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Primer

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Asplenia and spleen hypofunction

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Abstract

Asplenia (the congenital or acquired absence of the spleen) and hyposplenism (defective spleen function) are common causes of morbidity and mortality. The spleen is a secondary lymphoid organ that is responsible for the regulation of immune responses and blood filtration. Hence, asplenia or hyposplenism increases susceptibility to severe and invasive infections, especially those sustained by encapsulated bacteria (namely, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b). Asplenia is predominantly due to splenectomy for either traumatic events or oncohaematological conditions. Hyposplenism can be caused by several conditions, including haematological, infectious, autoimmune and gastrointestinal disorders. Anatomical disruption of the spleen and depletion of immune cells, especially IgM memory B cells, seem to be predominantly responsible for the clinical manifestations. Early recognition of hyposplenism and proper management of asplenia are warranted to prevent overwhelming post-splenectomy infections through vaccination and antibiotic prophylaxis. Although recommendations are available, the implementation of vaccination strategies, including more effective and immunogenic vaccines, is needed. Additionally, screening programmes for early detection of hyposplenism in high-risk patients and improvement of patient education are warranted.

Sections

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Introduction

The term asplenia refers to the congenital (extremely rare) or acquired (most commonly after surgery) absence of the spleen, whereas the term hyposplenism (also known as spleen hypofunction or defective spleen function) refers to the acquired impairment of spleen functions[1]. The aetiological causes of asplenia and hyposplenism are multiple and complex[2–4] (Box 1). Both conditions are associated with several disorders, including innate, immune-mediated, hepatic, haemolytic, autoimmune and circulatory disorders. In addition, gastrointestinal and infectious diseases may predispose individuals to spleen hypofunction[1,5]. Taken together, these are common conditions worldwide; however, hyposplenism remains largely underdiagnosed as only in the past 20 years has it been recognized as a specific nosological entity leading to the definition of its predisposing factors and disease associations[2,6,7].

The term hyposplenism was first used in 1913 to indicate, improperly, a general 'post-splenectomy' state[8]. Only later, was the modern concept of hyposplenism introduced, in analogy to thyroid hypofunction, that is, hypothyroidism[9]. We now know that asplenia and hyposplenism represent a great disease burden for patients because they predispose to the lifelong development of severe and systemic infections (termed overwhelming post-splenectomy infection (OPSI)), especially those sustained by encapsulated bacteria (specifically, *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b)[10–12]. Autoimmunity and thromboembolism also seem to be of concern in these patients, although evidence is more incomplete[1], and the causes of these phenomena are still poorly understood. Although some progress has been made in early recognition of these conditions and in tailoring health-care pathways to improve their clinical management, including leaflets, awareness campaigns, and spleen registries, most physicians and members of the public are still not fully aware of the clinical significance of asplenia and hyposplenism, and their consequences[13].

Most of our knowledge about the spleen derives from studies conducted in the past century[7]. The spleen is a secondary lymphoid organ that is located in a privileged anatomic location in the abdomen, strictly communicating with the digestive system through the hepatic portal system that is formed by the superior and inferior mesenteric veins and the spleen vein[14] (Fig. 1). Hence, several gastrointestinal diseases may be associated with hyposplenism for both anatomical and functional reasons. The spleen has two main functions: blood filtering, which is necessary for removing old erythrocytes (haemocatheresis) and other blood cells, and mounting immune responses against pathogens through both the innate and adaptive immune system branches[1]. These functions take place in two different anatomical parts of the spleen, that is the red pulp, which is a sponge-like structure through which the blood is continuously filtered in sinuses and cords, and the white pulp, where several immune cells and adaptive immune responses occur (Fig. 1). A heterogeneous group of IgM memory B cells are located in the extreme periphery of the white pulp, named the marginal zone[1,15,16]. IgM memory B cells are central to mounting prompt responses against both viral and bacterial pathogens, and to maintaining T cell-independent immune responses, even after vaccination[1,15]. The increasing availability of unconjugated and conjugate vaccines against encapsulated bacteria[17], as well as new insights gained through the coronavirus disease 2019 (COVID-19) pandemic and on the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on spleen function[18,19], have fuelled great interest in the study of patients with asplenia or hyposplenism.

In this Primer, we review the latest knowledge on asplenia and hyposplenism, including epidemiology, pathophysiology, diagnosis, vaccination strategies for preventing OPSI, overall management and patient quality of life (QOL). We also discuss the most compelling issues that will drive future strategies for early recognition and appropriate management of these conditions.

Epidemiology

The epidemiology of asplenia and the epidemiology of hyposplenism are linked with the prevalence and global distribution of the various associated aetiological factors (Box 1). Due to this broad association with other diseases, its under-recognition and the lack of extensive epidemiological studies, the global prevalence of asplenia and hyposplenism cannot be estimated. Hence, we report the epidemiology depending on the specific aetiologies of asplenia and hyposplenism.

Congenital

Asplenia may be congenital, being typically inherited as an autosomal dominant trait[20]. Congenital asplenia is rare but has been linked to several disorders, with variable penetrance. For example, Ivemark syndrome, a heterotaxy estimated to occur in 1 per 40,000 live births[21], is associated with asplenia in almost all cases. In children with congenital heart disease (with a prevalence in newborns of 0.75–0.9%), splenic malformations or asplenia occur in 1 per 5,000–7,000 of these newborns[22]. Isolated congenital asplenia (ICA) is defined as being born without a spleen in the absence of any other developmental anomalies. The incidence of ICA is relatively low, occurring in 1 per 600,000 to 0.51 per million births[23,24]. However, this is thought to be an underestimation due to poor diagnostic protocols[25], and ICA is often diagnosed accidentally in adulthood[23,25,26]. According to these available studies, splenic atrophy and asplenia have been reported to be common in autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) syndrome, but the exact estimate is not known. APECED syndrome, caused by mutations in *AIRE*, occurs worldwide. The prevalence of APECED is highest in Iranian Jews at 1 per 9,000 and ranges from 1 per 14,500 to over 1 per 10 million in other ethnic populations[27,28]. Other congenital abnormalities that may include asplenia are fetal hydantoin syndrome, Stormorken syndrome and congenital cyanotic heart disease[1].

Trauma

The most common cause of asplenia is surgical removal of the spleen following trauma-related injuries[1]. In the USA, an estimated 40,000 splenic injuries occur annually with 10–15% requiring emergency splenectomy[29,30]. In Australia, the incidence of traumatic splenectomy is ~6.4 per million annually[31]. In a retrospective study from China focusing on military hospitals, almost 8,000 splenic injuries occurred during ~10 years, most of which were treated surgically[32]. In France, across 16 institutions, in the context of a clinical trial, 133 cases of splenic trauma were reported in the period 2014–2017 (ref.[33]). By contrast, there is a paucity of data on trauma-related splenectomy from other geographic areas, such as Africa[34–37]. A retrospective survey from South Africa showed that ~10% of trauma patients needing surgery required splenectomy[34], whereas in retrospective studies in Nigeria 60% of cases involved splenectomy[38] with more conservative management in children[39].

Blood disorders

The second leading cause of surgical asplenia is related to the treatment of certain blood disorders, such as sickle cell disease (SCD), hereditary spherocytosis, Wiskott–Aldrich syndrome, immune thrombocytopenic purpura (ITP) and warm autoimmune haemolytic anaemia (AIHA)[1]. In these conditions, secondary hyposplenism may also occur as part of their natural history. It was initially thought that nearly all children

Box 1

Main causes of asplenia and hyposplenism

Causes of asplenia

Congenital asplenia

Premature birth
Isolated congenital asplenia
Ivemark syndrome
APECED syndrome
Type I autoimmune polyendocrine syndrome
Hypoparathyroidism–retardation–dysmorphism
Stormorken syndrome
Foetus hydantoin syndrome
Teratogenic warfarin effect
Cyanotic heart disease
Fanconi anaemia

Surgical splenectomy

Causes of hyposplenism

Gastrointestinal diseases

Coeliac disease
Inflammatory bowel disease
Whipple disease
Dermatitis herpetiformis
Intestinal lymphangiectasia
Idiopathic ulcerative enteritis
Primary eosinophilic gastrointestinal disorders
Autoimmune gastritis

Liver diseases

Alcoholic liver disease
Chronic active hepatitis
Liver cirrhosis and portal hypertension
Primary biliary cholangitis

Oncohaematological diseases

Haemoglobin S disease
Haemolytic anaemias (including warm autoimmune haemolytic anaemia)
Graft-versus-host disease
Acute leukaemia
Chronic myeloproliferative disease
Lymphoproliferative disease
Idiopathic thrombocytopenic purpura
Systemic mastocytosis
Langerhans cell histiocytosis
Breast cancer
Spleen cancer (primary and secondary)

Immune-mediated diseases or immune deficiencies

Systemic lupus erythematosus
Rheumatoid arthritis
Glomerulonephritis
Granulomatosis with polyangiitis
Goodpasture syndrome
Antiphospholipid syndrome
Sjögren syndrome
Polyarteritis nodosa
Connective tissue disease
Autoimmune thyroid disease
Sarcoidosis
Multiple sclerosis
Isolated IgA deficiency
Common variable immune deficiency

Infectious diseases

HIV infection and AIDS
Pneumococcal meningitis
Malaria
Babesiosis
SARS-CoV-2 infection

Iatrogenic causes

α-Methyldopa
High-dose steroids
Total parenteral nutrition
Splenic radiotherapy

Splenic vascular alterations

Splenic artery thrombosis
Splenic vein thrombosis
Coeliac artery thrombosis

Various

Amyloidosis
Hyposplenism owing to ageing
Hypopituitarism
Primary pulmonary hypertension

APECED, autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

with SCD develop splenic infarctions leading to auto-splenectomy in early life or have progressively worsening spleen function requiring late splenectomy[40,41]. However, a systematic review of several studies found that African patients with SCD have persistence of the spleen into late childhood and adulthood[40], similar to other populations displaying high fetal haemoglobin levels and coinheritance of the α-thalassaemia trait[42,43]. Globally, ~300,000 children with SCD are born each year, and >90% of affected individuals live in sub-Saharan Africa[44,45]. Hereditary spherocytosis and ITP are rare haematological disorders with an incidence of 1 per 2,000 for hereditary spherocytosis and 0.2–0.7 per 10,000 for ITP among individuals of European descent in the USA and Europe[46–48]. The treatment protocols for both hereditary spherocytosis

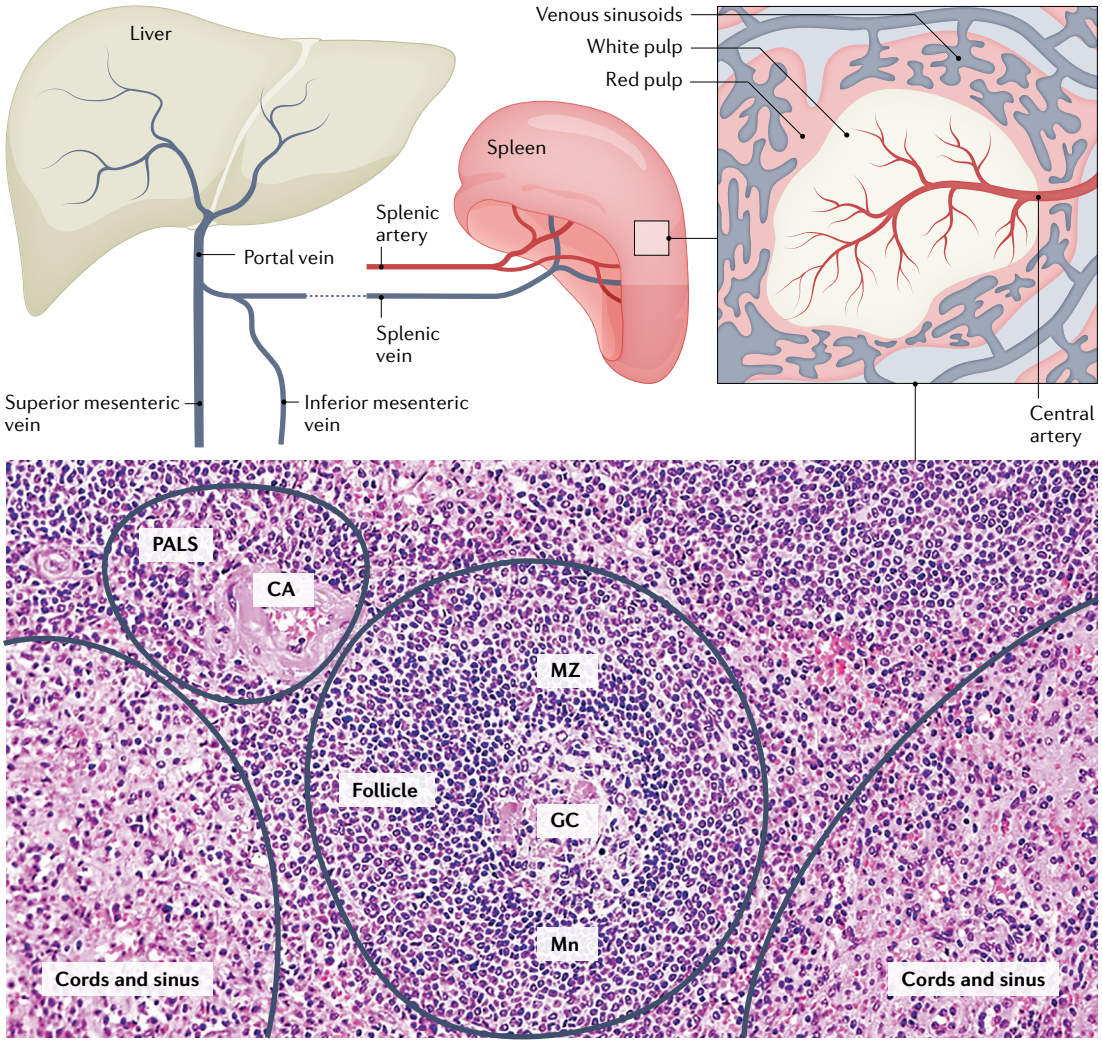

Fig. 1 | Anatomy, vascularization and histology of a healthy spleen. The spleen is a lymphoid organ 8–12 cm in length in adults. One or more accessory spleens may also be present. The spleen is strictly linked to the gastrointestinal tract through the portal venous system, which is composed of three main vein branches (the splenic vein, the inferior mesenteric vein and the superior mesenteric vein) that drain blood from the spleen, pancreas, stomach and small bowel. These veins converge into the portal vein that carries blood to the liver. The internal structure of the spleen comprises the red pulp that consists of cords and sinuses in which blood is filtered and white pulp that consists of lymphoid structures specialized in mounting immune responses. Follicles in the white pulp are composed of the germinal centre (GC), the marginal zone (MZ) and the mantle zone (Mn; also termed the corona). The MZ contains mostly B lymphocytes and represents the interface between the white and the red pulp of the spleen. The central arteriole (CA) is surrounded by a periarteriolar lymphoid sheath (PALS) that contains mostly T lymphocytes. Histology image: haematoxylin and eosin stain, ×10. Histological sample, image courtesy of V. Villanacci.

and ITP include splenectomy in severe or treatment-resistant disease, which accounts for 10–30% of cases[46–48]. In African populations, hereditary spherocytosis and ITP are thought to be much less prevalent than other haematological diseases, such as SCD. An average of ten new cases of ITP were reported from two hospitals in Nigeria over an 11-year period[49,50]. Finally, warm AIHA is an autoimmune disorder that results in excessive destruction of red blood cells by antibodies with or without complement activation. The estimated annual incidence is one to three cases per 100,000 (refs.[51,52]). Splenectomy as a therapy for warm AIHA was once considered the most effective second-line therapy (70–80% response rate)[53]. However, other treatments, such as the monoclonal antibody rituximab, are now preferred[54].

