Transfusion requirements for haemoglobinopathy patients

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Haemoglobinopathies (Sickle Cell and Thalassaemia) are the commonest genetic disorders in the UK

Increasing prevalence:
- Babies identified though newborn screening
- Immigration into UK
- Improved survival with medical treatment

National antenatal and newborn screening programmes are in place.
Abnormal haemoglobin polymerises at low oxygen tension

Red cells become rigid

Haemolysis

Vaso-occlusion
National Standards and Guidelines in Sickle Cell Disease
Sickle cell disease: clinical problems

- Anaemia
  - Hb 7-9g/dl
- Infections
- Painful crises
- Stroke
- Leg ulcers
- Priapism
- Visual loss
- Chronic organ damage
  - Kidneys, lungs, joints, heart
## Acute complications: how common?

Data from the Cooperative Study of Sickle Cell Disease (CSSCD)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Beta Globin Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SS</td>
</tr>
<tr>
<td>Painful Episodes</td>
<td>80</td>
</tr>
<tr>
<td>Acute Chest Syndrome</td>
<td>12.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6</td>
</tr>
</tbody>
</table>

All rates expressed per 100 patient-years.
<table>
<thead>
<tr>
<th>TCD Velocity (cm/s)</th>
<th>Interpretation</th>
<th>Yearly Risk of Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 170</td>
<td>Normal</td>
<td>~1%</td>
</tr>
<tr>
<td>≥ 170 and &lt; 200</td>
<td>Conditional</td>
<td>intermediate</td>
</tr>
<tr>
<td>≥ 200</td>
<td>Abnormal</td>
<td>~10%</td>
</tr>
</tbody>
</table>
Blood transfusion in stroke

- The role of blood transfusion in secondary stroke prevention is standard care.

- All patients with abnormal Transcranial Doppler scan should be offered prophylactic blood transfusion (STOPI and STOPII).

- Improved outcomes with transfusion for silent cerebral infarcts (SITT Trial 2014).

- Hydroxycarbamide? Not shown to prevent stroke (TWITCH and SWITCH studies).
Transfusion in SCD

Purpose:

- To treat anaemia and improve oxygen carrying capacity of blood

- Prevent or reduce painful/vaso-occlusive or sequestration complications by lowering proportion of Hb S relative to Hb A (aim < 30% acute or < 50% in some chronic situations)
Complications of transfusion 1

Alloimmunisation:

- Incidence prior to Rh and K matching up to 36% (USA) but some become undetectable
- Lower in UK
- Usually anti- C E and K
  - All patients should have full red cell phenotype/ genotype
  - Choose blood matched for Rh genotype and Kell
Complications of transfusion 2

- Haemolytic transfusion reactions
  - Classical 7-10 days
  - Hyperhaemolysis
    - destruction of donor and recipient cells.
    - Post transfusion Hb < Pre Tx
    - No Hb A detected
    - Reticulocytopenia
    - Acute<7days DAT neg, no new allo-ab identified
    - Delayed> 7 days DAT, new allo-ab found
    - Treat with steroids and IvIg
Complications of transfusion 3

- Hyperviscosity
- Iron Overload
- Transfusion transmitted infection
Sickle haemoglobin has much greater viscosity especially in the deoxygenated state.

Increasing Hb over 10g/dl carries risk of hyperviscosity symptoms in presence of large quantities of Hb S.
### Top up or exchange?

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Top Up</th>
<th>Exchange</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technically easier and needs fewer resources</td>
<td></td>
<td>Better control of Hb S</td>
</tr>
<tr>
<td>Less blood required</td>
<td></td>
<td>Avoids hyperviscosity</td>
</tr>
<tr>
<td>Quicker</td>
<td></td>
<td>Less iron accumulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron accumulation</td>
<td>Needs more resources (machine, trained nurse)</td>
</tr>
<tr>
<td>Cannot achieve acute Hb S &lt;30% without risk of hyperviscosity</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>Venous access problematic</td>
</tr>
<tr>
<td></td>
<td>More donor exposure</td>
</tr>
<tr>
<td>Top up</td>
<td>Exchange</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>Acute Chest Syndrome</td>
</tr>
<tr>
<td>Red cell aplasia</td>
<td>Acute stroke</td>
</tr>
<tr>
<td>Splenic sequestration</td>
<td>Acute hepatic sequestration</td>
</tr>
<tr>
<td></td>
<td>Severe sepsis</td>
</tr>
<tr>
<td></td>
<td>Acute multi organ failure</td>
</tr>
<tr>
<td></td>
<td>Progressive intrahepatic cholestasis</td>
</tr>
</tbody>
</table>
## Possible indications for elective blood transfusions

