenital and mostly post-surgical. Although hyposplenism and asplenia might predispose individuals to thromboembolic events, in this Review we focus on infectious complications, which are the most widely recognised consequences of these states. Because of the high mortality, the fulminant course, and the refractoriness to common treatment of overwhelming infections caused by encapsulated bacteria, prevention through vaccination and antibiotic prophylaxis is the basis of the management of patients who have had splenectomy or have hyposplenism. In this Review, we critically assess clinical and diagnostic aspects of splenic dysfunction and highlight new perspectives in the prevention of overwhelming post-splenectomy infections.

Introduction

The initial experimental evidence of the protective role of the spleen against infections was provided in the early 1900s by Morris and Bullock,¹ who indicated that splenectomised rats had a significantly higher post-surgical mortality than did rats who had sham operations, and this high mortality was attributed to sepsis by the bacillus that causes rat plague. Many years afterwards, the crucial function of the spleen in immune defence emerged as a result of two brief studies. King and Schumacker² reported a series of cases of overwhelming post-splenectomy infections (OPSI) caused by encapsulated bacteria in a cohort of children who had had splenectomy. Dameshek³ coined the term hyposplenism to describe a patient with coeliac disease in whom Howell-Jolly bodies were detected on peripheral blood smear and an atrophic spleen was confirmed at post-mortem examination. Hyposplenism is now regarded as an acquired disorder, potentially associated with several diseases and sometimes accompanied by a reduction in spleen size. Asplenia refers to the absence of the spleen, a disorder that is rarely congenital and is more frequently a result of surgery.

Although basic research has provided detailed information on the role of the spleen in the immune response,^{4,5} and data from many studies have confirmed the association of asplenia or impaired splenic function with increased morbidity and mortality from infectious complications,⁶ this information has not been sufficiently translated into appropriate clinical practice. Most physicians are unaware of the diseases for which a

systematic search for splenic dysfunction should be done, what the clinical predictors of this dysfunction and the means for assessing it are, what the real risks of sepsis are, and what would be the best ways to prevent sepsis. Treatment of post-splenectomy thrombotic complications has been recently reviewed;⁷ in this Review, we clarify the risk factors for splenic dysfunction, clinical signs, diagnostic techniques, and prophylaxis options against infection.

Immunological function of the spleen

The spleen consists of three functional inter-related compartments—the red pulp, white pulp, and marginal zone (figure 1).⁴ The red pulp is a sponge-like structure filled with blood flowing through sinuses and cords. The white pulp is distributed along the central arteriole branching from the splenic artery. T cells form an envelope (the periarteriolar lymphoid sheath) around the central arteriole, and also surround the B-cell follicle in a thin layer. This thin layer is formed by an outer dark zone—the mantle zone, containing dominantly proliferating small B lymphocytes—and a light central zone—the germinal centre, the area of B-cell selection. The marginal zone, containing memory B cells, is the extreme periphery of the white pulp in direct contact with the perifollicular area, where macrophages and fibroblasts positive for mucosal addressin cell adhesion molecule 1 are located.

The spleen functions as a phagocytic filter, removing senescent and damaged cells (culling), solid particles from the cytoplasm of erythrocytes (pitting), and blood-borne microorganisms, and also produces antibodies. When blood enters the splenic cords of the red pulp and passes through the fenestrated epithelium going into the venous sinus, the flow slows down, which helps the removal of defective erythrocytes and bacteria by splenic macrophages. Some bacteria are recognised directly by macrophages, but many first need to be opsonised, during which the bacterial surface is coated by complement or other spleen-derived opsonising molecules (properdin, tuftsin), which in turn interact with receptors on phagocytes.⁸ Opsonised bacteria are removed efficiently by macrophages in the spleen and liver. However, poorly opsonised bacteria, such as encapsulated bacteria—in

Search strategy and selection criteria

We searched Medline by using the medical subject heading terms “asplenia”, “hyposplenism”, “pneumococcal vaccination”, “splenectomy”, “splenic atrophy”, and “splenosis” for articles published between January, 1998, and June, 2010, but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of review articles on splenectomy and hyposplenism for additional papers we judged to be relevant to this Review.

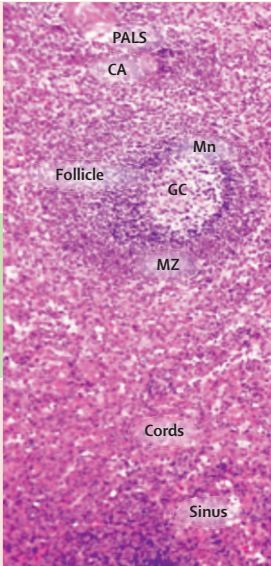
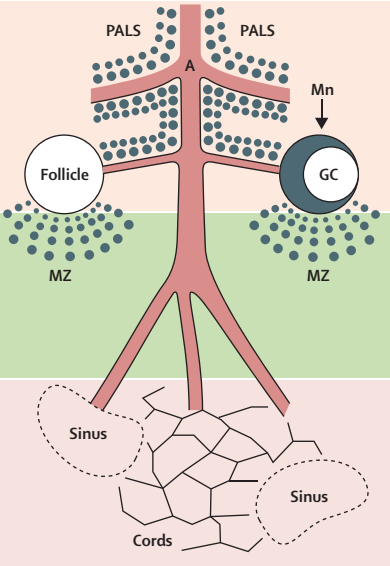
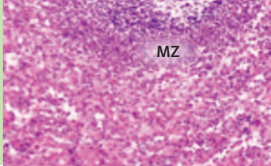
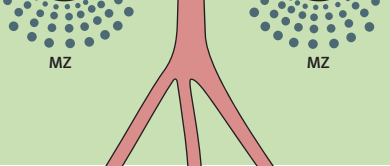
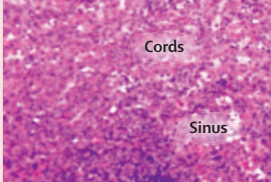
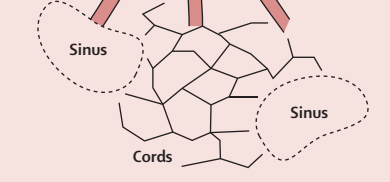
| Compartment | Histology | Structure | Function | Cell |
|---------------|---|---|--|---|
| White pulp |  |  | Adaptive response (antigen specific) consequent to interaction between antigen-presenting cells (dendritic cells or marginal zone B lymphocytes) and B lymphocytes or T lymphocytes | PALS (T-cell dependent) Small CD4 ⁺ T lymphocytes Dendritic cells B lymphocytes Macrophages Plasma cells Follicle (B-cell dependent) B lymphocytes or plasma cells Dendritic cells |
| Marginal zone |  |  | Innate response (first-line defence, non-antigen specific) characterised by IgM-memory B-lymphocyte production of natural antibodies | Resident B lymphocytes Macrophages In transit CD4 ⁺ T lymphocytes CD27 ⁺ memory B lymphocytes Dendritic cells |
| Red pulp |  |  | Innate response characterised by activation of macrophages in cords Adaptive response characterised by plasma-cell migration from the white pulp after antigen-specific differentiation in follicles Blood filter (pitting, culling) | Cords of Billroth CD8 ⁺ T lymphocytes Fibroblasts Macrophages Natural killer cells Sinusoids CD8 ⁺ endothelial cells |

Figure 1: Structure, function, and cell populations of the three functional compartments of the spleen

The histology panel shows a haematoxylin and eosin-stained section of normal spleen. CA=central arteriola. GC=germinal centre. Mn=mantle zone. MZ=marginal zone. PALS=periarteriolar lymphoid sheath. The structure panel provides a schematic representation of the spleen. The function panel lists a concise description of the roles of each compartment of the spleen. The last panel provides a description of the different cells within each compartment.

particular *Streptococcus pneumoniae* whose polysaccharide capsule impedes binding of complement or prevents complement assembled on the capsule from interacting with macrophage receptors—are only cleared by the spleen. For removal of these bacteria in the course of initial infection, natural antibodies are needed, which are pentameric IgM able to facilitate phagocytosis either directly or via complement deposition on the capsule and are produced by IgM memory B cells—a unique B-cell population in the marginal zone of the spleen. The key role of the spleen in initiating an immune response against encapsulated bacteria is indicated by the large reduction of IgM memory B cells after removal of the spleen.^{5,9}