Other medical conditions

The prevalence of hyposplenism varies in other conditions, but a true figure cannot be estimated as most knowledge is derived from case reports, case series or small cohort studies. In gastrointestinal diseases, hyposplenism is rather common. Using pitted red cell (PRC) count, the gold standard test for assessing spleen function by counting circulating red blood cells displaying membrane 'pits', hyposplenism is estimated to affect 37–100% of patients with alcoholic liver disease[55,56], 33–76% of those with coeliac disease[57–59], and 47% of those with Whipple disease[60]. These figures are rather high compared with the estimated prevalence of hyposplenism in haematopoietic stem cell transplant recipients, which is around 40%[61,62]. Among patients with coeliac disease, those

who have refractory disease, ulcerative jejuno-ileitis, or enteropathy-associated T cell lymphoma have the highest risk of hyposplenism[57,58], whereas hyposplenism is always absent in children. In addition, a proportion of patients with inflammatory bowel disease, specifically, 35–45% with ulcerative colitis and 9–37% with Crohn's disease, experience mild-to-moderate hyposplenism[63,64]. Anecdotally, hyposplenism has been observed in patients with autoimmune gastrointestinal disorders, including autoimmune gastritis, autoimmune enteropathy and autoimmune liver disease[65,66], although the clinical significance of this finding remains unclear.

Of note, hyposplenism has also been found in patients with several infectious diseases. Preliminary investigations conducted in 2020–2021 demonstrated spleen hypofunction in association with SARS-CoV-2 infection[18]. SARS-CoV-2 primarily causes a respiratory tract infection, with a broad range of clinical pictures. In a substantial number of patients, it may cause a systemic inflammatory response with multiple organ involvement, including the spleen, due to 'viral sepsis'[67]. Small independent studies in high-income and middle-income settings have found impaired spleen function, especially involving the white pulp, in 29–100% of patients with COVID-19 (refs.[18,19,68]), which was generally associated with an unfavourable outcomes. There are no data from Africa regarding the number of patients experiencing spleen hypofunction following COVID-19.

Splenic infarctions, causing spleen hypofunction or spleen atrophy, have been documented in patients with several infectious diseases, including malaria, HIV infection and babesiosis. Malaria is the leading cause of morbidity in sub-Saharan Africa and splenomegaly occurs in 70–80% of patients with acute disease[69]. Splenic enlargements typically return to normal following treatment. However, ~8.8% of non-immune individuals who develop abdominal pain following malaria suffer splenic rupture[70]. Among people living with HIV, the prevalence of hyposplenism is ~36%[71,72]. Furthermore, the risk of malaria and HIV co-infections in Africa is a concern. One study demonstrated a link between mortality and defective spleen function associated with malaria and HIV co-infections[73]. Babesiosis has been linked to splenic infarctions, but this is considered a rare occurrence[74,75].

Finally, hyposplenism has also been anecdotally reported in patients with autoimmune diseases. For example, <7% of patients with systemic lupus erythematosus were reported to have spleen hypofunction[76].

Overwhelming post-splenectomy infections

The incidence of OPSI in individuals who have undergone splenectomy is well established (~0.13 per 100 person-years)[77], but the risk of OPSI is not known, although probably lower, in those with hyposplenism[1]. For this reason, the term OPSI was initially coined for severe infections occurring after surgical splenectomy and was later extended to include other causes of asplenia or hyposplenism[1,2,7]. The factors associated with the severity and risk of OPSI include immune status, underlying disease, age and the microorganism involved, with *S. pneumoniae, N. meningitidis* and *H. influenzae* being among the most commonly identified[1,2,78]. Other associated microorganisms include *Pseudomonas aeruginosa*, *Capnocytophaga canimorsus*, *Bartonella* spp. and *Babesia* spp.[78]. Finally, OPSI may develop from gastrointestinal infections, which are rather common in asplenia[79], possibly due to the decreased levels of mucosal IgA. Of note, epidemiological studies showed that 90% of OPSI are caused by *S. pneumoniae*, whereas *H. influenzae* accounts for only ~6% of OPSI, followed by *N. meningitidis* and other bacteria. The incidence of fulminant sepsis is generally low (around 3–7%) but mortality from sepsis is up to 70%[10,11].

Haematological diseases, such as thalassaemia, SCD and warm AIHA, and immunosuppressive treatments have been associated with the development of OPSI and its related mortality to different extents[1,6]. OPSI-associated mortality in patients who have undergone splenectomy owing to autoimmune thrombocytopenia is similar to that of patients who have undergone splenectomy owing to trauma, but lower than that of patients who have undergone splenectomy owing to oncohaematological diseases, such as Hodgkin disease[80].

The risk of OPSI seems to increase with age, and the reported number of infections increase during the first 3 years after splenectomy and remain mostly stable thereafter[81]. Nevertheless, in 30–40% of affected patients, OPSI has been found to occur >5 years after splenectomy, and rarely has been found to occur >40 years after splenectomy, indicating a long-lasting risk of infections in these patients[80].

Mechanisms/pathophysiology

The spleen lymphocyte milieu is highly organized and complex (Fig. 2), reflecting the privileged anatomical position of the spleen, which is immunologically linked with the gut. There is evidence of shared roles of the gut and spleen in B cell development from both mouse models and studies of human tissues[82–84]. Unfortunately, for most conditions, the causes leading to hyposplenism are largely unknown. Some general mechanisms, such as spleen atrophy or severe architectural distortion, and/or suppression of the B cell milieu, are shared by virtually all conditions, such as haematological diseases, coeliac disease and other gastrointestinal disorders, autoimmune disorders and infectious diseases, including HIV infection[1,6]. This section focuses on the pathophysiological bases of defective spleen function and asplenia, in relation to the lymphocyte populations resident in the spleen.

IgM memory B cell depletion and other cell subsets

The unique splenic architecture regulates B cell function. In the spleen, B and T cells reside in the white pulp in primary follicles, germinal centres and T cell areas, forming structures similar to those found in the lymph nodes. B cell follicles and germinal centres are surrounded by the marginal zone (Fig. 2), a reservoir of $CD27^+$ memory B cells, mostly expressing IgM and IgD[85]. This cell population, also known as IgM[86], marginal zone[87] or innate[88,89] memory B cells, depend on the spleen for their generation, survival and function, and are depleted in asplenic and splenectomized individuals[86]. In the marginal zone, IgM memory B cells are in direct contact with the blood, which flows slowly in the open circulation of the splenic red pulp[85]. This strategic location favours the rapid encounter with blood-borne pathogens captured by marginal zone macrophages, triggering the immediate recruitment of memory B cells[1]. The mucosal vascular addressin cell adhesion molecule 1 (MAdCAM1) is expressed by the fibroblasts at the border between the follicles and the marginal zone. MAdCAM1 (refs.[90,91]) is also expressed in endothelial cells of mucosa-associated lymphatic tissues, such as Peyer's patches or mesenteric lymph nodes, and in the high endothelial venules of intestinal villi[85]. Memory B cells of the marginal zone express the MAdCAM1 ligand integrin $\alpha_4\beta_7$. Loss of MAdCAM1 disrupts the splenic architecture, abolishes the marginal zone[92] and, in the gut, drastically reduces the size of the associated lymphoid tissue and the number of mucosal IgA plasma cells[93].

The role of the spleen in the survival and function of memory B cells and in pathogen clearance. IgM memory B cells act as the first-line defence against infections by secreting natural IgM[94–96] and by generating most of the IgA plasma cells at mucosal sites[97]. In the mouse, B1 cells, the population functionally equivalent to human IgM memory

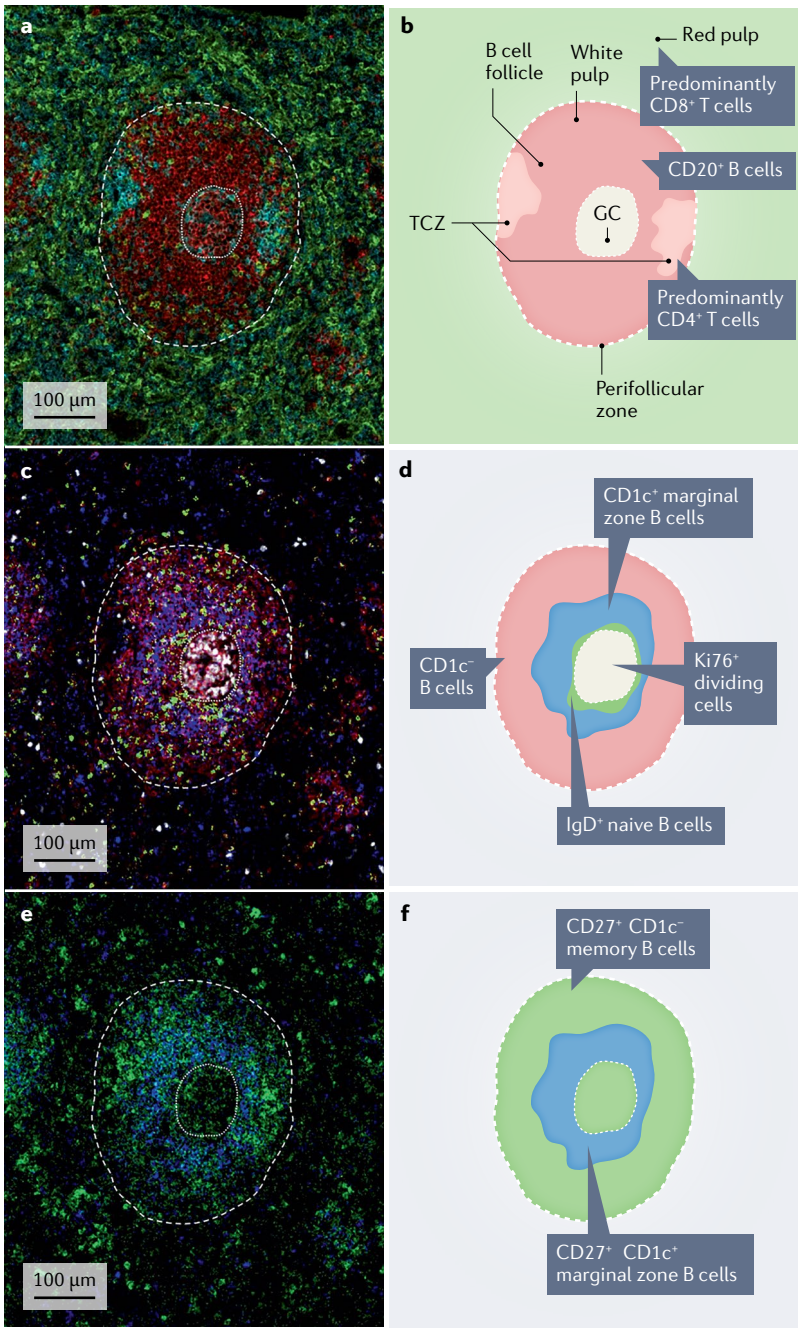

Fig. 2 | Immune cell composition of the healthy spleen. Normal human spleen visualized using imaging mass cytometry and corresponding schematic representations that approximate zones defined by the phenotype of the cells they contain. The boundaries between the red pulp and white pulp and the germinal centre (GC) within the white pulp are indicated by dashed lines. Of note, positioning and relative size of zones differ in every B cell follicle. Usual distribution of B and T cells (parts **a** and **b**). B cells (CD20; red) occupy most of the white pulp area. $CD4^+$ T cells (CD4; cyan) comprise most of the T cells in the T cell zone (TCZ) of the white pulp, whereas $CD8^+$ T cells (CD8; green) are relatively more abundant in the red pulp. Sinusoidal lining cells of the human red pulp also express CD8. B cell subsets within the follicle (parts **c** and **d**). Dividing cells are predominantly located in the GC (Ki76; white). Naive B cells, which have the highest IgD (green) expression levels, are located close to the GC. Marginal zone B cells, which commonly express CD1c (blue), surround the region of strongest IgD expression. B cells (CD20; red) on the outer region of the white pulp are $CD1c^-$. Distribution of memory B cells within the follicle (parts **e** and **f**). CD27-expressing cells (CD27; green), which are often considered to be memory B cells, extend to the boundary between the white pulp and red pulp, whereas $CD1c^+$ cells of the marginal zone are not found in the peripheral boundary. B cells occupying the marginal zone are, therefore, heterogeneous.

B cells, are derived from a stem cell originating from the fetal liver and residing in the spleen. Similar to IgM memory B cells, B1 cells secrete natural IgM, respond to encapsulated bacteria polysaccharides[98], and generate most of the IgA plasma cells in the gut[82].

In humans, IgM memory B cells of splenic origin develop without T cells in the absence of cognate B cell–T cell interactions, and therefore belong to a separate T cell-independent lineage[99] generated in the spleen[86,88]. In neonates, IgM memory B cells are the only memory B cell type in the peripheral blood[88]. Owing to the production of natural IgM in the serum and natural IgA at mucosal sites and owing to the ability to respond to T cell-independent antigens, innate memory B cells that originate in the spleen have the primary function of first-line protection against newly encountered pathogens[94]. Immunoglobulin sequence analyses in patients without the spleen showed that, in older children and adults, innate IgM memory B cells can be recruited to the germinal centre reaction, acquire somatic mutations, and are remodelled to increase their specificity[100]. Additionally, the interplay between IgM memory B cells and switched memory B cells maintains the stability and rapidity of the response of the B cell memory pool, serving as a substrate for the generation of highly specific switched memory B cells[98].

Switched memory B cells are the second major population of human memory B cells[101]. They are generated only in individuals

with perfectly functional germinal centres and in patients without a spleen[86]. The adaptive immune reaction can be initiated by naive B cells that acquire somatic mutations, undergo antigen selection and, finally, differentiate into high-affinity switched memory B cells and plasma cells[88]. The number of switched memory B cells is not substantially affected by splenectomy[88]. Germinal centres in the mesenteric lymph nodes and Peyer's patches generate high-affinity IgA plasma cells[102].

