Consult. Confirm. CONTROL:

with NovoSeven® (Recombinant Factor VIIa) in acquired haemophilia (AH)[1]

Henry, 78 years old, *presented with severe and extensive skin bruising and blood in the stool. Henry had no prior history of bleeding.*

This advertisement is intended for Healthcare Professionals

Your primary treatment objective in AH is to STOP THE BLEED*

NovoSeven® is one of the first-line treatment options in AH based on:†[2,3]

• Rapid bleed control with consistently high efficacy[4-11] • Established tolerability profile[1,4,12-15] • Simple, rapid reconstitution and administration‡ and convenient storage[1]

*Published guidelines also recommend eradicating the inhibitor with immunosuppressive therapy.
†Other first-line haemostatic treatments are also recommended.
‡NovoSeven® vial-to-vial reconstitution 2–5 mins to infuse.

Prescribing Information NovoSeven® Eptacog alfa (activated); recombinant Factor VIIa (rFVIIa) **Please refer to Summary of Product Characteristics for full information. Presentation:** Powder (vial) and solvent (pre-filled syringe) for solution for injection. Available in packs containing 1, 2, 5 or 8 mg rFVIIa (8 mg only available in the UK). **Uses:** Treatment of bleeding episodes and prevention of bleeding during surgery or invasive procedures in patients with:- congenital haemophilia with inhibitors to coagulation FVIII or FIX > 5 BU or who are expected to have a high anamnestic response to FVIII or FIX; - acquired haemophilia; - congenital FVII deficiency; - Glanzmann's thrombasthenia with past or present refractoriness to platelet transfusions, or where platelets are not readily available. **Dosage:** The rFVIIa is dissolved in the accompanying solvent before use. After reconstitution the solution contains 1 mg rFVIIa/ml. Administer by intravenous bolus injection over 2-5 minutes; must not be mixed with infusion solutions or given in a drip. NovoSeven® should be administered as early as possible after the start of a bleeding episode. *Haemophilia A or B with inhibitors or expected to have high anamnestic response* Initial dose of 90 µg/kg body weight. Duration of, and interval between, repeat injections dependent on severity of haemorrhage or procedure/surgery performed. Paediatric population: Clinical experience does not warrant a general differentiation in dosing between children and adults. Children have faster clearance than adults and higher doses may be needed to obtain similar plasma concentrations as in adults. For mild to moderate bleeding episodes (including home therapy): Two dosing regimens can be recommended: i) Two to three injections of 90 µg/kg body weight administered initially at 3-hour intervals. If further treatment is required, one additional dose of 90 µg/kg can be administered. ii) One single injection of 270 µg/kg body weight. Duration of home therapy should not exceed 24 hours. Only after consultation with the haemophilia treatment centre can continued home treatment be considered. For serious bleeding episodes, initial dose 90 µg/kg body weight; dose every two hours until clinical improvement. If continued therapy indicated, dosage interval can be increased successively. Major bleeding episode may be treated for 2-3 weeks or longer if clinically warranted. For invasive procedures/surgery administer initial dose of 90 µg/kg body weight immediately before the procedure. Repeat dose at 2-3 hour intervals for first 24-48 hours. In major surgery continue dosing at 2-4 hour intervals for 6-7 days. Dosage interval may then be increased to 6-8 hours for further 2 weeks. Treatment may be up to 2-3 weeks until healing has occurred. *Acquired haemophilia* Initial dose of 90 µg/kg body weight. Further injections may be given if required. Initial dose interval should be 2-3 hours. Once haemostasis achieved, the dose interval can be increased successively *Factor VII deficiency* For bleeding episodes and for invasive procedures/surgery, in adults and children, administer 15-30 µg/kg body weight every 4-6 hours until haemostasis achieved. Adapt dose and frequency to individual. Limited clinical experience in long term prophylaxis has been gathered in paediatrics below 12 years of age, with severe clinical phenotype. *Glanzmann's thrombasthenia* For bleeding episodes and for invasive procedures/surgery administer 90 µg/kg body weight (range 80-120 µg) every 2 hours (1.5-2.5 hours). At least three doses should be administered to secure effective haemostasis. For patients who are not refractory platelets are first line treatment. In all conditions the dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred. **Contra-indications:** Known hypersensitivity to active substance, excipients, or to mouse, hamster or bovine protein may be a contraindication to the use of NovoSeven®. **Precautions:** Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. For severe bleeds NovoSeven® should only be administered in hospitals specialised in the treatment of patients with coagulation factor FVIII or FIX inhibitors or in close collaboration with a physician specialised in treatment of haemophilia. No clinical experience with administration of single dose of 270 µg/kg body weight in elderly patients. Home therapy should not exceed 24 hours. Possibility of thrombogenesis or induction of DIC in conditions in which tissue factor could be expected in circulating blood, e.g. advanced atherosclerotic disease, crush injury, septicaemia, or DIC. Since NovoSeven® may contain trace amounts of mouse, bovine and hamster proteins there is a remote possibility of the development of hypersensitivity. Monitor FVII deficient patients for prothrombin time and FVII coagulant activity; suspect antibody formation if FVIIa activity fails to reach expected level or bleeding not controlled with recommended doses. Thrombosis in FVII deficient patients receiving NovoSeven® during surgery has been reported but risk is unknown. Avoid simultaneous use of prothrombin complex concentrates, activated or not. Based on a non-clinical study it is not recommended to combine rFVIIa and rFXIII. **Interactions: (Irish requirement only)** Risk of a potential interaction between NovoSeven® and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided. Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in haemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and rFVIIa treatment is however limited. **Fertility, pregnancy and lactation:** Only administer to pregnant women if clearly needed. Not known if excreted in human milk; a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with NovoSeven® should be made taking into account the benefit of breast-feeding to the child and the benefit of NovoSeven® therapy to the woman. Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility. **Side Effects:** The frequencies of both serious and non-serious adverse drug reactions are: Uncommon (≥ 1/1,000, < 1/100): venous thromboembolic events (deep vein thrombosis, thrombosis at i.v. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia); rash (including allergic dermatitis and rash erythematous); pruritus and urticaria; therapeutic response decreased - it is important that the dosage regimen of NovoSeven® is compliant with the recommended dosage; pyrexia. Rare (≥1/10,000, <1/1,000): disseminated intravascular coagulation and related laboratory findings including elevated levels of D-dimer and decreased levels of AT; coagulopathy; hypersensitivity; headache; arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia); angina pectoris; nausea; injection site reaction including injection site pain; increased fibrin degradation products; increase in alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin. Adverse drug reaction reported post-marketing only (i.e. not in clinical trials) are presented with a frequency of not known. Not known: anaphylactic reaction; intracardiac thrombus, flushing; angioedema. *Inhibitory antibody formation:* Post-marketing there have been no reports of inhibitory antibodies against NovoSeven® or FVII in patients with haemophilia A or B. Development of inhibitory antibodies to NovoSeven® has been reported in post-marketing observational registry of congenital FVII deficient patients. Patients with FVII deficiency, formation of antibodies against NovoSeven® and FVII is the only adverse drug reaction reported (frequency: common (≥ 1/100 to < 1/10)). Risk factors may have contributed to antibody development including previous treatment with human plasma and/or plasma-derived FVII, severe mutation of FVII gene, and overdose of NovoSeven®. Patients with FVII deficiency treated with NovoSeven® should be monitored for FVII antibodies. *Thromboembolic events:* When NovoSeven® is administered outside approved indications, arterial thromboembolic events are common (≥ 1/100 to < 1/10). A higher risk of arterial thromboembolic adverse events (5.6% in patients treated with NovoSeven® versus 3.0% in placebo-treated patients) has been shown in trials conducted outside current approved indications. Safety and efficacy of NovoSeven® have not been established outside approved indications; NovoSeven® should not be used in these cases. Thromboembolic events may lead to cardiac arrest. *Patients with acquired haemophilia:* Clinical trials showed certain adverse drug reactions were more frequent (1% based on treatment episodes): arterial thromboembolic events (cerebral artery occlusion, cerebrovascular accident), venous thromboembolic events (pulmonary embolism and deep vein thrombosis), angina pectoris, nausea, pyrexia, erythematous rash and investigation of increased levels of fibrin degradation products. The Summary of Product Characteristics should be consulted for a full list of side effects. **Marketing Authorisation numbers:** NovoSeven® 1 mg (50 KIU) EU/1/96/006/008 NovoSeven® 2 mg (100 KIU) EU/1/96/006/009 NovoSeven® 5 mg (250 KIU) EU/1/96/006/010 NovoSeven® 8 mg (400 KIU) EU/1/96/006/011 (UK only) **Legal Category:** POM **(UK ONLY)- Basic NHS Price:** NovoSeven® 1 mg £525.20 NovoSeven® 2 mg £1,050.40 NovoSeven® 5 mg £2,626.00 NovoSeven® 8 mg £4,201.60 For complete prescribing information, please refer to The Summary of Product Characteristics which is available: **For Ireland from** - www.medicines.ie or by email from info@novonordisk.ie or from Medical Department, Novo Nordisk Limited, 1st Floor, Block A, The Crescent Building, Northwood Business Park, Santry, Dublin 9, Ireland; Tel: 1 850 665 665 **For UK from** – www.medicines.org.uk or from Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA; Tel: 01293 613555 or Fax: 01293 613535

