Transfusion in Sickle Cell Disease
What the guidelines [are likely to] say

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Background to BCSH Guideline

Rationale
Current guidance in disparate publications
Concise evidence-based guideline needed
Essentials of transfusion practice in SCD and thalassaemia
Written with practitioners in low prevalence areas in mind
5,000 words long

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Transfusion in SCD

Strategies
- Episodically for acute complications
- Electively on long-term basis to prevent complications

Methods
- Simple or top up transfusion
- Exchange transfusion
Benefits versus Risks

**Benefits**

- May be life saving in acute situations
- Can reduce mortality and morbidity from post-op complications
- Effective in primary and secondary stroke prevention
- In selected patients, can ameliorate severe disease

**Risks**

- Greater risk of haemolytic transfusion reactions
  - Peculiar problems related to alloimmunisation
  - Increased rate of out of hours transfusion
  - Patients often present acutely to different hospitals

- Special requirements
- Iron overload
- Increased donor exposure
Aims of blood transfusion in SCD

- To correct anaemia and so improve the oxygen-carrying capacity of blood

- To treat or prevent complications by lowering the percentage of HbS relative to HbA
Indications for emergency transfusion

**Established**
- ACS with hypoxia
- Acute splenic sequestration
- Aplastic crisis
- Acute hepatic sequestration
- Acute ischaemic stroke
- Acute multi-organ failure

**Not indicated/ Uncertain**
- Uncomplicated vaso-occlusive crisis (N)
- Mild drop in Hb with no symptoms (N)
- Severe sepsis (U)
- Haemorrhagic stroke (U)
## Indications for elective transfusion

### Established
- Primary stroke prevention in children
- Secondary stroke prevention
- Pre-operatively
  - HbSS and HbSβ⁰ thalassaemia undergoing low and medium risk surgery

### Possible
- Pregnancy
  - Not for uncomplicated pregnancy
  - Consider for variety of other clinical situations
- Repeated painful crises or acute chest syndrome
- Leg ulceration resistant to intensive local measures
- Pulmonary hypertension
- Chronic priapism refractory to medical treatment
Transfusion practice in SCD

• Transfusing the acutely ill patient

• Chronic blood transfusion

• Make blood available in timely manner
• Minimise risk – alloimmunisation, HTRs
• Specify blood is for sickle patient
Transfusion practice in SCD

- Target Hb and HbS concentrations
- Volumes for complete exchange
- Manual exchange protocol
Oxygen transport versus haemoglobin in SCD

Sickle Cell Anemia
$H_b_{\text{max}} \sim 10-11$

2° Polycythemia ($H_b_{\text{max}} \sim 20-22$)

Normal $H_b_{\text{max}} \sim 14-16$

Swerdlow, Hematology 2006
Stroke recurrence in SCD patients on chronic transfusions

Exchange transfusion or top up?

- Hyperviscosity
- Venous access
- Maintaining iron balance
- Alloimmunisation
- Clinical indication
- Clinical status of the patient
Average Liver Iron Concentration

- > 43.0 mg/g dry tissue (NR: 0.17-1.8)
- > 769 mmol/kg dry tissue (NR: 3-33)

Normal range (NR) is taken from Bassoff et al., Hepatology 1996; 6: 24-29.

Transverse Relaxation Rate (R2) Image

Voxels Transverse Relaxation Rate (R2) Distribution

Distribution Mean ± SD: 309.9 ± 25.1

LIC Historic Values

<table>
<thead>
<tr>
<th>Scan Date</th>
<th>LIC mg/g dry tissue</th>
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</thead>
<tbody>
<tr>
<td>07 Oct 2009</td>
<td>&gt;43</td>
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<tr>
<td>13 Dec 2010</td>
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</table>

LIC Historic Plot
Average Liver Iron Concentration

24.2 mg/g dry tissue  (NR: 0.17-1.8)
434 mmol/kg dry tissue  (NR: 3-33)

Normal range (NR) is taken from Bassett et. al., Hepatology 1986; 6: 24-29.
**LIC Historic Values**

<table>
<thead>
<tr>
<th>Scan Date</th>
<th>LIC (mg Fe/g dw)</th>
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<tbody>
<tr>
<td>07 Sep 2009</td>
<td>12.7</td>
</tr>
<tr>
<td>11 May 2011</td>
<td>2.2</td>
</tr>
<tr>
<td>18 Apr 2012</td>
<td>0.9</td>
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</tbody>
</table>

**LIC Historic Plot**

![Graph showing LIC historic values over time]
Top up v Exchange

**Top up**
- Technically easier
- Fewer resources required
- Reduced donor exposure
- Faster rate of iron accumulation
- Difficult to achieve HbS <30% without increasing blood viscosity

**Exchange**
- Slower rate of iron accumulation
- Better control of desired HbS
- Reduced risk of hyperviscosity
- Vascular access problems
- Complications associated with long lines
- More resources
- Increased donor exposure
Manual v Automated Exchange

**Manual**
- Relatively less equipment
- Can be done at bedside
- Partial exchange (30% of blood volume can be achieved quickly)
- Rapid reversal of ACS with partial exchange
- Can maintain HbS < 30% if done every 4 weeks
- Different units have different protocols

**Automated**
- Relatively quick procedure
- Can achieve HbS < 30% within 2 hours
- Can be programmed to achieve final Hb, HbS and net fluid balance
- Hypocalcaemia and thrombocytopenia can occur
- Use limited in many parts of the country
Laboratory Aspects