Most infections start at mucosal sites, where the immune system controls pathogen spread and limits the damage by mounting a local response that is mostly sufficient to prevent organ invasion or sepsis. B cell-derived plasma cells contribute to local defences by producing secretory IgA, the only antibody in direct contact with the external world, positioned on the surface of epithelial cells of the airways, gut and genitourinary tract[103].

In individuals without a spleen, most of these early defence mechanisms are severely impaired and immune responses depend on adaptive immune pathways, which develop slowly, leaving these individuals unprotected in the first stages of an infection[1]. The lack of early defence barriers explains the increased susceptibility to the rapid development of lethal sepsis in this population[10].

Pathogen clearance from the bloodstream is central to impeding the systemic dissemination of several infections, and both the liver and the spleen, through the portal vein axis, play a major role in this process[104]. Splenic phagocytes are responsible for blocking pathogen dissemination that can be intercepted by flowing through the sinuses of the red pulp, while dendritic cells can mount an adaptive T cell response[105]. In patients without a spleen, these mechanisms are completely lacking, which may be central to promoting the dissemination of infections; however, there are no studies assessing these mechanisms in individuals with hyposplenism.

Hyposplenism or splenectomy due to haematological diseases

Patients with some inherited haematological or immune disorders are offered splenectomy to treat or alleviate disease-related symptoms. For example, several studies support the use of splenectomy in hereditary spherocytosis, transfusion-dependent thalassaemia or ITP[1–6]. Although splenectomy is not needed in all patients with hereditary spherocytosis, the treatment is indicated in those with severe anaemia requiring frequent transfusions or those with a poor QOL. Partial splenectomy should be recommended in patients <5 years of age and in those with autosomal dominant hereditary spherocytosis[106]. Splenectomy is also indicated in patients with severe transfusion-dependent thalassaemia, with the goal of reducing excessive blood consumption and consequent severe iron overload[107]. In addition to OPSI, negative effects of splenectomy in patients with transfusion-dependent thalassaemia include an increased risk of thrombotic complications and pulmonary hypertension, possibly owing to the augmented number of circulating platelets and immature erythrocytes, associated with alteration of the endothelial function, enhanced platelet activation, and decreased levels of proteins C and S[107]. Splenectomy is also performed in patients with ITP, especially in those with chronic or severe disease[47,108]. Usually, the recommendation for splenectomy is made much more conservatively in children than in adults with ITP[108]. The use of splenectomy in patients with ITP has decreased in the past decade, owing to the availability of alternative, more conservative, therapeutically effective options, including B cell-depleting antibodies (for example, rituximab) or thrombopoietin mimetic agents[108]. Splenectomy has been reported to increase platelet count in boys with Wiskott–Aldrich syndrome; however, the benefit of thrombocytopenia improvement derived from splenectomy has to be weighed against the augmented risk of infections in a condition already characterized by impaired immune function, including reduced antibody production[109].

Hyposplenism due to SARS-CoV-2 infection

Although based on preliminary observations, SARS-CoV-2 infection seems to cause hyposplenism in a substantial proportion of hospitalized patients, leading to unfavourable outcomes[18]. In 63 patients with COVID-19, 55 (87.3%) had IgM memory B cell depletion of whom 18 (32.7%) died during hospitalization[18]. According to autopsy studies in patients who died from COVID-19, SARS-CoV-2 has a high tropism for the spleen, as demonstrated by high virus RNA levels in this organ[110–113]. In addition to several unspecific alterations involving both the splenic vascularization and the red pulp, SARS-CoV-2 seems to specifically affect the white pulp by altering the germinal centre and the marginal zone architecture and by selectively depleting IgM memory B cells[18]. The mechanisms leading to this selective depletion are not known, and whether this mechanism is reversible still needs confirmation. Of note, the haemocatheretic function of the spleen, as assessed by PCR count, does not seem to be affected, at least in the acute phase of the infection[18]. This observation is the only known case of dissociation between the impairment of the white and the red pulp. This finding needs to be confirmed in larger studies.

Complications

As already mentioned, OPSI is the most threatening complication of splenectomy, owing to the lack of IgM memory B cells[1–6]. In addition, an increased risk of both venous and arterial vascular complications may result from splenectomy, especially when performed in patients with a haematological disorder[1–6]. Thromboembolic events following splenectomy are multifactorial, and are a consequence of a hypercoagulability state, thrombocytosis and platelet activation, altered blood viscosity, endothelium activation and dyslipidaemia. Particularly, in patients who have undergone splenectomy owing to thalassaemia intermedia, an increased incidence of thromboembolism has been reported[114]. In a study including 8,860 patients with thalassaemia, those with thalassaemia intermedia had a high prevalence of thromboembolism (4%)[115]. Although there are no prospective studies, some authors recommend thromboprophylaxis (that is, anticoagulation or antiplatelet agents) after splenectomy, especially in case of thalassaemia[116,117]. In coeliac disease, which is frequently associated with hyposplenism, an increased but modest risk of thromboembolism has been found in a large registry study from Sweden[118]. However, the authors concluded that this may have been due to a surveillance bias, and pathophysiological bases of this observation have not been tested.

Diagnosis, screening and prevention

Asplenia, either congenital or after surgery, is easily diagnosed through imaging techniques, including abdominal ultrasonography, CT and MRI[119], which will all show the anatomical absence of the spleen. Other congenital spleen anatomical variants or abnormalities can be diagnosed, such as accessory spleen(s), polysplenia (the presence of multiple spleens, usually associated with other congenital abnormalities) and splenosis, which is an acquired condition due to seeding and implantation of splenic tissue occurring either after a traumatic splenic rupture or intentionally performed during splenectomy to, at least partially, preserve spleen function[119,120]. By contrast, the diagnosis of hyposplenism, which requires the assessment of spleen function, is more demanding, as the gold standard diagnostic test, PRC count, is not widely available in clinical practice.

Diagnosis

The diagnosis of defective spleen function is mostly based on the assessment of the filtering function in the red pulp, through either radioisotopic methods or by searching for erythrocyte morphological alterations. Radioisotopic methods, which enable morphological and functional evaluation of the spleen, have been abandoned as they are impractical in a clinical setting, incur high costs and expose the patient to ionizing radiation, resulting in a poor safety profile[1]. Table 1 summarizes all the diagnostic techniques for the assessment of hyposplenism.

The evaluation of erythrocyte alterations is more feasible, safe and less expensive in a clinical setting than radioisotopic assessment[121,122]. Different red cell alterations can be seen in a blood smear from a patient with asplenia, including Howell–Jolly bodies (red cells with nuclear remnants), acanthocytes (red cells with spiked cell membrane), spherocytes (sphere-shaped red cells), spiculated spherocytes, target cells (red cells with the appearance of a shooting target), stomatocytes (red cells with a linear central pallor, which gives the appearance of coffee beans or kissing lips) and PRCs[1–6,123]. Other non-erythrocyte cell alterations can also be noticed, such as thrombocytosis. Among these alterations, only PRC count is considered accurate enough for diagnosing defective spleen function, as other aberrations can also be seen in several haematological disorders. PRCs are erythrocytes with characteristic pits or vacuoles that can be seen with a phase interference microscope equipped with Nomarski optics (Fig. 3). In the case of normal spleen function, abnormal erythrocytes are removed in the spleen (culling function) and particles and impurities can be removed from erythrocytes without destroying them (pitting function)[124]. Defective spleen function leads to progressive accumulation of PRCs. In healthy individuals, PRC count is <4% and a count of >4% is, therefore, considered indicative of hyposplenism[125]. As erythrocytes take 100–120 days before becoming senescent and being removed in the spleen, PRC count may increase only after 100–120 days after hyposplenism has occurred. Before PRC count, Howell–Jolly body count was used for assessing spleen function. However, although the results from the two methods are highly correlated, Howell–Jolly body counts were found not to be sensitive enough to detect low-level splenic hypofunction, especially in patients with slight increases in PRC count of 4–8%[126].

Counting circulating IgM memory B cells, which are either generated or stored in the white pulp of the spleen, has also been proposed for the assessment of spleen function. These cells can be detected through flow cytometry analysis for the cell surface markers CD22, CD27 and IgM[127]. Peripheral B cell populations have been thoroughly studied and quantified in both healthy[128] and pathological[129] conditions. As flow cytometry is widely available and PRC and IgM memory B cell values are well correlated[59], counting IgM memory B cells should be considered a reliable test for assessing spleen function. The lower normal limit for IgM memory B cells is 26 per microlitre, which is equivalent to <9% of total B cells[95].

Screening

The development of proactive screening strategies for early diagnosis of hyposplenism has been hampered for several reasons: although PRC count is inexpensive and highly reproducible, it is not widely available in routine clinical practice; the long-term effects of hyposplenism are yet to be fully understood; and extensive epidemiological studies assessing hyposplenism and its complications both in the general population and in high-risk populations are lacking. Until more evidence is available, we would recommend screening for hyposplenism in patients with certain congenital, gastrointestinal and liver, oncohaematological, immune-related and infectious diseases, those with certain splenic vascular alterations, and those with certain conditions of iatrogenic origin and some others (Box 1).

Clinically, the diagnosis of asplenia is usually straightforward, as the absence of the spleen is easily diagnosed through radiological imaging. By contrast, the detection of hyposplenism and the assessment of its severity are far more difficult, partly because patients with hyposplenism may not have symptoms, and partly because spleen function may be impaired even in individuals with a spleen of regular size.

Although OPSI has been extensively described in surgical and congenital asplenia[1,21], the evidence for increased risk of OPSI in hyposplenism is poor and the risk usually depends on the severity of spleen impairment.

Table 1 | Diagnostic techniques for the assessment of spleen function

Technique	Brief description	Comments
Technetium-99m-labelled sulfur colloidal scintigraphy	Splenic uptake of colloidal sulfur particles reflects spleen function	Radiation exposure; might be inaccurate in the presence of hepatomegaly or splenomegaly; now abandoned
Technetium-99m-labelled or rubidium-81-labelled heat-damaged autologous erythrocyte clearance	Dynamic evaluation of spleen function through measurement of erythrocytes clearance time from the spleen	Very low accuracy due to high false-positive or false-negative results; now abandoned
Serum tuftsin	Tuftsin is a tetrapeptide on the surface of neutrophils and is decreased after splenectomy	Not widely available in a clinical setting; no standardized reference values; may be altered in other conditions; mainly confined to research settings
Diagnostic imaging, including abdominal ultrasonography, CT and MRI	Identification and measurement of spleen size, as well as anatomical and structural abnormalities	Gold standard for the diagnosis of asplenia; spleen size does not accurately reflect spleen function, as hypofunction may occur in a normal-sized spleen
Howell–Jolly bodies count	Red cells with nuclear remnants observable in the peripheral blood	Not sensitive enough to detect low-level splenic hypofunction, especially in mild hyposplenism; standardized reference values do not exist; may increase in several haematological disorders
Pitted red cell count	Peripheral blood erythrocytes with characteristic pits or vacuoles observable with a phase interference microscope equipped with Nomarski optics	Gold standard for the diagnosis of hyposplenism; although inexpensive, not widely available; may have high inter-observer variability
IgM memory B cell count	IgM memory B cells detectable with flow cytometry	Gold standard for the diagnosis of hyposplenism; more expensive than pitted red cell count

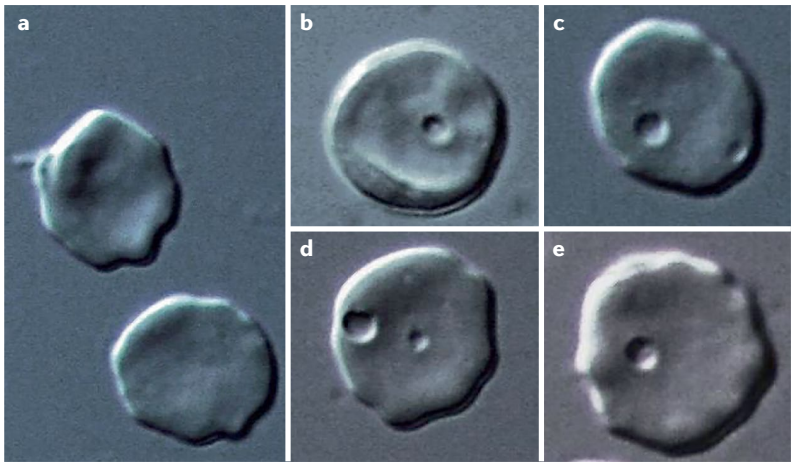

Fig. 3 | Healthy erythrocytes and pitted red cells. Representative phase interference (Nomarski optics) microscopic images of healthy erythrocytes (part **a**) and erythrocytes showing pits or vacuoles (parts **b**–**e**) known as pitted red cells (PRCs) in the blood of a patient who has undergone splenectomy. A PRC may have one or more pits on its surface. PRCs are usually removed by a healthy spleen and the PRC count should be <4% in individuals with normal spleen function. Parts **a**–**e**, ×100.

OPSI is far more common within the first 3–5 years after splenectomy, but may start at any time after defective spleen function has occurred. Various definitions of OPSI have been released[1,130,131], but they are usually defined by a rapid onset, fulminant septic shock, frequently leading to death within 24–48 h, and mostly sustained by encapsulated bacteria[132]. The site of infection is often cryptic, and prodromic symptoms are unspecific. Indeed, OPSI is a recognized complication in patients with SCD or other severe haematological diseases who usually have severe spleen dysfunction[5,133], comparable to that in patients who have undergone splenectomy. In patients with coeliac disease, the risk of OPSI is unclear but they have a clearly increased risk of pneumococcal infections; thus, vaccination is warranted[134,135]. In other conditions, such as inflammatory bowel disease, the risk of severe infections by encapsulated bacteria is not clear and may be biased by the concomitant use of immunosuppressants or biological drugs and by disease activity[136].

Thromboembolism is another clinical manifestation that may potentially occur in patients with asplenia or hyposplenism, but the available evidence relating to its epidemiology and risk factors is even more scarce than that regarding OPSI. An increased risk of thromboembolic events has certainly been found in patients who have undergone splenectomy, and this increased risk seems to be, at least partially, independent of the typical reactive thrombocytosis noted in these patients[137,138]. The patients included in the studies were hospitalized, which may have affected the risk of thromboembolism. In patients with hyposplenism, the contribution of the defective spleen function in determining thrombotic events remains unclear.

A certain association between the development of autoimmunity and defective spleen function has been postulated, particularly in coeliac disease, in which this risk depends on the duration of gluten-containing diet before diagnosis[59]. Additionally, patients with uncomplicated coeliac disease were found to have a lower prevalence of hyposplenism than those with other associated autoimmune conditions[57]. Hence, patients with coeliac disease who have additional autoimmune conditions should be screened for hyposplenism.

