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## Recommendations regarding splenectomy in hereditary hemolytic anemias

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### ABSTRACT

Hereditary hemolytic anemias are a group of disorders with a variety of causes, including red cell membrane defects, red blood cell enzyme disorders, congenital dyserythropoietic anemias, thalassemia syndromes and hemoglobinopathies. As damaged red blood cells passing through the red pulp of the spleen are removed by splenic macrophages, splenectomy is one possible therapeutic approach to the management of severely affected patients. However, except for hereditary spherocytosis for which the effectiveness of splenectomy has been well documented, the efficacy of splenectomy in other anemias within this group has yet to be determined and there are concerns regarding short- and long-term infectious and thrombotic complications. In light of the priorities identified by the European Hematology Association Roadmap we generated specific recommendations for each disorder, except thalassemia syndromes for which there are other, recent guidelines. Our recommendations are intended to enable clinicians to achieve better informed decisions on disease management by splenectomy, on the type of splenectomy and the possible consequences. As no randomized clinical trials, case control or cohort studies regarding splenectomy in these disorders were found in the literature, recommendations for each disease were based on expert opinion and were subsequently critically revised and modified by the Splenectomy in Rare Anemias Study Group, which includes hematologists caring for both adults and children.

## Introduction

Hereditary hemolytic anemias are a group of disorders with a variety of causes, including red cell membrane defects, enzyme disorders, congenital dyserythropoietic anemias, and hemoglobinopathies. Given the rarity of these disorders, their optimal management has yet to be determined. Splenectomy has been suggested as a possible therapeutic approach to manage severely affected patients, based on the evidence that abnormal or damaged red blood cells passing through the spleen red pulp are removed by the splenic macrophage system. However, although splenectomy has been commonly used in recent decades in the clinical management of patients with severe hematologic phenotypes, its efficacy in many of these disorders has yet to be determined. Additionally, concerns remain regarding short- and long-term infectious complications, and increased risk of cardiovascular complications in later life, including thrombosis and pulmonary hypertension.<sup>1</sup>

We first reviewed the literature in PubMed in order to generate recommendations regarding splenectomy in hereditary hemolytic anemias. Since no randomized clinical trials, case-control or cohort studies were identified, the level of evidence considered was lowered to that from non-analytic studies and case series. Expert recommendations were developed, and subsequently critically revised and modified by the Splenectomy in Rare Anemias Study Group in order to achieve the greatest possible agreement, which was classified as "full consensus" (100% agreement) or "consensus" (>80% agreement). None of the core statements achieved a degree of consensus below 80%. The Grading of Recommendation Assessment, Developing and Evaluation (GRADE) system was used to rate the quality of evidence and strength of recommendations (see *Online Supplementary Information*).<sup>2</sup>

We first present general considerations on the possible complications of splenectomy, including post-splenectomy infections and acute and long-term thromboembolic complications, and types of splenectomy (laparotomic, laparoscopic and partial). We then discuss the advantages and complications of splenectomy for each of the specific hereditary hemolytic anemia disorders, concluding with specific recommendations when possible.

## Splenectomy complications

### Post-splenectomy infections

Given the role of the spleen in immune competence and blood filtration, there is a risk of overwhelming post-splenectomy infection (OPSI), which is highest with encapsulated micro-organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*.<sup>3</sup> Asplenia is also an important risk factor for serious infections with *Plasmodium*, *Capnocytophaga canimorsus* and *C. cynodegmi* (after an animal bite), *Babesia spp.* (after a tick bite), and *Bordetella holmesii*.<sup>4,6</sup> The risk of post-splenectomy sepsis may vary according to the indication for splenectomy (intermediate risk in spherocytosis and higher in other inherited anemias),<sup>7</sup> patient's age at the time of surgery (highest before the age of 5 years),<sup>3</sup> and time since the splenectomy was performed (risk highest during the first year after the intervention). However, the risk proba-

bly remains elevated for life.<sup>8,9</sup> Given the high risk of OPSI at a young age, splenectomy should not normally be performed before 5 years of age.

It is difficult to estimate the current risk of OPSI in subjects aged >5 years as most studies are retrospective and include patients with heterogeneous diseases who were not fully immunized. It is possible that the widespread use of conjugated vaccines will significantly reduce the risk of OPSI. In fact, a recent retrospective study in which 141 consecutive children undergoing splenectomy during 1991-2010 were analyzed indicated that ten of the 11 patients who developed post-splenectomy sepsis had an additional underlying immune deficiency.<sup>10</sup> However, in a recent prospective, multicenter cohort study of German patients with severe sepsis or septic shock, *S. pneumoniae* sepsis was more frequent among splenectomized patients than among those with a normal functional spleen (42% versus 12%, respectively;  $P < 0.001$ ). It is of note that less than half of the OPSI patients in this study had received pneumococcal vaccination before splenectomy, despite national and international guidelines.<sup>11</sup>

Strategies to reduce the development of OPSI include: (i) patient's education, including advice to take urgent action in response to febrile episodes; (ii) vaccination and (iii) prophylactic anti-microbial therapy. Detailed guidelines regarding the prevention and treatment of infections in splenectomized or asplenic patients are available through the British Committee for Standards in Haematology<sup>12</sup> and American Academy of Pediatrics (Red Book 30<sup>th</sup> edition, 2015), to which the reader is referred.