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NovoSeven® Recombinant Factor VIIa

Guidelines on red cell transfusion in sickle cell disease Part II: indications for transfusion

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Red cell transfusion has an important role in the management of sickle cell disease (SCD) in both emergency and elective settings. However, because of insufficient randomised data, it is not always clear when or how to use red cell transfusion. A companion guideline, Guidelines on red cell transfusion in sickle cell disease Part I: principles and laboratory aspects, addresses the general principles of transfusion practice in SCD (Davis *et al*, 2016, *BJH in press*). The present guideline examines current available evidence on indications for transfusion in SCD. This may not be appropriate for all clinical scenarios and clinical decisions must be based on individual patient considerations.

In both guidelines, the term sickle cell disease refers to all genotypes of the disease, and sickle cell anaemia to the homozygous state (SS).

Methods

The writing group was selected by the British Committee for Standards in Haematology (BCSH) General Haematology and Transfusion Task Forces with input from other experts in Haemoglobinopathy. PubMed, MEDLINE and Embase were searched systematically for publications on red cell transfusion in SCD from 1960 to May 2016 using a combination of search terms related to: (i) sickle cell (including sickle, sickle cell, sickle cell disease, sickle cell anaemia, haemoglobin SC disease, sickle cell crisis), (ii) transfusion (including transfusion, blood transfusion, red cell transfusion), (iii) transfusion indications (including aplastic crisis, parvovirus, sequestration (splenic, liver, hepatic), acute chest syndrome (ACS), stroke, silent cerebral infarcts, multi-organ failure, girdle syndrome, intrahepatic cholestasis, surgery, pregnancy, and (iv) transfusion complications (including alloimmunisation, haemolytic transfusion reactions, iron overload, viral infections). Opinions were also sought from experienced haematologists with a special interest in the care of SCD patients. The guideline was reviewed by the members of the General Haematology Task Force of the BCSH prior to being sent to a sounding board of approximately 50 UK haematologists, the BCSH and the British Society for Haematology (BSH) Committee. Comments were incorporated where appropriate. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria are specified in the BCSH guidance pack http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html and the GRADE working group website http://www.gradeworkinggroup.org.

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Key recommendations

Consideration of sickle cell patients for transfusion, particularly long-term regimens, should weigh up the potential benefits against potential risks (Grade 1C).

Cerebrovascular disease. **Regular transfusion to maintain HbS <30% should be offered as initial treatment to children with SS or S/β^0 thalassaemia aged 2–16 years judged to be at high risk for a first stroke on the basis of Transcranial Doppler ultrasonography (TCD) (Grade 1A).**

Hydroxycarbamide treatment should be considered for the primary prevention of stroke in children with sickle cell anaemia and high TCD velocities but not severe Magnetic Resonance Angiography (MRA)-defined cerebral vasculopathy after an initial period of transfusions (Grade 1A). The duration of the initial period of transfusion should be tailored to the individual patient but should be for a minimum of 1 year; the transition to

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hydroxycarbamide should be done gradually and transfusion should be withdrawn after the hydroxycarbamide has been escalated to the maximum tolerated dose.

Regular transfusion to maintain HbS <30% effectively reduces the incidence of recurrence of cerebral infarction (defined as a stroke or a new or enlarged silent cerebral infarct) in children with sickle cell anaemia and S/β^0 thalassaemia aged 5–15 years. Treatment options including transfusion should be discussed with families of children who are found to have silent cerebral infarcts. Transfusion should be offered to children who are identified to be at greatest risk for recurrence of infarction after discussion of its benefits and risks (Grade 1A).

Long-term transfusion to maintain HbS <30% is recommended for the prevention of recurrent ischaemic stroke due to sickle cell disease in both children and adults (Grade 1B).

Adults or children who present with signs or symptoms suggestive of acute ischaemic stroke should be transfused without any delay to maintain HbS <30% pending further investigation. Those with confirmed stroke due to sickle cell disease should continue regular transfusions long-term (Grade 1B).

Surgery. **Preoperative transfusion is recommended for SS patients undergoing medium-risk surgery (e.g. abdominal, tonsillectomy, orthopaedic) (Grade 1A).**

Preoperative transfusion is recommended for SC patients undergoing medium-risk surgery (e.g. abdominal, tonsillectomy, orthopaedic) (Grade 1C).

Transfusion is recommended for sickle cell patients of all genotypes requiring high-risk surgery (e.g. cardiovascular, brain) (Grade 1C).

All sickle cell patients with other genotypes undergoing surgery should be individually assessed, taking into account previous history and complexity of surgery, and a management plan should be formulated to include the need for transfusion (Grade 1C).

Particular care should be taken to ensure that all aspects of perioperative care, including oxygenation, hydration, warmth and anaesthetic and surgical technique, are optimised in all sickle cell patients undergoing surgery (Grade 1C).

For patients requiring emergency surgery, the urgency and complexity of the procedure should be taken into account in the timing of perioperative transfusion. Simple transfusion should be given preoperatively if Hb <90 g/l provided this will not result in undue delay to surgery. If transfusion is likely to cause an unacceptable delay to surgery, it is reasonable to proceed to surgery while arranging to transfuse the patient intra- or post-operatively if necessary (Grade 1D).

Acutely ill patients. **Transfusion is recommended and may be life-saving in acute sickle complications such as splenic sequestration, hepatic sequestration, aplastic crisis and severe acute chest syndrome (Grade 1B).**

Transfusion should be considered in the unwell patient with acute multi-organ failure, mesenteric syndrome (Grade 1C) and patients with severe sepsis (Grade 2C). Such cases should be discussed with the specialist haemoglobinopathy team (SHT).

Transfusion for other causes of acute anaemia requires individual assessment and should be discussed with the SHT. Transfusion may be given by simple transfusion (top up) or exchange depending on clinical severity under the guidance of the SHT (Grade 2C).

Pregnancy. **Prophylactic transfusion is not routinely required for sickle pregnancy, but should be considered for women with:**

- **previous or current medical, obstetric or fetal problems related to SCD**
- **women previously on hydroxycarbamide because of severe disease**
- **multiple pregnancy (Grade 1C).**

Women on long-term transfusions for stroke prevention or for amelioration of severe sickle complications should continue with regular transfusions throughout pregnancy (Grade 1B).

Transfusion should be considered in women with worsening anaemia or those with acute SCD complications (acute chest syndrome, stroke etc.) (Grade 1B).

Amelioration of severe disease. **In selected patients with severe disease, blood transfusion can be effective in ameliorating disease, resulting in reduction in hospital bed days. Hydroxycarbamide is recommended as first line treatment for prevention of recurrent acute chest syndrome or repeated painful episodes associated with chest syndrome (Grade 1A). Regular transfusion should be considered for patients failing this treatment or for whom hydroxycarbamide is contraindicated or not acceptable (Grade 1B).**

Other indications. **Transfusion is not recommended to treat steady state anaemia provided that Hb has not fallen over a period of time to symptomatic levels (e.g. with developing chronic kidney disease) (Grade 1C).**

There is no evidence that transfusion shortens the duration of a painful crisis.

Transfusion is not recommended in uncomplicated painful crises but should be considered if there is a substantial drop in Hb from baseline (e.g. >20 g/l or to Hb <50 g/l), haemodynamic compromise or concern about impending critical organ complications (Grade 1C).

The benefit of transfusion to relieve established acute priapism has not been shown in randomised controlled trials. Many patients require a shunt or drainage procedure under general anaesthesia, which may require a transfusion. Such cases should be discussed with the SHT (Grade 2C).

Transfusion has been shown to reduce the incidence of symptomatic avascular necrosis in children receiving regular

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transfusions to maintain HbS <30% for prevention of recurrence of cerebral infarction (Grade 1A). However, there is no consensus on the use of transfusion for the sole purpose of preventing this complication in routine practice.