Hyposplenism should always be suspected in those with mesenteric lymph node cavitation syndrome, which is a very rare syndrome associated with coeliac disease, often refractory or complicated by enteropathy-associated T cell lymphoma, and spleen atrophy in most cases[139]. In this syndrome of unknown aetiology, the mesenteric lymph nodes show pseudocystic lesions with a large central cavity, surrounded by abundant fibrous tissue, and the spleen is often atrophic and small.

Finally, although spleen size does not necessarily correlate with its function, hyposplenism should be ruled out in patients with an incidental finding of a small-sized spleen (length <8 cm in men and <7.5 cm in women) on radiological imaging[140]. In fact, according to a study including 4,585 patients undergoing abdominal ultrasonography, 128 had a small spleen and 85 (66%) were hyposplenic (PCR count > 4%)[140]. Several causes of hyposplenism were identified, including oncological, haematological, and gastrointestinal diseases, and some of these patients had had previous severe infections.

Prevention

Strategies to prevent negative effects of spleen absence or hypofunction differ between patients in whom the spleen has been surgically removed and those with hyposplenism. Spleen function can be partially preserved in patients who have undergone splenectomy. Those undergoing splenectomy for trauma can develop spontaneous splenosis, which is the seeding of spleen tissue within the peritoneal cavity[141], that occurs soon after spleen rupture. Splenosis can also be deliberately performed by the surgeon to preserve minimum spleen function after spleen removal. It has been estimated that at least 20–30 cm^3 of spleen tissue are needed to restore normal spleen function[142].

Strategies aiming at preventing hyposplenism in specific clinical conditions have been poorly addressed. Generally, it is reasonable to assume that the treatment of the underlying disease could at least improve spleen impairment if it cannot revert it. For example, in coeliac disease, reducing diagnostic delay and starting a gluten-free diet early may prevent the development of hyposplenism[58]. Defective spleen function can be reverted by medical therapy (for example, with the use of steroids in patients with primary eosinophilic gastrointestinal disorders[143] and the use of infliximab in patients with Crohn's disease[144]). No evidence is available for other conditions associated with hyposplenism. Figure 4 schematically summarizes a diagnostic and overall management algorithm for patients with asplenia and hyposplenism.

Management

Long-term management of asplenia and hyposplenism

Long-term management strategies are mainly aimed at preventing sepsis and OPSI. Patient education, vaccination and antibiotic chemoprophylaxis are recommended for all individuals with asplenia to prevent infections. Although patients with hyposplenism compared

with those with asplenia could potentially have a lower risk of getting such complications, we would still recommend adopting these precautions until more solid evidence is available for this population. In particular, several clinical and behavioural norms should be adopted to prevent OPSI (Box 2).

OPSI is usually promptly recognized when a patient with a known history of asplenia or hyposplenism presents with signs and symptoms of an acute febrile condition. In particular, fever is the cardinal symptom of infection in these patients, although it may be mild at onset and may be preceded by more subtle and unspecific symptoms, including skin colour alterations, weight loss, gastrointestinal symptoms (for example, abdominal pain, altered bowel movements and dyspepsia) and headache[132]. As OPSI has a rapid and fulminant course, usually evolving in 24–48 h, if fever develops, emergency antibiotics should be self-administered, and individuals should present immediately to the closest emergency department for prompt management[145]. Prompt medical attention should be sought in the case of an animal bite or scratch, and counselling should be provided about household pets and exposure to animals. Blood culture tests and a peripheral blood smear should be performed as early as possibly to identify the responsible pathogen. In the meantime, broad spectrum antibiotics should be prescribed, such as ceftriaxone plus vancomycin or teicoplanin plus rifampicin if there is suspicion of highly resistant pneumococci[145]. Thereafter, antibiotic therapy can be tailored depending on the antibiogram. If septic shock develops, the guidelines of the Survival Sepsis Campaign should be followed[146]. The management of septic shock, characterized by severe hypotension often followed by multiorgan failure, consists of early recognition (ideally <1 h after onset), removal of risk factors (for example, infected foreign bodies, such as catheters or implantable devices), identification of the pathogen, antibiotic therapy, fluid therapy and noradrenaline administration[146].

In the following sections, we discuss the available strategies for the long-term prevention of OPSI and for optimizing the overall management of patients with asplenia and hyposplenism. The management of hyposplenism in people living with HIV infection is summarized in Box 3 (refs.[71,72,147–162]).

Vaccinations

Recommended vaccines for individuals with asplenia and hyposplenism target particularly encapsulated bacteria, that is, *S. pneumoniae*, *N. meningitidis* and *H. influenzae* type b that are commonly implicated in OPSI[163–165].

Guidelines recommend the use of both conjugate and unconjugated polysaccharide vaccines at the time of diagnosis of hyposplenism or asplenia and subsequently. A conjugate vaccine combines the antigen that elicits the immune response against a specific pathogen with a carrier protein that amplifies its immunogenicity and, therefore, its efficacy[166,167]. Generally, conjugate vaccines are preferred over polysaccharide vaccines as their mechanism bypasses the T cell-independent pathway of initiating immunological memory and instead

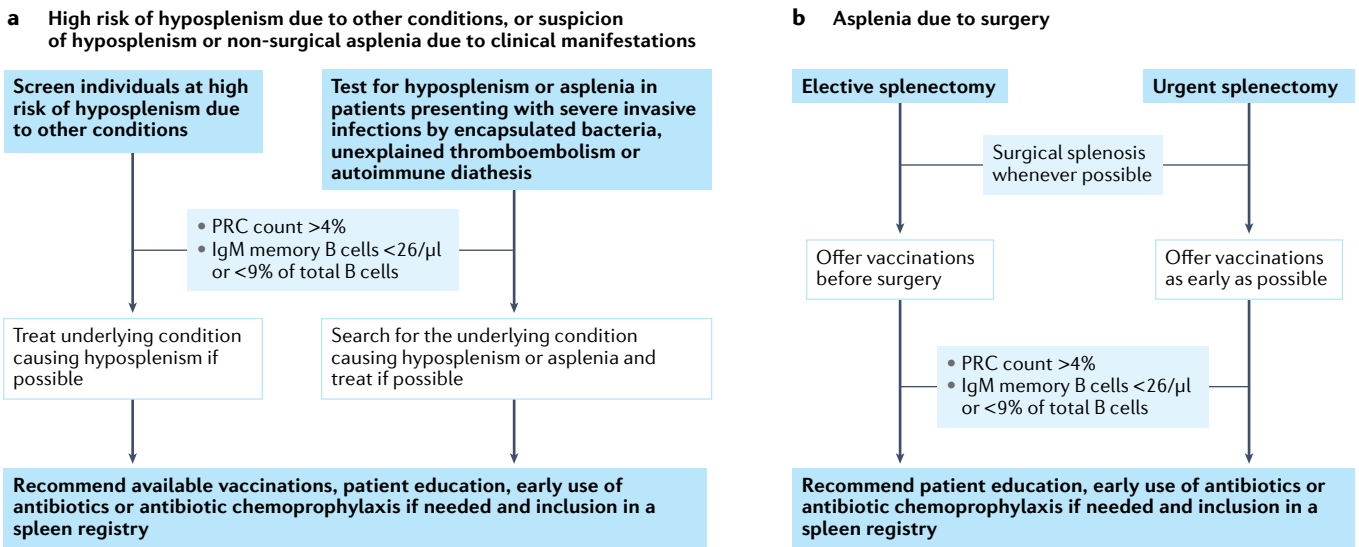

Fig. 4 | Diagnostic and management algorithm for patients with asplenia and hyposplenism. Asplenia or hyposplenism may predominantly be suspected in three different scenarios: individuals at risk owing to other conditions, individuals at risk owing to specific clinical manifestations, and individuals undergoing splenectomy. **a**, All individuals at high risk of hyposplenism (Box 1) should ideally be screened for hyposplenism by means of pitted red cell (PRC) count and/or IgM memory B cell count. In some conditions, such as coeliac disease and inflammatory bowel disease, the treatment of the disease causing hyposplenism may improve spleen function, at least partially. Individuals at risk owing to severe invasive infections, thromboembolism with no known predisposing factors, and autoimmune diathesis should undergo careful clinical evaluation after the formal diagnosis of hyposplenism. In both clinical scenarios, radiological imaging, such as abdominal ultrasonography, abdominal CT or abdominal MRI, is useful for assessing the presence of the spleen, its morphology and its size. **b**, The management of individuals undergoing surgical spleen removal depends on the reason for surgery and on its timing. If splenectomy is elective, the recommended vaccinations should be given before surgery, whereas, if splenectomy is urgent, they should be given as soon as possible after surgery. Splenosis, which is the surgical implantation of spleen tissue in the abdomen, should always be performed when feasible, to preserve some spleen function. The assessment of PRC and/or IgM memory B cell counts is useful for evaluating residual spleen tissue function. In all the three clinical scenarios, patients should be included in a spleen registry, should receive information for preventing infections, as well as chemoprophylaxis and vaccinations (including booster doses) according to guidelines. Patients should also be educated on how to promptly recognize signs and symptoms of an infection.

relies on the T cell-dependent pathway, which induces long-term protection and immunological memory[166,167]. By contrast, polysaccharide vaccines (licensed for use in individuals >2 years of age) rely on the T cell-independent pathway to initiate memory, which requires functioning memory B cells to develop an effective response. Thus, the sequential use of conjugate and unconjugated vaccines is now generally recommended in patients with hyposplenism or asplenia[157,158].

In addition, booster vaccinations are required to maintain long-term protection, owing to waning immunity. Immune waning is associated with loss of antibodies; thus, booster doses are necessary to keep up a certain antibody level for protection[168–172]. Additionally, tolerance induction or hyporesponsiveness occurs if polysaccharide vaccines are repeated at intervals of <5 years[168–172]. Conjugate vaccines are preferred, particularly in individuals with impaired B cell immunity, as they have been shown to provide better immune responses[173] and are not associated with the same long-term protection issues as are polysaccharide vaccines. Several other differences between conjugate and unconjugated vaccines exist[173–179] (Box 4) and these differences must be taken into account when vaccinating patients with asplenia or hyposplenism.

Pneumococcal vaccines. Both unconjugated and conjugate polysaccharide pneumococcal vaccines are widely available and used. The conjugate vaccine has evolved from an initial seven-valent vaccine to 20-valent vaccines. The unconjugated 23-valent pneumococcal polysaccharide vaccine (PPV23) has been available the longest; it covers a broad spectrum of 23 pneumococcal serotypes (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). Disadvantages of this vaccine are that children <2 years of age cannot mount antibody responses to polysaccharides and that patients with hyposplenism or asplenia do not show adequate IgG antibody induction after PPV23 vaccination. To overcome these problems, conjugate pneumococcal vaccines were developed, starting with a 7-valent vaccine followed by a 10-valent and a 13-valent vaccine (PCV13). PCV13 provides serotype coverage for 11 shared pneumococcal serotypes and two additional serotypes (1, 3, 4, 5, 6A, 6B, 7F, 8C, 9V, 14, 19A, 19F and 23F) and, therefore, provides a better and longer-lasting immune response than the earlier vaccines with a narrower coverage[169,180–185]. In 2021 and 2022, a 15-valent and a 20-valent conjugate pneumococcal vaccine were licensed by the EMA and FDA. The 15-valent vaccine (PCV15) additionally covers serotype 22F and 33F, and the 20-valent vaccine (PCV20) further includes the serotypes 8, 10A, 11A, 12F and 15B. Both vaccines are licensed for use in adults >18 years of age[186–189].

Meningococcal and *Haemophilus influenzae* type b vaccines. Quadrivalent meningococcal vaccines are available in conjugated form and cover the *N. meningitidis* serogroups A, C, W and Y[157]. The quadrivalent meningococcal conjugate vaccine is widely available and it has superseded the conjugate meningococcal C vaccine. Meningococcal B disease is preventable using recombinant meningococcal B vaccines[157]. *H. influenzae* type b vaccines — either as combination vaccine for use in infants, or as a monovalent form also licensed for use in adults — are available in conjugated formulations[157].

Influenza vaccines. Patients with hyposplenism or asplenia do not have an increased risk of influenza infection, but yearly vaccination against influenza is highly recommended in these patients owing to possible complications in those with secondary bacterial infections, particularly with *S. pneumoniae*[190,191]. Clinical observations clearly indicate a predisposition to pneumococcal infections following influenza. For example, the nasopharyngeal carriage of pneumococcal bacteria in children is increased after influenza infections[192]. A >50% reduction in mortality has been linked to influenza vaccination in patients with hyposplenism or asplenia[193].

SARS-CoV-2 vaccines. Although the effects of COVID-19 in individuals with hyposplenism or asplenia have not been clearly defined, these patients have been identified as frail patients who should be prioritized for receiving SARS-CoV-2 vaccination[68]. Studies assessing the efficacy of the available SARS-CoV-2 vaccines in this population, in both the short term and long term, are warranted.

Box 2

Recommended clinical and behavioural norms in patients with asplenia or hyposplenism

Screening for hyposplenism and preservation of the spleen
- Evaluate splenic function in patients at risk by counting pitted red cells
- Preserve as much spleen tissue as possible during surgery or implement splenosis when feasible

Patient and physician education
- Educate patients, family members and physicians about the risk of overwhelming post-splenectomy infection (OPSI)
- Provide patients and physicians with written information notes
- Notify the general practitioner and facilitate multidisciplinary meetings with other specialists
- Alert the general practitioner immediately if fever is present
- Apply precautions for travelling abroad, and against animal bites and other possible sources of infection

Antibiotic prophylaxis
- Amoxicillin or phenoxymethylpenicillin
- Consider other antibiotics in patients allergic to penicillin
- Continuous prophylaxis in selected patients with immune deficiencies

Vaccine prophylaxis
- Pneumococcal
- Meningococcal
- Anti-*Haemophilus influenzae* type b
- Anti-influenza[a]
- Anti-SARS-CoV-2[a]
- Other vaccinations recommended for the general population

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. [a]Vaccination against influenza virus is recommended to reduce the risk of a superimposed bacterial infection. Patients with hyposplenism or asplenia are considered in the frail category and should be prioritized for receiving anti-SARS-CoV-2 vaccination.

Recommendations. Current vaccination recommendations involve both the conjugate and unconjugated pneumococcal vaccines, quadrivalent conjugate meningococcal vaccine and recombinant meningococcal B vaccine, a conjugated *H. influenzae* type b vaccine, and the annual influenza vaccine[183,184]. The timing of vaccination seems to be important, particularly in relation to surgical splenectomy. Vaccination is recommended at least 2 weeks before elective splenectomy, and at least 2 weeks after emergency splenectomy to ensure optimal antibody function and slower waning of antibody levels[194,195].