### Post-splenectomy thromboembolic complications

It has been reported that, following splenectomy, there is an increased risk of early and late venous and arterial thrombosis,<sup>13</sup> including acute splenic and portal vein thrombosis (SPVT)<sup>14</sup> and delayed severe life-long complications.<sup>15</sup>

#### Acute splenic and portal vein thrombosis

Acute SPVT after splenectomy is an early and life-threatening complication, which can lead to bowel ischemia and/or portal hypertension. This complication has been related to stasis in the splenic vein remnant.<sup>14</sup> The risk varies depending on the underlying disorder. In 2008, Krauth *et al.* reviewed prospective and retrospective studies and found that 11/89 patients with hemolytic disease developed SPVT (12.3%) while only 2/118 patients (1.7%) of those with immune thrombocytopenia had SPVT. None of 122 patients who underwent splenectomy because of trauma developed this complication.<sup>14,15</sup> Large spleen size has also been identified as a risk factor for the development of SPVT. Although there are no well-designed randomized trials comparing the risk of SPVT after open splenectomy versus laparoscopic splenectomy, the surgical approach does not seem to affect the incidence of SPVT.<sup>16</sup> Screening for thrombophilia has not been shown to allow early identification of patients at risk of SPVT after splenectomy.<sup>17</sup>

A study in which contrast-enhanced computed tomography was used for the diagnosis of SPVT showed that the median time between splenectomy and the appearance of asymptomatic SPVT was 6 days (range, 3-11 days).<sup>18</sup> A Canadian study of 40 patients suggested that an appropriate time for Doppler/ultrasound surveillance to diagnose SPVT is 1 week following splenectomy.<sup>19</sup>

Most patients with documented SPVT are treated with anticoagulant therapy (i.e. intravenous heparin followed by oral anticoagulants) for a variable period ranging between 3 to 6 months. In one study, the majority of treated patients had documented complete (57/90, 63.3%) or at least partial (13.3%) resolution of the thrombus. However, 7.7% of this latter population showed persistence of thrombus, while 15.5% developed a cavernoma or portal hypertension.<sup>14</sup>

The role of prophylactic antithrombotic therapy is unknown as strategies in the various cohorts or case reports were extremely heterogeneous in terms of duration of prophylaxis. A randomized study comparing different durations of postoperative antithrombotic prophylaxis after laparoscopic abdominal surgery was terminated early due to the low incidence of thrombosis.<sup>16</sup>

#### Late cardiovascular events

##### Arterial and venous thromboembolism

An increased risk of vascular complications after splenectomy was first described in a group of 740 World War II veterans whose spleen was removed because of trauma. It was seen that these subjects had a significantly increased risk of death from ischemic heart disease compared to controls (relative risk, 1.85).<sup>15</sup> Data from a Danish Registry identifying all splenectomized patients from 1996-2005 showed that the long-term (>1 year) risk of venous thromboembolism remained approximately 3-fold higher in patients who had undergone splenectomy because of trauma than in the general population.<sup>20</sup> The contribution of other trauma complications to thrombotic risk was not, however, evaluated. The long-term risk of venous thromboembolism was highest in patients splenectomized for malignant hematologic disorders and hemolytic anemias.

##### Pulmonary arterial hypertension

Splenectomy has been reported to be a risk factor for the development of pulmonary arterial hypertension,<sup>21</sup> particularly in patients with hemolytic disorders.<sup>22-24</sup> Loss of splenic function is associated with increased numbers of platelets and also enhances their activation, promoting pulmonary microthrombosis and adhesion of red cells to the endothelium.<sup>25</sup> The spleen also plays a critical function in the removal of senescent and damaged erythrocytes.

#### Splenectomy recommendations

-For prompt diagnosis of SPVT at least one Doppler ultrasound study should be carried out on day 7 after splenectomy (agreed by 86% of experts) (grade 2 recommendation, grade C evidence).