Nearly half of the total B cells in the blood express the memory marker CD27 and carry somatic mutations, and are therefore thought to be memory B cells. Two populations of memory B cells have been identified in human beings—switched memory B cells and IgM memory B cells. Switched memory B cells, which are the final product of germinal centre reactions, produce high-affinity antibodies and have a protective function against reinfection.¹⁰ IgM memory B cells, which need the spleen for their survival and generation, have a unique ability to produce natural antibodies, including those directed against *S pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b, and can initiate T-cell-independent immune responses on infection or vaccination with capsular polysaccharide antigens. A decreased number of IgM memory B cells has been reported in children younger than 2 years because of

marginal zone immaturity, and in patients with common variable immunodeficiency, splenectomised patients, individuals with congenital asplenia or hyposplenism, and elderly people. All these patients have an increased susceptibility to infections by encapsulated bacteria because of their inability to initiate a protective antibody response to polysaccharide vaccines.^{5,11,12} However, the role of IgM memory B cells is debatable after results in *SCID/SCID* mice transplanted with human B-lymphocyte subsets and immunised with pneumococcal capsular polysaccharides¹³—the data from this study seem to contradict the belief that the IgM memory B-cell pool participates in only T-cell-independent immune response.¹³ These results, together with the report that splenectomy alone might not be the only reason for loss of IgM memory B cells and reduced IgM antipneumococcal antibodies,¹⁴ suggest that additional work to understand the role of IgM-positive CD27⁺ memory B cells is needed. In mice, the spleen is a reservoir for a specific population of monocytes that deploy to distant sites to favour wound healing.¹⁵

Diagnosis of spleen dysfunction

Diagnosis of spleen dysfunction is generally based on assessment of the spleen's filtering function by radioisotopic methods or quantitation of erythrocyte morphological abnormalities (table 1). Radioisotopic methods enable a morphofunctional assessment of the spleen by injection, uptake, and clearance of particulate substances or radiolabelled tracers.^{16,17} However, their use in clinical practice is limited by their high costs and some technical difficulties. Detection methods of

| | Description | Comments |
|--|---|---|
| | Technetium-99m-labelled sulphur colloidal scintiscan ¹⁶ | Quantitation of splenic uptake of colloidal sulphur particles enables a fairly accurate static assessment of spleen function |
| | Technetium-99m-labelled or rubidium-81-labelled heat-damaged autologous erythrocyte clearance ¹⁷ | Measurement of clearance time allows a dynamic evaluation of spleen function |
| | Detection of Howell-Jolly bodies ^{18,19} by staining | Erythrocytes with nuclear remnants |
| | Detection of pitted erythrocytes ²⁰ by phase-interference microscopy | Erythrocytes with membrane indentations (4% upper limit of the normal range) |
| | | Hypertrophy of the left hepatic lobe might be a limiting factor (this technique does not clearly show whether the mass originated in the liver or the spleen in the presence of an overlapping hypertrophic left hepatic lobe) |
| | | Pre-existing erythrocyte defects, difficult erythrocyte incorporation of the radioisotope, false positive or negative results in relation to excessive or insufficient heat damage make the test not suitable for clinical practice |
| | | No need for special equipment; inaccurate in the quantitation of splenic hypofunction |
| | | Need for phase-interference microscopy; counts enable a wide range of measurements and correlate with radioisotopic methods |

Table 1: Diagnostic techniques for and features of spleen dysfunction

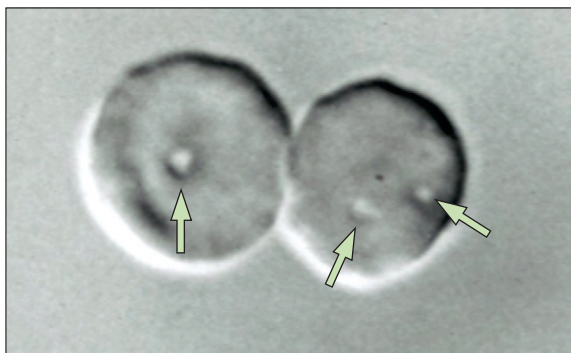


Figure 2: Characteristic pitted erythrocytes

A pitted erythrocyte is recognisable on phase-interference microscopy by the characteristic "pit" on the cell membrane (arrows).

morphological alterations of erythrocytes are more suitable for clinical use because these tests are easy to do, are inexpensive, and are less invasive than radio-labelling. The detection of **Howell-Jolly bodies** (ie, erythrocytes with **nuclear remnants**) is a useful method of screening for asplenia,¹⁸ although the specificity¹⁹ and sensitivity^{18,21} of this test has been disputed, particularly in the quantitation of mild forms of hyposplenism. In one uncontrolled study,²² quantitation of Howell-Jolly bodies by flow cytometric analysis was proposed.

Erythrocytes with characteristic membrane **pits**, visible with phase-interference microscopy (figure 2), were originally reported in premature neonates and splenectomised adults.²³ Because one of the **functions** of the spleen is the **removal** of **pits** from the circulating erythrocytes (pitting), asplenia and hyposplenism cause an increased number of circulating pitted erythrocytes. Because pitted erythrocyte counting is a simple, repeatable, and quantitative test, which accurately correlates with spleen volume,^{20,24} this test is regarded as the gold standard for the assessment of spleen dysfunction in most studies. However, pitted erythrocyte counting needs specific equipment (Nomarski optics), which explains its **limited use** in clinical practice. The inverse correlation seen between pitted erythrocytes and IgM memory B cells in

splenectomised and hyposplenic patients indicates that the impairment of the filtering function, as defined by pitted erythrocyte counting, might mirror a parallel impairment of the immunological compartment.^{25,26}

The incidental finding of a small spleen during an abdominal imaging procedure should always prompt clinicians to undertake one of the appropriate tests for quantitation of splenic dysfunction.

Splenectomy

In tertiary referral centres, the frequency of splenectomy for haematological, immunological, or oncological reasons (54%) is substantially higher than that for trauma surgery (16%),²⁷ although this ratio might be different in non-academic settings. The increasing awareness of the risk of OPSI²⁸ has led to a more conservative approach, and a notable reduction in the incidence of splenectomy for trauma was recorded in children between 1970 and 2000.²⁹ In 2005, the Society for Surgery of the Alimentary Tract provided guidelines according to which post-traumatic splenectomy is only indicated if the patient is haemodynamically unstable, if the patient has lost more than 1000 mL of blood, if transfusion of more than two units of erythrocytes is needed, or if there is evidence of bleeding in progress. Therefore, current approaches use haemostatic repair agents on tissue lacerations, ligation and partial angioembolisation of the splenic artery, simple splenorrhaphy, and partial splenectomy. Partial splenectomy leads to only a transitory depression of humoral immunity and enables an adequate phagocytic response.³⁰ In patients with thalassaemia who have had partial splenectomy, the risk of OPSI was lower than in those undergoing total removal of the spleen,³¹ and results from long-term follow-up studies did not indicate a significantly increased frequency of infections.³² However, no definite information is available as to whether antibiotic treatment or pneumococcal vaccination is necessary in patients who undergo conservative surgery. Thus, the same measures recommended for total splenectomy should also be adopted for patients undergoing partial removal of the spleen.

When the extent of the traumatic lesions makes removal of the whole spleen necessary, deliberate heterotopic autotransplantation of splenic tissue in omental pockets might lead to sufficient maintenance of splenic function.³³ The spontaneous occurrence of this phenomenon, after rupture of the splenic capsule, was first reported in 1939³⁴ and is known as splenosis. Splenic nodules, which consist of vital and functioning splenic tissue, are usually numerous, measure from a few mm to a few cm in diameter, and stain the omentum, the peritoneum, and the mesentery (figure 3). These nodules can be distinguished from accessory spleens by their high number, the absence of hilum, capsule, and trabeculae, the vascularisation provided by small omental vessels, and their localisation that is often separate from the splenopancreatic and gastro-splenic ligaments.³³

A high frequency of splenosis, confirmed by the reduction of circulating pitted erythrocytes, was found in children splenectomised for trauma (59% of 22 patients).³⁵ Additionally, normal pitted erythrocyte counts were reported in patients after partial splenectomy or splenorrhaphy, whereas patients with deliberate autotransplantation or spontaneous splenosis had pitted erythrocyte counts intermediate between normal counts and counts seen in splenectomised patients without splenosis.³⁶

In splenectomised patients with splenosis, the proportion of pitted erythrocytes is indicative of the volume of regenerated splenic tissue, and it has been calculated that 30 mL is the minimum volume of reimplanted splenic tissue needed to ensure a return of splenic function sufficient to guarantee some protection.³⁷

Although there is evidence that reimplantation of splenic tissue ensures a good antibody response after pneumococcal vaccination, splenosis does not seem to guarantee full protection against OPSI. Possible factors that restrict the defensive efficacy of the splenic nodules include, in addition to their small size, poor vascularisation, which reduces the contact between particulate antigens and splenic phagocytes.

