Rationale for RBC Transfusion in SCD

- Dilution of HgbS-containing RBCs via the addition of HgbA-containing cells from the blood of normal donors
- Suppression of erythropoietin release caused by the rise in Hgb, thereby reducing the production of new HgbS-containing cells
- Decrease in percentage of HgbS-containing cells due to the longer circulating lifespan of HgbA-containing cells
- Increase in Hgb oxygen saturation levels by approximately 1 to 6 percent, which increases oxygen delivery to the tissues

Evidence-Based Indications for RBC Transfusion in SCD

- Avoid simple transfusion for uncomplicated vaso-occlusive pain episode without symptomatic anemia
  - no evidence that simple transfusion therapy will abate the pain episode
  - there is a finite risk of transfusion-related complications
- Acute therapeutic transfusion indicated for:
  - Acute Stroke
  - Acute Chest Syndrome
  - Acute multi-organ failure (unrelated to DHTR/hyperhemolysis)
  - Acute symptomatic anemia (> 2gm/dL drop from baseline with onset of symptoms such as heart failure, dyspnea, hypotension, marked fatigue)
  - Hepatic or splenic sequestration
  - A significant drop in baseline reticulocyte count most commonly associated with infection, particularly parvovirus B19 infection

Evidence-Based Indications for RBC Transfusion in SCD

- Prophylactic transfusion indicated for:
  - Stroke (secondary prevention)
  - Prevent recurrent silent cerebral infarcts in children
  - Prevent recurrent ACS despite hydroxyrurea therapy in severely affected individuals
  - Vaso-occlusive pain episodes that are severe, frequent, and not responsive to maximum tolerated doses of hydroxyurea
  - Recurrent priapism.
  - Pulmonary hypertension (PH) with progressive clinical symptoms or increasing pulmonary artery pressures PH who are not benefitting from hydroxyurea therapy

Guidelines* for RBC Transfusion in SCD

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

* *British Journal of Haematology*, 2017, **176,** 192–209

Guidelines* for RBC Transfusion in SCD

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.

* *British Journal of Haematology*, 2017, **176,** 192–209

Overview of RBC Transfusion in SCD

- Avoid unnecessary transfusions:
  - Reduce risk of complications (iron overload, fluid overload, transfusion reactions, infections)
  - Reduce alloimmunization
- (Using a white blood cell filter to decrease the rate of febrile non-hemolytic transfusion reactions)
- (Chelation therapy if iron stores reach a selected threshold)
- Matching for minor RBC antigens (C, E, and Kell) to reduce the risk of alloimmunization
  - In US the ethnic mismatch between donor and recipients increases the likelihood of alloimmunization because the frequency of minor RBC antigens is heavily influenced by ethnic origin.
  - In US ~20-70% will develop alloimmunization with only ABO and D versus 5-15% with limited phenotype matching for C, E, K
  - In Uganda prevalence of alloimmunization ~6% but this may reflect a decreased rate of RBC transfusion (including anti-S)

Higher incidence of Delayed Hemolytic Transfusion Reaction and Hyperhemolytic Transfusion Reaction in SCD

- King's College Hospital, London over 5 year period
  - evidence of DHTR 7.7% SCD patients or 23/2158 (1.1%) transfusion episodes – 5 severe DHTRs and 2 deaths
- Henri Mondor Hospital, France during 12 years
  - 99 cases in 69 adult sickle cell patients – 6 deaths

Habibi et al. AJH 2016; 91:989-994. Vidler et al. BJH 2015; 169: 746-753. King K and Shirey RS. Transfusion 2010; 50: 2-4.

Laboratory Investigation

Required	Additional Considerations
• Clerical check • Visual inspection of the unit • Posttransfusion serum hemoglobin (qualitative) • Posttransfusion direct antiglobulin test (DAT) • Confirmation of posttransfusion ABO/Rh • Repeat pretransfusion ABO/Rh • Pre- and posttransfusion antibody screen • Repeat special antigen typing • Crossmatch with pre-and postreaction specimens	• Antibody identification panels on pre- and postreaction samples • Enhanced antibody screening method: PEG, gel, enzymes) • Enhanced crossmatches: PEG, enzymes • Red cell eluate on pre- and postreaction samples • Serum haptoglobin • Serum bilirubin • Urine hemoglobin and hemosiderin • Culture and gram stain of the blood bag • DAT on donor units • Investigation of additional products transfused within 24 hrs

Hemolytic Transfusion Reactions (HTR)