### Surgical approach

#### Laparotomic splenectomy

The traditional approach to splenectomy has been by laparotomy. This approach allows for a careful search for an accessory spleen which, if left behind, may cause recurrence of anemia.<sup>10</sup> The disadvantages of open splenectomy are mainly surgical morbidity and abdominal wall scarring.<sup>26</sup> Laparoscopic splenectomy has become feasible with progress in minimally invasive techniques.<sup>27</sup>

#### Laparoscopic splenectomy

Laparoscopic splenectomy is currently considered the gold standard technique for removal of a normal sized or slightly enlarged spleen and is preferred to open splenectomy. Compared to open splenectomy, laparoscopic splenectomy: (i) is less traumatic; (ii) is associated with fewer complications; (iii) requires shorter hospital stays; (iv) has a better cosmetic outcome; and (v) overall, has a lower cost. However, it should only be performed by experienced surgeons.<sup>28</sup> Nowadays, laparoscopic splenectomy is possible and safe also for massively enlarged spleens, but in such cases is associated with longer operating times and longer stays in hospital.<sup>29</sup> Perioperative splenic artery embolization has been found to be useful and reduces the complications of massive spleen laparoscopic splenectomy.<sup>30</sup> Moreover, selective splenic artery embolization, carried out in steps, will reduce spleen size and alleviate cytopenias.<sup>31</sup>

A preoperative assessment of splenic size by ultrasound is recommended. Although three-dimensional computed tomography is considered to be more accurate, it does not provide significant advantage in estimating spleen size and its use should be limited to those cases in which additional information about the anatomy is required prior to surgery.<sup>32</sup>

**Table 1.** Summary of splenectomy recommendations for hemolytic disorders.

Disease	When splenectomy recommended? *
Hereditary spherocytosis	Patient is transfusion-dependent or suffers severe anemia. Patient has moderate disease: decision based on spleen size and quality of life parameters. No need to perform cholecystectomy.
Pyruvate kinase deficiency	Consider if patient is transfusion-dependent or severely anemic. Cholecystectomy should be performed at time of splenectomy.
Splenectomy in congenital non-spherocytic hemolytic anemia due to G6PD deficiency	Consider if patient is transfusion-dependent and/or has massive splenomegaly and/or has symptomatic splenomegaly.
Hereditary stomatocytosis	Contraindicated.
Congenital dyserythropoietic anemia type II	Consider if patient is transfusion-dependent and/or has symptomatic splenomegaly.
Sickle cell disease	Patient has had two acute splenic sequestration crises and/or has massive splenomegaly and/or suffers symptomatic hypersplenism.
Unstable hemoglobin	Consider only if patient has transfusion-dependent anemia and/or symptomatic splenomegaly.

\*For all indications splenectomy should be performed after 6 years of age. G6PD: glucose-6-phosphate dehydrogenase.

### Partial splenectomy

In an attempt to reduce the infectious risk of total splenectomy, especially for children less than 6 years of age who suffer severe anemia or are transfusion-dependent, partial splenectomy has been increasingly used in recent years. In partial splenectomy, usually 80-90% of the enlarged spleen is removed. Partial splenectomy was initially performed using an open splenectomy approach but laparoscopic and robotic approaches have recently been introduced.<sup>35</sup> Nevertheless, partial splenectomy should always be performed by an experienced surgeon.

### Disease-specific recommendations

A detailed discussion of the clinical pictures of and diagnostic approaches to hereditary hemolytic disorders is beyond the scope of this manuscript. Data available on the advantages and complications of splenectomy in hereditary hemolytic anemias and expert recommendations are summarized in Table 1. It should be appreciated that data for some disorders are so sparse that no recommendations could be generated.

### Hereditary spherocytosis

Following thalassemia syndrome and sickle cell disease (SCD), hereditary spherocytosis (HS) is the most common form of congenital hemolytic anemia with an incidence of approximately 1:2000 and a dominant transmission in about 70-80% of cases. HS is caused by mutations in genes encoding  $\alpha$ - and  $\beta$ -spectrin and other proteins involved in the attachment of the cytoskeleton to the overlying lipid bilayer (ankyrin, band 3 and protein 4.2). Defects in these structural proteins render the red blood cells spherical, rigid and susceptible to premature destruction in the spleen.<sup>34-37</sup> Clinically, patients with HS are grouped into three categories according to disease severity: mild, moderate and severe (Table 2).<sup>36</sup>

#### Long-term thrombotic complications of splenectomy

In 1997, Schilling found that the rate of arteriosclerotic events (stroke, myocardial infarction, coronary or carotid artery surgery) in patients older than 40 years of age with HS was 5.6-fold higher in asplenic patients than in HS patients with an intact spleen, with the first event occurring one or more decades following splenectomy.<sup>38</sup> This was further confirmed in his follow-up study in which the hazard ratio for arterial events was 7.2 in HS patients who underwent splenectomy compared to affected patients who did not undergo splenectomy. In addition, affected patients who underwent splenectomy had a hazard ratio of 3 for developing venous events as compared to HS patients who did not undergo splenectomy.<sup>39</sup>