Hyposplenism

The natural history of many diseases, including congenital, haematological, immunological, gastroenterological, infectious, and iatrogenic disorders, can be complicated by splenic abnormalities ranging from a reversible mild hyposplenism to severe splenic atrophy (panel).⁶ In most of these conditions, the pathogenesis of hyposplenism is mostly unknown.⁸ Table 2 describes the main clinical aspects of the most frequent diseases complicated by splenic hypofunction or atrophy. Because of the relevance of hyposplenism and its consequences in sickle-cell anaemia, bone marrow transplantation, graft-versus-host disease, coeliac disease, and HIV infection, we discuss these disorders in more detail in this section.

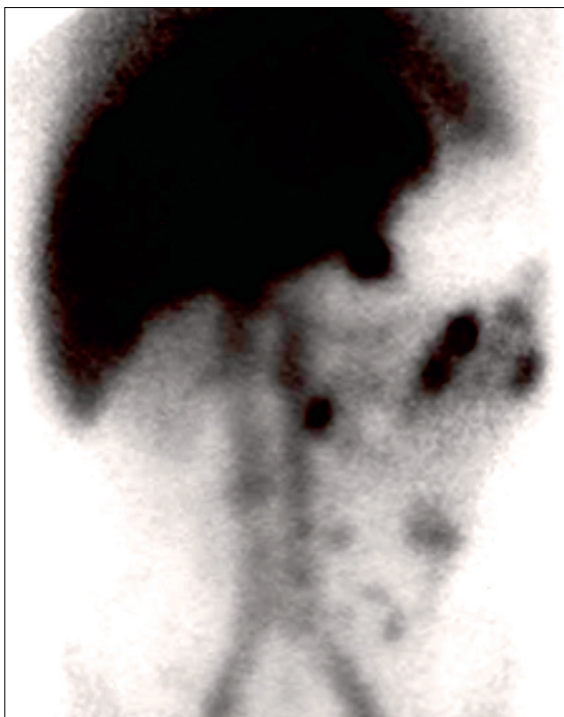


Figure 3: Splenosis in a splenectomised patient

Posteroanterior technetium-99m heat-damaged erythrocyte scan shows at least ten splenic nodules in the left-upper abdomen of a patient undergoing deliberate splenic autotransplantation after splenectomy.

Sickle-cell anaemia

Sickle-cell anaemia is invariably associated with severe splenic dysfunction.³⁸ In the first years of life of patients with sickle-cell anaemia, the size of the spleen increases because of vaso-occlusive congestion secondary to recurrent episodes of erythrocyte sickling. These events lead to engorgement of the sinusoids, although severe functional hyposplenism is already present and documented by scintiscan and pitted erythrocyte count.³⁹ As a consequence, patients are highly susceptible to sepsis by encapsulated bacteria, particularly before 3 years of age, reaching a risk level of sepsis or meningitis that is about 300–600 times higher than in the general population.⁶⁶

Sustained high concentrations of haemoglobin F ($\geq 20\%$) are recognised as a protective factor against impaired splenic function and are associated with mild disease and low mortality.⁴⁰ Drugs that substantially increase production of haemoglobin F, such as hydroxy-carbamide, can improve clinical outcomes in patients with sickle-cell anaemia. Both treatment with hydroxy-carbamide and blood transfusions revert hyposplenism in young children.^{41–43} Hypertransfusion therapy even reversed splenic involution and fibrosis in some children with sickle-cell anaemia.

Although the general outcome of children with sickle-cell anaemia has substantially improved as a result of better comprehensive care, transfusion therapy, and

Panel: Diseases associated with hyposplenism or splenic atrophy**Congenital forms**

- Normal and premature neonates
- Isolated congenital hyposplenism
- Ivemark's syndrome
- Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome
- Hypoparathyroidism syndrome
- Stormorken's syndrome

Gastrointestinal disorders

- Coeliac disease
- Inflammatory bowel diseases
- Whipple's disease
- Dermatitis herpetiformis
- Intestinal lymphangiectasia
- Idiopathic chronic ulcerative enteritis

Hepatic disorders

- Active chronic hepatitis
- Primary biliary cirrhosis
- Hepatic cirrhosis and portal hypertension
- Alcoholism and alcoholic hepatopathy

Oncohaematological disorders

- Haemoglobin S diseases
- Bone marrow transplantation
- Chronic graft-versus-host disease
- Acute leukaemia
- Chronic myeloproliferative disorders

Autoimmune disorders

- Systemic lupus erythematosus
- Rheumatoid arthritis
- Glomerulonephritis
- Wegener's granulomatosis
- Goodpasture's syndrome
- Sjögren's syndrome
- Nodous polyarteritis
- Thyroiditis
- Sarcoidosis

Infectious diseases

- HIV/AIDS
- Pneumococcal meningitis
- Malaria

Iatrogenic forms

- Exposure to methyl dopa
- High-dose steroids
- Total parenteral nutrition
- Splenic irradiation

Alteration in splenic circulation

- Thrombosis of splenic artery
- Thrombosis of splenic vein
- Thrombosis of coeliac artery

Miscellaneous

- Amyloidosis

treatment with hydroxycarbamide,⁴⁴ repeated splenic infarcts and the consequent fibrosis lead to spleen atrophy (autosplenectomy) and irreversible hyposplenism.⁴⁵ However, prophylactic treatment with benzylpenicillin, vigilance at times of fever, and vaccination can reduce this risk. Acute chest syndrome and multiorgan failure syndrome are now the leading causes of death in this disorder rather than bacterial sepsis.⁴⁴

All the above reported data refer to individuals who are homozygous for the haemoglobin S gene or who are affected by haemoglobin S β^0 -thalassaemia. The splenic deficit is less severe in patients who are homozygous for the haemoglobin S gene associated with α -thalassaemia, in individuals with haemoglobin S β^+ -thalassaemia, and in patients with haemoglobin SC disease.³⁹

Bone marrow transplantation and graft-versus-host disease

After earlier case reports, results from two studies using pitted erythrocyte counting and Howell-Jolly bodies detection indicated that functional hyposplenism might complicate 15–40% of allogeneic bone marrow transplantation.^{46,67} Additionally, a positive correlation was identified between reduction in spleen size, the duration of chronic graft-versus-host disease, and an increased

risk of life-threatening pneumococcal infections.⁴⁷ The report of deficiency of IgM memory B cells in allogeneic haemopoietic stem-cell transplantation recipients⁴⁸ might provide a pathophysiological explanation for the high susceptibility of these patients to infections by encapsulated bacteria, mainly *S pneumoniae*. *S pneumoniae* causes severe and sometimes fatal invasive infections months or years after transplantation, with an incidence of up to 27% in long-term survivors.⁴⁹ In conclusion, functional impairment of the spleen should be carefully taken into account in all individuals who undergo allogeneic bone marrow transplantation, especially in those who develop chronic graft-versus-host disease; furthermore, these patients have been proposed to receive life-long antibiotic prophylaxis.⁶⁸