Where transfusion is considered for indications where there is insufficient evidence for its benefit (e.g. leg ulcers, pulmonary hypertension, end stage renal or liver disease, progressive sickle cell retinopathy), a full risk-benefit assessment should be carried out in liaison with the SHT and each case should be considered on its own merits (Grade 2C).

Indications for transfusion in sickle cell disease

The indications for red cell transfusion in SCD range from those in which transfusion can be strongly recommended to those where its use is unproven or controversial. A case-by-case detailed analysis of risk and benefit of red cell transfusion should be undertaken for unproven or controversial indications.

The indications can be broadly categorised into conditions in which correction of anaemia is the main goal and those where reduction of sickle haemoglobin (HbS) may be more appropriate (see Table I). In both categories, transfusion is either performed acutely, as part of the management of an acute complication of SCD, or electively for the prevention or management of disease complications. Elective transfusions may be one-off (e.g. preoperative) or be part of a long-term transfusion programme.

The decision to transfuse any patient with SCD should be taken by senior medical staff, ideally at consultant level with the appropriate experience. Long-term elective transfusions should usually be initiated by or in consultation with a SHT.

It should be recognised that the low steady state Hb in SCD is the result of the low oxygen affinity of haemoglobin S and is therefore not in itself an indication or transfusion.

Table I. Indications for blood transfusion in sickle cell disease.

Indications where primary goal of transfusion is to correct acute anaemia	GRADE evaluation	Type of transfusion*
Aplastic crisis	1B	Simple (top up)
Acute splenic sequestration	1B	Simple
Acute hepatic sequestration	1B	Simple
Delayed haemolytic transfusion reaction (transfusion should be avoided unless the anaemia is severe or life-threatening)	1C	Simple
Indications where primary goal of transfusion is to reduce HbS concentration in relation to HbA	**GRADE evaluation**	**Type of transfusion***
ACS	1B	Simple or exchange[†]
Acute stroke or other neurological deficit (e.g. TIA)	1B	Exchange
Acute multi-organ failure	1C	Exchange
Mesenteric/girdle syndrome	1C	Exchange
Severe sepsis	2C	Exchange
Acute intrahepatic cholestasis	1C	Exchange
Primary stroke prevention	1A	Simple or exchange
Prevention of silent cerebral infarct recurrence	1A	Simple or exchange
Secondary stroke prevention	1B	Simple or exchange
Surgery		
• SS patients – elective low or medium risk surgery	1A	Simple or exchange
• SC patients – elective low or medium risk surgery	1C	Exchange
• All sickle genotypes – elective high risk surgery	1C	Exchange
• Emergency surgery	1D	Individual considerations[‡]
Pregnancy		
• Sickle complications (e.g. painful crises, ACS, stroke)	1B	Simple or exchange
• Severe anaemia	1C	Simple
• High obstetric, medical or fetal risk	1C	Simple or exchange
Recurrent ACS[§]	2C	Simple or exchange
Recurrent painful crises[§]	2C	Simple or exchange

ACS, acute chest syndrome; TIA, transient ischaemic attack.

*Consensus recommendations - individual patient factors and consideration of complications such as iron overload must be taken into account.

[†]Simple (top up) transfusion may abrogate mild cases of ACS but exchange transfusion should be performed from the outset in severe cases or if there is progression despite initial top up transfusion in mild cases.

[‡]Decisions to transfuse or choice of type of transfusion should be based on individual patient factors and considerations such as urgency or complexity of surgery.

[§]Hydroxycarbamide is first-line treatment. Transfusion should be considered for those failing or not accepting hydroxycarbamide or if it is contraindicated.

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Indications for emergency transfusion

Emergency transfusion with the primary aim of correcting acute anaemia

Ascertaining the cause of anaemia. Acute anaemia in SCD has been defined as a fall in haemoglobin ≥20 g/l below the steady state value (Emond *et al*, 1985; NHLBI, 2014). Understanding the cause of the anaemia is essential for appropriate management. Causes broadly include: decreased haemoglobin production, sequestration and increased haemolysis. Initial assessment should include: history of recent transfusion, haemodynamic status, spleen and liver size, full blood count and reticulocyte count. Any decision to transfuse should take into consideration the likely cause, haemodynamic status and degree of anaemia relative to baseline.

Aplastic crisis. Aplastic crisis should be suspected in patients with acute exacerbation of steady state anaemia with reticulocytopenia and is usually due to infection with human erythrovirus (formerly parvovirus) B19 (Pattison *et al*, 1981; Serjeant *et al*, 1981, 1993; Goldstein *et al*, 1987). Anaemia is usually severe with a mean fall of approximately 40 g/l below steady state values (Goldstein *et al*, 1987; Serjeant *et al*, 2001).

Simple transfusion to steady state level is usually all that is required to maintain the oxygen carrying capacity of blood (Goldstein *et al*, 1987; Serjeant *et al*, 1993; Smith-Whitley *et al*, 2004). Spontaneous resumption of erythropoiesis tends to occur within 7–10 days of aplasia (Anderson *et al*, 1985), restoring the Hb to the steady state value. Most patients will be close to spontaneous marrow recovery at the time of clinical presentation with development of reticulocytosis and recovery of Hb occurring <7 days from presentation (Serjeant *et al*, 1993).

Erythrovirus B19 may occasionally present with serious and potentially life-threatening complications, including acute splenic sequestration, ACS (Lowenthal *et al*, 1996; Smith-Whitley *et al*, 2004) or acute neurological syndromes including stroke (Balkaran *et al*, 1992; Wierenga *et al*, 2001). In such cases, exchange transfusion after initial simple transfusion may be more appropriate.

Acute splenic sequestration. Acute splenic sequestration is characterised by an acute fall in Hb ≥20 g/l, reticulocytosis and sudden splenic enlargement (Emond *et al*, 1985) and, in severe cases, may result in circulatory failure and even death (Rogers *et al*, 1978; Emond *et al*, 1985). Although splenic sequestration typically occurs in the first 5 years of life (Topley *et al*, 1981) before the spleen has spontaneously infarcted, it may occasionally occur later, particularly in those with milder disease such as SC disease in whom splenic infarction may not occur until later in life (Roshkow & Sanders, 1990; Aslam *et al*, 2005). Immediate management consists of simple transfusion to raise the Hb to steady state level (Emond *et al*, 1985). Transfusion with emergency (O Rh (D) negative) or ABO- and Rh (D)-specific uncrossmatched blood may occasionally be necessary to treat shock and anaemia *in extremis*. In many cases, however, cautious transfusion of small red cell volumes to raise the haemoglobin to the steady state level is sufficient to reverse the process and correct hypovolaemia and anaemia. Transfusion of large volumes of red cells (to Hb levels >80 g/l) should be avoided due to the risk of hyperviscosity when sequestered red cells return to the circulation (Kinney *et al*, 1990; Wanko & Telen, 2005; Josephson *et al*, 2007; Quirolo, 2010; NHLBI 2014).

All patients with previous splenic sequestration should be discussed with the SHT. There is a high recurrence rate (Emond *et al*, 1985; Brousse *et al*, 2012) and splenectomy is advised in patients who have recurrent episodes (two or more). Splenectomy is not associated with an increased long-term risk of bacteraemic episodes or death (Wright *et al*, 1999). Regular transfusion to maintain HbS <30% did not reduce the risk of recurrence or need for splenectomy after splenic sequestration compared to clinical observation in a retrospective observational study (Kinney *et al*, 1990).

Acute hepatic sequestration. Acute hepatic sequestration presents with acute hepatic enlargement associated with a fall in Hb ≥20 g/l and rise in the reticulocyte count. It usually responds to simple transfusion or exchange transfusion (Gutteridge *et al*, 1985; Hatton *et al*, 1985); spontaneous resolution has been reported (Hatton *et al*, 1985). As in acute splenic sequestration, the return of sequestered red cells into the circulation may cause acute hyperviscosity (Lee & Chu, 1996) and cautious transfusion of small volumes of red cells is recommended.

Delayed haemolytic transfusion reaction (classical and hyperhaemolysis syndrome). A delayed haemolytic transfusion reaction (DHTR) (classical or hyperhaemolysis) must be strongly suspected in patients presenting with acute anaemia with/without pain typical of vaso-occlusive crisis following a recent transfusion (Milner *et al*, 1985; King *et al*, 1997; Petz *et al*, 1997). Hyperhaemolysis may be missed because it is assumed that the patient's symptoms are due entirely to a painful crisis. The investigation and management of these two syndromes have been described in the companion guideline, Guidelines on red cell transfusion in sickle cell disease Part I: principles and laboratory aspects (Davis *et al*, 2016*; BJH in press*).