PCV13, which is routinely recommended in children to prevent invasive pneumococcal disease (IPD), is also recommended as a primary vaccination to prevent IPD in individuals with asplenia in guidelines globally[182,183]. Following initial vaccination with PCV13, individuals receive vaccination with PPV23 2 months later which is repeated every 5 years to ensure broad serotype coverage[182,183]. PPV23 doses should be limited to a total of two lifetime doses, with an interval of at least 6 years to avoid immune tolerance, which is commonly seen with repeated polysaccharide vaccination[157,196]. Although current data on sequential vaccination with either PCV15 or PCV20 followed by PPV23 are sparse, general guidelines are likely to change to schedules using the higher valent vaccines.

Box 3

Hyposplenism in HIV infection

People living with HIV infection (PLWH) should receive vaccines recommended for the general population including vaccines for SARS-CoV-2 and seasonal influenza virus, as well as HIV-specific vaccines for pneumococcal and meningococcal infections, and hepatitis A and B. Live attenuated vaccines should be avoided in those with low CD4 counts or uncontrolled HIV infection[147–149]. Similar to individuals with hyposplenism, the incidence of invasive pneumococcal infection is increased[150] and vaccination responses are impaired in PLWH compared with HIV-negative individuals[151–154]. Vaccination with combined conjugate and polysaccharide vaccine schedules is recommended for PLWH[154,155]. However, waning immunity with an increasing risk of infection is of concern and may warrant antibody level monitoring and revaccination[156]. Recommended schedules for pneumococcal and meningococcal vaccination are the same for PLWH and individuals with asplenia or hyposplenism within regional guidelines in the USA, Europe and Australasia[147–149,157–160]. However, as there are small differences in recommendations in regional guidelines to account for available vaccines and endemic pathogens, clinicians should refer to their national guidelines for immunization recommendations for PLWH.

Chemoprophylaxis for PLWH targets opportunistic infections and is recommended based on CD4 counts and exposure risk[161]. Penicillin chemoprophylaxis is not routinely recommended for all PLWH, but only in selected individuals depending on additional risk factors (for example, exposure to syphilis)[147]. To date, no studies have evaluated the use of penicillin chemoprophylaxis in PLWH for prevention of pneumococcal infection. Additionally, trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis, routinely used as pneumocystis pneumonia prophylaxis in this group, is associated with increased antibiotic resistance to TMP-SMX, penicillin and rifampicin in pneumococcal isolates[162].

Currently, no recommendations for routine monitoring of serotype-specific antibody levels in individuals with asplenia exist despite strong evidence of waning immunity. Furthermore, evidence that suggests a need for revaccination with conjugate vaccines is limited, particularly in settings where newer vaccines with broader serotype coverage are available[157,196]. To cover a very broad spectrum of serotypes and to induce strong vaccine responses, the international guidelines for patients who are immunocompromised recommend a sequential immunization strategy in patients with hyposplenism or asplenia[184,185].

Regarding prevention of invasive meningococcal diseases, patients with hyposplenism or asplenia should receive both the quadrivalent (ACWY) meningococcal and the meningococcal B vaccine. As immune responses to meningococcal C vaccine have been shown to decline earlier in individuals with hyposplenism or asplenia than in individuals with a functioning spleen[197], two doses of the ACWY vaccine at an interval of 4 or 8 weeks are commonly recommended[183] The meningococcal B vaccine should be given according to the age-specific recommendation in the product information. Despite lack of data, immunological considerations suggest that booster vaccinations should be administered every 5 years[198].

H. influenzae less frequently causes OPSI in patients with hyposplenism or asplenia than pneumococcal bacteria, but mortality owing to *H. influenzae* infection is high at 31%[11]. Thus, *H. influenzae* type b vaccination is recommended in all patients with hyposplenism or asplenia, but may not be required as it is routinely administered in infants and children[183]. Whether repeated vaccinations in adulthood are required is currently unclear.

Vaccination recommendations for children vary and, if a patient is diagnosed with asplenia or hyposplenism as a child, advice from infectious disease and haematology specialists should be sought and local vaccination guidelines should be consulted[182,199].

Chemoprophylaxis

Recommendations for penicillin chemoprophylaxis began following the observation that children with asplenia or hyposplenism had serious infections when they did not receive oral penicillin[200,201]. Daily penicillin chemoprophylaxis is recommended in individuals with asplenia who are immunocompromised or have a previous history of OPSI, and in the first 2–3 years following splenectomy[183]. The benefit of daily chemoprophylaxis in adults with asplenia outside these settings is unclear. Daily penicillin has been shown to prevent OPSI in randomized controlled trials including children with SCD[202]. A large cohort study in patients with asplenia may be able to evaluate the effectiveness of antibiotics and other preventive measures.

Individuals with hyposplenism or asplenia are recommended to carry a supply of antibiotics and should present to their nearest hospital for prompt treatment in the event of fever[183]. Penicillin antibiotics are usually preferred for emergency management. In individuals with non-severe penicillin allergy, use of a cephalosporin, such as cefuroxime or cefdinir, is considered safe[203]. For appropriate choice of antibiotic, appropriate local guidelines should be consulted or expert advice sought for common local pathogens and their antibiotic sensitivity or resistance profiles.

Hyposplenism in patients with SCD results in poor clearance of malaria-infected erythrocytes and patients may succumb to overwhelming infection with worsening anaemia[204,205]. Hence, in addition to prophylaxis for bacterial infections, these individuals should use insecticide-treated bed nets and malaria chemoprophylaxis, according to national guidelines, in malaria-endemic countries[206].

Education

It is imperative that patients are well educated and informed of the potential lifelong risk of OPSI associated with hyposplenism or asplenia. Despite extensive guidelines globally that recommend strategies for prevention[183,184], effective education and adherence to vaccination and chemoprophylaxis are necessary to ensure optimal prevention of OPSI. Similar to other chronic conditions, adherence falters particularly as time passes from diagnosis. Furthermore, adherence is poorer in individuals who have undergone non-elective splenectomy[207], which may be due to delayed commencement of prophylactic strategies, as vaccination in this setting occurs at least 2 weeks after splenectomy, or to poor initial education[207]. Patients should be educated about the need for initial and ongoing vaccinations, when to use emergency antibiotics and to take daily penicillin chemoprophylaxis, if appropriate.

Travel advice including additional vaccinations and additional antibiotics should be provided to any individual with hyposplenism or asplenia before travel, depending on the local infection risk (for example, yellow fever, malaria, cholera, hepatitis A and other infections). Before travelling to a malaria-endemic region, counselling on the risk of malaria and appropriate malaria prevention should be provided. Vaccination status of the individual should opportunistically be reviewed at this consultation and outstanding vaccines should be provided if appropriate.

Optimizing prevention and minimizing risk of OPSI requires a multidisciplinary approach. Connecting the patient and the patient's community with appropriate services optimizes effective long-term care. This includes treating physicians, pharmacists, community practitioners, patients themselves and their support networks (family and friends) and a spleen registry where available.

Spleen registries

Dedicated outpatient programmes including a spleen registry can be pivotal in optimizing long-term care of patients with asplenia or hyposplenism. These programmes have been shown to improve uptake of recommended preventive strategies[208–210], to reduce rates of IPD[211] and to improve the overall management of these patients[211–215].

Studies have shown that individuals who undergo emergency splenectomy are less likely to be vaccinated[207], probably because patients are discharged from hospital before reaching the 2-week mark for vaccination. The spleen registry addresses this problem, as eligible patients are registered at the time of diagnosis, or in anticipation of planned splenectomy or after emergency splenectomy. The registry provides information packs to registrants and sends reminders to patients and their general practitioner to ensure that vaccinations are given according to appropriate schedules. The registry also records vaccination administration dates, which enables long-term follow up. Patient compliance is further supported through annual newsletters and a mobile phone application that notifies when vaccinations are due.

Spleen Australia (https://spleen.org.au/) was the first large clinical registry for individuals with asplenia[212] and focuses on patient education in addition to monitoring vaccination uptake. Other registries for individuals with asplenia exist, including those in the UK[213,214] and New Zealand[216].

Quality of life

When assessing QOL, the risk profile associated with the underlying condition leading to asplenia must also be considered. For example, individuals who had undergone splenectomy owing to a haematological malignancy were found to have a higher risk of infections than those who had undergone splenectomy owing to other diseases[142,163]. Thus, to comprehensively investigate QOL, individuals from different cohorts should be identified and investigated separately.

Consequences of asplenia, including sepsis and OPSI, can lead to lifelong disability and increased risk of death[217,218]. Spleen-preserving therapies, such as splenic artery embolization or alternative repair procedures, can be used to prevent post-splenectomy associated complications[219,220], when feasible. In hereditary spherocytosis, splenectomy can

Box 4

Differences between conjugate and unconjugated vaccines

Conjugate vaccines consist of a capsular polysaccharide covalently linked to a carrier protein. They are preferred over unconjugated or polysaccharide-only vaccines owing to their stronger immunogenicity in vulnerable groups, such as individuals with asplenia or hyposplenism.

Polysaccharide antigens are type 2 T cell-independent antigens which cause a rapid initial humoral (B cell) response[174]. However, in the absence of a functioning spleen, the rapid humoral response following polysaccharide antigen presentation does not occur[175], as this response is driven by splenic marginal zone B cells[176–179]. Given their proximity and duration of exposure to blood from the red pulp, these cells are one of the first immune cells that pathogens come into contact with in the spleen. In their absence, not only is the rapid humoral response attenuated but the first line immunological response to blood-borne pathogens is also impaired. Furthermore, polysaccharide antigens are poorly internalized by B cells, and unable to engage T helper cells; thus, they do not generate high-affinity memory B cells. Consequently, the B cells undergo apoptosis[174]. However, when conjugated with a protein, it becomes a T cell-dependent antigen and can effectively engage B cells and T cells to produce long-lasting memory.

Conjugate vaccines do not rely on functioning splenic marginal zone B cells. When the polysaccharide antigen is conjugated to a carrier protein (such as the diphtheria carrier protein, in the case of the *Haemophilus influenzae* type b vaccine), both B cells and T helper cells are engaged, forming a germinal centre with the follicular dendritic cell. As antibodies are produced in the germinal centre, they also undergo class switching. With the assistance of T helper cells, B cells undergo cycles of replication producing efficient affinity maturation and long-term survival and, subsequently, long-term immunological memory[174].

A more effective immunological response to conjugate vaccination than to polysaccharide-only vaccination has been demonstrated in individuals with asplenia[173]. In vaccination against pneumococcus, currently the broadest serotype pneumococcal conjugate vaccine is the 13-valent pneumococcal conjugate vaccine, whereas the polysaccharide vaccine is the 23-valent pneumococcal vaccine. Broader spectrum conjugate vaccines are under development. However, despite suboptimal responses to vaccine, the 23-valent polysaccharide pneumococcal vaccine currently provides the broadest serotype coverage.

provide considerable improvements in QOL, and is indicated in those with moderate to severe disease in whom symptomatic splenomegaly and transfusion-dependent anaemia can occur[221]. In patients with mild and moderate disease, splenectomy is often driven by QOL considerations[222], and results in an improvement or resolution of haemolysis and anaemia[221] and can reduce or eliminate transfusion requirements. Similarly, in patients with transfusion-dependent thalassaemia, splenectomy is performed to reduce transfusion requirements[223]. As splenectomy is often performed in children with transfusion-dependent thalassaemia, the intervention enables improved lifelong QOL.

Although QOL research in individuals with asplenia and hyposplenism is overall limited, outcomes and complications associated with the immunocompromised state are well described[217,218]. Splenectomy is associated with increased rates of infection and sepsis, most prominently in the first few years after surgery, but also lifelong[163,164,224]. Furthermore, individuals with asplenia and hyposplenism present to hospital more frequently than the general population[79]. In addition, individuals with asplenia seem to be at increased risk of hospitalization and death owing to COVID-19 infection[225].

Indeed, optimal patient care requires good levels of health literacy[226], and improved awareness and health literacy is associated with improved clinical outcomes, including a better QOL, and reduced mortality[226–228]. Formal future QOL research in asplenia and hyposplenism would be highly valuable.

Outlook

Over the past decades, the management of patients with asplenia and hyposplenism has considerably improved, also owing to dedicated management guidelines. However, many actions should be taken in the near future to advance our knowledge about the pathogenesis, prevention and overall management of asplenia and hyposplenism, the main stakeholders being basic scientists, immunologists, clinicians and patients.

Screening programmes for early detection of hyposplenism are currently lacking, even in high-risk patients, which might have different reasons. First, the natural history of hyposplenism is unclear and the real incidence of the most threatening complications is largely unknown. Second, studies assessing the potential benefits of such screening programmes are lacking. Third, PRC count is not widely available, although it is inexpensive and non-invasive, and it may be subject to inter-observer variability. IgM memory B cell flow cytometric count should be considered as a valid alternative in clinical practice, although more expensive. To overcome these obstacles, prospective, long-term studies, focusing on conditions associated with hyposplenism are warranted. The non-invasive assessment of spleen function should be implemented worldwide, starting with education on these techniques at medical schools.

Vaccination strategies in these patients are another key issue that must be addressed. In fact, many recommendations are based on immunological considerations only, rather than on validated immunological data. Although it is intuitive that the correct timing of vaccination and the specific type of vaccination are crucial for determining an adequate and protective immune response, few scientific data are available in this population. Prospective studies assessing the immunological response to vaccinations and the actual rate of infections in a real-life setting are warranted.

Widening the use of spleen registries in the future may improve several patient outcomes. In particular, useful leaflets should be given to patients, with specific recommendations about antibiotic chemoprophylaxis or early use of antibiotics in the event of a suspected infection. In addition, providing health education about the potential immune and infectious sequelae associated with asplenia better equips patients to recognize and respond to sepsis at an early stage, increasing the likelihood that they survive sepsis and OPSI[226]. Hence, the use of dedicated outpatient services or registries should be considered a method to improve uptake of preventive strategies and health education and, in turn, reduce infectious complications associated with asplenia or hyposplenism. International, collaborative registries across continents may also greatly enhance research activities in this field.

Finally, the COVID-19 pandemic has fuelled research in both immunology and vaccinology. Particularly, as SARS-CoV-2 can cause hyposplenism during the infection[18], studies assessing the long-term effects on the spleen are needed. In addition, the efficacy of the novel mRNA-based vaccines against SARS-CoV-2 infection in patients with hyposplenism or asplenia needs to be determined. Whether mRNA-based vaccines against the pathogens typically involved in OPSI will be developed and whether this would translate into a benefit for these patients remains a matter of future investigation.