Coeliac disease

Coeliac disease, an immune-mediated enteropathy induced in genetically susceptible individuals by the ingestion of gluten,⁶⁹ is the most frequent disorder associated with hyposplenism.⁵⁰ Splenic hypofunction, with or without splenic atrophy, is a frequent complication of coeliac disease, with a prevalence ranging from 33% to 76%.^{51,52} When these data are categorised according to clinical severity, the prevalence

| | Diagnostic method | Prevalence of hyposplenism (%) | Degree of hyposplenism | Evidence of OPSI | Additional information |
|--|---|--------------------------------|--------------------------|------------------|---|
| Sickle-cell anaemia ³⁸⁻⁴⁵ | Pitted erythrocyte count | 100 | Severe | +++ | Hyposplenism worsens with decreasing concentrations of haemoglobin F |
| Bone marrow transplantation or GVHD ⁴⁶⁻⁴⁹ | HJB detection; pitted erythrocyte count | 40; 15 | Moderate to severe | +++ | Hyposplenism is more frequent in patients with extensive GVHD; need for antibiotic prophylaxis |
| Coeliac disease ⁵⁰⁻⁵⁵ | Pitted erythrocyte count | 33-76 | Moderate to severe | +++ | Hyposplenism reversible after gluten-free diet; decreased concentrations of IgM memory B cells; poor prognosis in patients with splenic atrophy |
| HIV/AIDS ⁵⁶⁻⁶⁰ | Pitted erythrocyte count | 36 | Moderate to severe | +++ | Decreased concentrations of IgM memory B cells |
| Alcoholic liver disease ⁶¹ | Pitted erythrocyte count | 37-100 | Moderate to severe | +++ | Abstinence improves splenic function |
| Inflammatory bowel disease ⁶² | Pitted erythrocyte count | 35-45 (UC); 9-37 (CD) | Mild to moderate (UC>CD) | ++ | Decreased concentrations of IgM memory B cells; poor prognosis in patients with splenic atrophy |
| Whipple's disease ⁶³ | Pitted erythrocyte count | 47 | Mild | - | Thrombocytosis; thrombotic events |
| Primary amyloidosis ⁶⁴ | HJB detection | 28 | Moderate | ++ | Poor prognosis in hyposplenic patients |
| Systemic lupus erythematosus ⁶⁵ | HJB detection; pitted erythrocyte count | 7; 5 | Mild to moderate | ++ | Hyposplenism unrelated to disease activity |

--no evidence. +=weak evidence. ++=moderate evidence. +++=strong evidence. OPSI=overwhelming post-splenectomy infections. GVHD=graft-versus-host disease. HJB=Howell-Jolly bodies. UC=ulcerative colitis. CD=Crohn's disease.

Table 2: Clinical features of the most common hyposplenism-associated disorders

of hyposplenism increases from 19% in patients with uncomplicated disease, to 59% in those with associated autoimmune diseases, and up to 80% in those with premalignant or malignant complications.²⁵ Hyposplenism does not complicate coeliac disease in infancy, and its occurrence in adults correlates with the duration of pre-exposure to gluten.³¹ A gluten-free diet is effective in restoring splenic function except in patients who already have an irreversible loss of splenic tissue.^{52,53} Splenic atrophy, which is now recognised as an indicator of poor prognosis in patients with coeliac disease and is often associated with mesenteric lymph node cavitation (figure 4), affects the size of both the marginal zone and the white pulp B-cell compartment, and causes splenic IgM memory B-cell deficiency. This B-cell deficiency might contribute to the increased susceptibility of patients with coeliac disease to severe infections. This predisposition is supported by data from two ad-hoc studies, which indicate a substantially higher relative risk of pneumococcal sepsis in adult patients with coeliac disease than in the general population.^{54,55} These data are in accordance with the increased mortality reported in these patients because of major infections.⁷⁰

HIV infection

Impaired reticuloendothelial function was first reported in patients with AIDS in 1985,⁵⁶ and data from a subsequent study that used pitted erythrocyte counting

confirmed that functional hyposplenism can affect patients who are HIV positive, with a prevalence of 36%.⁵⁷ Moreover, in patients with AIDS, splenic function was correlated with the activity of the spleen-derived opsonising factor tuftsin.⁵⁸ More recently, depletion of IgM memory B cells has been reported in untreated patients with HIV who have a CD4 T-cell count of less than 300 cells per μL .⁵⁹ This depletion might be a risk factor for pneumococcal disease, which occurs in patients with HIV with an incidence that is 100-times greater than in the general population. Antiretroviral therapy seems to be effective in restoring the IgM memory B-cell pool,⁵⁹ which might partly explain the low rates of pneumococcal disease in patients with HIV receiving this therapy. In another series,⁶⁰ 70% of 84 patients with HIV had similar numbers of IgM memory B cells to those in splenectomised individuals, and this loss was associated with diminished vaccination responses to both T-cell-dependent and T-cell-independent antigens.

OPSI

The term OPSI defines fulminating sepsis, meningitis, or pneumonia triggered mainly by *S pneumoniae*, *N meningitidis*, and *H influenzae type b* in splenectomised and hyposplenic individuals.²⁹ Although data from several studies⁶ have confirmed that asplenia and hyposplenism are major risk factors for sepsis, prevention of these infections is often overlooked. Nevertheless, extrapolation

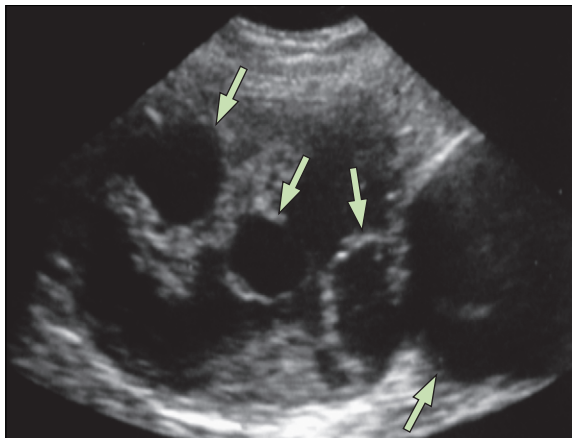


Figure 4: Mesenteric lymph node cavitation in a patient with refractory coeliac disease complicated by ulcerative jejunoileitis and splenic atrophy. Multiple cavitations of mesenteric lymph nodes appear on abdominal bowel sonography as anechoic cystic masses with posterior acoustic enhancement (arrows).

of definite figures on the epidemiology of OPSI from a series of retrospective studies is difficult because of the tendency to over-report the events, the variability in the selection and inclusion criteria, and the differences in the duration of the follow-up and in the stratification of patients by age, underlying disease, and type of splenectomy. Similarly, the distinction in terms of risk of OPSI between splenectomised patients and patients with acquired hyposplenism is not possible because of the absence of comparable data.

An analysis of 78 studies done between 1966 and 1996 enabled investigation of 19 680 splenectomised patients for a mean period of 6.9 years.²⁸ The prevalence of infections was 3.2% with a mortality rate of 1.4%. A more detailed analysis was only possible in a few patients, in whom there was an unexpected similar prevalence of infections between children (3.3%) and adults (3.2%), with a higher mortality rate in children (1.7% vs 1.3%). The risk of sepsis and death was strongly associated with the reason why splenectomy was done. The indications for splenectomy most frequently associated with a risk of infection and death were thalassaemia major (8.2% and 5.1%, respectively), sickle-cell anaemia (7.3% and 4.8%), Hodgkin's lymphoma (4.1% and 1.9%), spherocytosis (3.1% and 1.3%), and idiopathic thrombocytopenic purpura (2.1% and 1.2%). The prevalence of OPSI and the mortality rate in splenectomy for trauma were 2.3% and 1.1%, respectively. The results of this analysis do not noticeably differ from those of the individual studies analysed, but might underestimate the risk of OPSI because of the short duration of the follow-up in many of the studies. The opinion that OPSI occur in the first few years after surgery⁷¹ is not universally shared.⁷² The risk of sepsis in the absence of the spleen is a permanent condition; cases of OPSI have been described 20–40 years after removal of the spleen,⁷³ and the cumulative

prevalence of infections needing admission to hospital rose progressively from 17% at 1 year to 33% at 10 years.⁷⁴ The underlying disease and concomitant factors that depress the immune system (malnutrition, chemotherapy, alcoholism, diabetes) have an important role. The rare Wiskott-Aldrich syndrome, which was not included in Bisharat and colleagues' survey,²⁸ was reported as the disorder with the highest risk of post-splenectomy infection (30.7%) and death (12.8%).⁷⁵ Finally, in patients who had splenectomy because of idiopathic thrombocytopenic purpura, the not-infrequent coexistence of common variable immunodeficiency substantially increased the risk of sepsis.