All cases of DHTR should be discussed with the SHT both for advice on management and because of the long-term implications of alloimmunisation and risk of hyperhaemolysis recurrence.

Increased haemolysis during painful crises. Transfusion is not recommended in uncomplicated painful crises. Although Hb often drops to slightly below steady state levels, transfusion is typically not required and Hb will return to baseline as the

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crisis abates. Transfusion may be indicated if there is a substantial drop in Hb from baseline (e.g. >20 g/l or Hb < 50 g/l), haemodynamic compromise or concern about impending critical organ complications (see below).

Other causes of exacerbation of anaemia. An acute decline in Hb due to haemolysis is common in acute sickle complications, such as ACS (Howard *et al*, 2015) and acute multi-organ failure syndrome (Hassell *et al*, 1994). The role of transfusion in these two syndromes is described in sections Acute chest syndrome (ACS) and Acute multi-organ failure syndrome. Urgent transfusion is indicated for acute blood loss.

Severe anaemia during hydroxycarbamide therapy requiring transfusion is usually due to an acute intercurrent illness, such as acute splenic sequestration, aplastic crisis or ACS rather than the myelosuppressive effects of the drug (Scott *et al*, 1996; Kinney *et al*, 1999; Wang *et al*, 2001; Gulbis *et al*, 2005; Hankins *et al*, 2005a). The effects of myelosuppression are usually reversible rapidly upon reduction of the dose or temporary cessation of hydroxycarbamide but full recovery may not occur for several weeks (Wang *et al*, 2001; Hankins *et al*, 2005a).

In patients with sickle cell nephropathy, a slow decline of haemoglobin concentration occurs as the renal disease progresses and the anaemia may be severe enough to compromise cardiovascular function (Serjeant & Serjeant, 2001).

Recommendations

Simple transfusion to steady state haemoglobin concentration is indicated for patients with acute exacerbation of anaemia as a result of aplastic crisis or sequestration crisis (Grade 1B). Over-transfusion (to Hb > 80 g/l) should be avoided in sequestration crises because of the risk of hyperviscosity due to the re-entry of sequestered red cells into the circulation.

Transfusion is not recommended in uncomplicated vaso-occlusive crisis but should be considered if there is worsening anaemia, haemodynamic compromise or concern about impending critical organ complications (Grade 1C).

Transfusion for other causes of acute anaemia requires individual assessment and should be discussed with the SHT (Grade 1C).

Emergency transfusion with the primary aim of reducing HbS in relation to HbA

Transfusion to reduce the %HbS is indicated where there is evidence of acute critical organ complications, especially ACS and ischaemic stroke.

Acute chest syndrome (ACS). ACS usually develops during a painful crisis and should be suspected in patients presenting with fever and/or respiratory symptoms, together with clinical signs of lung consolidation (Howard *et al*, 2015). Early recognition of ACS and intervention with blood transfusion can be life-saving.

ACS can develop rapidly and progress to acute respiratory failure within a few hours. It is advisable to plan to have blood available if early signs of ACS occur, even if other measures subsequently render transfusion unnecessary. Both simple and exchange transfusion rapidly improved oxygenation with similar efficacy in non-randomised studies (Vichinsky *et al*, 2000; Turner *et al*, 2009). A simple transfusion aiming for a target Hb 100–110 g/l is effective in preventing progression to acute respiratory failure in SS patients with mild ACS if it is given early in the illness (Emre *et al*, 1995) and should be considered in patients with a PaO_2 < 9·0 kPa on room air, but may also be needed at less severe degrees of hypoxaemia, depending on the individual patient's history and clinical features, or if the patient's oxygen requirements are increasing (Howard *et al*, 2015). Exchange transfusion is recommended in patients with features of severe ACS, those who fail to respond to initial simple transfusion, or patients with a higher Hb (>90 g/l) where there is little leeway for simple transfusion (Emre *et al*, 1995; Vichinsky *et al*, 1997; NHLBI 2014; Howard *et al*, 2015).

There is no evidence as to the optimal %HbS target post-exchange transfusion. In practice, a target of <30–40% is often used, but clinicians should be guided by the clinical response (Howard *et al*, 2015).

Guidelines for the diagnosis and management of ACS are available from the BCSH (Howard *et al*, 2015).

Acute ischaemic stroke. The value of transfusion and the comparative effects of exchange versus simple transfusion in acute ischaemic stroke have not been evaluated in randomised trials. Emergency exchange transfusion to reduce HbS to <30% is recommended for acute ischaemic stroke (RCP, 2004; Sickle Cell Society 2008; NHLBI 2014). Initial simple transfusion should be given if the stroke has occurred in the context of severe acute anaemia (e.g. in aplastic crisis) (RCP 2004). Although there are no controlled trials on the effect of transfusion on the stroke itself, red cell transfusion may potentially minimise morbidity and mortality by improving perfusion and oxygenation to the brain, thereby preventing extension of an infarct. There is evidence from a retrospective cohort study that exchange transfusion for a first overt stroke at the time of stroke presentation is associated with a lower risk of a subsequent stroke compared to simple transfusion (Hulbert *et al*, 2006). It is important to avoid hypovolaemia during the procedure and to keep the post-transfusion Hb at a target of 100 g/l, as a high haematocrit associated with hyperviscosity may worsen the neurological insult.

Current pathways for acute stroke care in the UK require adult patients with suspected stroke to be admitted directly to specialist stroke units (hyperacute stroke units) (NICE,

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2008). National Health Service (NHS) Trusts must ensure that governance arrangements are in place to provide specialist haemoglobinopathy care for SCD patients with suspected stroke who are admitted to hyperacute stroke units, so that emergency exchange transfusion can be provided in a timely manner. Although this model of care has not been developed for paediatrics, NHS Trusts must develop local protocols with the collaboration of their SHT so that SCD children with acute stroke can receive appropriate care, including timely exchange transfusion and specialist neurology advice (RCP 2004; Dick, 2010).

There are currently no data to support the use of red cell transfusion either in the acute management of haemorrhagic stroke or to prevent its recurrence and it is recommended that specialist advice should be sought for individual cases.

Acute multi-organ failure syndrome. This is a severe life-threatening syndrome that may complicate a severe painful crisis. It is particularly likely to occur in patients with otherwise mild SCD and a relatively high haemoglobin concentration. The patient presents with multi-organ failure with associated fever, rapid decrements in Hb and platelet count, non-focal encephalopathy and rhabdomyolysis. The syndrome usually responds to aggressive exchange transfusion (Hassell *et al*, 1994).

Mesenteric ("girdle") syndrome. This is a rare severe sequestration syndrome characterised by simultaneous or consecutive sickling and sequestration in the mesenteric vascular bed, liver and lungs (Brozovic *et al*, 1987). Preceding pain in the abdomen, lumbar spine and limbs is common. Sickling in the abdomen can present with tenderness and rigidity, mimicking peritonitis and progressing to ileus, with a silent distended abdomen and dilated loops of bowel on X-ray. ACS frequently develops due to splinting of the chest wall. Acute exchange blood transfusion is indicated.

Severe sepsis. Severe sepsis often engenders a vicious circle of tissue hypoxia, acidosis and sickling. An exchange transfusion or simple transfusion may be useful in correcting anaemia, improving microvascular blood flow, tissue oxygenation and the patient's overall clinical condition (Ohene-Frempong, 2001).

Acute intrahepatic cholestasis. This is a rare and little understood complication that presents with extreme hyperbilirubinaemia (mainly conjugated) (Banerjee *et al*, 2001; Gardner *et al*, 2014), marked elevation of the alkaline phosphatase and variable rises in transaminase levels. There is a high mortality from liver failure or bleeding. There is no established treatment but exchange transfusion appears to be beneficial (Shao & Orringer, 1995).

Acute priapism. The treatment of priority in acute fulminant priapism is penile aspiration/irrigation followed by the intracavernosal injection of sympathomimetic drugs if aspiration fails to resolve the problem (Montague *et al*, 2003). This initial urological intervention should not be delayed while a transfusion is arranged.

Neither simple nor exchange transfusion have been evaluated for acute management of priapism in randomised controlled trials. Small case series and literature reviews provide no evidence of amelioration of pain or duration of priapism once this has been established (McCarthy *et al*, 2000; Merritt *et al*, 2006). Surgical management is indicated if initial urological measures are not effective (Montague *et al*, 2003). Shunt procedures for the relief of acute priapism require a general anaesthetic so that the patient may benefit from transfusion, as with other surgical procedures (Howard *et al*, 2013). If patients do not respond to initial shunt procedures there may be benefit from exchange transfusion to decrease %HbS. Local hospitals should develop referral pathways so that patients requiring specialist surgery are transferred promptly to tertiary centres. Such patients must be discussed with the SHT with regards to possible transfusion preoperatively.

