The spleen and sickle cell disease: the sick(led) spleen

Valentine Brousse,1,2,3 Pierre Buffet4,5 and David Rees6

1Department of Paediatrics, Reference Centre for Sickle Cell Disease, Hôpital Universitaire Necker-Enfants Malades, APHP, 2Université Paris Descartes, 3Laboratory of Excellence GR-Ex, 4Centre d’Immunologie et des Maladies Infectieuses de Paris, CIMI-PARIS, U1135 INSERM/UPMC Université Paris VI, 5Service de Parasitologie, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France and 6Department of Paediatric Haematology, King’s College Hospital NHS Foundation Trust, King’s Health Partners, Denmark Hill, London, UK

Summary

The spleen has a combined function of immune defence and quality control of senescent or altered red cells. It is the first organ injured in sickle cell anaemia (SCA) with evidence of hyposplenism present before 12 months in the majority of children. Repeated splenic vaso-occlusion leads to fibrosis and progressive atrophy of the organ (autosplenectomy), which is generally complete by 5 years in SCA. The precise sequence of pathogenic events leading to hyposplenism is unknown. Splenic injury is generally silent and progressive. It can be clinically overt with acute splenic sequestration of red cells, an unpredictable and life-threatening complication in infants. Splenomegaly, with or without hyposplenism, can also occur and can coexist with loss of function. Hyposplenism increases the susceptibility of SCA children to infection with encapsulated bacteria, which is notably reduced by penicillin prophylaxis and immunization. Whether hyposplenism indirectly increases the risk of vaso-occlusion or other circulatory complications remains to be determined.

Keywords: spleen, sickle cell disease, hyposplenism, acute splenic sequestration, childhood.

Over the years, the human spleen has received attention in the literature, mostly from poets and philosophers as the seat of melancholy and bad temper (Baudelaire, 1869). In English ‘spleen’ is still used to refer to anger, and in French, the same word means sadness. In physiology, the spleen has been described as early as Galen’s era and, despite further insight in the 1970s into its sophisticated ultra structural microanatomy (Chen & Weiss, 1972), the spleen continues to remain a mysterious organ, often considered as an unnecessary reservoir. Progressive evidence is pointing, however, to the role of the spleen as a major contributor to immune, vascular and blood homeostasis. Hyposplenism, therefore, is increasingly recognized as a pathological condition with potentially major consequences, such as vascular complications and immune dysfunction, in addition to the long identified susceptibility to encapsulated bacteria. In sickling disorders, the spleen is prone to early injury and hyposplenism is consequently a major feature of the disease, and a constant one in homozygous and S-beta-thalassaemia patients. This review summarizes the up to date knowledge on the physiological role of the spleen and its dysfunction in sickling disorders. The main consequences related to spleen dysfunction, susceptibility to infections, disease expression and vascular risk are highlighted. Principles of management in sickle cell disease (SCD) are discussed.

Functions of the spleen

The spleen is a uniquely adapted lymphoid organ dedicated to the clearance of blood cells, microorganisms and blood-borne antigens. It is a major filter of the blood, which initiates and links innate and adaptive immune responses against pathogens. The spleen is histologically divided in three functional interconnected compartments: the white pulp, essentially dedicated to adaptive immunity, the red pulp, which is essentially dedicated to a filtering function and the marginal zone (or perifollicular zone) lying in-between, connecting both functions. Due to its location on the blood mainstream, as opposed to other secondary lymphoid organs, the spleen filters approximately 5% of the cardiac output every minute (William & Corazza, 2007). Blood entering the spleen through the splenic artery is distributed through the trabecular arteries that branch throughout the parenchyma to a terminating arteriole called the central arteriole, surrounded by lymphoid cells. The arteriole can either drain directly into the venous sinuses, which are vascular channels lined by endothelial cells, or alternatively terminate within the parenchyma and discharge its blood content into the cords of the red pulp. In this latter case, blood cells and blood-borne bacteria are in close and prolonged contact with specialized macrophages and resident spleen cells. This interaction triggers phagocytosis of pathogens or red blood cells (RBC).
whenever activating signals are present on the cell surface. Farther in their progression along this un-endothelialized space, the remaining cells will re-enter into the venous system after squeezing through narrow (1–3 μm wide), inter-endothelial slits in the wall of venous sinuses. At this ultimate checkpoint, red cells may be retained upstream from the sinus wall if they are not deformable enough. They can also be ‘pitted’ if they contain abnormal material like nuclear remnants or altered parasites (Buffet et al., 2006; Safeukui et al., 2008). During this pitting process, the red cell is groomed of its unwanted material by squeezing through inter-endothelial slits. If this pitting capacity is altered, red cells containing abnormal material are found in the circulation. Ten percent of the blood circulating in the spleen flows with reduced velocity and high haematocrit in the open and slow pathway, whilst 90% flows through in the fast closed pathway, bypassing the filtration beds. Red cell velocity in the slow pathway is in the range of 7 μm/s vs. 100 times greater in the sinus. Additional resistance due to the dynamic properties of both the endothelial cells and specialized fibroblasts (Donald & Aarhus, 1974) may play an important role in regulating blood filtration and possibly be dysfunctional in pathological conditions like SCD.

