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 hydroxyurea 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.

<table>
<thead>
<tr>
<th>Indications where primary goal of transfusion is to correct acute anaemia</th>
<th>GRADE evaluation</th>
<th>Type of transfusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aplastic crisis</td>
<td>1B</td>
<td>Simple (top up)</td>
</tr>
<tr>
<td>Acute splenic sequestration</td>
<td>1B</td>
<td>Simple</td>
</tr>
<tr>
<td>Acute hepatic sequestration</td>
<td>1B</td>
<td>Simple</td>
</tr>
<tr>
<td>Delayed haemolytic transfusion reaction (transfusion should be avoided unless the anaemia is severe or life-threatening)</td>
<td>1C</td>
<td>Simple</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications where primary goal of transfusion is to reduce HbS concentration in relation to HbA</th>
<th>GRADE evaluation</th>
<th>Type of transfusion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>1B</td>
<td>Simple or exchange †</td>
</tr>
<tr>
<td>Acute stroke or other neurological deficit (e.g. TIA)</td>
<td>1B</td>
<td>Exchange</td>
</tr>
<tr>
<td>Acute multi-organ failure</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Mesenteric/girdle syndrome</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>2C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Acute intrahepatic cholestasis</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>Primary stroke prevention</td>
<td>1A</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Prevention of silent cerebral infarct recurrence</td>
<td>1A</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>1B</td>
<td>Simple or exchange</td>
</tr>
</tbody>
</table>

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*British Journal of Haematology, 2017, 176, 192–209*
Guidelines* for RBC Transfusion in SCD

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SS patients – elective low or medium risk surgery</td>
<td>1A</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>• SC patients – elective low or medium risk surgery</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>• All sickle genotypes – elective high risk surgery</td>
<td>1C</td>
<td>Exchange</td>
</tr>
<tr>
<td>• Emergency surgery</td>
<td>1D</td>
<td>Individual considerations†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy</th>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sickle complications (e.g. painful crises, ACS, stroke)</td>
<td>1B</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>• Severe anaemia</td>
<td>1C</td>
<td>Simple</td>
</tr>
<tr>
<td>• High obstetric, medical or fetal risk</td>
<td>1C</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Recurrent ACS§</td>
<td>2C</td>
<td>Simple or exchange</td>
</tr>
<tr>
<td>Recurrent painful crises§</td>
<td>2C</td>
<td>Simple or exchange</td>
</tr>
</tbody>
</table>

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.

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

## Laboratory Investigation

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

<table>
<thead>
<tr>
<th></th>
<th>Acute &lt; 24 hrs</th>
<th>Delayed &gt; 24 hrs up to 6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravascular hemolysis</strong></td>
<td>Life threatening</td>
<td>Extravascular hemolysis</td>
</tr>
<tr>
<td></td>
<td>Hemoglobinemia</td>
<td>Shortened RBC survival</td>
</tr>
<tr>
<td></td>
<td>Hemoglobinuria</td>
<td></td>
</tr>
</tbody>
</table>

**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

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

**Good outcome**
- Persistence of transfused RBCs
- HbA% ++
- Total Hb ++

**Mild Outcome** (Mild VOC, Dark urine)
- Destruction of transfused RBCs
- HbA% ±
- Total Hb ±
- LDH +

**Severe Outcome** (VOC, Anemia, Dark Urine, MOF, Death)
- Destruction of transfused and autologous RBCs
- Hyperhemolysis
- HbA% none
- Total Hb decreased from pre-transfusion
- Reticulocytopenia
- LDH +++

Adapted from France Pirenne, AABB 2016
### Common clinical findings during DHTR in Sickle Cell Disease

<table>
<thead>
<tr>
<th>Finding</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobinuria/dark urine</td>
<td>96%</td>
</tr>
<tr>
<td>Pain</td>
<td>89%</td>
</tr>
<tr>
<td>Fever</td>
<td>64%</td>
</tr>
<tr>
<td>Anemia signs</td>
<td>44%</td>
</tr>
</tbody>
</table>

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

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

Table I. Differentiating DHTR from VOC episodes in SCD.

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

DHTR, delayed haemolytic transfusion reaction; VOC, veno-occlusive crisis; SCD, sickle cell disease; RBC, red blood cell; LDH, lactate dehydrogenase; DAT, direct antiglobulin test.
SCD patient unwell (VOC pain, haemoglobinuria, fever) and 1-21 days post-transfusion

- No → Treat as usual VOC
- Yes → Hb drop ≥25% from post-transfusion Hb or Hb below pre-transfusion Hb levels
  - No → Treat as usual VOC
  - Yes → Evaluate for DHTR

Evaluate for DHTR

- Serology: New red cell alloantibodies, DAT positive
- Evidence of severe haemolysis: Haemoglobinuria, Marked LDH increase (≥2 baseline)
- Sequential HPLC: HbA/HbS ratios
- ? Relative reticulocytopenia

- Exclude other causes of Hb drop: Bleeding, Infection, G6PD-deficiency

DHTR diagnosed. First steps:
- Avoid transfusion: communicate this to other colleagues
- Serial monitoring: clinical and laboratory parameters
- Supportive care: renal function, pain, alert for other complications

Patient deterioration
- First line immunosuppression: steroids & IVIg
- Optimize erythropoiesis: high dose ESA, IV iron
- Transfusion if life-threatening anaemia

Further patient deterioration → Immunosuppression: rituximab

Patient stabilized
- Continue monitoring until clinical and laboratory improvement (reticulocyte count and Hb)

Long-term management
- Documentation: DHTR episodes, new alloantibodies detected
- Patient awareness: antibody card
- Consider hydroxycarbamide, ESA long term

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.