Recommendations

Transfusion is recommended in cases of acute chest syndrome with hypoxia. Transfusion may be given by simple or exchange transfusion depending on clinical severity under the guidance of the SHT (Grade 1B).

Adults or children with signs or symptoms suggestive of acute ischaemic stroke should be transfused to sickle haemoglobin (HbS) <30% pending further investigation. Those with confirmed stroke due to sickle cell disease should continue regular transfusions indefinitely (Grade 1B).

Transfusion should be considered in the unwell patient with acute multi-organ failure, mesenteric syndrome (Grade 1C) and patients with severe sepsis (Grade 2C). Such cases should be discussed with the SHT.

The benefit of transfusion to relieve established acute priapism has not been shown in randomised controlled trials. Many patients require a shunt or drainage procedure under general anaesthesia, which may require a transfusion. Such cases should be discussed with the SHT (Grade 2C).

Indications for chronic transfusion

The best data to support chronic transfusion programmes are for the primary prevention of stroke (Adams *et al*, 1998; Adams & Brambilla, 2005) and secondary prevention of silent cerebral infarcts in paediatric populations (DeBaun *et al*, 2014). There is also good evidence for the effectiveness of transfusions in preventing recurrent stroke in children (Pegelow *et al*, 1995; Scothorn *et al*, 2002).

Chronic exchange transfusion has been utilised for a wide variety of indications, including prevention of recurrent vaso-occlusive crises and recurrent chest syndrome. In many

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of these circumstances there is also evidence of benefit of hydroxycarbamide therapy (Charache *et al*, 1995; Thornburg *et al*, 2012) and chronic transfusion should only be contemplated where hydroxycarbamide is ineffective or contra-indicated.

Where chronic transfusion is initiated outside the context of paediatric stroke, the parameters to assess efficacy should be clearly documented and the risks and benefits for the patient regularly reviewed. Outcomes of chronic transfusion programmes should be regularly audited across centres. Decisions to initiate chronic transfusion should be made by the SHT.

Primary and secondary stroke prevention

Long-term red cell transfusion is the mainstay of treatment for the primary and secondary prevention of stroke due to SCD. Evidence for the efficacy of transfusion for primary stroke prevention is available only for children but the principles may be relevant for adult patients (over 16 years).

Primary stroke prevention in children with SCD. Regular red cell transfusion to maintain HbS level <30% is indicated for the primary prevention of stroke in children (2–16 years) with SS or S/β^o thalassaemia with time averaged mean TCD velocities of ≥200 cm/s in the internal carotid or middle cerebral artery (Stroke Prevention Trial in Sickle Cell Anemia study – STOP) (Adams *et al*, 1998). Regular red cell transfusion reduced the risk of an initial stroke by 92% (Adams *et al*, 1998), This was confirmed in the Optimizing Primary Stroke Prevention in Sickle Cell Anemia (STOP2) Trial, where children whose transfusions were discontinued were more likely to have a stroke or to revert to abnormal TCD velocities than those who continued on regular transfusion (Adams & Brambilla, 2005).

The role of hydroxycarbamide in maintaining normal TCD velocities in children without severe cerebral vasculopathy or prior transient ischaemic attack (TIA) who have received transfusions for at least 1 year (mean 4 years) for primary stroke prevention has recently been investigated in the TCD With Transfusions Changing to Hydroxyurea (TWiTCH) trial (Ware *et al*, 2016). In this randomised trial, hydroxycarbamide at maximum tolerated dose (alternative group) was compared to standard transfusions (standard group) after patients randomised to hydroxycarbamide had been slowly weaned off transfusions over 4–9 months. This trial showed that hydroxycarbamide is non-inferior to transfusions for the maintenance of TCD velocities and can be used as a substitute to help prevent primary stroke after discontinuation of initial transfusion therapy.

Recommendations

Transfusion to maintain HbS <30% should be offered to children at high risk of stroke following Transcranial Doppler (TCD) screening. Transfusion is the recommended initial treatment to prevent stroke in such children (Grade 1A).

Hydroxycarbamide treatment should be considered for the primary prevention of stroke in children with high TCD velocities but not severe MRA-defined cerebral vasculopathy after an initial period of transfusion of at least 1 year (Grade 1A). The duration of the initial period of transfusion should be tailored to the individual patient; the transition to hydroxycarbamide should be done gradually and transfusion should be withdrawn after the hydroxycarbamide has been escalated to the maximum tolerated dose.

Secondary prevention of silent cerebral infarction in children with SCD. The role of transfusion in the management of children with sickle cell anaemia aged 5–15 years (median 10 years) with silent cerebral infarcts was investigated in the Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) (DeBaun *et al*, 2014). In this randomised trial, children with SS or S/β^o thalassaemia with silent cerebral infarcts and normal or conditional TCD velocities were randomised to receive monthly transfusions to a target Hb of 90 g/l and HbS <30% or standard care (observation group) for 3 years. The primary endpoint was recurrence of infarction, defined as a stroke, or new or enlarged silent cerebral infarct. The transfused group had a relative risk reduction of recurrence of infarction of 58% compared to the observation group; however, this was mainly due to a reduction in stroke incidence rather than a reduction in silent infarcts by transfusions. The authors recommended a screening Magnetic Resonance Imaging (MRI) scan of the brain to identify children who may benefit from medical or educational intervention (DeBaun *et al*, 2014). However, MRI is difficult to perform without sedation in children <7 years old, the age group in which the majority of silent cerebral infarcts occur.

Recommendation

Treatment options including transfusion should be discussed with families of children who are found to have silent cerebral infarcts. Transfusion should be offered to children who are identified as being at greatest risk for recurrence of infarction after discussion of its benefits and risks (Grade 1A).

Secondary prevention of overt stroke in children with SCD. The risk of recurrent stroke in children with SCD is very high. In a natural history study of 35 patients with a history of one or more strokes, the recurrence rate was 67% over a 9-year period, with 80% of the recurrent episodes occurring within 36 months of the initial event (Powars *et al*, 1978).

There have been no randomised trials comparing the use of transfusion to no intervention for prevention of recurrent stroke in SCD. Several single centre studies (Lusher *et al*,

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1976; Sarnaik *et al*, 1979; Russell *et al*, 1984; Balkaran *et al*, 1992) and two multi-centre retrospective studies (Pegelow *et al*, 1995; Scothorn *et al*, 2002) all reported a clear benefit of transfusion in reducing the risk of recurrence in patients who had suffered one or more previous episodes of cerebral infarction.

In the Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial, a non-inferiority trial that compared transfusion to HbS <30% plus chelation with hydroxycarbamide plus phlebotomy for the composite endpoint of secondary stroke prevention and improved control of iron overload, there were no cases of recurrent stroke in the transfused patients compared with 10% in the hydroxycarbamide/phlebotomy arm (Ware *et al*, 2012). The trial was closed early because even though the increased stroke risk in the hydroxycarbamide arm was within the predicted 12% rate, it was not offset by a reduction in iron overload through phlebotomy. Therefore, the authors concluded that transfusion and chelation remain a better way to manage children with sickle cell anaemia, stroke and iron overload.

Although the risk of stroke is not completely eliminated by regular transfusions (Pegelow *et al*, 1995; Scothorn *et al*, 2002; Hulbert *et al*, 2011), transfusions to maintain HbS <30% remains the recommended intervention to prevent stroke recurrence in children with SCD. There is some evidence from a small observational study that patients on transfusion programmes for secondary stroke prevention may be maintained on a less rigorous target of HbS <50% with little increased risk of stroke recurrence, provided they have been neurologically stable for at least 4 years after the initial stroke (Cohen *et al*, 1992).

Recommendation

Long-term transfusion to maintain HbS <30% is recommended for the prevention of recurrent ischaemic stroke due to sickle cell disease in children (Grade 1B).

Primary stroke prevention in adults with SCD. Adults with sickle cell anaemia are at increased risk of ischaemic and haemorrhagic stroke; the risk of ischaemic stroke is highest after the age of 30 years, whereas haemorrhagic stroke is most common in the 20–29 year age group (Ohene-Frempong *et al*, 1998). TCD has not been validated in adults and there is currently no tool for systematically assessing stroke risk. Studies to evaluate the efficacy of transfusion for primary stroke prevention in defined adult SCD populations have not been undertaken. There are no studies on the management of patients who, having been on long-term transfusions for primary stroke prevention since childhood, have crossed the transition threshold and become adults. Management of such patients is a subject for individual assessment, and discussion with young adults and carers should take place concerning the benefits and risks of remaining on transfusion or substituting with hydroxycarbamide.