The risk of OPSI in splenectomised patients is more than 50-times higher than in the general population,²⁹ and *S pneumoniae* is the most common causal organism (50–90% of cases), followed by *H influenzae* type b and *N meningitidis*.⁷¹ A predominant pneumococcal serotype has not been documented, and serotype distribution did not differ between OPSI and other forms of pneumococcal infections. Two surveys on invasive pneumococcal disease reported different results: one concluded that host factors are more important than isolate serotype in establishing the severity and outcome of infections,⁷⁶ whereas the other reported that serotypes 18C, 9N, 6B, 16F, 23A, 19F, and 3 are those most commonly associated with increased case-fatality rates.⁷⁷ The prominence of *Salmonella* sp in patients with sickle-cell disease, which mostly causes osteomyelitis, seems to be associated with further determinants in addition to impaired splenic function—eg, abnormal humoral immunity, bone ischaemia, or infarction.⁷⁸ Causative organisms that are less frequently implicated are *Escherichia coli*, *Pseudomonas aeruginosa*, *Capnocytophaga animorsus* (transmitted by dog bites), and, more rarely, *Enterococcus* sp, *Bacteroides* sp, and *Bartonella* sp.

OPSI is a medical emergency for which only prompt diagnosis and immediate treatment can reduce mortality.⁷⁹ The clinical course of OPSI is measured in hours rather than days. The mortality rate is 50–70%, and most deaths occur within the first 24 h.⁷¹ Bacteraemia commonly has an unknown origin; after a brief prodrome characterised by fever, shivering, myalgia, vomiting, diarrhoea, and headache, septic shock develops in just a few hours, with anuria, hypotension, hypoglycaemia, and, commonly, disseminated intravascular coagulation and massive adrenal gland haemorrhage (Waterhouse-Friderichsen syndrome), to multiorgan failure and death.⁷⁹

In patients at risk and with indicative symptoms of OPSI, particularly fever, treatment with empirical antibiotics is essential, and involves infusion with third-generation cephalosporins (cefotaxime 2 g every 8 h or ceftriaxone 2 g every 12 h), combined with gentamicin (5–7 mg/kg every 24 h) or ciprofloxacin (400 mg every 12 h) if a possible urinary or intestinal focus is suspected, or vancomycin (1–1.5 g every 12 h) in case of resistance to benzylpenicillin.⁷⁹ While waiting for the results of

blood-culture tests, bacteria can be visualised by Gram or Wright staining in the buffy-coat, or even in the peripheral blood smear. This empirical approach can be changed to a more specific treatment once the nature of the pathogen is known. A real-time PCR test, which enables the simultaneous identification of the three main encapsulated bacteria causative for OPSI, is available.

Prevention of OPSI

Education

Up to 84% of splenectomised individuals are thought to be unaware of their increased susceptibility to severe sepsis,⁸⁰ and provision of proper information reduces infectious complications.⁸¹ In particular, patients and relatives should be instructed to notify their physicians of any acute febrile illness, especially if associated with rigor and systemic symptoms,⁸¹ and of visits to tropical countries because of the high risk of parasitic infections, such as malaria or babesiosis. In particular, travellers should take preventive measures such as antimalarial prophylaxis, mosquito repellents, and other barrier precautions. Other measures include immediate treatment in the event of dog bites or bites of other animals, although there is no consensus on the need for prophylactic antibiotics in case of dental procedures. Disappointingly, these recommendations are ignored by doctors themselves,⁷² whereas constant monitoring is essential because the risk of OPSI is long term, compliance with prevention tends to decrease over time, and vaccination itself might gradually lose efficacy. Careful monitoring of these patients would be greatly helped by specific registers, and this approach has a favourable cost-benefit ratio, in terms of prevention and reduction of mortality.⁸²

Antibiotic prophylaxis

The use of antibiotics for the prevention of OPSI is not evidence based. The actual effectiveness of antibiotics is unknown and there is no agreement on how long these drugs should be taken for or which subgroups to treat, especially when factors such as poor compliance and possibility of favouring the development of resistant bacterial strains in the long term are taken into account.⁸³ Moreover, antibiotics might reduce but not abolish the risk of OPSI. Apart from data from two controlled trials published in the 1980s that indicated the efficacy of prophylactic benzylpenicillin against pneumococcal infections in children with sickle-cell anaemia,^{84,85} we are not aware of any study that has assessed antibiotic prophylaxis in other subgroups of asplenic or hyposplenic individuals. Furthermore, we identified only two retrospective studies done on large cohorts of splenectomised children, which reported a substantial reduction of the occurrence of OPSI during treatment with benzylpenicillin.^{86,87} Most of the patients, however, had concomitant pneumococcal vaccination, which makes estimation of the contribution of antibiotics difficult.

Compliance with long-term antibiotic treatment is often inadequate and remains suboptimal in children even after ad-hoc education of parents.⁸¹ Guidelines recommend antibiotic prophylaxis in children younger than 5 years, but there is no agreement between Canadian, British, and American guidelines on when to discontinue prophylactic benzylpenicillin. In adults, guidelines recommend prophylaxis with 250–500 mg per day of amoxicillin or 500 mg per day phenoxymethylpenicillin. In children allergic to these antibiotics, possible alternatives are co-trimoxazole or erythromycin, although these options are becoming less effective because of the increasing development of resistant pneumococcal strains.⁸³ Although there is no consensus on the duration of treatment, the British guidelines propose life-long treatment with regards to the persistent risk of sepsis. Long-term treatment is recommended in patients with concomitant haematological diseases or an impaired immune system. Episodic short-term antibiotics at the time of febrile illnesses might be a useful strategy in asplenic patients, although robust data are needed.

Vaccine prophylaxis

Vaccines used in patients at risk of OPSI are the 23-valent pneumococcal polysaccharide vaccine (PPV-23; serotypes include 1–5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), the 7-valent diphtheria cross-reactive material 197 (CRM197) protein-conjugate pneumococcal vaccine (PCV-7; serotypes include 4, 6B, 9V, 14, 18C, 19F, and 23F), the *H influenzae* type b conjugate vaccine, and the meningococcal vaccine.

Although PPV-23 reduces (but does not abolish) the occurrence of OPSI in splenectomised patients,⁸¹ this vaccine is not commonly used. In 2005 in England and Wales, only 366 (13·2%) of 2770 splenectomised patients had been vaccinated in the previous 12 months and 1479 (53·4%) had been vaccinated in the previous 5 years.⁸⁸ For patients with sickle-cell anaemia, 473 (13·2%) had been vaccinated in the previous 12 months and 1914 (53·4%) had been vaccinated in the previous 5 years. Of the 3584 patients with either sickle-cell disease or coeliac disease, 154 (4·3%) had been vaccinated in the previous 12 months, and 570 (15·9%) had been vaccinated in the previous 5 years.

The protective action of PPV-23 is based on the production of opsonising anticapsular antibodies by means of a T-cell-independent mechanism.⁸⁹ PPV-23 is recommended for adults or children older than 5 years who are scheduled for elective splenectomy. This vaccine should be given at least 2 weeks before surgery or, in the event of emergency splenectomy, 2 weeks after surgery.⁹⁰ PPV-23 provides protection against many capsulated antigens, albeit only temporarily. Therefore, revaccination after 5 years is advisable, although the serological response declines more rapidly and frequent reimmunisation in specific subgroups is needed (eg, sickle-cell anaemia, myeloproliferative diseases,

and lymphoproliferative diseases). However, these recommendations are made despite only few data on antibody persistence after vaccination and on antibody responses to revaccination. Monitoring of antibody titres at intervals with ELISA might be helpful for the assessment of whether revaccination is needed; measurement of functional antibody titres by opsonophagocytic assay seems to be preferable to ELISA to predict the extent of protection or to establish an ad-hoc retreatment schedule,⁹¹ although the availability of this assay is limited to a few research laboratories at present because of the increased technical difficulty.

