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Recommendations for splenectomy in hereditary hemolytic anemias

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Abstract

Hereditary hemolytic anemias are a group of disorders including red cell membrane defects, red blood cells enzyme disorders, congenital dyserythropoietic anemias, thalassemia syndromes and haemoglobinopathies. As damaged red blood cells passing through the spleen red pulp are efficiently 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 (EHA) Roadmap we generated specific recommendations for each disorder that will enable clinicians to achieve better informed decisions on disease management by splenectomy, on the type of splenectomy and possible consequences. Guidelines for thalassemia syndromes that have been previously established were excluded from the current work. As no randomized clinical trials, case control or cohort studies regarding splenectomy in those disorders were found in the literature, recommendations for each disease were based on expert opinion, which were subsequently critically revised and modified by the Splenectomy in Rare Anemias Study Group including both adult and pediatric hematologists.

Introduction

Hereditary hemolytic anemias are a group of disorders including red cell membrane defects, enzyme disorders, congenital dyserythropoietic anemias, and haemoglobinopathies. Due to the rarity of these diseases optimal therapy 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 efficiently removed by the splenic macrophage system. Although in recent decade splenectomy has been commonly used in the clinical management of patients with severe hematologic phenotypes, the efficacy of splenectomy in many of these disorders has yet to be determined. Additionally, concern remain regarding short- and long-term infectious complications, and increased risk of cardiovascular complications in later life, including thrombosis and pulmonary hypertension.[1]

We first reviewed the literature in PubMed in order to generate recommendations for splenectomy in these disorders. No randomized clinical trials, case control or cohort studies were identified lowering the level of evidence to 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 highest possible agreement that was classified as "full consensus" (100%) agreement or “consensus” (>80%). 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 quality of evidence and strength of recommendations (see supplementary

document).[2]

In the present manuscript, we first present possible general complications of splenectomy including, post splenectomy infections and thromboembolic complications, then discuss the advantages and complications of splenectomy for each of the specific hereditary hemolytic anemia disorders prior to generating specific recommendations.

Splenectomy Complications

Post Splenectomy Infections

Due to the role of the spleen in immune competence and blood filtration, post splenectomy there is a risk of overwhelming infection (OPSI) which is highest with encapsulated organisms such as *S. pneumoniae*, *N.meningitis* and *H. influenza*.[3] Asplenia is also an important risk factor for serious infection with *Plasmodium*, *Capnocytophaga canimorsus* and *cynodegmi* (after an animal bite), Babesia (after a tick bite), and *Bordetella holmesii*.[4-6] The risk of post-splenectomy sepsis may vary according to the indication for splenectomy [intermediate for spherocytosis and higher for other inherited anemias],[7] patient's age at the time of surgery [highest before age of 5],[3] and interval since splenectomy was performed [highest during the first year]. However, an elevated risk probably remains for life.[8,9] Due to 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 at age >5 years as most studies are retrospective and include patients with heterogeneous diseases who were not fully immunized. It is possible that the wide use of conjugated vaccines will significantly reduce the risk of OPSI. In fact, a recent retrospective study analyzing 141 consecutive children undergoing

splenectomy during 1991-2010 suggested that 10 of 11 patients suffering from post-splenectomy sepsis had an additional underlying immune deficiency.[10] However, in a recent prospective multicenter cohort study of German patients, who underwent splenectomy due to variety of causes, *S. pneumoniae* sepsis was more frequent than in patients with a normal functional spleen (42% *vs* 12% respectively; $P < .001$). It is of note that less than half of the OPSI patients in the above study received pneumococcal vaccination before splenectomy, despite national and international guidelines.[11]

Strategies to reduce the risk of OPSI include: (i) patient's education including urgent action in response to febrile episodes; (ii) vaccination and (iii) prophylactic anti-microbial therapy. As detailed guidelines regarding prevention and treatment of infections in splenectomized or asplenic patients are available through the British Committee for Standards in Haematology[12] and American Academy of Pediatrics (Red Book 30th edition, 2015), the reader is referred to those publications for detailed instructions.