Secondary stroke prevention in adults with SCD. Whilst neurological events, such as TIA or seizures, may be the initial presentation of sickle cell cerebrovascular disease, adults experiencing such episodes should be fully investigated for other possible causes (e.g. atrial fibrillation, carotid artery stenosis). Data on transfusion for secondary stroke prevention in adult SCD is limited. An observational study (Powars *et al*, 1978) that included some adult subjects strongly suggests that the risk of further strokes is likely to be high without intervention. Current practice is to perform chronic transfusions in adults who have suffered a stroke attributable to SCD (Sickle Cell Society 2008; NHLBI 2014).

Recommendation

Long-term transfusion to maintain HbS <30% is recommended for the prevention of recurrent ischaemic stroke due to sickle cell disease in adults (Grade 1B).

Duration of transfusions for stroke prevention. The optimal duration of transfusion is uncertain. Data from the STOP 2 trial indicated that patients who were maintained on transfusion for a follow up period of 65 months for primary stroke prevention had a 93% lower stroke risk than patients who discontinued transfusions after 30 months (Adams & Brambilla, 2005). The results of the TWiTCH trial show that hydroxycarbamide is efficacious and non-inferior to blood transfusions for primary stroke prevention in children without severe cerebral vasculopathy or prior TIA who have been on transfusion for at least a year (mean 4 years) (Ware *et al*, 2016). However, the trial did not establish the optimal duration of transfusions prior to the switchover to hydroxycarbamide. Therefore, we suggest that the duration of this initial period of transfusions is assessed on a case-by-case basis.

For patients who have had a stroke, the risk of recurrent stroke is highest in the first 3 years after the initial event (Powars *et al*, 1978; Russell *et al*, 1984; Balkaran *et al*, 1992; Pegelow *et al*, 1995), suggesting that maintaining a HbS level <30% is especially important during this period. The benefits of transfusions beyond this period are debatable. Recurrent stroke has been reported within 12 months of prospectively stopping transfusions in 5 out of 10 children who had been on a transfusion programme for as long as 9·5 years (Wang *et al*, 1991). Therefore, transfusion for secondary stroke prevention may need to continue indefinitely (Sickle Cell Society 2008; NHLBI 2014), but the decision to continue transfusions should be tailored to the needs of individual patients; it should be regularly reviewed and risk/benefit considerations must be discussed with the patient and/or parents. It has been suggested that where the stroke has occurred in the context of acute illness (e.g. aplastic crisis), transfusions may be discontinued after 2 years if repeat vascular imaging is normal at that time (RCP 2004).

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Recommendation

Transfusion is the recommended initial treatment of choice for children at high risk of stroke based on TCD screening (Grade 1A). Provided there is no concomitant severe cerebral vasculopathy or prior history of TIA, hydroxycarbamide may be offered to such children after at least 1 year of transfusions (Grade 1A) but the exact duration of transfusions should be tailored to the individual patient.

Long-term transfusion should be offered to children and adults who have suffered a previous ischaemic stroke due to sickle cell disease (Grade 1B).

Recurrent ACS

Acute chest syndrome is a marker of SCD severity, being a risk factor for early death in SS patients >20 years (Castro *et al*, 1994; Platt *et al*, 1994) and 44% of patients will have recurrent episodes (Castro *et al*, 1994). Evidence suggests that chronic transfusion therapy is effective in reducing incidence and hospitalisation due to ACS (Styles & Vichinsky, 1994; Miller *et al*, 2001; Hankins *et al*, 2005b). In the SIT trial, ACS was significantly reduced in comparison with untransfused patients with an incidence rate ratio of 0·13 (DeBaun *et al*, 2014). However, given that there is a clear benefit of hydroxycarbamide for ACS prevention (Charache *et al*, 1995; Thornburg *et al*, 2012), transfusion should be considered only if hydroxycarbamide is ineffective or contraindicated.

Recommendation

Hydroxycarbamide is recommended as first line treatment for recurrent acute chest syndrome or repeated painful episodes. Regular transfusion should be considered for patients failing this treatment or for whom it is contraindicated (Grade 1B).

Frequent painful crises

The frequency of sickle cell painful crises is a marker of disease severity; SS patients who are admitted to hospital ≥3 times a year because of vaso-occlusive crises are at increased risk of early death (Platt *et al*, 1991). Prolonged hospitalisations and high readmission rates are also associated with a higher mortality (Houston-Yu *et al*, 2003; Ballas & Lusardi, 2005).

Long-term transfusion may be of benefit in patients with recurrent painful crises. In a retrospective study, long-term blood transfusion significantly reduced the hospital admission frequency for vaso-occlusive crises from 2·20 to 0·21 per patient per year (Styles & Vichinsky, 1994). In the STOP trial, the hospital admission rate for vaso-occlusive crises in chronically transfused patients was significantly less than for patients on standard care (9·7 vs. 27·1 events per 100 patient years) (Miller *et al*, 2001). In the SIT trial, incidence rates of painful crises were significantly reduced by transfusion with an incidence rate ratio of 0·41 (DeBaun *et al*, 2014).

However, hydroxycarbamide is very effective in reducing the rate of painful crises and ACS in both adults and children (Charache *et al*, 1995; Scott *et al*, 1996; Olivieri & Vichinsky, 1998) and improves survival (Steinberg *et al*, 2003, 2010). Therefore, hydroxycarbamide is the first line therapy for patients with frequent vaso-occlusive crises with transfusion being reserved for those who do not respond or in whom hydroxycarbamide is contraindicated.

Recommendation

Transfusion, either by simple or exchange transfusion, should be considered in patients with frequent painful episodes where hydroxycarbamide is ineffective or contraindicated (Grade 1B).

Other possible indications

Transfusion has been used in a variety of sickle cell related problems, where clinical experience or case reports/series have suggested benefit. In patients with renal disease, transfusion may be considered in end stage renal disease, in those awaiting a renal transplant and post-renal transplant (Sharpe & Thein, 2014). Transfusion has also been used in patients undergoing liver transplantation in the peri-transplant setting (Blinder *et al*, 2013; Gardner *et al*, 2014). Blood transfusion in the treatment of pulmonary hypertension seems theoretically reasonable, with the aim of decreasing haemolysis and thereby nitric oxide scavenging and consequent pulmonary vasoconstriction, and has been recommended for this purpose (Machado & Gladwin, 2005; Cho & Hambleton, 2011).

The incidence of priapism and symptomatic avascular necrosis was significantly decreased by transfusion in the randomised SIT trial with incidence rate ratios of 0·13 and 0·22, respectively (DeBaun *et al*, 2014), but its benefit in the management of patients with established disease has not been proven in randomised trials.

Transfusion has been used for other conditions including leg ulcers (Minniti *et al*, 2010; Delaney *et al*, 2013) and progressive sickle retinopathy (Gustave *et al*, 2013; McKinney *et al*, 2015). In some cases the reported benefit from transfusion has seemed dramatic, but specific recommendations must await more extensive data.

Recommendation

Transfusion for indications where evidence is limited should be based on a case-by-case assessment after full risk-benefit analysis (Grade 2C).

Preoperative transfusion

Anaesthesia and surgery increase sickle-related complications, particularly ACS, while transfusion reduces the risk of perioperative complications (Vichinsky *et al*, 1995; Howard *et al*,

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2013). Meticulous attention should be paid to optimising all aspects of perioperative care including oxygenation, hydration and warmth, as well as anaesthetic and surgical technique. Close liaison between anaesthetist, surgeon and haematologist is essential to ensuring good outcomes. Complicated surgical procedures should be undertaken in centres where there is specialist haemoglobinopathy support.

With regards to transfusion, the two key questions to consider are:

1 Should SCD patients be transfused routinely preoperatively?
2 If transfused, what is the optimal regimen?

Role of routine preoperative transfusion

This has long been controversial with insufficient randomised trial data impacting on variability in practice across hospitals in England (Buck *et al*, 2005) and in other studies (Table II). There have been advocates both of routine pre-operative transfusion (Janik & Seeler, 1980; Fullerton *et al*, 1981; Derkay *et al*, 1991; Bhattacharyya *et al*, 1993) and selective transfusion (Oduro & Searle, 1972; Homi *et al*, 1979; Bischoff *et al*, 1988; Griffin & Buchanan, 1993; Fu *et al*, 2005; Leff *et al*, 2007). A large observational study showed that perioperative transfusion was associated with a significantly lower rate of SCD-related postoperative complications for SS patients undergoing low-risk procedures and for SC patients at all surgical risk levels (Koshy *et al*, 1995). However, these findings suggested that not all patients should routinely be transfused preoperatively. Another study showed that those receiving "no transfusion" suffered the highest overall SCD-related complication rate (32%), chest syndrome rate (19%) and mortality rate (5%) but without significant difference between those randomised to aggressive or simple transfusion regimens (Haberkern *et al*, 1997).