In addition to the limited persistence of circulating antibodies post-vaccination, other factors that counteract effectiveness of PPV-23 are acquired immune deficiency, increasing age, and a genetically determined inability to respond to most or all polysaccharides contained in this vaccine. Ineffectiveness of this vaccine might also occur when bacteraemia is caused by a serotype not included in PPV-23.⁹²

The more recent and costly conjugate vaccines protect against fewer serotypes than does PPV-23 but are more immunogenic.⁹³ In PCV-7, conjugation of polysaccharides to the CRM197 protein changes the antipolysaccharide response from T-lymphocyte-independent responses to T-lymphocyte-dependent ones. This effect makes this vaccine particularly suitable for infants, especially those younger than 2 years who still have an immature B-cell-dependent splenic compartment, and for patients who have already undergone splenectomy or have hyposplenism. In these groups, the pre-existing deficit of IgM memory B cells might be an additional cause of ineffectiveness of PPV-23,⁵ which has been repeatedly reported in hyposplenic and splenectomised patients.^{72,94} By contrast, there was an adequate immune response after PCV-7 in both experimental and human asplenia,^{95,96} and vaccination of splenectomised patients who had invasive pneumococcal disease despite previous PPV-23 immunisation was protective.⁹⁷ Finally, combined use of PCV-7 followed by PPV-23 was effective in hyposplenic patients with sickle-cell anaemia,⁹⁸ HIV infection,⁹⁹ and individuals splenectomised for β -thalassaemia.¹⁰⁰ The explanation for this effectiveness is the less prominent role of the spleen in the anamnestic response in comparison to the generation of the primary response to polysaccharides.⁹⁵

The novel protein-conjugate vaccine PCV-13 (serotypes include 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F)¹⁰¹ offers coverage against several additional pneumococcal strains in comparison to PCV-7 or PCV-10 (serotypes include 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F),¹⁰² and is expected to replace these other pneumococcal vaccines.¹⁰³ PCV-13 includes all seven serotypes most frequently involved in antibiotic resistance (6A, 6B, 9V, 14, 19A, 19F, 23F).¹⁰⁴ Finally, conjugating capsular polysaccharides to pneumococcal surface peptides might offer new therapeutic options in the future.

Current guidelines recommend immunisation against *H influenzae* type b and *N meningitidis*, for adults and children. The *H influenzae* type b conjugate vaccine was immunogenic in splenectomised patients, although the antibody response was lower and faded more rapidly in these patients than in control individuals.¹⁰⁵ There is no agreement on the need for reimmunisation in children, and a single vaccination in adults seems sufficient. For meningococcal immunisation, the conventional tetravalent vaccine protects against strains A, C, Y, and W135 capsular polysaccharides. Independent of T cells, this vaccine has little efficacy in infants younger than 2–3 years,¹⁰⁶ whereas a conjugate vaccine against meningococcal serogroup C is highly immunogenic in the first few months of life and in adults. A single dose of this vaccine is thought to be sufficient,¹⁰⁷ but because revaccination increases the effective antibody response from 80 to 93%, revaccination has been proposed if protective titres are not achieved. The availability of a new tetravalent conjugate meningococcal vaccine¹⁰⁸ might be useful, especially for hyposplenic or splenectomised patients who travel to countries in which *N meningitidis* is hyperendemic or epidemic.

Conclusions

Although post-splenectomy and hyposplenic states might predispose individuals to thromboembolic complications, the main adverse events are immunological and infectious. Spleen-preserving surgical techniques have become increasingly common both for emergency and elective splenectomy; however, the morbidity and mortality associated with the absence and the dysfunction of the spleen are still unacceptably high. In disorders associated with hyposplenism, spleen function should be assessed by means of an appropriate technique (scintiscan, pitted erythrocyte counting, or Howell-Jolly body detection), and, if splenic function is reduced—particularly if associated with atrophy—then all preventive measures against OPSI should be adopted. For children scheduled for splenectomy, postponement of the operation is advisable when possible until the age of 6–12 years. During splenectomy for trauma, surgeons should try to save as much tissue as possible, resorting to deliberate splenosis if necessary. In view of the high mortality rate of OPSI, prophylaxis against encapsulated bacteria is an unavoidable option, and the choice of the most appropriate vaccine is secondary to awareness that vaccination is necessary. Clear clinical and experimental evidence suggests that conjugate vaccines are preferable to the traditional PPV-23 in young children, although there are as yet insufficient data to recommend the use of these vaccines in splenectomised patients and in those with major hyposplenism. Patients, family members, and general practitioners need to be aware of the long-term risk of OPSI and of the advisability of antibiotic treatment not only in children soon after surgery and in patients who

are immunologically impaired, but also in particular situations such as animal bites and visits to at-risk countries. In asplenic or hyposplenic states, any fever must be promptly and carefully assessed and treated.

Contributors

ADS and GRC wrote the clinical part of the Review. ADS and RC wrote the immunological part of the Review. RC participated in writing the section on pneumococcal vaccines.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We thank Vincenzo Villanacci (Second Department of Pathology, Spedali Civili, Brescia, Italy) for providing the histological picture of the spleen shown in figure 1.