The white pulp selectively clears lymphocytes and accessory cells from the blood and allows the spleen to initiate an adaptive immune response. It is divided into T lymphocyte zones around the artery (periarteriolar lymphocyte sheath, PALS) and follicles composed of B cells, in addition to dendritic cells and macrophages.

The spleen contains distinct B cell lineages: follicular and marginal zone B cells. Follicular B cells recirculate as plasmacytes, producing high affinity antibodies and participate mainly in T cell-dependent immune responses upon re-infection or immunization. Marginal zone B cells and dendritic cells capture antigens and promote both T cell-independent and -dependent immune responses. Marginal zone B cells (immunoglobulin (Ig)M memory B cells) express the memory cell marker CD27, high surface IgM and low levels of IgD (Weller et al., 2004). These cells can provide early T cell independent responses by producing natural anti polysaccharide IgMs, which are essential to the phagocytosis of otherwise poorly opsonised encapsulated bacteria, such as Streptococcus pneumoniae, Nesseria meningitidis and Haemophilus influenza type b (Hib). The splenic marginal zone is central to the generation and the maintenance of IgM memory B cells.

Macrophages exerting discrete functions are present in all compartments. Marginal zone macrophages express unique pattern-recognition receptors and contribute to the clearance of blood-borne bacteria and regulate tolerance to antigens. Macrophages in the filtration beds are specialized in erythropagocytosis, scavenging blood-borne debris and recycling iron (den Haan & Kraal, 2012).

The main clinical consequences of defective spleen function derive from the alteration of both the filtering and immune functions, leading to increased susceptibility to bacterial infection, increased risks of vascular complications and autoimmunity, all of which are further discussed in the section Consequences of hyposplenism in SCA.

Measuring splenic function

Unlike tests of renal function for instance, there is no direct way of assessing splenic output, and both biological and imaging tools are imperfectly suited for functional evaluation.

Blood markers, such as Howell–Jolly bodies (HJB) or pitted cells (PIT) (Figs 1 and 2, respectively) have been used to assess the filtering function of the spleen whereas counts of specific B cell subsets or measures of immune response following vaccination have been used to assess its immunological function.

Howell–Jolly bodies are nuclear remnants in circulating mature red cells, which are, in physiological conditions, groomed or pitted by the spleen. The circulating number of HJB can be counted on blood smears or by flow cytometry (Harrod et al., 2007) and has therefore been used as a marker of splenic dysfunction. A HJB count of ≥665/10^6 RBC is con-

Fig 1. Howell–Jolly bodies (black arrows) on blood smear stained by May–Grunwald Giemsa, original magnification ×1000, light microscopy.
Sickle cell anaemia (SCA) is a condition where splenic hypofunction is constant. However, unlike other conditions, such as coeliac disease or inflammatory bowel disease in which hyposplenism results from splenic atrophy (Di Sabatino et al., 2011), SCA may combine, notably in infancy, functional hyposplenism and splenomegaly. At birth, the spleen in SCA is morphologically and functionally normal. Progressive injury occurs when the haemoglobin switch initiates the multiple changes in the sickle RBC’s adherence, plastic and signalling properties.