Acute < 24 hrs	Delayed > 24 hrs up to 6 weeks
Intravascular hemolysis • Life threatening • Hemoglobinemia • Hemoglobinuria	**Extravascular hemolysis** • Shortened RBC survival
Symptoms	
• Fever ±chills/rigors • Pain (infusion site, back, chest, flank, groin, HA) • Nausea/vomiting • Dyspnea • Hypotension • Tachycardia	• Fever ± chills • Jaundice • Hypotension (very rare)
Complications	
• Activation of complement → hypotension and shock • Impaired renal function (multifactorial) • DIC	• Impaired renal function • Anemia
Outcome	
• May be fatal	• Rarely fatal

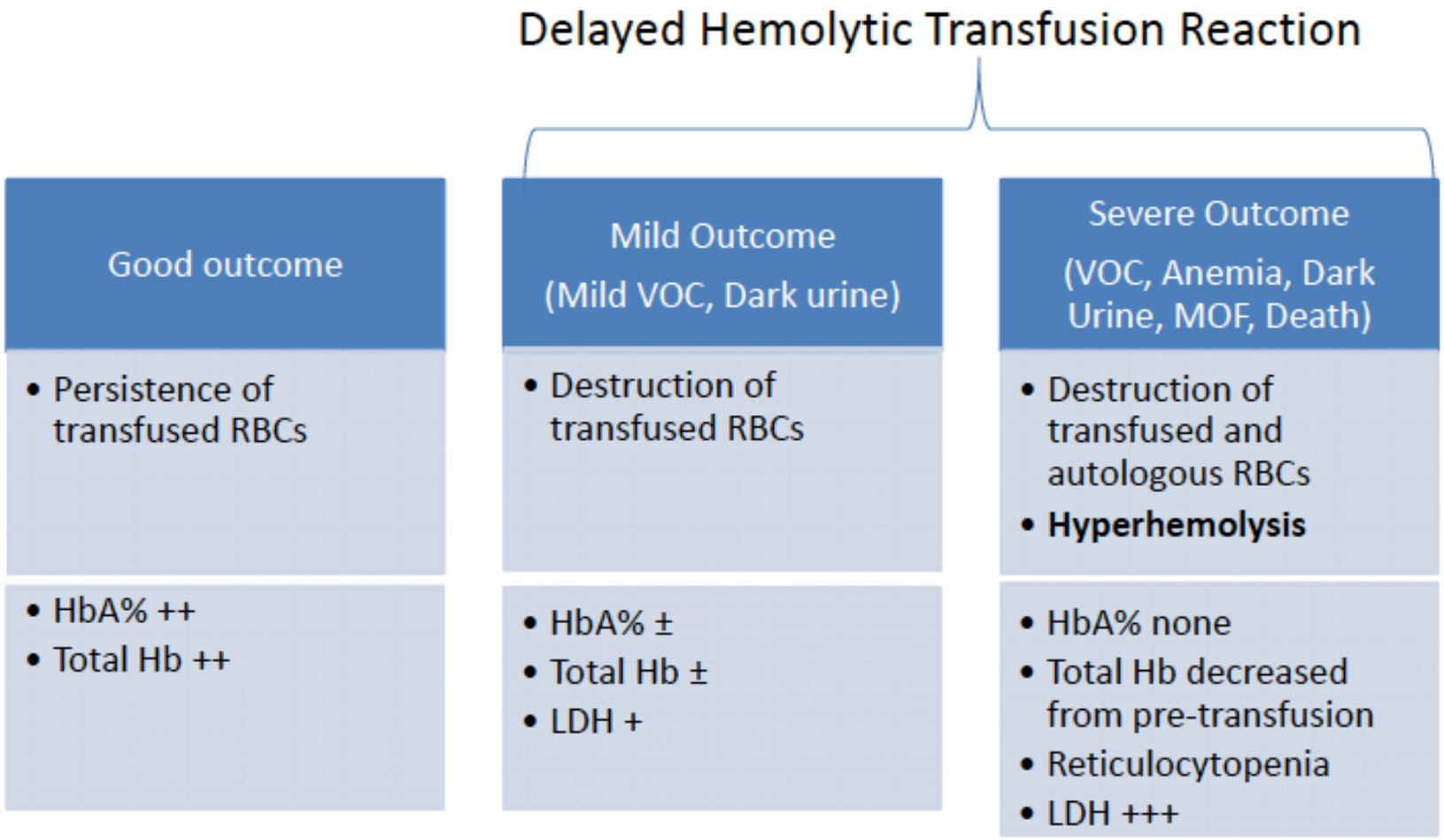
Diagnosis of HTRs

AHTRs	DHTRs	Delayed Serologic TRs (DSTR)
• Positive DAT (IgG or C3) • Positive elution test- alloantibody on RBCs • Increased LDH • Increased Bilirubin • Low Haptoglobin • Hemoglobinuria • Low Fibrinogen • Increased Plasma hemoglobin	• Positive DAT- 24 hours-28 days after cessation of transfusion • Positive elution test • Inadequate rise of Hb • Unexplained appearance of spherocytes	• Demonstration of new clinically-significant alloantibodies that were not present on the pre-transfusion specimen (24hrs-28 days) • Positive DAT • Newly positive Ab screen with newly identified RBC alloantibody