The most compelling evidence to support preoperative transfusion comes from the Transfusion Alternatives Preoperatively in Sickle Cell Disease (TAPS) trial (Howard *et al*, 2013). This was a randomised controlled trial in which a total of 67 SS and Sβ^o thalassaemia patients undergoing low risk surgery (e.g. adenoidectomy, dental procedures) and medium risk surgery (e.g. joint replacement, cholecystectomy, tonsillectomy) were randomly assigned to either no transfusion or transfusion (simple transfusion if Hb <90 g/l, exchange transfusion if Hb ≥90 g/l to achieve estimated HbS <60%) (Howard *et al*, 2013). Classification of surgical risk was in accordance with the Cooperative Study of Sickle Cell Disease criteria (Koshy *et al*, 1995). Significantly greater clinically important complications (39% vs. 15%) and serious adverse events (30% vs. 3%) were found in untransfused SS and S/β^o-thalassaemia compared to transfused patients undergoing low-risk and medium-risk surgery. The most common serious adverse event was ACS, accounting for 91% of all serious events occurring in 27% of untransfused patients compared with 3% in transfused patients. Intraoperative or postoperative transfusion was increased in the patients who had not been transfused preoperatively (Howard *et al*, 2013).

Although the final number of subjects recruited into the trial at its termination was small, the TAPS study provided good evidence to support preoperative transfusion in SS patients undergoing low- and medium-risk surgical procedures.

Optimal preoperative transfusion regimen

In a study of SS and S/β^o-thalassaemia patients (Vichinsky *et al*, 1995), a top-up transfusion regimen to haemoglobin 100 g/l was reported to be as effective as exchange transfusion to attain haemoglobin 100 g/l and HbS <30% in preventing perioperative complications and was associated with a 50% lower risk of transfusion-related complications. However, it must be noted that the type of exchange transfusion procedure was not described and some of the exchange transfused patients required repeated simple transfusion. Furthermore, in 14% of patients in the exchange transfusion arm, post-transfusion %HbS was substantially higher than the 30% target for a number of reasons including inadequate transfusion. Moreover, in the simple transfusion group, nearly 43% of the patients received "minimal transfusion therapy". Despite these limitations, the authors concluded that simple transfusion was as effective as exchange transfusion.

The issue of whether simple or aggressive transfusion had better outcomes was not addressed in the TAPS trial, where the transfusion regimen was either simple transfusion if Hb <90 g/l or partial exchange transfusion if Hb ≥90 g/l, to a target Hb of 100 g/l and estimated HbS <60% (Howard *et al*, 2013). Seventy-six per cent of transfused patients received simple transfusion, providing support for the efficacy of a conservative transfusion regimen in reducing post-operative complications for the relevant surgical procedures reported in the trial.

It is not possible to give dogmatic guidelines regarding the choice of type of preoperative transfusion and transfusion targets; these should be tailored to the individual patient, taking into account factors such as the type of surgery, the severity of the patient's SCD and co-morbidities (see section Deciding which patients may benefit from preoperative transfusion, Role of transfusion in surgery for sickle genotypes other than SS). However, it is reasonable to undertake simple transfusion for low and moderate risk surgery if Hb is <90 g/l to achieve a post-transfusion Hb of 100 g/l. An exchange transfusion should be considered for patients undergoing high-risk surgery, patients with severe SCD and those with significant co-morbidities.

Emergency surgery

Evidence for the role of transfusion in emergency surgery is very limited. In the largest study on surgery in SCD, 717

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Table II. Studies on preoperative transfusion in sickle cell disease.

Reference Study type Period of observation	Genotypes	Surgical procedures (*n*)	Risk category of procedures	Elective procedures (*n*)	Emergency Procedures (*n*)	Transfusion practice
Howard *et al* (2013) RCT 2007–2011	SS: *N* = 54 Sβ°thal: *N* = 13	67	Low & moderate risk	67	0	Transfusion (top up or partial exchange) versus no transfusion
Vichinsky *et al* (1995) RCT 1988–1993	SS: *N* = 604	604	All risk levels	604	0	Aggressive versus conservative transfusion
Koshy *et al* (1995) Observational, natural history 1978–1988	SS: *N* = 553 SC: *N* = 102 Sβ°thal: *N* = 41 Sβ⁺thal: *N* = 21	1079	All risk levels	806	271	Majority transfused Low risk 63·1% Moderate risk 90%
Haberkern *et al* (1997) [Subgroup of Vichinsky *et al* (1995)] RCT plus two non-randomised groups 1988–1993	SS and Sβ°thal: genotype numbers not given	364	Moderate risk, (Cholecystectomy only)	364	0	Aggressive versus conservative transfusion 2 non-randomised groups: No transfusion (*N* = 37) and transfusion
Vichinsky *et al* (1999) [Subgroup of Vichinsky *et al* (1995)] RCT plus two non-randomised groups 1988–1993	SS: *N* = 127 Sβ°thal: *N* = 11	138	Low and moderate risk orthopaedic surgery	138	0	Aggressive versus conservative transfusion 2 non-randomised groups: No transfusion (*N* = 24) and transfusion
Waldron *et al* (1999) [Subgroup of Vichinsky *et al* (1995)] RCT plus two non-randomised groups 1988–1993	SS and Sβ°thal: genotype numbers not given	165	Low and moderate risk ENT surgery	165	0	Aggressive versus conservative transfusion 2 non-randomised groups: No transfusion (*N* = 20) and transfusion
Neumayr *et al* (1998) Prospective, observational 1988–1993	SC: *N* = 75 Sβ⁺thal: *N* = 11 *Other: *N* = 6	92 (in SC patients)	All risk levels	92	0	35 patients (38%) transfused
Homi *et al* (1979) Retrospective, Observational 1958–1978	SS: *N* = 211 SC: *N* = 51 Sβ°thal: *N* = 14 Sβ⁺thal: *N* = 8	284	All risk levels	242	42	Selective transfusion
Bischoff *et al* (1988) Retrospective, Observational 1978–1986	SS: *N* = 50 SC: *N* = 13 Sβthal: *N* = 3	82	All risk levels	54	28	Pre-op transfusion *N* = 48 No transfusion *N* = 16
Fullerton *et al* (1981) Prospective, Observational 1964–1979	SS: *N* = 50	67	All risk levels	67	0	Exchange transfusion versus top up transfusion

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Table II. (*Continued*)

Reference Study type Period of observation	Genotypes	Surgical procedures (*n*)	Risk category of procedures	Elective procedures (*n*)	Emergency Procedures (*n*)	Transfusion practice
Fu *et al* (2005) Retrospective, Observational 1991–2003	SS: $N = 28$	38	Low risk	38	0	Non-transfusion strategy No transfusion in 85% of cases
Griffin and Buchanan (1993) Retrospective, Observational 1975–1990	SS: $N = 43$ SC: $N = 8$ $S\beta^0$thal: $N = 2$ $S\beta^+$thal: $N = 1$	66	All risk levels	66	0	Non-transfusion strategy
Oduro and Searle (1972) Observational 1970–1972	SS: $N = 17$ SC: $N = 21$ Sβthal: $N = 2$ SHPFH: $N = 1$	42	All risk levels	36	6	Selective transfusion

ENT, ear, nose and throat; N, number; RCT, randomised controlled trial; SS, sickle cell anaemia; SC, compound heterozygosity for haemoglobin S and haemoglobin C; $S\beta^0$thal, haemoglobin S/β^0 thalassaemia; $S\beta^+$thal, haemoglobin S/β^+ thalassaemia; SHPFH, haemoglobin S/hereditary persistence of fetal haemoglobin.
*Other, comprises haemoglobin S/hereditary persistence of fetal haemoglobin, haemoglobin S/haemoglobin Lepore and haemoglobin S/haemoglobin O-Arab.

patients underwent 1079 surgical procedures of which 271 (25%) were emergency procedures (Koshy *et al*, 1995). When all procedures (elective + emergency) were considered, most patients undergoing cholecystectomy and splenectomy were transfused preoperatively (94% of SS and 82% of SC) as were those undergoing Caesarean section or hysterectomy (91% of SS and 72% of SC). As the data for postoperative outcomes were analysed together for elective and emergency procedures (rather than separately), it is not possible to assess the effect on transfusion on outcomes for SCD patients undergoing emergency surgery in this study.