The first histological description of the spleen in SCA was published in 1935 (Diggs, 1935) and describes ‘Splenic cords stuffed with entangled masses of greatly elongated, pointed, curved and bizarre shaped erythrocytes (…). The lesions do not all progress at the same rate.’ Granuloma-like nodules, known as Gamma–Gandy bodies, are characteristic, resulting from periarteriolar haemorrhage followed by fibrosis and impregnation of iron pigments (Piccin et al., 2012). The precise sequence of pathogenic events leading to splenic alterations in SCA patients is however still hypothetical and is thought to be a randomly located sequence of vaso-occlusion followed by ischaemia, leading to progressive fibrosis and atrophy (Fig 3), resulting in ‘autosplenectomy’.

The spleen is indeed prone to injury in SCA: the specific slow and open microcirculation favours in vivo deoxygenation and therefore sickling, which in turn favours RBC adhesion to the spleen matrix or macrophages due to increased expression of adhesion molecules and activation of usually quiescent proteins. Several sickle red cell adhesion molecules have been identified (Wandersee et al., 2005). The interaction of sickle red cells with laminin via the B-CAM/LU receptor is the best characterized adhesion phenomenon (El Nemer et al., 1998). Non-receptor mechanisms include proadhesive roles for red cell sulphated glycolipids and phosphatidyl serine promoting direct clearance through phagocytosis (death signal). This enhanced clearance contributes to the shortened life span of sickle RBC. In addition, impaired deformability of sickled RBC promotes their trapping upstream by the narrow inter endothelial slits (Fig 4).

The concept of functional asplenia based on the finding of a palpable spleen without scintigraphic uptake was first iden-
The pathophysiology of functional hyposplenism is hypothetical but two non-mutually exclusive mechanisms have been proposed resulting from the congestion of the red pulp: one is the haemodynamic diversion of blood flow to the closed pathway, thus shunting blood away from the filtration beds, and the other is due to the limitation of erythrophagocytosis by red pulp macrophages overwhelmed by sickled red cells.

Whatever the precise mechanism, spleen injury occurs very early in SCA with a sharp rise in PIT counts after 6 months of age (Brown et al, 1994). In a recent study, loss of splenic function was found to begin before 12 months of age in 86% of SCA infants assessed by 99mTc sulphur-colloid liver scintigraphy. Out of 44 infants aged 15–18 months, only four had normal splenic uptake (Rogers et al, 2011).

In the majority of patients, vaso-occlusive events in the spleen are clinically silent and result in progressive atrophy of the organ. Autosplenectomy is thought to be complete by 3–5 years of age in SS or S beta° patients (Brown et al, 1994). In a small fraction of children, acute splenic sequestration may precipitate hyposplenism, although the nature of the causal relationship between these conditions remains to be determined. Of note splenomegaly, hypersplenism and functional hyposplenism are not mutually exclusive and may coexist. Enhanced retention of altered red cells may indeed lead to splenomegaly and anaemia (hypersplenism), while impairing the filtering function of the spleen, an effect leading to an increased risk of infection and reduced pitting rates (hyposplenism).

Clinical manifestations of splenic injury in SCA

In children with SCA, the spleen can either be clinically palpable or not, functional or not, with no correlation between size and function.

Splenomegaly

Moderate splenomegaly (1–2 cm below the left costal margin) with no haematological consequence is classically described early in life before atrophy occurs. It is hypothesized that splenomegaly results from the progressive yet moderate trapping of sickled red cells in the red pulp. In a large Jamaican cohort, the spleen was palpable in 93% of infants by the age of 1 year decreasing to 16% at 10 years (Serjeant, 2001). In a North American setting, the mean spleen volume, assessed by sonography in 199 SCA infants aged 7–18 months, was 105 ml vs. 18 ml in 18 height-matched healthy children. Spleen volume was significantly associated with palpated spleen size (McCarville et al, 2011).

The prevalence of splenomegaly in SCA is however difficult to interpret because it may depend on interfering genetic or infectious factors. Persistent high fetal haemoglobin (HbF) levels promote persistent splenomegaly, as illustrated by a study in Saudi Arabia that assessed 363 patients (mean age 16 years) by ultrasound. Only 24 (6.6%) patients had autosplenectomy i.e. no visible spleen. HbF levels were higher in patients with marked or massive splenomegaly than in those with autosplenectomy. In this cohort, estimated splenic volume increased with age until about 40 years and then gradually decreased (Al-Salem et al, 1998). Co-inheritance of alpha thalassaemia may also prolong the function of the spleen (Higgs et al, 1982). Infectious agents may further interfere with spleen size, notably in malaria-endemic countries. In Kenya, for instance, in a total of 124 SCA children, splenomegaly was present in 41 (33%) subjects at a median age of 6-3 years (Sadaranagani et al, 2009).
**Hypersplenism**