References

- Morris DH, Bullock FD. The importance of the spleen in resistance to infection. *Ann Surg* 1919; **70**: 513–21.
- King H, Schumacker HB. Splenic studies. I. Susceptibility to infection after splenectomy performed in infancy. *Ann Surg* 1952; **136**: 239–42.
- Dameshek W. Hyposplenism. *JAMA* 1955; **157**: 613.
- Mebius RE, Kraal G. Structure and function of the spleen. *Nat Immunol* 2005; **5**: 606–16.
- Kruetzmann S, Rosado MM, Weber H, et al. Human immunoglobulin M memory B cells controlling *Streptococcus pneumoniae* infections are generated in the spleen. *J Exp Med* 2003; **197**: 939–45.
- William BM, Thawani N, Sae-Tia S, Corazza GR. Hyposplenism: a comprehensive review. Part II. Clinical manifestations, diagnosis and management. *Hematology* 2007; **12**: 89–98.
- Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. *Blood* 2009; **114**: 2861–68.
- William BM, Corazza GR. Hyposplenism: a comprehensive review. Part I. Basic concepts and causes. *Hematology* 2007; **12**: 1–13.
- Weller S, Braun MC, Tan BK, et al. Human blood IgM “memory” B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. *Blood* 2004; **104**: 3647–54.
- Weller S, Faili A, Garcia C, et al. CD40-CD40L independent Ig gene hypermutation suggests a second B cell diversification pathway in humans. *Proc Natl Acad Sci USA* 2001; **98**: 1166–70.
- Carsetti R, Pantosti A, Quinti I. Impairment of the antipolysaccharide response in splenectomized patients is due to the lack of immunoglobulin M memory B cells. *J Infect Dis* 2006; **193**: 1189–90.
- Shi Y, Yamazaki T, Okubo Y, et al. Regulation of aged humoral immune defense against pneumococcal bacteria by IgM memory B cell. *J Immunol* 2005; **175**: 3262–67.
- Moens L, Wuyts M, Meyts I, De Boeck K, Bossuyt X. Human memory B lymphocyte subsets fulfill distinct roles in the anti-polysaccharide and anti-protein immune response. *J Immunol* 2008; **181**: 5306–12.
- Wasserstrom H, Bussel J, Lim LC, Cunningham-Rundles C. Memory B cells and pneumococcal antibody after splenectomy. *J Immunol* 2008; **181**: 3684–89.
- Swirski FK, Nahrendorf M, Etzrodt M, et al. Identification of splenic reservoir monocytes and their deployment to inflammatory sites. *Science* 2009; **325**: 612–16.
- Spencer RP, Gupta SM. The spleen: diagnosis of splenic diseases using radiolabeled tracers. *Crit Rev Lab Sci* 1989; **27**: 299–318.
- Peters AM, Ryan PFJ, Klonizakis I, Elkon KB, Lewis SM, Hughes GRW. Measurement of splenic function in humans using heat damaged autologous red blood cells. *Scand J Haematol* 1981; **27**: 374–80.
- Corazza GR, Ginaldi L, Zoli G, et al. Howell-Jolly body counting as a measure of splenic function. A reassessment. *Clin Lab Haematol* 1990; **12**: 269–75.
- Sills RH. Splenic function: physiology and splenic hypofunction. *Crit Rev Oncol Hematol* 1987; **7**: 1–36.
- Corazza GR, Bullen AW, Hall R, Robinson PJ, Losowsky MS. Simple method of assessing splenic function in coeliac disease. *Clin Sci* 1981; **60**: 109–13.
- Dhawan V, Spencer RP, Pearson HA, Sziklas JJ. Functional asplenia in the absence of circulating Howell-Jolly bodies. *Clin Nucl Med* 1977; **2**: 395–96.
- Harrod VL, Howard TA, Zimmerman SA, Dertinger SD, Ware RE. Quantitative analysis of Howell-Jolly bodies in children with sickle cell disease. *Exp Hematol* 2007; **35**: 179–83.
- Holroyde CP, Oski FA, Gardner FH. The pocked erythrocyte: red-cell surface alterations in reticuloendothelial immaturity of the neonate. *N Engl J Med* 1969; **281**: 516–20.
- Lane PA, O’Connell JL, Lear JL, et al. Functional asplenia in hemoglobin SC disease. *Blood* 1995; **85**: 2238–44.
- Di Sabatino A, Rosado MM, Cazzola P, et al. Splenic hypofunction and the spectrum of autoimmune and malignant complications in celiac disease. *Clin Gastroenterol Hepatol* 2006; **4**: 179–86.
- Di Sabatino A, Rosado MM, Ciccocioppo R, et al. Depletion of immunoglobulin M memory B cells is associated with splenic hypofunction in inflammatory bowel disease. *Am J Gastroenterol* 2005; **100**: 1788–95.
- Melles DC, de Marie S. Prevention of infections in hyposplenic and asplenic patients: an update. *Neth J Med* 2004; **62**: 45–52.
- Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *J Infect* 2001; **43**: 182–86.
- Hansen K, Singer DB. Asplenic-hyposplenic overwhelming sepsis: post-splenectomy sepsis revisited. *Pediatr Dev Pathol* 2001; **4**: 105–21.
- Bader-Meunier B, Gauthier F, Archambaud F, et al. Long-term evaluation of the beneficial effect of subtotal splenectomy for management of hereditary spherocytosis. *Blood* 2001; **97**: 399–403.
- Sheikha AK, Salih ZT, Kasnazan KH, et al. Prevention of overwhelming postsplenectomy infection in thalassemia patients by partial rather than total splenectomy. *Can J Surg* 2007; **50**: 382–86.
- Timens W, Leemans R. Splenic autotransplantation and the immune system. Adequate testing required for evaluation of effect. *Ann Surg* 1992; **215**: 256–60.
- Fremont RD, Rice TW. Splenosis: a review. *South Med J* 2007; **100**: 589–93.
- Buchbinder JH, Lipkoff CJ. Splenosis: multiple peritoneal splenic implant following abdominal injury: a report of a case and review of the literature. *Surgery* 1939; **6**: 927–34.
- Pearson HA, Johnston D, Smith KA, Touloukian RJ. The born-again spleen. Return of splenic function after splenectomy for trauma. *N Engl J Med* 1978; **298**: 1389–92.
- Traub A, Giebink GS, Smith C, et al. Splenic reticuloendothelial function after splenectomy, spleen repair, and spleen autotransplantation. *N Engl J Med* 1987; **317**: 1559–64.
- Corazza GR, Tarozzi C, Vaira D, Frisoni M, Gasbarrini G. Return of splenic function after splenectomy: how much tissue is needed? *BMJ* 1984; **289**: 861–64.
- Pearson HA, Spencer RP, Cornelius A. Functional asplenia in sickle-cell anemia. *N Engl J Med* 1969; **281**: 923–26.
- Pearson HA, McIntosh S, Ritchey AK. Developmental aspects of splenic function in sickle cell anemia. *Blood* 1979; **53**: 358–65.
- Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? *Blood* 1984; **63**: 921–26.
- Pearson HA, Gallagher D, Chilcote R, et al. Developmental pattern of splenic dysfunction in sickle cell disorders. *Pediatrics* 1985; **76**: 392–97.
- Barrios NJ, Livaudais F, McNeil J, Humbert JR, Corrigan J. Reversible splenic hypofunction in hypertransfused children with homozygous sickle cell disease. *J Natl Med Assoc* 1993; **85**: 677–80.
- Santos A, Pinheiro V, Anjos C. Scintigraphic follow-up of the effects of therapy with hydroxyurea on splenic function in patients with sickle cell disease. *Eur J Nucl Med Mol Imaging* 2002; **29**: 536–41.
- Quinn CT, Rogers ZR, McCavit TL, Buchanan GR. Improved survival of children and adolescents with sickle cell disease. *Blood* 2010; **115**: 3447–52.
- Wang WC, Wynn LW, Rogers ZR, Scott JP, Lane PA, Ware RE. A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *J Pediatr* 2001; **139**: 790–96.
- Cuthbert RJ, Iqbal A, Gates A, Toghil PJ, Russell NH. Functional hyposplenism following allogeneic bone marrow transplantation. *J Clin Pathol* 1995; **48**: 257–59.