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References

1. Di Sabatino, A., Carsetti, R. & Corazza, G. R. Post-splenectomy and hyposplenic states. *Lancet* **378**, 86–97 (2011).
2. William, B. M. & Corazza, G. R. Hyposplenism: a comprehensive review. Part I: basic concepts and causes. *Hematology* **12**, 1–13 (2007).
3. Quinti, I. & Paganelli, R. in *Stiehm's Immune Deficiencies* 1st edn Ch. 45 (eds Sullivan, K. E. & Stiehm, E. R.) 835–844 (Academic, 2014).
4. Pulvirenti, F. et al. in *Stiehm's Immune Deficiencies* 2nd edn Ch. 48 (eds Sullivan, K. E. & Stiehm, E. R.) 1021–1033 (Academic, 2020).
5. Kirkineska, L., Perifanis, V. & Vasiliadis, T. Functional hyposplenism. *Hippokratia* **18**, 7–11 (2014).
6. William, B. M., Thawani, N., Sae-Tia, S. & Corazza, G. R. Hyposplenism: a comprehensive review. Part II: clinical manifestations, diagnosis, and management. *Hematology* **12**, 89–98 (2007).
7. Riva, M. A., Ferraina, F., Paleari, A., Lenti, M. V. & Di Sabatino, A. From sadness to stiffness: the spleen's progress. *Intern. Emerg. Med.* **14**, 739–743 (2019).
8. Eppinger, H. Zur pathologie der milzfunktion [German]. *Klin. Wochenschr.* **50**, 1509–1512 (1913).
9. Weber, F. P. Hypersplenism and hyposplenism and splenectomy. *Br. Med. J.* **1**, 766 (1929).
10. Sinwar, P. D. Overwhelming post splenectomy infection syndrome–review study. *Int. J. Surg.* **12**, 1314–1316 (2014).
11. Chong, J., Jones, P., Spelman, D., Leder, K. & Cheng, A. C. Overwhelming post-splenectomy sepsis in patients with asplenia and hyposplenia: a retrospective cohort study. *Epidemiol. Infect.* **145**, 397–400 (2017).
12. Di Sabatino, A. et al. Vaccination coverage and mortality after splenectomy: results from an Italian single-centre study. *Intern. Emerg. Med.* **12**, 1139–1147 (2017).
13. Di Sabatino, A., Lenti, M. V. & Corazza, G. R. Spleen registry: still a chimera. *Clin. Infect. Dis.* **67**, 562–563 (2018).
14. Mebius, R. E. & Kraal, G. Structure and function of the spleen. *Nat. Rev. Immunol.* **5**, 606–616 (2005).
15. Tangye, S. G. & Good, K. L. Human IgM+CD27+ B cells: memory B cells or "memory" B cells? *J. Immunol.* **179**, 13–19 (2007).
16. Siu, J. H. I. et al. Two subsets of human marginal zone B cells resolved by global analysis of lymphoid tissues and blood. *Sci. Immunol.* **7**, eabm9060 (2022).
17. Salehen, N. & Stover, C. The role of complement in the success of vaccination with conjugated vs. unconjugated polysaccharide antigen. *Vaccine* **26**, 451–459 (2008).
18. Lenti, M. V. et al. Depletion of circulating IgM memory B cells predicts unfavourable outcome in COVID-19. *Sci. Rep.* **10**, 20836 (2020).
A study that provides the first evidence of a role of IgM memory B cell depletion in determining unfavourable clinical outcomes in COVID-19.
19. Cococcia, S. et al. Liver–spleen axis dysfunction in COVID-19. *World J. Gastroenterol.* **27**, 5919–5931 (2021).
20. Ahmed, S. A., Zengeya, S., Kini, U. & Pollard, A. J. Familial isolated congenital asplenia: case report and literature review. *Eur. J. Pediatr.* **169**, 315–318 (2010).
21. Rose, V., Izukawa, T. & Moës, C. A. Syndromes of asplenia and polysplenia. A review of cardiac and non-cardiac malformations in 60 cases with special reference to diagnosis and prognosis. *Br. Heart J.* **37**, 840–852 (1975).
22. Hrusca, A. et al. Ivemark syndrome–a rare entity with specific anatomical features. *Rev. Méd. Chil.* **143**, 383–386 (2015).

23. Bolze, A. et al. Incomplete penetrance for isolated congenital asplenia in humans with mutations in translated and untranslated RPSA exons. *Proc. Natl Acad. Sci. USA* **115**, e8007–e8016 (2018).
24. Mahlaoui, N. et al. Isolated congenital asplenia: a French nationwide retrospective survey of 20 cases. *J. Pediatr.* **158**, 142–148 (2011).
25. Dinis-Ferreira, S. et al. Isolated congenital asplenia in an asymptomatic patient: a very rare diagnosis. *Eur. J. Case Rep. Intern. Med.* **7**, 001429 (2020).
26. Bolze, A. et al. Ribosomal protein SA haploinsufficiency in humans with isolated congenital asplenia. *Science* **24**, 976–978 (2013).
27. Choudhary, S., McLeod, M., Torchia, D. & Romanelli, P. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J. Clin. Aesthet. Dermatol.* **5**, 18–22 (2012).
28. Kibirige, D. & Kambugu, F. Autoimmune polyglandular syndrome type 1 in a 12-year-old Ugandan girl. *JEMDSA* **18**, 65–67 (2013).
29. Zarzaur, B. L. & Rozycki, G. S. An update on nonoperative management of the spleen in adults. *Trauma. Surg. Acute Care Open* **2**, 000075 (2017).
30. Santorelli, J. E. et al. Readmission after splenic salvage: how real is the risk? *Surgery* **171**, 1417–1421 (2022).
31. Luu, S. et al. Prevalence and distribution of functional splenic tissue after splenectomy. *Int. Med. J.* **50**, 556–564 (2020).
32. Chen, Y., Qiu, J., Yang, A., Yuan, D. & Zhou, J. Epidemiology and management of splenic injury: an analysis of a Chinese military registry. *Exp. Ther. Med.* **13**, 2102–2108 (2017).
33. Arvieux, C. et al. Effect of prophylactic embolization on patients with blunt trauma at high risk of splenectomy: a randomized clinical trial. *JAMA Surg.* **155**, 1102–1111 (2020).
This study was a large trial assessing splenic arterial embolization for sparing splenectomy after trauma.
34. Rhimes, P. et al. The spectrum of blunt abdominal trauma in Pietermaritzburg. *S. Afr. J. Surg.* **59**, 90–93 (2021).
35. Iribhogbe, P. E. & Okolo, C. J. Management of splenic injuries in a university teaching hospital in Nigeria. *West Afr. J. Med.* **28**, 308–312 (2009).
36. Conradie, B. et al. Retrospective cohort study of paediatric splenic injuries at a major adult trauma centre in South Africa identifies areas of success and improvement. *ANZ J. Surg.* **91**, 1091–1097 (2021).
37. Choua, O., Rimtebbaye, K., Yamingue, N., Moussa, K. & Kaboro, M. Epidemiological, clinical and therapeutic aspects of blunt abdominal trauma in patients undergoing surgery at the General Hospital of National Reference of N'Djamena, Chad: about 49 cases [French]. *Pan. Afr. Med. J.* **26**, 50 (2017).
38. Akinkuolie, A. A., Lawal, O. O., Arowolo, O. A., Agbakwuru, E. A. & Adesunkanmi, A. R. Determinants of splenectomy in splenic injuries following blunt abdominal trauma. *S. Afr. J. Surg.* **48**, 15–19 (2010).
39. Chukwubuike, K. E. Pattern and outcome of splenic injury in children. *Ann. Afr. Surg.* **18**, 150–154 (2021).
40. Ladu, A. I., Aiyenigba, A., Adekile, A. & Bates, I. The spectrum of splenic complications in patients with sickle cell disease in Africa: a systematic review. *Br. J. Haematol.* **193**, 26–42 (2021).
41. Al-Salem, A. H. Splenic complications of sickle cell anemia and the role of splenectomy. *ISRN Hematol.* **2011**, 864257 (2011).
42. Adekile, A. D. et al. Influence of α-thalassemia trait on spleen function in sickle cell anemia patients with high HbF. *Am. J. Hematol.* **53**, 1–5 (1996).
43. Wali, Y. A. et al. Splenic function in Omani children with sickle cell disease: correlation with severity index, hemoglobin phenotype, iron status, and α-thalassemia trait. *Pediatr. Hematol. Oncol.* **19**, 491–500 (2002).
44. Aygun, B. & Odame, I. A global perspective on sickle cell disease. *Pediatr. Blood Cancer* **59**, 386–390 (2012).
45. Piel, F. B., Steinberg, M. H. & Rees, D. C. Sickle cell disease. *N. Eng. J. Med.* **376**, 1561–1573 (2017).
46. Casale, M. & Perrotta, S. Splenectomy for hereditary spherocytosis: complete, partial or not at all? *Exp. Rev. Hematol.* **4**, 627–635 (2011).
47. Matzdorff, A. et al. Immune thrombocytopenia – current diagnostics and therapy: recommendations of a joint working group of DGHO, ÖGHO, SGH, GPOH, and DGTI. *Oncol. Res. Treat.* **41** (Suppl. 5), 1–30 (2018).
48. Michel, M. Immune thrombocytopenic purpura: epidemiology and implications for patients. *Eur. J. Haematol.* **82**, 3–7 (2009).
49. Hassan, A. et al. Clinical feature and management of immune thrombocytopenic purpura in a tertiary hospital in Northwest Nigeria. *Niger. Med. J.* **58**, 68–71 (2017).
50. Salawu, L. & Durosinmi, M. A. Immune thrombocytopaenic purpura: 11-year experience in Ile-Ife, Nigeria. *Afr. J. Med. Med. Sci.* **30**, 99–103 (2001).
51. Barcellini, W., Zaninoni, A., Giannotta, J. A. & Fattizzo, B. New insights in autoimmune hemolytic anemia: from pathogenesis to therapy stage 1. *J. Clin. Med.* **9**, 3859 (2020).
52. Barcellini, W. & Fattizzo, B. How I treat warm autoimmune hemolytic anemia. *Blood* **137**, 1283–1294 (2021).
53. Barcellini, W., Giannotta, J. & Fattizzo, B. Autoimmune hemolytic anemia in adults: primary risk factors and diagnostic procedures. *Expert. Rev. Hematol.* **13**, 585–597 (2020).
54. Brodsky, R. A. Warm autoimmune hemolytic anemia. *N. Engl. J. Med.* **381**, 647–654 (2019).
55. Li, L. et al. The spleen in liver cirrhosis: revisiting an old enemy with novel targets. *J. Transl Med.* **15**, 111 (2017).
56. Muller, A. F. & Toghill, P. J. Functional hyposplenism in alcoholic liver disease: a toxic effect of alcohol? *Gut* **35**, 679–682 (1994).
57. Di Sabatino, A. et al. Splenic hypofunction and the spectrum of autoimmune and malignant complications in celiac disease. *Clin. Gastroenterol. Hepatol.* **4**, 179–186 (2006).
58. Corazza, G. R., Zoli, G., Di Sabatino, A., Ciccocioppo, R. & Gasbarrini, G. A reassessment of splenic hypofunction in celiac disease. *Am. J. Gastroenterol.* **94**, 391–397 (1999).
This is a landmark study assessing splenic function in patients with coeliac disease.
59. Di Sabatino, A., Brunetti, L., Maffè, G. C., Giuffrida, P. & Corazza, G. R. Is it worth investigating splenic function in patients with celiac disease? *World J. Gastroenterol.* **19**, 2313–2318 (2013).
60. Di Sabatino, A. et al. Splenic hypofunction in Whipple's disease. *Am. J. Gastroenterol.* **104**, 2641–2643 (2009).
61. Rozmus, J., Mallhi, K., Ke, J. & Schultz, K. R. Functional hyposplenism after hematopoietic stem cell transplantation. *Bone Marrow Transpl.* **50**, 1343–1347 (2015).
62. Cuthbert, R. J., Iqbal, A., Gates, A., Toghill, P. J. & Russell, N. H. Functional hyposplenism following allogeneic bone marrow transplantation. *J. Clin. Pathol.* **48**, 257–259 (1995).
This is a landmark study assessing splenic function after allogeneic bone marrow transplantation.
63. Mathur, A., McLean, M. H., Cao, H. & Vickers, M. A. Hyposplenism and gastrointestinal diseases: significance and mechanisms. *Dig. Dis.* **40**, 290–298 (2022).
64. Di Sabatino, A. et al. Depletion of immunoglobulin M memory B cells is associated with splenic hypofunction in inflammatory bowel disease. *Am. J. Gastroenterol.* **100**, 1788–1795 (2005).
65. Giuffrida, P. et al. Defective spleen function in autoimmune gastrointestinal disorders. *Intern. Emerg. Med.* **15**, 225–229 (2020).
66. Lenti, M. V. et al. Autoimmune gastritis. *Nat. Rev. Dis. Primers* **6**, 56 (2020).
67. Li, H. et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet* **395**, 1517–1520 (2020).
68. Lenti, M. V., Corazza, G. R. & Di Sabatino, A. COVID-19 and asplenia: a Janus-faced issue. *Intern. Emerg. Med.* **16**, 2341–2342 (2021).
69. Chaves, L. F., Taleo, G., Kalkao, M. & Kaneko, A. Spleen rates in children: an old and new surveillance tool for malaria elimination initiatives in island settings. *Trans. R. Soc. Trop. Med. Hyg.* **105**, 226–231 (2011).
70. Imbert, P., Rapp, C. & Buffet, P. A. Pathological rupture of the spleen in malaria: analysis of 55 cases (1958–2008). *Travel. Med. Infect. Dis.* **7**, 147–159 (2009).
71. Hart, M. 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.* **178**, 8212–8220 (2007).
72. Grotto, H. Z. & Costa, F. F. Hyposplenism in AIDS. *AIDS* **5**, 1538–1540 (1991).
73. Joice, R. et al. Evidence for spleen dysfunction in malaria–HIV co-infection in a subset of pediatric patients. *Mod. Pathol.* **29**, 381–390 (2016).
A study showing that malaria and HIV co-infections are associated with spleen hypofunction.
74. Sporn, Z. A., Fenves, A. Z., Sykes, D. B. & Al-Samkari, H. Severe babesiosis with associated splenic infarcts and asplenia. *Proc. (Bayl. Univ. Med. Cent.)* **34**, 597–599 (2021).
75. Alvi, A., Gupta, S., Goyal, P., Pichardo, J. & Mattana, J. Splenic infarction as a rare presentation of severe babesiosis. *IDCases* **15**, 00491 (2019).
76. Neilan, B. A. & Berney, S. N. Hyposplenism in systemic lupus erythematosus. *J. Rheumatol.* **10**, 332–334 (1983).
77. Sarangi, J., Coleby, M., Trivella, M. & Reilly, S. Prevention of post splenectomy sepsis: a population based approach. *J. Public. Health Med.* **19**, 208–212 (1997).
78. Tahir, F., Ahmed, J. & Malik, F. Post-splenectomy sepsis: a review of the literature. *Cureus* **12**, 6898 (2020).
79. Thomsen, R. W. et al. Risk for hospital contact with infection in patients with splenectomy: a population-based cohort study. *Ann. Intern. Med.* **151**, 546–555 (2009).
80. Serio, B. et al. OPSI threat in hematological patients. *Transl Med.* **6**, 2–10 (2013).
81. Madenci, A. et al. Incidence and risk factors for sepsis after childhood splenectomy. *J. Pediatr. Surg.* **54**, 1445–1448 (2019).
82. Rosado, M. M. et al. From the fetal liver to spleen and gut: the highway to natural antibody. *Mucosal. Immunol.* **2**, 351–361 (2009).
83. Rosser, E. C. et al. Regulatory B cells are induced by gut microbiota-driven interleukin-1β and interleukin-6 production. *Nat. Med.* **20**, 1334–1339 (2014).
84. Tull, T. J. et al. Human marginal zone B cell development from early T2 progenitors. *J. Exp. Med.* **218**, e20202001 (2021).
85. Steiniger, B., Timphus, E. M. & Barth, P. J. The splenic marginal zone in humans and rodents: an enigmatic compartment and its inhabitants. *Histochem. Cell Biol.* **126**, 641–648 (2006).
86. Kruetzmann, S. et al. Human immunoglobulin M memory B cells controlling *Streptococcus pneumoniae* infections are generated in the spleen. *J. Exp. Med.* **197**, 939–945 (2003).
This study demonstrated that IgM memory B cells directed against an infection sustained by encapsulated bacteria are produced in the spleen.
87. Weller, S. et al. Human blood IgM "memory" B cells are circulating splenic marginal zone B cells harboring a prediversified immunoglobulin repertoire. *Blood* **104**, 3647–3654 (2004).
88. Aranburu, A. et al. TLR ligation triggers somatic hypermutation in transitional B cells inducing the generation of IgM memory B cells. *J. Immunol.* **185**, 7293–7301 (2010).
89. Aranburu, A. et al. Human B-cell memory is shaped by age- and tissue-specific T-independent and GC-dependent events. *Eur. J. Immunol.* **47**, 327–344 (2017).