Hypersplenism classically refers to splenomegaly and any combination of anaemia, leucopenia and/or thrombocytopenia, with compensatory bone marrow hyperplasia for a sustained period, and improvement after splenectomy. In SCA patients, diagnosis is difficult because splenomegaly is frequent, anaemia pre-exists and defining a drop from baseline level of haemoglobin at young age is sometimes hazardous. Thrombocytopenia and ‘abnormally normal’ leucocyte count are therefore the main haematological signs. The prevalence of hypersplenism is unknown. It may occur in the absence of any identified triggering event or follow acute splenic sequestration. Excessive destruction of red cells in SCA children with prolonged hypersplenism may lead to subsequent growth impairment and bone marrow hyperplasia. Transfusion efficiency is usually reduced in SCA patients with hypersplenism.

**Acute splenic sequestration**

Acute splenic sequestration is defined as an acute splenic enlargement with a fall in the haemoglobin level of at least 20 g/l (or 20%) from baseline level and a normal or increased basal reticulocyte count (Topley et al., 1981). It occurs when RBCs are acutely trapped in the spleen resulting in abdominal pain and distension, pallor and haemodynamic symptoms (tachycardia, hypotension, lethergy). Severe episodes may lead to hypovolaemic shock and death from cardiovascular collapse, within a few hours. The diagnosis is based on clinical signs. Imaging is therefore not essential and, if performed, should be planned only after treatment has started. The precise sequence of pathogenic events leading to acute splenic sequestration is unknown. A precipitating event, such as fever or infection may trigger or amplify red cell sickling in the splenic red pulp. Upon random accumulation of sickle cells in a zone close to a draining vein, mechanical obstruction of blood flow would induce a drop in oxygen concentration leading to amplification and extension of sickling. This acute event may be self-limited and transient or lead to extensive irreversible infarction.

Acute splenic sequestration is the earliest life-threatening complication seen in SCA patients, with the first occurrence described as early as 5 weeks of age (Airede, 1992). The median age at first episode was 1.4 years (0.1–7) in a retrospective study of 190 cases (Brousse et al., 2012), with 75% of first cases occurring before 2 years. Acute splenic sequestration is rarely observed after 6 years (Emond et al., 1985) albeit in patients with high HbF levels or in those on regular blood transfusion (see Reversal of hypersplenism section).

The life-long prevalence of acute splenic sequestration ranges from 7 to 30% according to studies (Topley et al., 1981; Powell et al., 1992; Brousse et al., 2012). An associated clinical event is found in more than 50% of episodes: isolated fever, upper respiratory tract or gastro intestinal infection, vaso occlusive crisis. Whether these events are triggering or concomitant factors is unknown but this brings to light the need for medical and parental awareness of acute splenic sequestration occurrence in case of fever in SCA infants.

To date, no solid predictor of acute splenic sequestration has been identified. As for many other SCA complications, the time of occurrence of acute splenic sequestration is partly linked to the kinetics of the haemoglobin switch in infants and to the HbF level. Relapse of acute splenic sequestration is frequent with 50–75% of patients experiencing more than one episode (Emond et al., 1985; Brousse et al., 2012). In the French cohort, age at the first episode was the only factor predicting recurrence: the risk was lower when the first episode occurred after 2 years than before 1 year of age (hazard ratio, 0.60; 95% confidence interval, 0.41–0.88; P = 0.025).

Since the implementation of neonatal SCA screening programmes and subsequent parental education on the risk of acute splenic sequestration, related mortality rate has decreased sharply, as illustrated in a study showing a fall in mortality in the period spanning from June 1973 to December 1981 (Lee et al., 1995). In countries where SCA is diagnosed at birth and comprehensive care is available, mortality from acute splenic sequestration has now become very infrequent (Telfer et al., 2007; Quinn et al., 2010; van der Plas et al., 2011).