<table>
<thead>
<tr>
<th>Level A or B evidence available</th>
<th>Level A and B evidence unavailable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary stroke prevention</td>
<td>Fetal complications in pregnancy</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>Repeated severe painful crises</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Painful crises in pregnancy</td>
<td>Leg Ulcers</td>
</tr>
<tr>
<td></td>
<td>Priapism</td>
</tr>
</tbody>
</table>
Take home messages

- Transfusion is not required for steady state anaemia
- Transfusion in SCD should be discussed with haematologist
- Laboratory should be informed that blood is for a sickle cell patient so they can ensure correct blood requested
- Important to ask patient if they have had previous reactions to blood or carry a card
- Do not take Hb up to >90-100g/L
- Transfusion is lifesaving
Thalassaemia Standards 2008

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What is Thalassaemia?

- A group of inherited disorders resulting in reduced synthesis of one or more globin chains.
- This results in an imbalance of globin chains with the excess chain producing the pathological effects:
  - damage to red cell precursors → ineffective erythropoiesis
  - damage to mature red cells → haemolytic anaemia
Clinical Classification of Thalassaemia

- Thalassaemia Major
  - Transfusion dependent

- Thalassaemia Intermedia
  - Less severe anaemia and can survive without regular blood transfusions

- Thalassaemia Minor (trait, carrier)
  - Asymptomatic carrier
Consequences (cont)

- Failure to thrive
  - Fatigue
  - Poor feeding
  - Developmental delay
  - Poor growth
  - Splenomegaly
  - Facial appearance etc

Requires careful monitoring (monthly from diagnosis)
When to start transfusions?

- “Good clinical judgement cannot be replaced by any kind of clear instructions regarding decisions whether to transfuse a patient” [Loukopoulos, Palermo Conference]

- Genotype…
- Growth / thriving
- Hb levels as well

Earlier:
Before any problems / spleen enlarges etc

Later:
Parents accept child needs
Child may prove not to need

[best taken at Centre]
Standard: Red cell transfusions

- Haemoglobin levels should be maintained above 9.5-10g/dl.
- Cannulation will be undertaken by an experienced nurse or doctor.
- Pre-arranged transfusions should be started promptly.
- Good transfusion practice must be observed.
- Transfusions will be given on each occasion in a designated area with suitable facilities, experienced regular named nurses and familiar supervising medical team.
Transfusion therapy and monitoring iron loading in thalassaemia

- 1 blood unit contains 200 mg iron
- A 60 kg thalassaemia patient receiving 45 units of blood annually has transfusional iron intake of 9 g iron/year
  - 0.4 mg iron/kg body wt/day
- In addition, up to 4 mg/day may be absorbed from the gut
  - Up to 1.5 g iron/year

200–250 mg iron:
Whole blood: 0.47 mg iron/mL
‘Pure’ red cells: 1.16 mg iron/mL

Organ systems susceptible to iron overload

**Clinical sequelae of iron overload**

- **Pituitary** → Impaired growth, infertility
- **Heart** → Cardiomyopathy, cardiac failure
- **Liver** → Hepatic cirrhosis
- **Pancreas** → Diabetes mellitus
- **Gonads** → Hypogonadism
Repeated transfusions lead to iron overload