Delayed Hemolytic Transfusion Reaction

- Alloantibodies develop against antigens on transfused RBCs
- These alloantibodies are most often not detected in the serum during the pre-transfusion screening test:
  - result from remote antigenic exposure and waning of alloantibody titers
  - followed by increase in titer with immune re-stimulation with re-exposure.
- The most life-threatening consequence of allo-immunization in SCD is the development of DHTR with hyperhemolysis.
  - This type of hemolytic reaction is unpredictable and potentially under-recognized because its clinical presentation may resemble a vaso-occlusive crisis

Delayed Hemolytic Transfusion Reaction presents 1 to 21 days after transfusion



Adapted from France Pirenne, AABB 2016

Common clinical findings during DHTR in Sickle Cell Disease

Finding	Frequency
Hemoglobinuria/dark urine	96%
Pain	89%
Fever	64%
Anemia signs	44%

Habibi et al. AJH 2016; 91:989-994.

Key Clinical Features of DHTR/Hyperhemolysis Syndrome

- Fever and pain
  - Mimics sickle cell crisis
- Evidence of hemolysis
  - Hemoglobinuria
  - Hyperbilirubinemia
  - Elevated LDH
- Severe anemia
  - post-transfusion HCT/Hb measurement below pre-transfusion level
- Decreased absolute reticulocyte count
- **Exacerbation with transfusion**
- Early Recognition is Key
  - Difficult due to background chronic hemolysis and sickle cell pain crisis
- **Quickly evolves within a few hours:**
  - **Multiorgan failure**
  - **Death**

Win N. Expert Rev Hematol 2009; 2: 111-115.
Habibi et al. AJH 2016; 91:989-994.

Potential Mechanisms

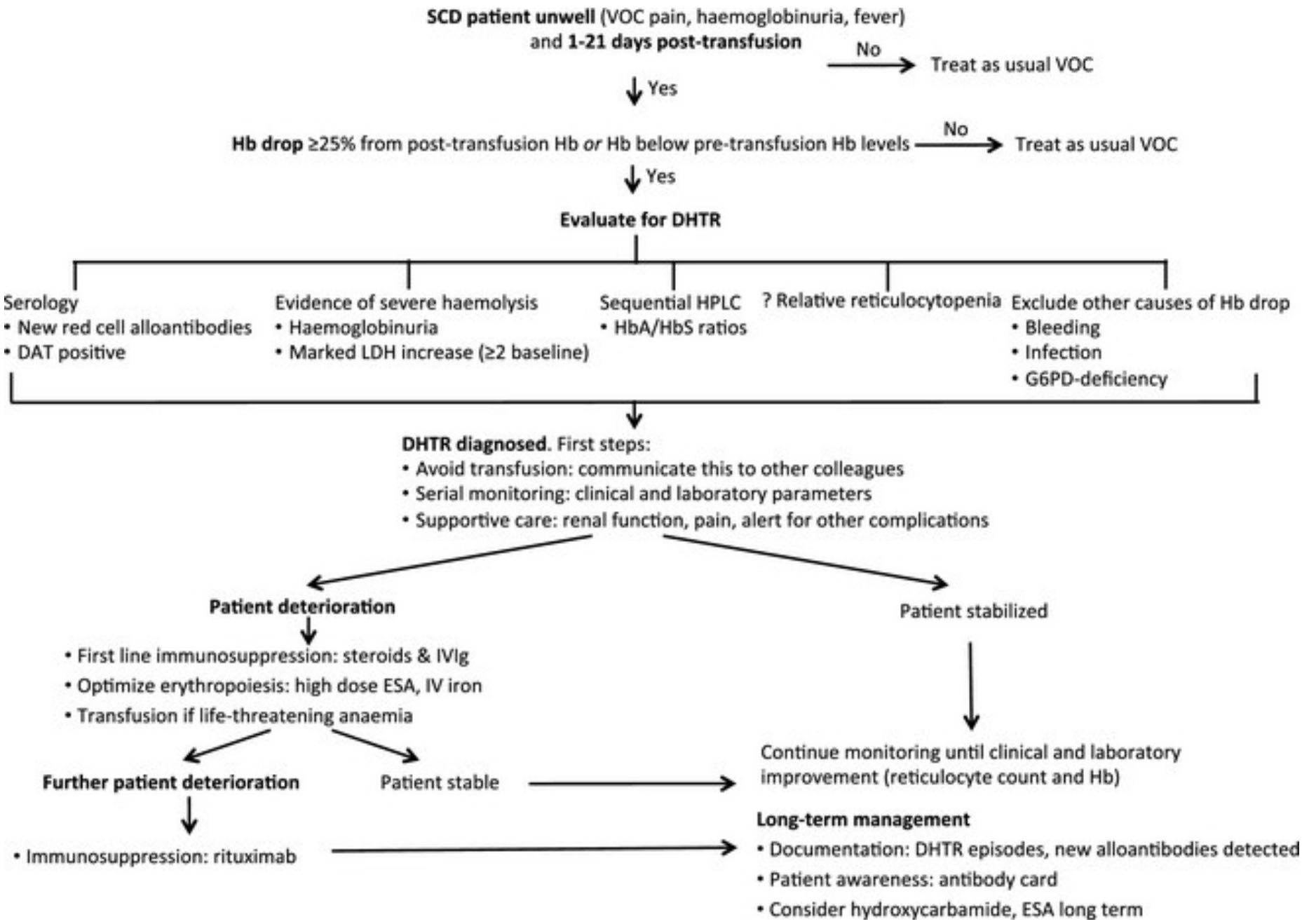
- Poorly understood
  - DAT positive and DAT negative described
  - Triggers: alloimmunization, hemoglobinopathy (sickle cell, thalassemia)
- Bystander hemolysis
  - Destruction of autologous RBCs
- Suppression of erythropoiesis
  - Reticulocytopenia
- Activated macrophages
  - Aid in destruction of RBCs