**Consequences of hyposplenism in SCA**

**Infectious susceptibility**

The spleen plays a major role in the defence against infection by combining the elimination of blood-borne bacteria by red pulp macrophages through direct recognition and phagocytosis, by the generation and maintenance of IgM memory B cells which produce natural IgM antibodies, and by allowing efficient T-dependent immune response which produce high affinity antibodies. Importantly, infants physiologically lack IgM memory B cells and consequently are not able to produce natural antibodies against poorly-opsonized encapsulated bacteria, such as Streptococcus pneumoniae, Nesseria meningitidis and Hib. This feature, which may be viewed as physiological splenic immaturity, explains the early susceptibility to pneumococcal infections in infants. Immunization against encapsulated bacteria in infants <2 years of age relies therefore on conjugated vaccines, which allow a T-dependent response that does not require IgM memory B cells and, consequently, an intact spleen to be efficient (Rosado et al., 2013).

In infants with SCA, early injury of the spleen decreases the trapping of blood-borne bacteria, further impairs the generation or maintenance of IgM memory B cells and dramatically increases the risk of life-threatening infections with encapsulated bacteria. Before pneumococcal immunization
and prophylactic antibiotics were implemented, the relative risk of infection with *Streptococcus pneumoniae* in young SCA children compared to normal controls was about 300, with a 15% mortality rate. Similarly, the relative risk of invasive infection with *Haemophilus influenzae* was 20–100, with a mortality rate of about 20% (Barrett-Connor, 1971). The widespread use of the conjugated vaccine over the past two decades has virtually eliminated invasive *H. influenzae* type b disease where it is used (Ram et al, 2010).

About 10% of healthy humans carry meningococci in their nasopharynges. About 50% of carriage isolates are unencapsulated, while almost every strain recovered from the bloodstream or the cerebrospinal fluid is encapsulated. Most invasive isolates of meningococcal disease belong to the serogroups A, B, C, W-135 and Y (Ram et al, 2010) for which a conjugated vaccine is now available.

In influenza infection, pneumococcal carriage increases and upper respiratory tract viral infection favours bacterial invasion (Rice et al, 2012), warranting annual immunization against influenza.

**Vascular complications**

Vascular complications, defined as any condition causing narrowing or occlusion of a blood vessel, have been associated with asplenia, notably following surgical splenectomy (Crary & Buchanan, 2009). An absent splenic filter allows particulate matter, damaged, adherent or sickled cells and procoagulant cell-derived microparticles to circulate (Fontana et al, 2008), resulting in injury and activation of the endothelium. In SCA, which combines asplenia, chronic haemolysis and sickling, the risk of vascular complications is, therefore, expected to be greatly increased. Additional endothelial dysfunction caused by the haemolysis-related nitric oxide depletion (Kato et al, 2009) and the basal hypercoagulable state further contribute to the pathogenesis of vascular complications.

The specific contribution of hyposplenism to arteriothrombotic complication in SCA is difficult to assess: cerebrovascular stroke is a major multifactorial complication in SCA with an overall prevalence rate of 4.01% (Ohene-Frempong et al, 1998). However, other arteriosclerotic events, such as myocardial infarction and coronary artery disease are infrequent.

Studies on the prevalence of venous thromboembolic complications in SCD have yielded conflicting results. The prevalence of deep venous thrombosis in SCD was not found to differ from aged-matched African Americans in a study based on National Hospital Discharge Survey Data (Stein et al, 2006). In contrast, this same study demonstrated a higher incidence of pulmonary embolism, suggesting a spleen-independent *in situ* thrombosis mechanism. In a retrospective cross-sectional study of 404 adult SCD patients (Naik et al, 2013), however, 25% of patients had a history of venous thromboembolism. Of note, the prevalence of non-catheter-related venous thromboembolism was significantly higher in patients with variant genotypes other than SS and Sbeta°. Whether thromboembolic complications in SCD are specifically related to spleen dysfunction is therefore difficult to determine.

Pulmonary arterial hypertension (PAH) is considered a potential complication of asplenia. In SCA, the prevalence of PAH is controversial, ranging from 30% (Gladwin et al, 2004) to 6% (Parent et al, 2011), depending on the investigational technique. Altogether, contradictory or limited data concerning hyposplenism-related vascular complications in SCA plead for further exploration of the role of the spleen in vascular homeostasis.