90. Steiniger, B., Rüttinger, L. & Barth, P. J. The three-dimensional structure of human splenic white pulp compartments. *J. Histochem. Cytochem.* **51**, 655–664 (2003).
91. Satoh, T., Oikawa, H., Yashima-Abo, A., Nishiya, M. & Masuda, T. Expression of mucosal addressin cell adhesion molecule-1 on the reticular framework between white pulp and the marginal zone in the human spleen. *J. Clin. Exp. Hematop.* **59**, 187–195 (2019).
92. Pabst, O., Förster, R., Lipp, M., Engel, H. & Arnold, H. H. NKX2.3 is required for MAdCAM-1 expression and homing of lymphocytes in spleen and mucosa-associated lymphoid tissue. *EMBO J.* **19**, 2015–2023 (2000).
93. Schippers, A. et al. Mucosal addressin cell-adhesion molecule-1 controls plasma-cell migration and function in the small intestine of mice. *Gastroenterology* **137**, 924–933 (2009).
94. Capolunghi, F., Rosado, M. M., Sinibaldi, M., Aranburu, A. & Carsetti, R. Why do we need IgM memory B cells? *Immunol. Lett.* **152**, 114–120 (2013).
95. Carsetti, R. et al. The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J. Allergy Clin. Immunol.* **115**, 412–417 (2005).
96. Rosado, M. M. et al. Preserved antibody levels and loss of memory B cells against pneumococcus and tetanus after splenectomy: tailoring better vaccination strategies. *Eur. J. Immunol.* **43**, 2659–2670 (2013).
97. Carsetti, R. et al. Lack of gut secretory immunoglobulin A in memory B-cell dysfunction-associated disorders: a possible gut–spleen axis. *Front. Immunol.* **10**, 2937 (2020).
98. Wardemann, H., Boehm, T., Dear, N. & Carsetti, R. B-1a B cells that link the innate and adaptive immune responses are lacking in the absence of the spleen. *J. Exp. Med.* **195**, 771–780 (2002).
99. Weller, S. et al. CD40-CD40L independent Ig gene hypermutation suggests a second B cell diversification pathway in humans. *Proc. Natl Acad. Sci. USA* **98**, 1166–1170 (2001).
100. Weller, S. et al. Somatic diversification in the absence of antigen-driven responses is the hallmark of the IgM+ IgD+ CD27+ B cell repertoire in infants. *J. Exp. Med.* **205**, 1331–1342 (2008).
101. Sanz, I. et al. Challenges and opportunities for consistent classification of human B cell and plasma cell populations. *Front. Immunol.* **10**, 2458 (2019).
102. Pabst, O. & Slack, E. IgA and the intestinal microbiota: the importance of being specific. *Mucosal. Immunol.* **13**, 12–21 (2020).
103. Corthésy, B. Multi-faceted functions of secretory IgA at mucosal surfaces. *Front. Immunol.* **4**, 185 (2013).
104. van Lookeren Campagne, M. & Verschoor, A. Pathogen clearance and immune adherence "revisited": immuno-regulatory roles for CRIg. *Semin. Immunol.* **37**, 4–11 (2018).
105. Jung, S. et al. In vivo depletion of CD11c+ dendritic cells abrogates priming of CD8+ T cells by exogenous cell-associated antigens. *Immunity* **17**, 211–220 (2002).
106. Rothman, J. A., Stevens, J. L., Gray, F. L. & Kalfa, T. A. How I approach hereditary hemolytic anemia and splenectomy. *Pediatr. Blood Cancer* **67**, 28337 (2020).
107. Taher, A., Tyan, P. I. & Cappellini, M. D. in *Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT)* 3rd edn Ch. 6 (eds Cappellini, M. D., Cohen, A., Porter, J., Taher, A. & Viprakasit, V.) (Thalassaemia International Federation, 2014).
108. Neunert, C. et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv.* **3**, 3829–3866 (2019).
109. Rivers, E., Worth, A., Thrasher, A. J. & Burns, S. O. How I manage patients with Wiskott Aldrich syndrome. *Br. J. Haematol.* **4**, 647–655 (2019).
110. Xu, X. et al. Pathological changes of the spleen in ten patients with new coronavirus infection by minimally invasive autopsies. *Zhonghua Bing Li Xue Za Zhi* **49**, 576–582 (2020).
111. Duarte-Neto, A. N. et al. Pulmonary and systemic involvement of COVID-19 assessed by ultrasound-guided minimally invasive autopsy. *Histopathology* **77**, 186–197 (2020).
112. Sekulic, M. et al. Molecular detection of SARS-CoV-2 infection in FFPE samples and histopathologic findings in fatal SARS-CoV-2 cases. *Am. J. Clin. Pathol.* **154**, 190–200 (2020).
113. Lax, S. F. et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann. Intern. Med.* **173**, 350–361 (2020).
114. Crary, S. E. & Buchanan, G. R. Vascular complications after splenectomy for hematologic disorders. *Blood* **114**, 2861–2868 (2009).
115. Taher, A. et al. Prevalence of thromboembolic events among 8860 patients with thalassaemia major and intermedia in the Mediterranean area and Iran. *Thromb. Haemost.* **96**, 488–491 (2006).
116. Mohren, M. et al. Thromboembolic complications after splenectomy for hematologic diseases. *Am. J. Hematol.* **76**, 143–147 (2004).
117. Eldor, A. & Rachmilewitz, E. A. The hypercoagulable state in thalassemia. *Blood* **99**, 36–43 (2002).
118. Ludvigsson, J. F., Welander, A., Lassila, R., Ekbom, A. & Montgomery, S. M. Risk of thromboembolism in 14,000 individuals with coeliac disease. *Br. J. Haematol.* **139**, 121–127 (2007).
119. Vancauwenberghe, T., Snoeckx, A., Vanbeckevoort, D., Dymarkowski, S. & Vanhoenacker, F. M. Imaging of the spleen: what the clinician needs to know. *Singap. Med. J.* **56**, 133–144 (2015).
120. Palas, J., Matos, A. P. & Ramalho, M. The spleen revisited: an overview on magnetic resonance imaging. *Radiol. Res. Pract.* **2013**, 219297 (2013).
121. Spencer, R. P. & Gupta, S. M. The spleen: diagnosis of splenic diseases using radiolabeled tracers. *Crit. Rev. Clin. Lab. Sci.* **27**, 299–318 (1989).
122. Peters, A. M. et al. Measurement of splenic function in humans using heat damaged autologous red blood cells. *Scand. J. Haematol.* **27**, 374–380 (1981).
123. Mohamed, M. Functional hyposplenism diagnosed by blood film examination. *Blood* **124**, 1997 (2014).
124. Crosby, W. H. Normal functions of the spleen relative to red blood cells: a review. *Blood* **14**, 399–408 (1959).
125. Corazza, G. R., Bullen, A. W., Hall, R., Robinson, P. J. & Losowsky, M. S. Simple method of assessing splenic function in coeliac disease. *Clin. Sci.* **60**, 109–113 (1981).
126. Corazza, G. R. et al. Howell-Jolly body counting as a measure of splenic function. A reassessment. *Clin. Lab. Haematol.* **12**, 269–275 (1990).
In this study, pitted red cell count proved the best laboratory test for assessing spleen function.
127. Seifert, M. & Küppers, R. Human memory B cells. *Leukemia* **30**, 2283–2292 (2016).
128. Carsetti, R. et al. Comprehensive phenotyping of human peripheral blood B lymphocytes in healthy conditions. *Cytom. A* **101**, 131–139 (2022).
129. Carsetti, R. et al. Comprehensive phenotyping of human peripheral blood B lymphocytes in pathological conditions. *Cytom. A* **101**, 140–149 (2022).
130. Kyaw, M. H. et al. Evaluation of severe infection and survival after splenectomy. *Am. J. Med.* **119**, 271–277 (2006).
131. Di Cataldo, A. et al. Splenic trauma and overwhelming postsplenectomy infection. *Br. J. Surg.* **74**, 343–345 (1987).
132. Okabayashi, T. & Hanazaki, K. Overwhelming postsplenectomy infection syndrome in adults–a clinically preventable disease. *World J. Gastroenterol.* **14**, 176–179 (2008).
133. Pearson, H. A., Spencer, R. P. & Cornelius, E. A. Functional asplenia in sickle-cell anemia. *N. Eng. J. Med.* **281**, 923–926 (1969).
134. Simons, M. et al. Celiac disease and increased risk of pneumococcal infection: a systematic review and meta-analysis. *Am. J. Med.* **131**, 83–89 (2018).
135. Zingone, F. et al. The risk of community-acquired pneumonia among 9803 patients with coeliac disease compared to the general population: a cohort study. *Aliment. Pharmacol. Ther.* **44**, 57–67 (2016).
136. Lenti, M. V. et al. Preventing infections by encapsulated bacteria through vaccine prophylaxis in inflammatory bowel disease. *Front. Immunol.* **11**, 485 (2020).
137. Lee, D. H. et al. Splenectomy is associated with a higher risk for venous thromboembolism: prospective cohort study. *Int. J. Surg.* **24**, 27–32 (2015).
138. Boyle, S., White, R. H., Brunson, A. & Wun, T. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. *Blood* **121**, 4782–4790 (2013).
139. Freeman, H. J. Mesenteric lymph node cavitation syndrome. *World J. Gastroenterol.* **16**, 2991–2993 (2010).
140. Di Sabatino, A., Carnevale Maffè, G., Brunetti, L., Guerci, M. & Corazza, G. R. Splenic hypofunction in patients with an incidental finding of small-sized spleen at abdominal ultrasound. *Intern. Emerg. Med.* **8**, 361–362 (2013).
141. Hathaway, J. M., Harley, R. A., Self, S., Schiffman, G. & Virella, G. Immunological function in post-traumatic splenosis. *Clin. Immunol. Immunopathol.* **74**, 143–150 (1995).
142. Corazza, G. R., Tarozzi, C., Vaira, D., Frisoni, M. & Gasbarrini, G. Return of splenic function after splenectomy: how much tissue is needed? *Br. Med. J.* **289**, 861–864 (1984).
This study demonstrated that splenosis is associated with spleen function preservation in a quantity-dependent manner.
143. Di Sabatino, A. et al. Association between defective spleen function and primary eosinophilic gastrointestinal disorders. *J. Allergy Clin. Immunol. Pract.* **6**, 1056–1058 (2018).
144. Di Sabatino, A. et al. Splenic function and IgM-memory B cells in Crohn's disease patients treated with infliximab. *Inflamm. Bowel Dis.* **14**, 591–596 (2008).
145. Davidson, R. N. & Wall, R. A. Prevention and management of infections in patients without a spleen. *Clin. Microbiol. Infect.* **7**, 657–660 (2001).
146. Evans, L. et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2021. *Crit. Care Med.* **49**, e1063–e1143 (2021).
147. Centers for Disease Control and Prevention. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. *ClinicalInfo.HIV.gov* https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection (2022).
148. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). HIV Management in Australasia: A guide for clinical care: summary of vaccination recommendations for HIV-infected adults. *ashm* https://hivmanagement.ashm.org.au/summary-of-vaccination-recommendations-for-hiv-infected-adults/ (2019).
149. European AIDS Clinical Society. Guidelines. Version 11.0. October 2021. *EACS* https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf (2021).
150. Garcia Garrido, H. M. et al. Incidence and risk factors for invasive pneumococcal disease and community-acquired pneumonia in human immunodeficiency virus–infected individuals in a high-income setting. *Clin. Infect. Dis.* **71**, 41–50 (2020).
151. Carson, P. J., Schut, R. L., Simpson, M. L., O'Brien, J. & Janoff, E. N. Antibody class and subclass responses to pneumococcal polysaccharides following immunization of human immunodeficiency virus-infected patients. *J. Infect. Dis.* **172**, 340–345 (1995).
152. Janoff, E. N., Fasching, C., Ojoo, J. C., O'Brien, J. & Gilks, C. F. Responsiveness of human immunodeficiency virus type 1-infected Kenyan women with or without prior pneumococcal disease to pneumococcal vaccine. *J. Infect. Dis.* **175**, 975–978 (1997).
153. Vardanjani, H. M., Borna, H. & Ahmadi, A. Effectiveness of pneumococcal conjugate vaccination against invasive pneumococcal disease among children with and those