However, only a few patients with HS who developed stroke, pulmonary emboli or pulmonary arterial hypertension following splenectomy have been reported.<sup>24,40-42</sup> Moreover, Buchanan *et al.* studied 39 adults with HS and found no evidence of thrombotic manifestations despite a long follow up (median 25 years).<sup>43</sup>

### Splenectomy

Splenectomy in HS usually results in disappearance of anemia and a clear decrease of hemolytic markers. In the large HS series reported by Mariani *et al.*, the median hemoglobin increase after splenectomy was 3 g/dL (10.8 to 13.9 g/dL), associated with a decrease of reticulocyte count (from 337 to 51×10<sup>9</sup>/L) and unconjugated bilirubin (from 32.5 to 12  $\mu$ mol/L).<sup>44</sup>

Due to increasing awareness of post-splenectomy complications, the rate of splenectomy has declined in the last decade. During the period from 1980 to 2005, splenectomy was performed in only 20% of HS patients.<sup>44</sup> In general, splenectomy is not indicated in patients with mild HS, whereas it is usually necessary in severe cases, albeit delayed if possible until the age of 6 years (Table 2). In the intermediate categories the indications for splenectomy are less clear. One indication is symptomatic/painful splenomegaly with associated thrombocytopenia or leukopenia that affects the patient's quality of life. For young adult patients, unacceptable cutaneous jaundice (usually in patients with concomitant Gilbert genotype) may become a social problem that balances a decision towards splenectomy.

#### Available guidelines for splenectomy

Guidelines for the diagnosis and management of HS, including splenectomy were published on behalf of the General Haematology Task Force of the British Committee for Standards in Haematology in 2004 and updated in 2011.<sup>45,46</sup> In agreement with previous recommendations, the laparoscopic approach is preferred if trained surgeons are available; in children undergoing splenectomy, the gall bladder should be removed concomitantly if symptomatic gallstones are present (Table 3). We referred to previously published guidelines when considering two particular clinical situations: (i) whether splenectomy should accompany cholecystectomy when biliary stones are present; and (ii) the role of partial splenectomy, particularly in children younger than 6 years of age with severe HS.

#### Splenectomy and cholecystectomy

It was previously suggested that there is an increased risk of intrahepatic choledocholithiasis following splenectomy<sup>44</sup> and the 2004 guidelines suggested that for children with HS who require cholecystectomy the spleen should

**Table 2.** Indications for splenectomy in hereditary spherocytosis based on severity of disease\*.

Disease severity	Hemoglobin (g/dL)	Reticulocyte count (%)	Bilirubin ( $\mu$ mol/L)	Indication for splenectomy
Severe	< 8	> 10	> 51	Indicated, delay until age >6 years
Moderate	8 - 12	> 6	> 34	Individually tailored based on spleen size and quality of life parameters
Mild	11 - 15	3 - 6	17 - 34	Not indicated

\*severity of disease based on reference 35.



**Table 3. Splenectomy guidelines in hereditary spherocytosis –2011 update<sup>45</sup> and the authors' recommendations.**

N.	Guidelines 2011	Authors' recommendations
1	The laparoscopic approach to splenectomy is associated with less pain, shorter hospital stay and better cosmetic appearance; but is dependent on the availability of appropriately trained surgeons, and suitable equipment (grade 1 recommendation, grade B evidence).	No change.
2	In children undergoing splenectomy, the gall bladder should be removed concomitantly if there are symptomatic gallstones (grade C evidence, grade 2 recommendation).	No change.
3	In children who require cholecystectomy for symptoms of gallstones the use of concurrent splenectomy is controversial. It may be associated with a decreased risk of common bile duct stones in the future, but is also associated with a risk of post-splenectomy sepsis (grade 2 recommendation, grade C evidence).	In children > 6 years of age concomitant splenectomy is indicated according to severity of anemia (Table 1).
4	When splenectomy is indicated, ideally it should be done after the age of 6 years (grade 2 recommendation, grade C evidence).	No change.
5	Partial splenectomy is theoretically associated with a decreased risk of post-splenectomy sepsis, but it is possible that further surgery may be needed for either recurrence of hematologic problems or symptomatic cholelithiasis (grade 2 recommendation, grade C evidence).	No consensus among our experts.