Win N. Expert Rev Hematol 2009; 2: 111-115.
Danaee A. et al. Transfusion Med Rev 2015; 220-230.
Habibi et al. AJH 2016; 91:989-994.

Table I. Differentiating DHTR from VOC episodes in SCD.

	DHTR	VOC episodes
Context	Recent RBC transfusion (within 2–21 d)	Any
Symptoms	Pain, fever, haemoglobinuria	Pain, fever
Reticulocytes	Variable – relative reticulocytopenia or elevated	Frequently elevated from baseline unless transient RBC aplasia from acute infection e.g. Parvovirus
LDH	Highly elevated (several times patient's baseline LDH)	Mildly elevated compared to patient's baseline LDH
Hb quantitation	Decrease in Hb to below post- and sometimes, pre-transfusion level, rapid clearance of HbA% with concomitant increase in HbS%	Unchanged or mild decrease from baseline (or if transfused, appropriate increase in Hb)
Immunohaematology	DAT positive (~75%) or negative (~25%); new RBC alloantibody detected in some cases May require RBC eluates	DAT negative

DHTR, delayed haemolytic transfusion reaction; VOC, veno-occlusive crisis; SCD, sickle cell disease; RBC, red blood cell; LDH, lactate dehydrogenase; DAT, direct antiglobulin test.



British Journal of Haematology, 2015, **170,** 745–756

Hematopoietic Cell Transplant in SCD: Limitations

- The clinical course of the disease is quite variable, and prognostic factors that might indicate which patients are most likely to develop advanced stage disease, and thus be candidates for HCT, are lacking.
- Patient eligibility is limited because of the presence of advanced stage symptomatic disease, often involving severe pulmonary and neurologic vasculopathy.
- Serious concerns about transplantation-related mortality, as well as the potential for treatment-induced malignancy, exist.

Hematopoietic Cell Transplant in SCD: Choice of Donor

- HLA-matched siblings are preferable as HCT donors for individuals with SCD because of the lower risks of graft-versus-host disease (GVHD) and graft failure/rejection with a related donor transplant.
  - Siblings without a sickle cell syndrome and siblings with sickle cell trait are acceptable as donors.
  - The safety and feasibility of peripheral blood stem cell mobilization with G-CSF in individuals with sickle cell trait has been established
  - Inclusion of siblings with sickle cell trait as potential donors expands the potential donor pool, although the proportion of individuals with suitable donors remains small.
  - Trials of matched unrelated donor with reduced intensity conditioning are underway
  - Trials of haploidentical donors with reduced intensity conditioning are underway

Hematopoietic Cell Transplant in SCD: Recommendations

- HCT is a potentially curative option in patients with SCD.
- Limitations to the use of HCT in patients with SCD include:
  - Variable clinical course, which preclude predictions of which patients might benefit from HCT
  - Transplant-related risks because of pulmonary and neurologic disease in patients with advanced SCD
  - Need for a HLA-matched sibling donor
- In several series of patients who have undergone HCT for SCD, five-year survival rates were 90 to 97 percent, and transplant-related mortality was 7 to 10 percent.
- Consider HCT for patients with severe symptoms of SCD that are unresponsive to treatment with transfusions and hydroxyurea if an HLA-matched sibling is available as a donor.