Similarly, in another observational study, no separate analyses were carried for patients undergoing emergency surgery (Bischoff *et al*, 1988). In a further retrospective study where perioperative transfusion was used selectively and sparingly (Homi *et al*, 1979), 5 postoperative deaths occurred in 28 patients undergoing emergency surgery; however, it is not clear if these patients were transfused preoperatively.

The important principle here is to not unnecessarily delay emergency surgery because of transfusion. A reasonable policy is to give a simple transfusion to patients who have Hb <90 g/l and then proceed to surgery with minimal delay. If the Hb is >90 g/l and the surgical procedure is low risk, it is reasonable to proceed to surgery without delay while arrangements are made to transfuse the patient intra- operatively or post-operatively if necessary.

Role of transfusion in surgery for sickle genotypes other than SS

There is a paucity of evidence relating specifically to SC and other sickle genotypes. One observational study suggested a benefit for transfusion in reducing the incidence of sickle cell-related postoperative complications for SC patients at all levels of surgical risk (Koshy *et al*, 1995), however, transfused SC patients undergoing low-risk surgery had higher rates of non-sickle cell postoperative complications (fever and bleeding) than untransfused patients. A further study demonstrated that preoperative transfusion was beneficial for moderate risk procedures, particularly abdominal surgery (Neumayr *et al*, 1998).

Deciding which patients may benefit from preoperative transfusion

The TAPS trial has provided evidence for the efficacy of preoperative transfusion only for SS patients with preoperative Hb 60–90 g/l undergoing a narrow range of elective medium-risk surgical procedures (Howard *et al*, 2013). The trial's findings may not be applicable to many other surgical situations. However, on the basis of the findings, it is recommended that preoperative transfusion to an Hb of 100 g/l be considered a standard intervention in SS undergoing elective low-risk or medium-risk surgery as defined in the study (Howard *et al*, 2013). For other patients it is recommended

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that each case is judged on its own merits in consultation with the SHT. Transfusion should be considered when the risk of post-operative chest infection or ACS is high, but this has yet to be clearly shown in prospective trials. Transfusion is also recommended for individuals with significant co-morbidities (e.g. abnormal pulmonary, cardiac, renal and hepatic function) and in those undergoing high-risk surgical procedures or having lengthy surgical procedures (Wun & Hassell, 2009).

The optimal method of transfusion remains an open question but currently available evidence indicates that simple transfusion is not inferior to exchange transfusion in low- to medium-risk surgery (Vichinsky *et al*, 1995; Howard *et al*, 2013), However exchange transfusion is recommended for patients undergoing high-risk surgery, although this has not been directly addressed in studies.

Recommendation

Preoperative transfusion (simple transfusion to Hb 100 g/l if Hb <90 g/l or partial exchange if Hb ≥90 g/l) is recommended for SS patients undergoing low and medium-risk surgery (Grade 1A).

Exchange transfusion is recommended for all patients with SS requiring high-risk surgery (Grade 1C).

Preoperative transfusion is recommended for patients with SC undergoing moderate risk surgery and high-risk surgery (Grade 1C).

All other patients undergoing surgery should be individually assessed, taking into account previous history and complexity of surgery, and a management plan should be formulated to include the need for transfusion (Grade 1C).

For patients requiring emergency surgery, the urgency and complexity of the procedure should be taken into account in the timing of perioperative transfusion. Provided transfusion will not result in undue delay to surgery, simple transfusion should be given preoperatively to a target Hb of 100 g/l if the Hb is low. If Hb ≥90 g/l and surgical risk is low but transfusion will result in an unacceptable delay to surgery, it is reasonable to proceed to surgery without delay while arrangements are made to transfuse the patient intra- operatively or post-operatively if necessary (Grade 1C).

Transfusion in pregnancy

Sickle cell disease in pregnancy is associated with an increased risk of both maternal and fetal complications (Smith *et al*, 1996; Serjeant *et al*, 2004; Villers *et al*, 2008; Oteng-Ntim *et al*, 2015a,b). Maternal complications include sickle-related problems (notably painful crises, ACS) and pregnancy-related syndromes, such as pre-eclampsia, preterm labour and an increased rate of Caesarean section (Villers *et al*, 2008; Oteng-Ntim *et al*, 2015b). Fetal complications include intra-uterine growth restriction, prematurity and increased rates of fetal loss (Serjeant *et al*, 2004; Oteng-Ntim *et al*, 2015b). In a UK-wide observational study of 109 pregnancies in SCD, 52% of women suffered painful crises during pregnancy and 13% within 6 weeks post-partum; 6% had ACS and 21% were admitted to intensive care (Oteng-Ntim *et al*, 2015a).

There is a single prospective randomised controlled study that compared 36 pregnant SS women who were transfused prophylactically (simple or partial exchange transfusion commencing in the first or second trimester; target Hb 100–110 g/l; target HbS <35%) to a control group of 36 SS women who received transfusion only for medical or obstetric emergencies (Koshy *et al*, 1988). This study found a significant reduction in the incidence of painful crises and substantial decrease in other SCD-related complications in the group receiving prophylactic transfusions but no difference in medical and obstetric complications or fetal outcome between the two groups. Additionally, satisfactory pregnancy outcomes were observed in a non-randomised group of SS, SC and S/β thalassaemia women who were transfused only for medical or obstetric emergencies. In view of these results, the authors concluded that omitting prophylactic transfusions was not harmful to pregnant patients with SCD or their offspring and thus routine use of transfusions in pregnancy was not justified. However, this study had a number of significant limitations including small sample size and high risk of bias (Malinowski *et al*, 2015).

Other uncontrolled studies have shown conflicting evidence, with some showing evidence for a benefit of transfusion (Cunningham *et al*, 1983; Morrison *et al*, 1991; Howard *et al*, 1995; Gilli *et al*, 2007; Asma *et al*, 2015; Benites *et al*, 2016) whilst others did not (Tuck *et al*, 1987; El-Shafei *et al*, 1995). The study by Howard *et al* (1995) demonstrated a trend for reduced SCD-related complications in the third trimester in patients on prophylactic exchange transfusions, leading the authors to recommend prophylactic transfusions from the 26th week of pregnancy onwards in SS patients. In a more recent retrospective study, high rates of painful sickle crises and other severe sickle complications occurred despite a policy of prophylactic partial exchange transfusions to maintain HbS <40% from 22 to 26 weeks onwards for all sickle patients (Ngo *et al*, 2010), but there was no control arm not receiving prophylactic transfusion for comparison.

A Cochrane review which examined evidence from two small studies of low quality concluded that other than a marginal reduction in the rate of painful crises, prophylactic transfusion conferred no clear advantage over selective transfusion with regards to pregnancy outcome (Okusanya & Oladapo, 2013). However, the findings of a more recent systematic review and meta-analysis, which included 11 cohort studies and the randomised controlled trial reported by Koshy *et al* (1988), suggested that prophylactic transfusion is associated with a reduction in vaso-occlusive episodes, maternal mortality, overall pulmonary complications, neonatal mortality and pre-term birth while acknowledging the

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methodological limitations of the original study designs (Malinowski *et al*, 2015).

As a result of the limited and sometimes conflicting data, the use of prophylactic transfusion varies between centres. There is a consensus however that pregnant women with a history of severe SCD-related complications, such as recurrent ACS and stroke, individuals on chronic transfusion prior to pregnancy, and those with repeated sickle cell crises or exacerbation of anaemia during pregnancy, should receive transfusion (Koshy, 1995; Sickle Cell Society 2008; RCOG, 2011). Prophylactic transfusion should also be considered for women with other serious medical or obstetric conditions or with a multiple pregnancy. (Koshy, 1995; ACOG, 2007; RCOG 2011).

It should be emphasised that pregnancy in women with SCD is high-risk and expert obstetric care is essential to achieving good outcomes. The ideal standard of care is joint management by obstetricians and haematologists who are experienced in the care of SCD patients.

Recommendations

Prophylactic transfusion is not routinely required for sickle pregnancy, but should be considered for women with:

- **previous or current medical, obstetric or fetal problems, related to SCD**
- **women previously on hydroxycarbamide because of severe disease**
- **multiple pregnancy (Grade 1C).**

Women on long-term transfusions for stroke prevention or for amelioration of severe sickle complications should continue with regular transfusions throughout pregnancy. (Grade 1B).

Transfusion should be considered in women with worsening anaemia or those with acute SCD complications (acute chest syndrome, stroke etc.) (Grade 1B).

Date for guideline review

This guideline will be reviewed within 5 years of completion of the final draft.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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