Post Splenectomy Thromboembolic Complications

An increased risk of early and late venous and arterial thrombosis was described after splenectomy,[1,13] including acute splenic and portal vein thrombosis (SPVT)[14] and delayed severe life-long complications.[15]

Acute Splenic and Portal Vein Thrombosis

Acute splenic and portal vein thrombosis (SPVT) after splenectomy is an early and life-threatening complication, which can lead to bowel ischemia and/or portal hypertension. These complications have been related to stasis in splenic vein remnant.[14] The risk varies with the underlying disorder. Krauth

et al in 2008 compiled 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 due to trauma developed this complication.[14,15] 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 for SPVT after open splenectomy (OS) versus laparoscopic splenectomy (LS), the surgical approach seems not to affect incidence of SPVT.[16] Screening for thrombophilia has not been shown to allow early identification of patients at risk for SPVT after splenectomy.[17]

A study with contrast-enhanced CT used for the diagnosis of SPVT showed a median time of 6 days (range 3-11 days) between splenectomy and the appearance of asymptomatic SPVT.[18] A Canadian study of 40 patients suggested that the timing for SPTV Doppler/ultrasound surveillance to diagnose SPVT is one week following splenectomy.[19]

Most patients with documented SPVT were treated with anticoagulant therapy (i.e. intravenous heparin followed by oral anticoagulants) for a variable time period ranging between 3 to 6 months. A documented complete (57/90, 63.3%) or at least partial resolution (13.3 %) of the thrombus was reported in the majority of treated patients. However, 7.7% of this latter population showed persistence of thrombus, while 15.5% developed a cavernoma or portal hypertension.[14]

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 thrombosis prophylaxis after

laparoscopic abdominal surgery was terminated early due to the low incidence of thrombosis.[16]

Late Vascular 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 for trauma. A significantly increased risk of death from ischemic heart disease compared to controls was described with a relative risk of 1.85.[15] Data from a Danish Registry identifying all splenectomized patients from 1996-2005 showed that the long-term (>1 year) risk of venous thromboembolism (VTE) remained approximately 3-fold higher in trauma patients undergoing splenectomy versus the general population.[20] However, the contribution of other trauma complications to thrombotic risk was not evaluated. The long-term risk was highest in patients splenectomized for malignant hematological disorders and hemolytic anemias.

Pulmonary Arterial Hypertension

Splenectomy has been reported to be a risk factor for the development of pulmonary arterial hypertension (PAH),[21] particularly in patients with hemolytic disorders.[22-24] Loss of splenic function is associated with increased number of platelets and also increases in their activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.[25] 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 post-splenectomy (agreed by 86% of experts) (Grade 2 recommendation, grade C evidence).

Surgical Approach

Laparotomy Splenectomy

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

Laparoscopic Splenectomy

Currently LS is considered the gold standard for normal size or slightly enlarged spleen and is preferred to OS. LS (i) is less traumatic; (ii) presents fewer complications; (iii) requires shorter hospital stays; (iv) has better cosmetic outcome, and an overall lower cost compared to OS. However, it should be performed only by experienced operators.[28] Nowadays, splenectomy is possible and safe also for massively enlarged spleen, but is associated with longer operative time and hospital stay.[29] Perioperative splenic artery embolization was also found to be useful and lower the complications of massive spleen LS.[30] Moreover, selective splenic artery embolization, carried out in steps, will reduce spleen size and alleviate cytopenias.[31]

A pre-operative assessment of splenic size by ultrasound is recommended. Although three dimensional CT scan 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 where additional information about the anatomy is required prior to surgery.[32]

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 (PS) has been increasingly used in recent years. In PS, 80-90% of the enlarged spleen is generally removed. PS was initially performed using an OS approach but laparoscopic and robotic approaches have recently been introduced.[33] Nevertheless, PS should always be performed by an experienced surgeon.

Disease Specific Recommendations

A detailed discussion of the clinical picture 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 for some disorders data is so sparse and that no recommendations could be generated.

Hereditary Spherocytosis

General

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 for α- and β-spectrin and in genes encoding other proteins involved in the attachment of cytoskeleton to the overlying lipid bilayer (ankyrin, band 3 and protein 4.2). Defects in these structural proteins render the RBC

spherical, rigid and susceptible to premature destruction in the spleen.[34-37] Clinically, patients with HS are grouped into 3 categories according to the disease severity: mild, moderate and severe (Table 2).[36]

Long Term Thrombotic Complications of Splenectomy in Hereditary Spherocytosis

Schilling in 1997 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 compared to HS patients with intact spleen, with the first event occurring one or more decades following splenectomy.[38] This was further confirmed in his follow-up study in which arterial events in HS patients, had a hazard ratio of 7.2 compared to affected patients who did not undergo splenectomy. In addition, affected patients who underwent splenectomy had a hazard ratio of 3 for developing of venous events as compared to HS patients who did not undergo splenectomy. [39]

However, only few patients with HS who developed stroke, PE or PAH following splenectomy have been reported.[24,40-42] Moreover, Buchanan et al studied 39 adults with HS and found no evidence for thrombotic manifestations despite a long follow up (median 25 years).[43]

Splenectomy in Hereditary Spherocytosis

Splenectomy in HS usually results in disappearance of anemia and 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 51×10^9/L) and unconjugated bilirubin (from 32.5 to 12 µmol/L).[44]

Due to increasing awareness to post splenectomy complications, in the past decade the rate of splenectomy continues to declined. During 1980-2005, splenectomy was performed in only 20% of HS patients.[44] 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 impacts the patient's quality of life. For young adult patients, unacceptable cutaneous icterus (usually in patients with concomitant Gilbert genotype) may become a social problem that balances a decision towards splenectomy.