\* Reference 45 The Grading of Recommendation Assessment, Developing and Evaluation (GRADE) system was used to rate quality of evidence and strength of recommendations.

always be removed.<sup>45</sup> This recommendation was based on expert opinion despite little supportive data in the literature; the recommendation was changed in subsequent guidelines to indicate that this issue remains controversial.<sup>46</sup> In a recent study, of 32 pediatric patients with HS who underwent cholecystectomy, 27 underwent synchronous splenectomy. However, none of the five patients who underwent cholecystectomy without splenectomy experienced signs or symptoms consistent with gallstones over a median follow-up of 15.6 years.<sup>47</sup> Similarly, in a recent study of children aged 4-17 years studied during 2009-2012, simultaneous cholecystectomy (for cholelithiasis) and splenectomy was performed in fewer than half of the patients.<sup>48</sup> We recommend that indications for splenectomy when cholecystectomy is required should not differ from those for splenectomy when cholecystectomy is not planned (Tables 1 and 2).

### Partial splenectomy

In an attempt to reduce the infectious risk following total splenectomy, especially for children less than 6 years of age who suffer severe anemia or are transfusion-dependent, partial splenectomy has been increasingly performed in recent years. Several studies indicate that partial splenectomy reduces the rate of hemolysis and increases red blood cell lifespan while maintaining efficient splenic phagocytic function.<sup>49,50</sup> In a recently published follow-up study, Pincez *et al.* reported on 79 HS children who underwent partial splenectomy using an open splenectomy approach between 1985 and 2013. In this population, 39 children were less than 5 years of age at the time of splenectomy (mean age at surgery, 4.3±0.6 years) and most were transfusion-dependent (31/39). Following partial splenectomy (mean follow up of 12±0.9 years) there were drastic reductions in transfusion rate and increases in hemoglobin levels that were compatible with normal growth while maintaining efficient spleen function in 96% of cases.<sup>51</sup> On the other hand, this approach reduced but did not totally suppress hemolysis and was associated with later development of gallstones, and splenic remnant regrowth. Finally, 50% of the 39 severely affected young

HS children required total splenectomy in a median of 5 years following partial splenectomy at an age when total splenectomy was much safer.<sup>51</sup> Falling hemoglobin levels and discomfort due to spleen remnant regrowth were the most common indications for this procedure. A recently published systematic review and meta-analysis comparing HS patients undergoing total splenectomy (1941 children) *versus* partial splenectomy (283 children) confirmed that although total splenectomy was more effective than partial splenectomy in increasing hemoglobin levels (increases of 3.6 g/dL and 2.2 g/dL, respectively) and in reducing reticulocyte counts (by 12.5% and 6.5%, respectively), the outcome following partial splenectomy was stable for at least 6 years. There were no cases of OPSI.<sup>52</sup> In this meta-analysis, with an overall short follow-up, recurrence of symptoms following partial splenectomy was uncommon (5-10%) and secondary splenectomy was indicated in only 5% of children. Thus, partial splenectomy still needs to be evaluated in larger series with longer term follow-up. In view of these conflicting data no recommendations regarding partial splenectomy in HS could be generated by the group.

#### **Splenectomy recommendations**

- Splenectomy is recommended in HS patients who are transfusion-dependent or suffer severe anemia (agreed by 100% of experts) (Grade 2 recommendation, grade C evidence).

- Indications for splenectomy in the intermediate forms of HS should be individually tailored based on spleen size and quality of life parameters (agreed by 95% of experts) (grade 2 recommendation, grade C evidence).

### Pyruvate kinase deficiency

Pyruvate kinase (PK) deficiency is the most common glycolytic defect causing congenital non-spherocytic hemolytic anemia, having an incidence of 1:20,000 in white individuals.<sup>53</sup> PK converts phosphoenolpyruvate to pyruvate, generating 50% of the total red cell ATP. PK-deficient red blood cells are damaged due to lack of energy

**Table 4.** Indications for splenectomy in pyruvate kinase deficiency based on severity of disease\*.

Disease severity	Age at diagnosis	Clinical manifestations	Median hemoglobin (g/dL)	Transfusion requirement	Indication for splenectomy
Severe	Birth/infancy	Most patients suffer severe neonatal jaundice requiring exchange transfusion, median age at diagnosis 4, almost all transfusion-dependent	6.8	Transfusion-dependent	Indicated after age of 6 years
Moderate	Variable, childhood to adult	Moderate anemia occasional exacerbations	9	Confined to exacerbations	Not indicated
Mild	Variable, childhood to adult	Lifelong history of mild anemia	11	Rare	Not indicated

Severity of disease based on references 54 and 55.

to support membrane ion transport and to maintain membrane structure and are, therefore, cleared by the spleen and liver. Clinically, PK deficiency has been categorized into mild, moderate and severe forms (Table 4).<sup>54,55</sup>