- 47 Picardi M, Selleri C, Rotoli B. Spleen sizing by ultrasound scan and risk of pneumococcal infection in patients with chronic GVHD: preliminary observations. *Bone Marrow Transplant* 1999; **24**: 173–77.
- 48 D'Orsogna LJ, Wright MP, Krueger RG, et al. Allogeneic hematopoietic stem cell transplantation recipients have defects of both switched and IgM memory B cells. *Biol Blood Marrow Transplant* 2009; **15**: 795–803.
- 49 Engelhard D, Cordonnier C, Shaw PJ, et al. Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. *Br J Haematol* 2002; **117**: 444–50.
- 50 Ferguson A, Hutton MM, Maxwell JD, Murray D. Adult coeliac disease in hyposplenic patients. *Lancet* 1970; **295**: 163–64.
- 51 Corazza GR, Zoli G, Di Sabatino A, Ciccocioppo R, Gasbarrini G. A reassessment of splenic hypofunction in celiac disease. *Am J Gastroenterol* 1999; **94**: 391–97.
- 52 O'Grady JG, Stevens FM, Harding B, O'Gorman TA, McNicholl B, McCarthy CF. Hyposplenism and gluten-sensitive enteropathy. Natural history, incidence, and relationship to diet and small bowel morphology. *Gastroenterology* 1984; **87**: 1326–31.
- 53 Corazza GR, Frisoni M, Vaira D, Gasbarrini G. Effect of gluten-free diet on splenic hypofunction of adult coeliac disease. *Gut* 1983; **24**: 228–30.
- 54 Ludvigsson JF, Olen O, Bell M, Ekblom A, Montgomery SM. Coeliac disease and the risk of sepsis. *Gut* 2008; **57**: 1074–80.
- 55 Thomas HJ, Wotton CJ, Yeates D, Ahmad T, Jewell DP, Goldacre MJ. Pneumococcal infection in patients with coeliac disease. *Eur J Gastroenterol Hepatol* 2008; **20**: 624–28.
- 56 Bender BS, Frank MM, Lawley TJ, et al. Defective reticuloendothelial system Fc-receptor function in patients with acquired immunodeficiency syndrome. *J Infect Dis* 1985; **152**: 409–12.
- 57 Grotto HZ, Costa FF. Hyposplenism in AIDS. *AIDS* 1991; **5**: 1538–40.
- 58 Corazza GR, Zoli G, Ginaldi L, et al. Tuftsin deficiency in AIDS. *Lancet* 1991; **337**: 12–13.
- 59 D'Orsogna LJ, Krueger RG, McKinnon EJ, French MA. Circulating memory B-cell subpopulations are affected differently by HIV infection and antiretroviral therapy. *AIDS* 2007; **21**: 1747–52.
- 60 Hart M, Steel A, Clark SA, et al. Loss of discrete memory B cell subsets is associated with impaired immunization responses in HIV-1 infection and may be a risk factor for invasive pneumococcal disease. *J Immunol* 2007; **178**: 8212–20.
- 61 Muller AF, Toghiani PJ. Functional hyposplenism in alcoholic liver disease: a toxic effect of alcohol? *Gut* 1994; **35**: 679–82.
- 62 Foster KJ, Devitt N, Gallagher PJ, Abbott RM. Overwhelming pneumococcal septicaemia in a patient with ulcerative colitis and splenic atrophy. *Gut* 1982; **23**: 630–32.
- 63 Di Sabatino A, Vidali F, Cazzola P, et al. Splenic hypofunction in Whipple's disease. *Am J Gastroenterol* 2009; **104**: 2641–43.
- 64 Powsner RA, Simms RW, Chudnovsky A, Lee VW, Skinner M. Scintigraphic functional hyposplenism in amyloidosis. *J Nucl Med* 1998; **39**: 221–23.
- 65 Neilan BA, Berney SN. Hyposplenism in systemic lupus erythematosus. *J Rheumatol* 1983; **10**: 332–34.
- 66 Powars D, Chan LS, Schroeder WA. The variable expression of sickle cell disease is genetically determined. *Semin Hematol* 1990; **27**: 360–76.
- 67 Kalhs P, Panzer S, Kletter K, et al. Functional asplenia after bone marrow transplantation. A late complication related to extensive chronic graft-versus-host disease. *Ann Intern Med* 1988; **109**: 461–64.
- 68 Kulkarni S, Powles R, Treleaven J, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplants. *Blood* 2000; **95**: 3683–86.
- 69 Di Sabatino A, Corazza GR. Coeliac disease. *Lancet* 2009; **373**: 1480–93.
- 70 Peters U, Askling J, Gridley G, Ekblom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med* 2003; **163**: 1566–72.
- 71 Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg* 1991; **78**: 1031–38.
- 72 Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. *J Clin Pathol* 2001; **54**: 214–18.
- 73 Robinette CD, Fraumeni JF. Splenectomy and subsequent mortality in veterans of the 1939–45 war. *Lancet* 1977; **2**: 127–29.
- 74 Schwartz PE, Sterioff S, Mucha P, Melton LJ, Offord KP. Postsplenectomy sepsis and mortality in adults. *JAMA* 1982; **248**: 2279–83.
- 75 Mullen CA, Anderson KD, Blaese RM. Splenectomy and/or bone marrow transplantation in the management of the Wiskott-Aldrich syndrome: long-term follow-up of 62 cases. *Blood* 1993; **82**: 2961–66.
- 76 Alaneer SR, McGee L, Jackson D, et al. Association of serotypes of *Streptococcus pneumoniae* with disease severity and outcome in adults: an international study. *Clin Infect Dis* 2007; **45**: 46–51.
- 77 Jansen AG, Rodenburg GD, van der Ende A, et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. *Clin Infect Dis* 2009; **49**: e23–29.
- 78 Anand AJ, Glatt AE. Salmonella osteomyelitis and arthritis in sickle cell disease. *Semin Arthritis Rheum* 1994; **24**: 211–21.
- 79 Bridgen ML, Pattullo AL. Prevention and management of overwhelming postsplenectomy infection—an update. *Crit Care Med* 1999; **27**: 836–42.
- 80 Bridgen ML, Pattullo AL, Brown G. Pneumococcal vaccine administration associated with splenectomy: the need for improved education, documentation, and the use of a practical checklist. *Am J Hematol* 2000; **65**: 25–29.
- 81 El-Alfy MS, El-Sayed MH. Overwhelming postsplenectomy infection: is quality of patient knowledge enough for prevention? *Hematol J* 2004; **5**: 77–80.
- 82 Woolley I, Jones P, Spelman D, Gold L. Cost-effectiveness of a post-splenectomy registry for prevention of sepsis in the asplenic. *Aust NZ J Public Health* 2006; **30**: 558–59.
- 83 Kaplinsky C, Spierer Z. Post-splenectomy antibiotic prophylaxis—unfinished story: to treat or not to treat? *Pediatr Blood Cancer* 2006; **47**: 740–41.
- 84 John AB, Ramlal A, Jackson H, Maude GH, Sharma AW, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *BMJ* 1984; **288**: 1567–70.
- 85 Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. *N Engl J Med* 1986; **314**: 1593–99.
- 86 Pedersen FK, Henriksen J, Schiffman G. Antibody response to vaccination with pneumococcal capsular polysaccharides in splenectomized children. *Acta Paediatr Scand* 1982; **71**: 451–55.
- 87 Konradsen HB, Henriksen J. Pneumococcal infections in splenectomized children are preventable. *Acta Paediatr Scand* 1991; **80**: 423–27.
- 88 Pebody RG, Hippisley-Cox J, Harcourt S, Pringle M, Painter M, Smith G. Uptake of pneumococcal polysaccharide vaccine in at-risk populations in England and Wales 1999–2005. *Epidemiol Infect* 2008; **136**: 360–69.
- 89 French N. Use of pneumococcal polysaccharide vaccines: no simple answers. *J Infect* 2003; **46**: 78–86.
- 90 Shatz DV, Romero-Steiner S, Elie CM, Holder PF, Carlone GM. Antibody responses in postsplenectomy trauma patients receiving the 23-valent pneumococcal polysaccharide vaccine at 14 versus 28 days postoperatively. *J Trauma* 2002; **53**: 1037–42.
- 91 Vernacchio L, Romero-Steiner S, Martinez JE, et al. Comparison of an opsonophagocytic assay and IgG ELISA to assess responses to pneumococcal polysaccharide and pneumococcal conjugate vaccines in children and young adults with sickle cell disease. *J Infect Dis* 2000; **181**: 1162–66.
- 92 Shatz DV. Vaccination considerations in the asplenic patient. *Expert Rev Vaccines* 2005; **4**: 27–34.
- 93 Chan CY, Molrine DC, George S, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. *J Infect Dis* 1996; **173**: 256–58.
- 94 Ahonkhai VI, Landesman SH, Fikrig SM, et al. Failure of pneumococcal vaccine in children with sickle-cell disease. *N Engl J Med* 1979; **301**: 26–27.

- 95 Breukels MA, Zandvoort A, van Den Dobbelsteen GP, et al. Pneumococcal conjugate vaccines overcome splenic dependency of antibody response to pneumococcal polysaccharides. *Infect Immun* 2001; **69**: 7583–87.
- 96 Mikoluc B, Kayhty H, Bernatowska E, Motkowski R. Immune response to the 7-valent pneumococcal conjugate vaccine in 30 asplenic children. *Eur J Clin Microbiol Infect Dis* 2008; **27**: 923–28.
- 97 Musher DM, Ceasar H, Kojic EM, et al. Administration of protein-conjugate pneumococcal vaccine to patients who have invasive disease after splenectomy despite their having received 23-valent pneumococcal polysaccharide vaccine. *J Infect Dis* 2005; **191**: 1063–67.
- 98 Vernacchio L, Neufeld EJ, MacDonald K, et al. Combined schedule of 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal vaccine in children and young adults with sickle cell disease. *J Pediatr* 1998; **133**: 275–78.
- 99 Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. Enhanced antibody response to pneumococcal polysaccharide vaccine after prior immunization with conjugate pneumococcal vaccine in HIV-infected adults. *Vaccine* 2000; **19**: 886–94.
- 100 Orthopoulos GV, Theodoridou MC, Ladis VA, Tsousis DK, Spoulou VI. The effect of 23-valent pneumococcal polysaccharide vaccine on immunological priming induced by 7-valent conjugate vaccine in asplenic subjects with beta-thalassemia. *Vaccine* 2009; **27**: 350–54.
- 101 Scott DA, Komjathy SF, Hu BT, et al. Phase 1 trial of a 13-valent pneumococcal conjugate vaccine in healthy adults. *Vaccine* 2007; **25**: 6164–66.
- 102 Croxtall JD, Keating GM. Pneumococcal polysaccharide protein D-conjugate vaccine (Synflorix; PHiD-CV). *Paediatr Drugs* 2009; **11**: 349–57.
- 103 Lee CJ, Wang TR, Frasch CE. Immunogenicity in mice of pneumococcal glycoconjugate vaccines using pneumococcal protein carriers. *Vaccine* 2001; **19**: 3216–25.
- 104 Dagan R, Klugman KP. Impact of conjugate pneumococcal vaccines on antibiotic resistance. *Lancet Infect Dis* 2008; **8**: 785–95.
- 105 Cimaz R, Mensi C, D'Angelo E, et al. Safety and immunogenicity of a conjugate vaccine against *Haemophilus influenzae* type b in splenectomized and nonsplenectomized patients with Cooley anemia. *J Infect Dis* 2001; **183**: 1819–21.
- 106 Leach A, Twumasi PA, Kumah S, et al. Induction of immunologic memory in Gambian children by vaccination in infancy with a group A plus group C meningococcal polysaccharide-protein conjugate vaccine. *J Infect Dis* 1997; **175**: 200–04.
- 107 Borrow R, Andrews N, Goldblatt D, Miller E. Serological basis for use of meningococcal serogroup C conjugate vaccines in the United Kingdom: reevaluation of correlates of protection. *Infect Immun* 2001; **69**: 1568–73.
- 108 Centers for Disease Control and Prevention. Revised recommendations of the Advisory Committee on Immunization Practices to vaccinate all persons aged 11–18 years with meningococcal conjugate vaccine. *MMWR Morb Mortal Wkly Rep* 2007; **56**: 794–95.