Available Guidelines for Splenectomy in Hereditary Spherocytosis

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.[45-46] 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 refer to previously published guidelines asking if: (1) splenectomy should accompany cholecystectomy when biliary stones are present and (2) partial splenectomy be performed for children younger than 6 years of age with severe HS.

Should Splenectomy Accompany Cholecystectomy

It was previously suggested that there is an increased risk of intrahepatic choledocholithiasis following splenectomy[44] and the 2004 guidelines suggested that for children with HS who require cholecystectomy

the spleen should always be removed.[45] This recommendation was based on expert opinion despite little supportive data in the literature thereafter, the recommendation was changed in subsequent guidelines to indicate that this issue remains controversial.[46] 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 biliary stones over a median follow-up of 15.6 years.[47] Similarly, in a recent study of children aged 4-17 years studied during 2009-2012, simultaneous cholecystectomy (for cholelithiasis) and splenectomy were performed in fewer than half of the patients.[48] We recommend that indications for splenectomy when cholecystectomy is required should not differ from that for splenectomy with no cholecystectomy (Tables 1,2).

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 (PS) has been increasingly performed in recent years. Several studies indicate that partial splenectomy reduces the hemolytic rate and increases red cell lifespan while maintaining efficient splenic phagocytic function.[49-50] In a recently published follow-up study, Pincez et al. reported on 79 HS children who underwent partial splenectomy using an OS approach during 1985-2013. In this population, 39 children were less than 5 years of age at time of splenectomy (mean age at surgery 4.3±0.6 years) and most were transfusion–dependent (31/39). Following PS (mean follow up of 12±0.9 years) there was a drastic reduction in transfusion rate and increase in hemoglobin levels that were compatible

with normal growth while maintaining efficient spleen function in 96% of cases.[51] On the other hand, this approach reduced but did not totally suppress hemolysis and was associated with later development of biliary stones, and splenic remnant regrowth. Finally, 50% of the 39 severely affected young HS children required total splenectomy in a median of 5 years following PS at an age when total splenectomy was much safer.[51] Drop in 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 (1941 HS children) versus partial splenectomy (283 HS children), confirmed that although total splenectomy was more effective than PS in increasing Hb levels (3.6g/dl compared to 2.2g/dl, respectively) and in reducing reticulocyte counts (12.5% compared to 6.5% respectively), the outcome following PS was stable for at least 6 years. There were no cases of OPSI.[52] In this meta-analysis, with overall short follow-up length, recurrence of symptoms in PS 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 recommendation regarding PS in HS could have been 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

General

Pyruvate kinase deficiency (PKD) is the most common glycolytic defect causing congenital non‐spherocytic hemolytic anemia (CNSHA) with incidence of 1:20,000 in white individuals.[53] Pyruvate kinase converts phosphoenolpyruvate to pyruvate, generating 50% of the red cell total ATP. PK deficiency red blood cells, are damaged due to lack of energy to support membrane ion transport, and to maintain membrane structure and are therefore cleared by the spleen and liver. Clinically, PKD has been categorized into mild, moderate and severe forms (Table 4).[54-55]

Results of Splenectomy in Pyruvate Kinase Deficiency

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), 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.[54] Analysis of the results of a recent international, multicenter registry study with 144 patients,[56] 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 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 (2.6-60.4), of whom a splenectomy had been performed in 35 (37%). 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 in pyruvate Kinase Deficiency

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. It does not arrest hemolysis, however, 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.[54,55] 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 pyruvate Kinase Deficiency

As for HS, splenectomy should also be considered in patients requiring cholecystectomy to avoid a 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 in pyruvate Kinase Deficiency

Partial splenectomy was reported to be unsuccessful in two PK deficient cases, and effective in one patient with an increase in the baseline hemoglobin and reduction in transfusion rate.[57]

Other therapeutic options for PK deficiency that should be considered include HLA-matched sibling allogeneic transplant,[58] and new therapies

which are still under investigation including the enzyme activator (AG-348)[59] and gene therapy.[60]