#### Results of splenectomy

Small retrospective studies suggest that splenectomy may result in a moderate increase in hemoglobin levels of approximately 1.8 g/dL (range, 0.4–3.4 g/dL), together with a conspicuous rise of reticulocytes (up to 50–70%, a typical feature of PK deficiency) and increased amounts of indirect bilirubin, even if the anemia becomes less severe.<sup>54</sup> Analysis of the results of a recent international, multicenter registry study involving 144 patients<sup>56</sup> suggested that splenectomy was performed mainly to reduce transfusion burden and resulted in improved anemia, and thus enhanced quality of life. The median pre-splenectomy hemoglobin concentration was 7 g/dL and, surgery reduced the transfusion burden in 91% of cases. Fifty-three patients (66%) underwent cholecystectomy at a median age of 14 years (range, 2.6–60.4 years), of whom 35 (37%) were splenectomized. Importantly this study showed that transfusion-dependency and moderate anemia persisted despite splenectomy in more than half of the patients, suggesting that surgery is less effective in PK deficiency than in HS.

#### Indications for splenectomy

Splenectomy may be beneficial in patients with high transfusion requirements. It may also be considered in patients with low transfusion requirements who may subsequently become transfusion independent following splenectomy, although this is difficult to predict. Although splenectomy does not arrest hemolysis, it reduces and sometimes eliminates the transfusion requirement in most transfusion-dependent cases. The response to surgery of other affected family members may help in predicting the therapeutic efficacy of splenectomy.<sup>54,55</sup> Optimal timing of surgery is unclear and needs to be considered individually weighing up the life-long risks (infection, thromboembolism) against the likely benefits.

#### Cholecystectomy and splenectomy

As for HS, splenectomy should also be considered in patients requiring cholecystectomy to avoid second surgery. However, in contrast to HS, in PK deficiency gallstones are also common in splenectomized patients, and therefore cholecystectomy should accompany splenectomy.

#### Partial splenectomy

Partial splenectomy was reported to be unsuccessful in two patients with PK deficiency and effective in one patient, who achieved an increase in baseline hemoglobin and reduction in transfusion rate.<sup>57</sup>

Other therapeutic options for PK deficiency that should be considered include HLA-matched sibling allogeneic transplantation,<sup>58</sup> and new therapies which are still under investigation, including the enzyme activator (AG-348)<sup>59</sup> and gene therapy.<sup>60</sup>

#### Splenectomy recommendations

-Splenectomy should be considered in patients with PK deficiency who are transfusion-dependent or do not tolerate the anemia (agreed by 91% of experts) (grade 2 recommendation, grade C evidence).

-Cholecystectomy should be performed together with splenectomy (agreed by 86% of experts) (grade 2 recommendation, grade C evidence).

#### Congenital non-spherocytic hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency

Patients with glucose-6-phosphate dehydrogenase deficiency rarely suffer hemolytic anemia in the steady state and hemolysis is triggered by an exogenous factor. Some mutations of glucose-6-phosphate dehydrogenase do, however, result in chronic hemolysis without precipitating causes. These mutations are more severe than the more commonly occurring polymorphic forms of the enzyme. The severity of anemia ranges from borderline to transfusion-dependent. In 2004, Hamilton *et al.* identified nine transfusion-dependent patients in the literature: seven responded to splenectomy and became transfusion-independent.<sup>61</sup> Luzzatto and Poggi suggested that splenectomy should be performed if splenomegaly becomes a physical encumbrance, or if there is evidence of hypersplenism and if the anemia is severe.<sup>62</sup>

#### Splenectomy recommendations

-Splenectomy should be considered in patients with congenital non-spherocytic hemolytic anemia due to glucose-6-phosphate dehydrogenase deficiency who are transfusion-dependent and/or have symptomatic splenomegaly. (agreed by 100% of experts) (grade 2 recommendation, grade C evidence)

### Pyrimidine-5'-nucleotidase deficiency

Deficiency of erythrocyte pyrimidine-5'-nucleotidase is the most common inherited abnormality of nucleotide metabolism causing hemolytic anemia of moderate severity.<sup>55,63</sup> Transfusions are rarely required. Splenectomy has been associated with variable increases in hemoglobin levels.<sup>64-67</sup> Portosplenomesentric venous thrombosis was described in one patient with pyrimidine-5'-nucleotidase following splenectomy due to trauma.<sup>68</sup> As there are insufficient data regarding the efficacy and complications of splenectomy in this disorder no recommendations could be made.