**Autoimmunity**

The spleen contributes to tolerance to antigens by trapping particulate matter and circulating apoptotic cells. Tolerance to apoptotic cells is essential to prevent inflammatory pathology and development of autoimmunity. Antinuclear antibody positivity has been shown to be more common in SCD (Bethege et al, 1990). Clinical manifestations of immune disorders may have common features with clinical manifestations of SCD resulting in delayed diagnosis. A higher than expected incidence of connective tissue disease in SCD patients compared to the general population has been reported (Alkindi et al, 2012). Whether this higher incidence is related to spleen dysfunction remains speculative at this time.

**Reversal of hyposplenism**

Interestingly, hyposplenism has been demonstrated to be reversible, to a certain extent, in patients benefiting from transfusion therapy, hydroxyurea or HSCT. Transfusion therapy resulted in both reduction in PIT counts and increased scintigraphic uptake on 99mTc sulphur colloid scans in patients as old as 34 years in whom irreversible splenic atrophy would have been expected (Pearson et al, 1970; Barrios et al, 1993; Campbell et al, 1997). Along the same lines, HSCT in three SCA children aged 10–14 years, was associated with restoration of splenic filtering function as evidenced by realignment of splenic uptake on 99mTc scans and disappearance of HbJ (Ferster et al, 1993).

Anti-sickling agents, such as hydroxyurea, may also contribute to the preservation of splenic function. In a pilot trial evaluating the effect of hydroxyurea in 21 SCA infants (median age upon treatment initiation 15 months), splenic radionuclide uptake was observed in 53% of children while a 20% rate would have been predicted from historical data (Wang et al, 2001). However, in a subsequent randomized controlled trial of hydroxyurea *versus* placebo in 179 SCA infants (mean age at enrolment 13-6 months), hydroxyurea did not prevent the decline in splenic function as assessed by qualitative spleen scan uptake: 19 of 70 infants
patients presented decreased spleen function at exit in the hydroxyurea group vs. 28 of 74 patients in the placebo group, \( P = 0.21 \). Interestingly, episodes of splenic sequestration were equal in the two groups (Wang et al, 2011). Because the duration of the study was relatively short (2 years) these results do not rule out the possibility that hydroxyurea may also increase the risk of acute splenic sequestration in older children, by preserving splenic function.

Altogether, reversal of hyposplenism or preservation of spleen function following such treatments should be considered as potential beneficial effects, notably in terms of infectious protection. Hyposplenism, however, is not considered an indication for such interventions.

**Principles of management**

**Hyposplenism and infectious risk**

The reduction of infectious bacteria, particularly to encapsulated bacteria, is pivotal and based on antibiotic prophylaxis, vaccination and patient and/or parental education to seek prompt medical evaluation of febrile illness.

Daily oral penicillin has been shown to significantly reduce morbidity and mortality associated with pneumococcal infection in SCA infants with an 84% reduction in pneumococcal septicaemia (Gaston et al, 1986). Discontinuation of antibiotic prophylaxis is controversial and no evidence-based recommendation is available. (Hirst & Owusu-Ofori, 2012).

The immunization programme (Table I) should include pneumococcal, Hib, meningococcal and influenza vaccines. Immunization by protein conjugated vaccines, which are immunogenic in infants before 2 years of age, is completed by polysaccharidic vaccines after 2 years and in adults.

The introduction of a heptavalent pneumococcal conjugate vaccine (PCV) demonstrated a 65% decrease in the mean annual rate of hospitalization for invasive pneumococcal infection among children with SCA (Payne et al, 2013).

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Age given</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenza B</td>
<td>2, 3 and 4 months</td>
<td>Routine vaccination for all children in many countries</td>
</tr>
<tr>
<td>13-valent pneumococcal conjugated vaccine</td>
<td>2, 4 and 13 months</td>
<td>Routine vaccination for all children in many countries</td>
</tr>
<tr>
<td>Meningitis C conjugated vaccine</td>
<td>3 and 13 months</td>
<td>Routine vaccination for all children in many countries</td>
</tr>
<tr>
<td>23-valent polysaccharide pneumococcal vaccine</td>
<td>2 years, repeated every 3–5 years, life-long</td>
<td></td>
</tr>
<tr>
<td>Meningococcal ACWY conjugated vaccine</td>
<td>5 months</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>1 year, repeated annually</td>
<td>New vaccine produced each year</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>12, 13 and 18 months with booster depending on antibody levels</td>
<td>If likely to travel to countries with endemic Hepatitis B, and in regularly transfused cases</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>12, 13 and 18 months</td>
<td>If significant liver disease, travel, or regular transfusions</td>
</tr>
</tbody>
</table>