Splenectomy Recommendations

-Splenectomy should be considered in patients with PK 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 G-6PD Deficiency

G6PD deficiency patients rarely suffer hemolytic anemia in the steady state when not triggered by an exogenous factor. Some mutations of G6PD 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 between borderline to transfusion-dependent. Hamilton et al (2004) identified nine transfusion-dependent patients in the literature, seven responded to splenectomy and became transfusion-independent.[61] 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.[62]

Splenectomy Recommendation

-Splenectomy should be considered in patients with congenital non-spherocytic hemolytic anemia due to G6PD 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 P5'N is the most common inherited abnormality of nucleotide metabolism causing hemolytic anemia of moderate severity.[55,63] Transfusions are rarely required. Splenectomy has been associated with variable increase in hemoglobin levels.[64-67] Portosplenomesentric venous thrombosis was described in one P5'N patient following splenectomy due to trauma.[68] As there is insufficient data regarding efficacy and complications of splenectomy in this disorder no recommendations could be given.

Hereditary Stomatocytosis

Hereditary stomatocytosis **(**HSt) is a dominant disorder comprising both dehydrated (DHS) and overhydrated (OHS) types, which show alteration of the RBC membrane permeability to monovalent cation (Na+ and K+), with a consequent alteration in the intracellular cationic content and in red cell volume. DHS is the most highly represented among HSt disorders, with an incidence of approximately 1:50000 births. OHS is a very rare subtype among HSt disorders, with only 20 cases reported worldwide. The recent identification of genes mutated in HSt has improved diagnosis and understanding of the pathophysiology of this group of disorders. To date, a

total of five different genes encode for membrane proteins have been reported to be responsible for RBC volume alterations, three leading to OHSt (AE1 [also termed SLC4A1], RHAG and GLUT1 [also termed SCL2A1) [69,70] and two to DHSt (PIEZO1 and the Gardos Channel)[71-75]. Reviews on the clinical picture and molecular pathogenesis have recently been published.[37,76.]

Splenectomy in Hereditary Stomatocytosis

High risk of thromboembolic complications following splenectomy in hereditary stomatocytosis was first described by Stewart and colleagues (1996) in nine splenectomized adults.[77] In their seven families four had OHSt and the remaining DHSt. Both groups suffered from serious late thrombotic complications, sometimes recurrent over years, including DVT, pulmonary emboli (PE), superficial thrombophlebitis, portal vein thrombosis, intracardiac mural thrombosis, arterial thrombosis, and PAH. 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 OHSt or DHSt who developed severe thrombotic complications.[78-81]

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 OHSt and ineffective in DHSt, should be avoided. In patients with hereditary stomatocytosis who were mistakenly misdiagnosed as HS and underwent splenectomy life-long anti-coagulation should be considered.

Splenectomy Recommendations

- **In patients with hereditary stomatocytosis splenectomy is contra-indicated (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.[82] 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.[83] CDA II is the most common subtype, with more than 200 patients described in the literature followed by CDA I with approximately 100 patients.[82]

Splenectomy in CDA I

Two case series of 13 severely anemic mostly transfusion-dependent patients undergoing splenectomy were identified, who had undergone splenectomy.[84,85] 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 PAH and the other two due to overwhelming sepsis. Because of inconsistent response 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 is CDA I could be generated.

CDA II

Heimpel at al reported on 22 patients who underwent splenectomy at a median age of 19.9 years.[86] Hemoglobin concentration improved 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.[86] Russo et al reported that 36% (41/112) of their patients with CDAII 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).[87] 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).

Hemoglobinopathies

The authors decided not to discuss thalassemic syndromes since revised guidelines have recently been presented by TIF (please visit: www.tif.org).[88]

Sickle Cell Disease (SCD)

Sickle Cell Disease (SCD) is a worldwide distributed hereditary red cell disorder with an annual birth rate of 237,381; 11,143; and 1,939 in Africa, US

and Europe respectively.[89] SCD is caused by a point mutation in the β-globin gene resulting in the synthesis of pathological hemoglobin S (HbS).[90] Cyclic polymerization/depolymerization of deoxy-HbS generate dense, dehydrated red cells, playing a central role in acute and chronic clinical manifestations of SCD, in which intravascular sickling leads to vaso-occlusion (VOCs) and impaired blood flow with ischemic/reperfusion injury.[90] 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.[90,91]