### Hereditary stomatocytosis

Hereditary stomatocytosis (HSt), comprising both dehydrated and overhydrated types, is a dominantly inherited disorder in which there is altered red blood cell membrane permeability to monovalent cations (Na<sup>+</sup> and K<sup>+</sup>), with consequent changes in intracellular cation content and red cell volume. Dehydrated HSt is the most common form of HSt, with an incidence of approximately 1:50,000 births. Overhydrated HSt is a very rare subtype, with only 20 cases having been reported worldwide. The recent identification of genes mutated in HSt has improved the diagnosis and understanding of the pathophysiology of this group of disorders. To date, a total of five different genes encoding membrane proteins have been reported to be responsible for red blood cell volume alterations: three lead to overhydrated HSt [*AE1* (also termed *SLC4A1*), *RHAG* and *GLUT1* (also termed *SCL2A1*)<sup>69,70</sup> and two to dehydrated HSt (*PIEZO1* and *KCNN4*, encoding the Gardos channel)]<sup>71-75</sup>. Reviews on the clinical picture and molecular pathogenesis have recently been published.<sup>37,76</sup>

### Splenectomy

A high risk of thromboembolic complications following splenectomy in HSt was first described by Stewart and colleagues (1996) in nine splenectomized adults.<sup>77</sup> In their seven families four had overhydrated HSt and the remaining dehydrated HSt. Both groups suffered from serious late thrombotic complications, sometimes recurrent over years, including deep vein thrombosis, pulmonary emboli, superficial thrombophlebitis, portal vein thrombosis, intracardiac mural thrombosis, arterial thrombosis, and pulmonary arterial hypertension. Four of the nine patients died. No such complications were observed in six affected before splenectomy. Since this original observation there have been at least four additional reports of individuals with overhydrated or dehydrated HSt who developed severe thrombotic complications.<sup>78-81</sup>

Given the retrospective, incomplete, and anecdotal nature of the description of thromboembolic complications following splenectomy in HSt, it is impossible to estimate the precise risk of this procedure, but it is apparent that there is a high risk and that splenectomy, which is only partially effective in overhydrated HSt and ineffective in dehydrated HSt, should be avoided. In patients with HSt who were mistakenly misdiagnosed as having HS and underwent splenectomy, life-long anticoagulation should be considered.

### Splenectomy recommendations

- In patients with hereditary stomatocytosis, splenectomy is contraindicated (agreed by 100% of experts) (grade 2 recommendation, grade C evidence).

### Congenital dyserythropoietic anemia

Congenital dyserythropoietic anemia (CDA) is a group of rare red blood cell disorders characterized by ineffective erythropoiesis, pathognomonic cytopathology of nucleated red blood cells in bone marrow and increased iron absorption with secondary hemochromatosis.<sup>82</sup> Based on morphological criteria, subsequently supported by genetic analysis, three types have been described (I-III). More recently CDA IV was defined and several additional unclassified patients have been characterized.<sup>83</sup> CDA II is the most common subtype, with more than 200 patients described in the literature, followed by CDA I with approximately 100 patients.<sup>82</sup>

### Splenectomy in congenital dyserythropoietic anemia I

Two case series of 13 severely anemic, mostly transfusion-dependent patients who had undergone splenectomy were identified.<sup>84,85</sup> Six of those patients became transfusion-independent following splenectomy, while seven had no improvement in hemoglobin levels. Long-term follow-up of six patients revealed that three had died, one due to pulmonary arterial hypertension and the other two due to overwhelming sepsis. Because of inconsistent responses and possible complications, splenectomy should probably be reserved for patients manifesting worsening anemia, and/or significant thrombocytopenia or leukopenia or for patients with massive, painful splenomegaly. Due to paucity of data no recommendation regarding splenectomy in CDA I could be made.

### Splenectomy in congenital dyserythropoietic anemia II

Heimpel *et al.* reported on 22 patients who underwent splenectomy at a median age of 19.9 years.<sup>86</sup> Hemoglobin concentration increased in all patients from an average of 9.2 g/dL to 10.3 g/dL. However, in all but one patient, hemoglobin levels remained below sex-matched reference values.<sup>86</sup> Russo *et al.* reported that 36% (41/112) of their patients with CDA II underwent splenectomy and most (14/17) showed a similar, moderate increase in hemoglobin concentration (9.3±1.2 g/dL to 10.6±1.6 g/dL).<sup>87</sup> To date thrombosis has not been documented in patients with CDA II following splenectomy.

### Splenectomy recommendations

- In patients with CDA II splenectomy should be considered in severely anemic patients and/or in those with symptomatic splenomegaly (agreed by 95% of experts) (grade 2 recommendation, grade C evidence).