without HIV infection: a systematic review and meta-analysis. *BMC Infect. Dis.* **19**, 685 (2019).
154. Garcia Garrido, H. M. et al. Immunogenicity of the 13-valent pneumococcal conjugate vaccine followed by the 23-valent pneumococcal polysaccharide vaccine in people living with HIV on combination antiretroviral therapy. *Int. J. Antimicrob. Agents* **60**, 106629 (2002).
155. Garcia Garrido, H. M. et al. Immunogenicity of pneumococcal vaccination in HIV infected individuals: a systematic review and meta-analysis. *EClinicalMedicine* **29–30**, 100576 (2020).
156. Kerneis, S. et al. Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. *Clin. Infect. Dis.* **58**, 1130–1139 (2014).
157. Australian Government Department of Health and Aged Care. Vaccination for people who are immunocompromised. *Australian Government* https://immunisationhandbook.health.gov.au/contents/vaccination-for-special-risk-groups/vaccination-for-people-who-are-immunocompromised (2019).
158. UK Health Security Agency in *Immunisation Against Infectious Diseases: The Green Book* Ch. 25 (UKHSA, 2022).
159. UK Health Security Agency in *Immunisation Against Infectious Diseases: The Green Book* Ch. 22 (UKHSA, 2022).
160. Centers for Disease Control and Prevention. Pneumococcal Vaccination: Summary of Who and When to Vaccinate. *CDC* https://www.cdc.gov/vaccines/vpd/pneumo/hcp/who-when-to-vaccinate.html (2022).
161. Centers for Disease Control and Prevention. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: Tables. *CDC* https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/prophylaxis-prevent-first-episode (2022).
162. Soeters, H. M., von Gottberg, A., Cohen, C., Quan, V. & Klugman, K. P. Trimethoprim-sulfamethoxazole prophylaxis and antibiotic non susceptibility in invasive pneumococcal disease. *Antimicrob. Agents Chemother.* **56**, 1602–1605 (2012).
163. Dendle, C., Sundararajan, V., Spelman, T., Jolley, D. & Woolley, I. Splenectomy sequelae: an analysis of infectious outcomes among adults in Victoria. *MJA* **196**, 582–586 (2012).
164. Bisharat, N., Omari, H., Lavi, I. & Raz, R. Risk of infection and death among post-splenectomy patients. *J. Infect.* **43**, 182–186 (2001).
165. Waghorn, D. J. Overwhelming infection in asplenic patients: current best practice preventive measures are not being measured. *J. Clin. Pathol.* **54**, 214–218 (2001).
166. Vinuesa, C. G., De Lucas, C. & Cook, M. C. Clinical implications of the specialised B cell response to polysaccharide encapsulated pathogens. *Postgrad. Med. J.* **77**, 562–569 (2001).
167. Lexau, C. A. et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. *JAMA* **294**, 2043–2051 (2005).
168. Macintyre, C. R. et al. A randomized clinical trial of the immunogenicity of 7-valent pneumococcal conjugate vaccine compared to 23-valent polysaccharide vaccine in frail, hospitalized elderly. *PLoS ONE* **9**, e94578 (2014).
169. O'Brien, K., Hochman, M. & Goldblatt, D. Combined schedules of pneumococcal conjugate and polysaccharide vaccines: is hyporesponsiveness an issue? *Lancet Infect. Dis.* **7**, 597–606 (2007).
170. Mufson, M. A., Hughey, D. F., Turner, C. E. & Schiffman, G. Revaccination with pneumococcal vaccine of elderly persons 6 years after primary vaccination. *Vaccine* **9**, 403–407 (1991).
171. Musher, D. M. et al. Antibody persistence ten years after first and second doses of 23-valent pneumococcal polysaccharide vaccine, and immunogenicity and safety of second and third doses in older adults. *Hum. Vaccin.* **7**, 919–928 (2011).
172. Jackson, L. A. et al. Influence of initial vaccination with 13-valent pneumococcal conjugate vaccine or 23-valent pneumococcal polysaccharide vaccine on anti-pneumococcal responses following subsequent pneumococcal vaccination in adults 50 years and older. *Vaccine* **31**, 3594–3602 (2013).
173. Nived, P., Jørgensen, C. S. & Settergren, B. Vaccination status and immune response to 13-valent pneumococcal conjugate vaccine in asplenic individuals. *Vaccine* **33**, 1688–1694 (2015).
174. Rappuoli, R., Gregorio, E. D. & Costantino, P. On the mechanisms of conjugate vaccines. *Proc. Natl Acad. Sci. USA* **116**, 14–16 (2019).
175. Breukels, M. A. et al. Pneumococcal conjugate vaccines overcome splenic dependency of antibody response to pneumococcal polysaccharides. *Infect. Immun.* **69**, 7584–7587 (2001).
176. Amlot, P. L. & Hayes, A. E. Impaired human antibody response to the thymus-independent antigen, DNP-Ficoll, after splenectomy: implications for post-splenectomy infections. *Lancet* **325**, 1008–1011 (1985).
177. Zaandvoort, A. & Timens, W. The dual function of the splenic marginal zone: essential for initiation of anti-TI-2 responses but also vital in the general first-line defense against blood-borne antigens. *Clin. Exp. Immunol.* **130**, 4–11 (2002).
178. Claassens, E., Kors, N., Dijkstra, C. D. & Van Rooijen, N. Marginal zone of the spleen and the development and localization of specific antibody-forming cells against thymus-dependent and thymus independent type-2 antigens. *Immunology* **57**, 399–403 (1986).
179. Lane, P. J., Gray, D., Oldfield, S. & MacLennan, I. C. Differences in the recruitment of virgin B cells in antibody responses to thymus-dependent and thymus-independent type-2 antigens. *Eur. J. Immunol.* **16**, 1569–1575 (1986).
180. Musher, D. 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.* **191**, 1063–1067 (2005).
181. Stoehr, G. A. et al. Immunogenicity of sequential pneumococcal vaccination in subjects splenectomised for hereditary spherocytosis. *Br. J. Hematol.* **132**, 788–790 (2006).
182. Lee, G. M. Preventing infections in children and adults with asplenia. *Hematol. Am. Soc. Hematol. Educ. Program* **2020**, 328–335 (2020).
183. Kanhutu, K. et al. Spleen Australia guidelines for the prevention of sepsis in patients with asplenia and hyposplenism in Australia and New Zealand. *Intern. Med. J.* **47**, 848–855 (2017).
184. Rubin, L. G. et al. IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin. Infect. Dis.* **58**, 309–318 (2013).
185. Wiedermann, U. et al. Guidelines for vaccination of immunocompromised individuals [German]. *Wien. Klin. Wochenschr.* **128** (Suppl. 4), 337–376 (2016).
186. Food and Drug Administration. Vaxneuvance. *FDA* https://www.fda.gov/vaccines-blood-biologics/vaccines/vaxneuvance (2022).
187. European Medicines Agency. Vaxneuvance. *European Medicines Agency* https://www.ema.europa.eu/en/medicines/human/EPAR/vaxneuvance (2022).
188. Food and Drug Administration. Prevnar 20. *FDA* https://www.fda.gov/vaccines-blood-biologics/vaccines/prevnar-20 (2021).
189. European Medicines Agency. Apexxnar. *European Medicines Agency* https://www.ema.europa.eu/en/medicines/human/EPAR/apexxnar (2022).
190. Jochems, S. P. et al. Inflammation induced by influenza virus impairs human innate immune control of pneumococcus. *Nat. Immunol.* **19**, 1299–1308 (2018).
191. Martino, R. et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses in adult recipients of hematopoietic stem cell transplants for hematologic malignancies. *Biol. Blood Marrow Transpl.* **11**, 781–796 (2005).
192. Vu, H. T. et al. Association between nasopharyngeal load of *Streptococcus pneumoniae*, viral coinfection, and radiologically confirmed pneumonia in Vietnamese children. *Pediatr. Infect. Dis. J.* **30**, 11–18 (2011).
193. L'Huillier, A. G. & Kumar, D. Immunizations in solid organ and hematopoeitic stem cell transplant patients: a comprehensive review. *Hum. Vaccin. Immunother.* **11**, 2852–2863 (2015).
194. Shatz, D. V. et al. Immune responses of splenectomized trauma patients to the 23-valent pneumococcal polysaccharide vaccine at 1 versus 7 versus 14 days after splenectomy. *J. Trauma. Inj. Infect. Crit. Care* **44**, 760–766 (1998).
195. Konradsen, H. B., Rasmussen, C., Ejstrud, P. & Hansen, J. B. Antibody levels against *Streptococcus pneumoniae* and *Haemophilus influenzae* type b in a population of splenectomized individuals with varying vaccination status. *Epidemiol. Infect.* **119**, 167–174 (1997).
196. Caya, C. A., Boikos, C., Desai, S. & Quach, C. Dosing regimen of the 23-valent pneumococcal vaccination: a systematic review. *Vaccine* **33**, 1302–1312 (2015).
197. Meerveld-Eggink, A. et al. Impaired antibody response to conjugated meningococcal serogroup C vaccine in asplenic patients. *Eur. J. Clin. Microbiol. Infect. Dis.* **30**, 611–618 (2011).
198. Mbaeyi, S. A. et al. Meningococcal vaccination: recommendations of the Advisory Committee on Immunization Practices, United States, 2020. *MMWR Recomm. Rep.* **69**, 1–41 (2020).
199. Spleen Australia. Paediatric guidelines age 0 to 18 years. *Spleen Australia* https://spleen.org.au/wp-content/uploads/2020/03/RECOMMENDATIONS_Spleen_Registry_p.pdf (2019).
200. Lanzkowsky, P., Shende, A., Karayalcin, G. & Aral, I. Staging laparotomy and splenectomy: treatment and complications of Hodgkin's disease in children. *Am. J. Hematol.* **1**, 393–404 (1976).
201. Gaston, M. H. et al. Prophylaxis with oral penicillin in children with sickle cell anaemia. A randomized trial. *N. Engl. J. Med.* **314**, 1593–1599 (1986).
202. Cober, M. P. & Phelps, S. J. Penicillin prophylaxis in children with sickle cell disease. *J. Pediatr. Pharmacol. Ther.* **15**, 152–159 (2010).
203. Chaudhry, S. B., Veve, M. P. & Wagner, J. L. Cephalosporins: a focus on side chains and β-lactam cross-reactivity. *Pharmacy* **7**, 103 (2019).
204. Luzzatto, L. Sickle cell anaemia and malaria. *Mediterr. J. Hematol. Infect. Dis.* **4**, 2012065 (2012).
205. Brousse, V., Buffet, P. & Rees, D. The spleen and sickle cell disease: the sick(led) spleen. *Br. J. Haematol.* **166**, 165–176 (2014).
206. Federal Ministry of Health. National guideline for the control and management of sickle cell disease. *Federal Ministry of Health* http://scsn.com.ng/wp-content/uploads/2014/11/National-Guideline-for-the-Control-and-Management-of-Sickle-Cell-Disease.pdf (2014).
207. Ramachandra, J., Bond, A., Ranaboldo, C. & Cullis, J. An audit of post-splenectomy prophylaxis – are we following the guidelines? *Ann. R. Coll. Surg. Engl.* **85**, 252–255 (2003).
208. Rieg, S. et al. A single-center prospective cohort study on postsplenectomy sepsis and its prevention. *Open. Forum Infect. Dis.* **7**, ofaa050 (2020).
209. Luu, S., Dendle, C., Jones, P., Ojaimi, S. & Woolley, I. J. Impact of a spleen registry on optimal post-splenectomy vaccination and care. *Hum. Vaccin. Immunother.* **14**, 2894–2899 (2018).
210. Wang, J., Jones, P. A., Cheng, A. C. & Leder, K. Adherence to infection prevention measures in a statewide spleen registry. *Med. J. Aust.* **200**, 538–540 (2014).

211. Arnott, A. et al. A registry for patients with asplenia/hyposplenism reduces the risk of infections with encapsulated organisms. *Clin. Infect. Dis.* **67**, 557–561 (2018).
212. Denholm, J. T., Jones, P. A., Spelman, D. W., Cameron, P. U. & Woolley, I. J. Spleen registry may help reduce the incidence of overwhelming postsplenectomy infection in Victoria. *Med. J. Aust.* **192**, 49–50 (2010).
213. MacInnes, J., Waghorn, D. J. & Haworth, E. Management of asplenic patients in South Buckinghamshire: an audit of local practice. *Commun. Dis. Rep. Cdr. Rev.* **5**, 173–177 (1995).
214. Spickett, G. Northern Region asplenia register – analysis of first two years. *J. Clin. Pathol.* **52**, 424–429 (1999).
215. Watson, A. R. Pretravel health advice for asplenic individuals. *J. Travel. Med.* **10**, 117–121 (2006).
216. Starship. Splenectomy and management of the asplenic patient. *Starship* https://starship.org.nz/guidelines/splenectomy/ (2020).
217. Solverson, K. J. & Doig, C. J. A fatal case of pneumococcal sepsis years after splenectomy. *Can. Med. Assoc. J.* **189**, 800–802 (2017).
218. Urata, Y. et al. A fatal case of overwhelming postsplenectomy infection syndrome developing 10 years after splenectomy [Japanese]. *Nihon Rinsho Meneki Gakkai Kaishi* **20**, 184–190 (1997).
219. Cormack, R. J., Ferris, M. C. M., Wong, J. K. & Przybojewski, S. Splenic artery embolisation in the non-operative management of blunt splenic trauma in adults. *S. Afr. J. Radiol.* **20**, a1014 (2016).
220. Nakae, H. et al. Does splenic preservation treatment (embolization, splenorrhaphy, and partial splenectomy) improve immunologic function and long-term prognosis after splenic injury? *J. Trauma* **67**, 557–564 (2009).
221. Iolascon, A. et al. Recommendations regarding splenectomy in hereditary hemolytic anemias. *Haematologica* **102**, 1304–1313 (2017).
222. Mathew, S., Buchanan, G. R. & Crary, S. E. Medical and quality of life indications for splenectomy in children with hereditary spherocytosis. *Blood* **114**, 5082 (2009).
223. Cappellini, M.-D. et al. *Guidelines for the Clinical Management of Thalassaemia* 2nd revised edn (Thalassaemia International Federation, 2008).
224. Kang, J.-M. et al. Risk of invasive pneumococcal disease in patients with asplenia/hyposplenism: a nationwide population-based study in Korea, 2009–2018. *Intern. J. Infect. Dis.* **98**, 486–493 (2020).
225. Bojesen, A. B., Lund, A., Mortensen, F. V. & Kirkegård, J. A.-O. Splenectomy and risk of COVID-19 infection, hospitalisation, and death. *Infect. Dis.* **53**, 678–683 (2021).
226. El-Alfy, M. S. & El-Sayed, M. H. Overwhelming postsplenectomy infection: is quality of patient knowledge enough for prevention? *Hematol. J.* **5**, 77–80 (2004).
227. Hegarty, P. K., Tan, B., O'Sullivan, R., Cronin, C. C. & Brady, M. P. Prevention of postsplenectomy sepsis: how much do patients know? *Hematol. J.* **1**, 357–359 (2000).
228. Brigden, M. L. Overwhelming postsplenectomy infection still a problem. *West. J. Med.* **157**, 440–443 (1992).

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