Splenectomy in Sickle Cell Disease

Acute splenic sequestration crisis (ASSC) is defined as acute abdominal pain and distension associated with spleen enlargement, a decline in Hb levels of at least 2 g/dL and stable or high reticulocyte count compared to patient in steady state.[92] Even though the mortality rate of SCD patients has declined since the introduction of neonatal screening for SCD, vaccination program and parental education, ASSC is still a life-threatening complication.[93] The clinical management of ASSC with acute splenic sickling and spleen blood entrapment, is based on rapid correction of hypovolemic shock by crystalloid and packed red cell infusion. Although international guidelines or consensus are not available for management of ASSC, splenectomy is usually recommended after two ASSC episodes requiring urgent transfusion.[92-95]

Hypersplenism, defined as chronic splenic enlargement with decreased hemoglobin, platelet and leukocyte count, is the second major indication for splenectomy in SCD patients.[92-95] Splenectomy is usually

indicated if there is hypersplenism, pressure effects of the spleen or failure to thrive. Transfusion is often ineffective in such children due to RBC sequestration in the enlarged spleen.

Although splenectomy is the treatment for either recurrent ASSC or hypersplenism in SCD, there is no evidence that it improves the hemoglobin level, decrease the hemolysis or increases patient survival.[96] In addition, splenectomy may increase thromboembolism. Limited evidence is available about any possible increased incidence of PAH or pain frequency in SCD patients.[97]

In SCD children LS is generally used, after preoperative transfusion or exchange transfusion to decrease the HbS percentage. In SCD children, the major limitations for using a laparoscopic approach are the spleen size with its local adhesion and the longer length of operative time. Although LS has some positive aspects such as the shorter duration of hospitalization, its impact on the incidence of post-operative SCD-related severe acute complication, such as acute chest syndrome (ACS), is still unclear.[98,99] To date there are no real advantages in terms of hematologic phenotype and infective risk to partial splenectomy as compared to total splenectomy in SCD children.[100]

Thus, in SCD guidelines on clinical management for ASSC are needed, that present parameters and the timing for splenectomy, with accompanying surgical approaches. Indications are likely to vary depending on environmental factors, including the availability of safe blood transfusion and the spectrum of infection. Future multicenter studies should be designed to address these questions.

Splenectomy Recommendations

-In SCD children, splenectomy is recommended after two episodes of ASSC (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 chromic transfusion therapy. Following splenectomy thrombotic complications were described in nine patients (with Hb Bridlington/HbTaybe, Hb Taybe, Hb Mainz, Hb Olmsted, Hb Madrid and Hb Perth).[101-106] Thrombotic events including PE, PAH, arterial stroke and priapism occurring even 4-32 years after splenectomy have been described in all reported patients. Moreover, the majority of patients (7/9) had no improvement or only partial improvement in hemoglobin levels. Despite the anecdotal data splenectomy should be considered only when there is severe anemia and/or of 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).

Table 1: Summary of splenectomy recommendations for hemolytic disorders

Disease	**When is 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 kinas 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	Considered if patient is transfusion-dependent and/or has massive splenomegaly and/or has symptomatic splenomegaly.
Hereditary stomatocytosis	Contra-indicated.
Congenital dyserytrhopoietic anemia type II	Considered if patient is transfusion-dependent and/or has symptomatic splenomegaly.
Sickle cell disease	Patient had two episodes of acute splenic sequestration crisis and/or has massive splenomegaly and/or suffers symptomatic hypersplensim.

Unstable hemoglobin	Considered only if patient is transfusion-dependent anemia and/or symptomatic splenomegaly.

**For all indications splenectomy should be performed after 6 years of age.*

Table 2: Indications for splenectomy in HS based on severity of disease*

Disease severity	**Hemoglobin level (gr/dL)**	**Reticulocyte counts (%)**	**Bilirubin (µmol/l)**	**Indication for splenectomy**
Severe	< 8	> 10	> 51	Indicated, delayed 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* and authors' recommendations

No.	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 for post-splenectomy sepsis, but it is possible that further surgery may be needed for either recurrence of hematological 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.

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>6
Moderate	Variable, childhood to adult	Moderate anemia occasional exacerbations	9	Confined to exacerbations	Not indicated
Mild	Variable, childhood	Long live history of	11	Rare	Not indicated

	to adult	mild anemia			

Severity of disease based on references 54, 55.

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Supplementary document

Grading of Recommendations Assessment, Development and Evaluation (GRADE) (2)

Strength of Recommendation

Strong recommendations (grade 1): the evidence is high quality and the desirable effect clearly outweigh the undesirable effect.

Weak recommendations (grade 2): There is a close or uncertain balance

The quality of evidence

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations.

(C) Low: Further research is likely to have important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.