**SCA and Malaria**

The prevalence and density of malarial parasitaemia were lower in children with SCA than in patients without SCA in Kenya, with a trend toward a lower incidence of severe forms (Komba et al, 2009). In a large case-control study in Kenya there was no strong positive association between SCA and admission to hospital with either uncomplicated or severe *P. falciparum* malaria. However, protection was not complete, and *P. falciparum* carriage was significantly associated with severe malarial anaemia and death in SCA patients in Kenya (McAuley et al, 2010) and Tanzania (Makani et al, 2010). Malaria chemoprophylaxis is thus recommended in SCA patients living in malaria endemic regions (World Health Organization (WHO), 2010) despite limited evidence of a beneficial effect on sickle cell-related events. Reductions of blood transfusion requirements and, possibly, severe malarial anaemia have nevertheless been demonstrated (Ane-ni et al, 2013). Antimalarial chemoprophylaxis is also indicated for SCA patients from non-endemic countries travelling to endemic countries.

Interestingly, the prevalence of parasitaemia is generally identical or slightly greater in HbSS than in HbAS subjects,
when a stronger protection of HbSS subjects might be expected. Higher concentration of HbS should lead to stronger protection through impaired parasite growth, cytoadherence or enhanced adaptive response. SCD-induced hyposplenism may explain why protection is weaker than expected (Deplaine et al, 2011) but markers of hyposplenism have not been analysed yet in SCA patients with and without malaria.

Management of splenomegaly and hypersplenism:
Isoleted mild splenomegaly warrants no specific management apart from parental education on the risk of acute splenic sequestration. When the spleen is markedly enlarged with biological signs of hypersplenism, along with poor growth, bone marrow hyperplasia and abdominal distension, a supportive transfusion programme can be initiated or splenectomy performed if age allows. Violent sports should be restricted in order to avoid traumatic splenic rupture (Imbert et al, 2009).

Management of acute splenic sequestration
Early detection and parental education on the occurrence of acute splenic sequestration has had a major impact on the related mortality (Serjeant, 2001). It is a medical emergency that requires the immediate restoration of blood volume by fluids and, generally, blood transfusion. Blood transfusion usually releases the trapped RBC resulting in higher transfusion yields than expected, warranting caution on the amount of blood transfused in order to avoid a post-transfusional haematocrit above 35%. Management of acute splenic sequestration also includes treating an associated infectious cause.

A major concern following a first episode is preventing the risk of recurrence. Parental education about the importance of fever, spleen palpation, acute pallor and referral to hospital is pivotal.

Management of recurrent acute splenic sequestration
Possible strategies to manage recurrent episodes include watchful waiting, chronic transfusion and splenectomy. Indications are neither clearly defined nor evidence-based and should be individualized. Factors influencing the decision process include age, severity of episode, and medical and parental environment. A recent updated Cochrane review found no evidence in favour of splenectomy versus conservative management to improve survival and decrease morbidity from acute splenic sequestration, calling for randomized studies in order to define the best strategy (Owusu-Ofori & Hirst, 2013). An algorithm is proposed in Fig 5.

Prophylactic transfusion programmes may be started following the first episode or the first recurrence of acute splenic sequestration. The rationale is to allow permanent elevation of the haemoglobin level above the basal in order to prevent life-threatening anaemia in case of recurrence, rather than decreasing the HbS fraction, as the latter has not proven to decrease the risk of acute sequestration (Kinney et al, 1990). In addition, transfusion may temper the inflammatory status in SCD and prolong the spleen's immune function. On the other hand, it may prolong the spleen's potential for sequestration by delaying autosplenectomy, and lead to transfusion-related complications, such as iron overload, alloimmunization and bacterial and viral infections.