### Thalassemic syndromes

The authors decided not to discuss thalassemic syndromes since revised guidelines have recently been presented by the Thalassemia International Federation (please visit: [www.tif.org](http://www.tif.org)).<sup>88</sup>

### Sickle cell disease

SCD is a hereditary hemoglobinopathy with a worldwide distribution: projected numbers of births in 2010 were 237,381 in Africa, 11,143 in the USA and 1,939 in Europe.<sup>89</sup> SCD is caused by a point mutation in the  $\beta$ -globin gene resulting in the synthesis of a pathological hemoglobin, HbS.<sup>90</sup> Cyclic polymerization/depolymerization of deoxy-HbS generates dense, dehydrated red cells that play a central role in the acute and chronic clinical manifestations of SCD, in which intravascular sickling leads to vaso-occlusion and impaired blood flow with ischemic/reperfusion injury.<sup>90</sup> Some organs, such as the spleen, have been shown to be more vulnerable to damage from HbS polymerization than others organs, due to their peculiar anatomic organization mainly characterized by sluggish circulation, low pH and local high pro-oxidant environment.<sup>90,91</sup>

### Splenectomy

An acute splenic sequestration crisis is defined as acute abdominal pain and distension associated with spleen enlargement, a decrease in hemoglobin levels of at least 2 g/dL and stable or high reticulocyte count compared to that of the patient in steady state.<sup>92</sup> Even though the mortality rate of patients with SCD has declined since the introduction of neonatal screening for the disease, vaccination programs and parental education, acute splenic sequestration crisis is still a life-threatening complication.<sup>93</sup> The clinical management of such crises, with acute splenic sickling and spleen blood entrapment, is based on rapid correction of hypovolemic shock by infusion of crystalloids and packed red cells. Although international guidelines and consensus statements on the management of acute splenic sequestration crisis are not available, splenectomy is usually recommended after two such crises requiring urgent transfusion.<sup>92-95</sup>

Hypersplenism, defined as chronic splenic enlargement with lowered hemoglobin concentration and decreased platelet and leukocyte counts, is the second major indication for splenectomy in SCD patients.<sup>92-95</sup> Splenectomy is usually indicated if there is hypersplenism, pressure effects of the spleen or failure to thrive. Transfusion is often ineffective in such children because of red blood cell sequestration in the enlarged spleen.

Although splenectomy is the treatment for recurrent acute splenic sequestration crises and hypersplenism in SCD, there is no evidence that it increases hemoglobin level, decreases hemolysis or improves patients' survival.<sup>96</sup> Splenectomy may, however, increase thromboembolism. Limited evidence is available about any possible increased incidence of pulmonary arterial hypertension or pain frequency in SCD patients.<sup>97</sup>

Laparoscopic splenectomy is generally used in children with SCD. It is performed after preoperative transfusion or exchange transfusion to decrease the percentage of HbS. The major limitations to using a laparoscopic

approach in SCD children are the size of the spleen, with its local adhesions, and the longer duration of the operation. Although laparoscopic splenectomy has some positive aspects, such as the shorter duration of hospitalization, its impact on the incidence of post-operative severe, acute, SCD-related complications, including acute chest syndrome, is still unclear.<sup>98,99</sup> To date there are no real advantages, in terms of hematologic phenotype and infective risk, from partial splenectomy rather than total splenectomy in children with SCD.<sup>100</sup>

Thus, guidelines on the clinical management of acute splenic sequestration crisis in SCD are needed. The guidelines should present parameters for and timing of splenectomy, with accompanying surgical approaches. Indications are likely to vary depending on environmental factors, including the availability of safe blood transfusions and the spectrum of infections. Future multicenter studies should be designed to address these issues.

#### **Splenectomy recommendations**

*-In SCD children, splenectomy is recommended after two acute splenic sequestration crises (agreed by 100% of experts) (grade 2 recommendation, grade C evidence).*

*-In SCD children, splenectomy is also recommended in patients with massive splenomegaly and/or hypersplenism (agreed by 90% of experts) (grade 2 recommendation, grade C evidence).*

### Unstable hemoglobin

Globin mutations that destabilize hemoglobin tetramers constitute a very rare cause of hemolytic anemia. The clinical pattern of hemolytic anemia related to unstable hemoglobin is extremely variable. Severely affected patients, particularly those with hyperunstable hemoglobin, present early in childhood and may require chronic transfusion therapy. Thrombotic complications following splenectomy have been described in nine patients (with Hb Bridlington/HbTaybe, Hb Taybe, Hb Mainz, Hb Olmsted, Hb Madrid and Hb Perth).<sup>101-106</sup> The thrombotic events, including pulmonary emboli, pulmonary arterial hypertension, arterial stroke and priapism, occurred even 4-32 years after splenectomy. The majority of patients (7/9) had no or only partial improvement in hemoglobin levels. Given the anecdotal data, splenectomy should be considered only when there is severe anemia and/or massive or symptomatic splenomegaly.

#### **Splenectomy recommendations**

*-In patients with unstable hemoglobin splenectomy should be considered when the spleen is very large and/or there is evidence of hypersplenism (agreed by 95% of experts) (grade 2 recommendation, grade C evidence).*

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