Extended phenotype (or genotype) & compatibility testing

- Phenotype/genotype prior to transfusion
- Serological usually; molecular if recently transfused
- C c E e K k Jk^a Jk^b Fy^a Fy^b S s
- U typing if S-s-
- Fully automated systems for ABO grouping
- Antibody screening as standard
- Antibody identification if screen positive
- Antibody card if alloantibodies detected

Choice of blood product

- Match for Rh (D C c E e) and K as a minimum
- Select R0 blood for R0 individuals; use rr in emergency if R0 unavailable
- If antibodies, select blood that is negative for corresponding antigens
- HbS negative
- <14 days old; <7 days old for automated exchange if possible
The serious problem of alloimmunisation

- Reported frequency 18-36% in sickle cell disease
- 30% sickle v 5% non-sickle (Vichinsky, NEJM 1990)
- Likely an underestimate – 37% of antibodies undetectable (Rosse Blood 1990)
- K C E account for 66% of antibodies (Davies BJH, 1987; Vichinsky NEJM 1990)
- Higher rate of multiple alloantibodies (Rosse, Blood 1990)
- Increased rate of autoantibodies (Castellino, BJH 1999)

Factors implicated in alloimmunisation

- Phenotype differences between donors and recipients (Vichinsky, NEJM 1990)
- Greater number of transfusions (Rosse Blood 1990; Olujohungbe BJH 2001)
- Later start to transfusions (Spanos, Vox Sanguinis 1990)
## Red cell phenotypes (%) patients and donors

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>African</th>
</tr>
</thead>
<tbody>
<tr>
<td>*C</td>
<td>70 (68)†</td>
<td>30 (28)</td>
</tr>
<tr>
<td>*E</td>
<td>30 (35)</td>
<td>19 (24)</td>
</tr>
<tr>
<td>*K</td>
<td>9 (9)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Jk(^a)</td>
<td>77 (77)</td>
<td>92 (91)</td>
</tr>
<tr>
<td>*Jk(^b)</td>
<td>74 (72)</td>
<td>49 (39)</td>
</tr>
<tr>
<td>S</td>
<td>55 (55)</td>
<td>31 (26)</td>
</tr>
<tr>
<td>s</td>
<td>89 (94)</td>
<td>97 (95)</td>
</tr>
<tr>
<td>**U</td>
<td>&gt;99.9</td>
<td>99</td>
</tr>
<tr>
<td>*Fy(^a)</td>
<td>66 (67)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>*Fy(^b)</td>
<td>83 (82)</td>
<td>23 (11)</td>
</tr>
</tbody>
</table>

†Vichinsky NEJM 1990; 322:1617-21
## Frequency of alloantibodies in transfused sickle cell patients

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Frequency (%)</th>
<th>Specificity</th>
<th>Frequency (%)</th>
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<tbody>
<tr>
<td>K</td>
<td>26</td>
<td>Le&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>E</td>
<td>24</td>
<td>M</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>16</td>
<td>Fy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>Jk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>e</td>
<td>2</td>
</tr>
<tr>
<td>Fy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>Jk&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
</tr>
</tbody>
</table>

Vichinsky NEJM 1990; **322**:1617-21
Disappearing alloantibodies in SCD

Vichinsky  Semin Hematol, 2001
Minimising Alloimmunisation

Reduced use of transfusions

- Avoid transfusion unless absolutely necessary
- Incentive spirometry (Bellet, NEJM 1995)
- Hydroxyurea (Charache, NEJM 1995)

Give phenotype-matched blood

- Matching for K, C, E reduced alloimmunisation rate from 3% to 0.5% (Vichinsky, Transfusion 2001)
- 10x reduction if fully phenotyped (17 alloantigens) (Ambruso, Transfusion 1987)
Difficult to transfuse patients

Rare blood types
- Multiple alloantibodies – particular combinations may pose more difficulties
- Common phenotype in Blacks, rare in Caucasian donors (eg. Fy\textsuperscript{a-b-})
- Rare phenotype occurring exclusively in Blacks (S-s-U- and Js\textsuperscript{a+b-})

Hyperhaemolysis
- Technically not a rare blood group problem
- Problem of provoking or exacerbating life-threatening haemolysis
- Transfusion management during active haemolysis
  - Avoid transfusion if mild
  - Small volume top ups if severe, rapid haemolysis
Difficult to transfuse patients

Management

• Antibody and hyperhaemolysis cards

• Transfuse only with consultant authorisation

• Active involvement of NBS consultants

• Planning for elective transfusions eg. (pre-op)
  • Prevention of further alloimmunisations
  • Limiting blood loss at operations
  • Location of red cell units

• Planning for emergencies
National Transfusion Database for SCD

- No national database
  - Extended phenotype results
  - Alloimmunised patients
  - Hyperhaemolysis patients

- No centralised system for phenotyping or antibody identification
  - In-house
  - National Blood Service

- A central database – hospital transfusion labs can very easily access patients’ transfusion records
  - Telephone hotline
  - Directly by electronic means
Conclusions

• Transfusion is a major part of SCD management but has risks

• Risks can be minimised by attention to specific principles

• Guideline should help disseminate good practice

• A central database will facilitate transfusion management of sickle cell patients