Significant correlation between transfusion duration and liver iron on biopsy

<table>
<thead>
<tr>
<th>Causes of death in Thalassaemia</th>
<th>All patients (N=1073)</th>
<th>All patients born after 1970* (N=720)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>133</td>
<td>60.2</td>
</tr>
<tr>
<td>Infection</td>
<td>15</td>
<td>6.8</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>15</td>
<td>6.8</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>9</td>
<td>4.1</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>9</td>
<td>4.1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>8</td>
<td>3.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7</td>
<td>3.2</td>
</tr>
<tr>
<td>Accident</td>
<td>4</td>
<td>1.8</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>HIV / AIDS</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>Familial autoimmune disorder</td>
<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>221</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring iron overload

- Serum ferritin reflect current iron stores.
- Liver biopsy “gold standard” Invasive
- MRI techniques Standard of care
- End organ function Too late
Disease-free survival related to body iron levels assessed by serum ferritin

Cardiac disease-free survival in patients with:
- <33% ferritin measures >2500 ng/mL
- 33–67% ferritin measures >2500 ng/mL
- >67% ferritin measures >2500 ng/mL

Liver iron and risk from iron overload

Hepatic iron (µmol/g wet weight)

Age (years)

Hepatic iron (mg/g dry weight)

Threshold for cardiac disease and early death

Increased risk of complications

Optimal level in thalassaemia

Normal

Olivieri NF & Brittenham GM. Blood 1997;89:739–761
Relationship between myocardial T2* values and left ventricular ejection fraction. Below a myocardial T2* of 20 ms, there was a progressive and significant decline in left ventricular ejection fraction ($R=0.61$, $P<0.0001$).

Cardiac T2* value of 37 in a normal heart

Cardiac T2* value of 4 in a significantly iron overloaded heart

Goals of chelation therapy

Reduce patient morbidity and improve survival by:

- Avoiding accumulation of iron
- Removing accumulated iron
- Avoiding chelation toxicity
What is chelation therapy?

Chelator + Metal → Chelator-Metal → Excretion

Toxic
# Comparison of chelators

<table>
<thead>
<tr>
<th>Property</th>
<th>DFO</th>
<th>Deferiprone</th>
<th>Deferasirox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose (mg/kg/day)</td>
<td>25–60</td>
<td>75</td>
<td>20–30</td>
</tr>
<tr>
<td>Route</td>
<td>sc, iv (8–12 hours, 5 days/week)</td>
<td>Oral 3 times daily</td>
<td>Oral Once daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20–30 minutes</td>
<td>3–4 hours</td>
<td>12–16 hours</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, faecal</td>
<td>Urinary</td>
<td>Faecal</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Local reactions, ophthalmologic, auditory, growth retardation, allergic</td>
<td>Gastrointestinal disturbances, agranulocytosis/neutropenia, arthralgia</td>
<td>Gastrointestinal disturbances, rash, mild non-progressive creatinine increase, ophthalmologic, auditory</td>
</tr>
</tbody>
</table>
DFO therapy improves survival in regularly transfused thalassaemia patients

Kaplan-Meier analysis of survival in 257 consecutive thalassaemic patients according to the mean compliance with subcutaneous DFO therapy

Deferasirox effectively decreases LIC across a range of transfusion-dependent anaemias

Deferasirox was non-inferior to DFO at doses of >20 mg/kg/day.

Choice of chelator

- Decision based on
  - Tolerance of current treatment
  - Current iron stores as evidenced by serum ferritin levels and liver/heart imaging techniques
  - Trends in ferritin levels
  - Patient choice
Iron chelation in SCD

- Liver loading appears more important than cardiac loading
- Ferritin levels unreliable
- Liver MRI techniques now recommended
- Many patients have significant lifetime transfusion burden even if not on regular transfusions

Optimal iron chelation intensity unclear
Conclusions

- Transfusion may be lifesaving or reduce morbidity in Sickle Cell Disease or Thalassaemia.

- The number of patients on transfusion is likely to increase.

- National guidelines indicate which patients with SCD need transfusions.

- Iron accumulation is a significant problem for these patients and chelation should aim to prevent complications.

- Blood should be genotypically matched to prevent alloimmunisation.