Splenectomy in SCA
Given that the natural history of the spleen in SCA leads to autosplenectomy, no surgical procedure is required in the vast majority of cases. The question of splenectomy arises when strong evidence of sustained hypersplenism is present or life-threatening episodes of acute splenic sequestration occur. The underlying question regarding splenectomy is to what degree the surgical removal of the spleen will further increase the infectious risk, and therefore at what age the operation should be performed. There is no clear answer to this question. In a study of the post-splenectomy course of 53 children younger than 4 years (of which 60% were <2 years) (Lesher et al, 2009) a low risk of post-splenectomy sepsis was reported with 3 (5.7%) positive blood cultures and one documented pneumococcal sepsis, in 353 post-splenectomy admissions over a mean post-operative follow-up period of 5-6 years. Similarly, febrile events, bacteraemic episodes and mortality were not different between a cohort of 130 splenectomized SCA children and a control group matched for sex, age and duration of follow up (Wright et al, 1999).

Another question raised by this comparative study, however, was the significantly higher incidence of vaso-occlusive pain and acute chest syndrome in the splenectomized group. This increased prevalence was not explained by known determinants of bone pain or chest syndrome, such as high haemoglobin or low HbF, raising the hypothesis that splenic complications, such as acute splenic sequestration, may be a predictive factor of disease severity. A higher incidence of severe complications in the pre- versus post-splenectomy period was also reported (Kalpathi et al, 2010) in 58 children splenectomized at a median age of 2 years. However, considering the young age of these patients, a serious bias may well be the expected increasing incidence of these complications with age.

Laparoscopic splenectomy has become the procedure of choice for most children requiring splenectomy (Rescorla et al, 2007).

Partial splenectomy has also been proposed as an alternative treatment in very young children, because of the possibility that leaving a splenic remnant might preserve immune function. A retrospective web-based registry study comparing partial and total splenectomy in 26 children found similar laboratory and clinical haematological outcomes. No children had recurrent splenic sequestration during a 52-week follow-up. One fatal event with overwhelming sepsis has neverthe-
less been reported following partial splenectomy (Svarch et al, 1999).

Following splenectomy, leucocytosis and thrombocytosis are common findings and generally return to expected basal levels within a year. Whether this finding further contributes to vascular complications remains to be determined.

Altogether, there is no consensual answer as to the safest age at which splenectomy, if required, should be performed. This needs to be considered at an individual level, balancing relative risks and benefits by taking into account the indication, the medical environment, parental wishes and reliability, and the risks related to alternative treatment, such as chronic transfusions. An algorithm is proposed in Fig 5.

**Spleen dysfunction in HbSC disease**

Splenic dysfunction in HbSC disease is poorly characterized. It is generally believed that functional hyposplenism also occurs in the SC genotype, albeit later and to a lesser extent than in SCA. The majority of HbSC patients have normal splenic function assessed by PIT counts before 5 years and many maintain normal splenic function until the second decade of life (Pearson et al, 1985). In another study analysing PIT counts in 201 SC subjects aged 6 months to 90 years, no splenic dysfunction was found in children below 4 years of age. Functional asplenia was demonstrated in 42% of patients over 12 years of age (Lane et al, 1995).

The prevalence of splenomegaly by palpation or imaging has been reported in up to 50–60% of adult patients with HbSC disease. In a cohort of paediatric patients with HbSC, palpable splenomegaly was found in 34 of 100 children over 2 years of age (mean age 11·0 ± 5·4 years; range 2–23·8 years) (Zimmerman & Ware, 2000).

Acute splenic sequestration may also occur in HbSC patients but its prevalence is much lower than in SCA and generally later in life, possibly as late as the eighth decade (Koduri & Nathan, 2006). In a study of 271 patients with HbSC disease, 5% experienced acute splenic sequestration with the initial event occurring at a mean age of 8·9 years (range, 2–17 years). Of note, in two cases, this complication was life threatening, with a drop in the haemoglobin value to <20 g/l. In almost half the 13 cases (46%), splenomegaly was noted before the initial event. (Aquino et al, 1997). Overall, among the 271 patients, 3% underwent splenectomy. Most treatment recommendations concerning spleen dysfunction in HbSC patients have been extended from studies in SCA without an evidence-based rationale, and antibiotic prophylaxis and vaccination recommendations are the same. As acute splenic sequestration occurs later in life, splenectomy can usually be under-

---

**Fig 5.** Suggested algorithm for the management of acute splenic sequestration.

© 2014 John Wiley & Sons Ltd, *British Journal of Haematology*
References


Review

of splenic Gamma-Gandy bodies in sickle cell anemia. *Human Pathology*, **43**, 1028–1036.


