Why do we need to understand the complications of Sickle Cell Disease?

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What is Sickle Cell Disease?

- Haemolysis
- Anaemia
- Vaso-occlusion
  - Acute pain and complications
  - Chronic organ damage
Sickle Cell Disease is common

Carriers: 7% of population
270 million carriers

>300,000 births per year
2% of all births in West Africa
50-80% mortality by 5 years
15,000 affected in UK

¾ live in London

>300 births/year – 1/3 in South London
Indications for Transfusion

- Emergency
  - Top-up
  - Exchange
  - Acute Chest Syndrome
- Elective
  - One off
  - Exchange
  - Stroke Prevention
- Long term
  - Severe Symptoms
- Pre-operative

Rapid haemolysis

Red cell aplasia
Increasing blood usage

Drasar 2011
Increasing blood usage at GSTT

- Increase in numbers of patients on long term transfusion of 20-25% pa
- 2016 > 100 patients on long term transfusion
- Majority on long term red cell apheresis (NICE guidance)
  - Primary or secondary stroke prevention
  - Recurrent Pain or Acute Chest Syndrome despite hydroxycarbamide
  - Priapism, Pulmonary hypertension, liver hepatopathy, leg ulcers
Risks of transfusion

• Iron overload
  – Patients on chronic transfusion need monitoring with ferritin /MRI
  – Iron accumulation can occur with sporadic transfusion
• Alloimmunisation

• Availability and costs of blood
• Infection

• May be a high burden to patient – hospital visits, monitoring investigations
Alloimmunisation in SCD

- 20-50% of patients
  - >65% Rh and Kell
  - >60% are transitory
- Increased risk with increased number of units
- Risks
  - Delayed haemolytic transfusion reaction
  - Haemolytic disease of newborn
  - Patient rendered ‘untransfusible’

Rosse, Blood 1990
Reasons for increased antibody formation

Antigen disparity

Alloimmunization decreased in more racially homogenous populations:
Uganda 6.1%
Jamaica 2.6%
Reasons for increased antibody formation

Antigen disparity

Individual factors

HLA II genotype

Decreased Treg activity in Ab responders

Increased Th2 cells in Ab responders

SCD related factors

Increased inflammation

Genetic predictors: TRIM21
Strategies to prevent alloimmunization and DHTR

• Improve red cell matching for Rh (CDE) and Kell
  – Decreases alloimmunisation to Rh and Kell (BUT not completely)
  – Still have immunisation to other antigens

• Extend phenotyping further
  – Limitations of blood supply

• Persistence of Rh antibody formation despite phenotype matching
  – Mechanism: High levels of variant Rh antigens and of altered Rh antigens

• Red cell genotyping
  – 494 patients with SCD: 1.1% discrepancies found
Strategies to prevent alloimmunization and DHTR

• Improved transfusion records (National Record)
• Ab screening after each transfusion
• Improved donor recruitment
• Therapeutic methods to decrease alloimmunisation
• Use of genetic screening and risk factors
Delayed haemolytic transfusion reaction (DHTR) in Sickle Cell Disease

• DHTR
  – Immune destruction of transfused red cells by red cell antibodies
  – 5-15 days post transfusion
  – Mimics vaso-occlusive crisis or acute chest syndrome
  – Hb decreases to pretransfusion levels
  – Increased haemolysis (bilirubin, LDH, reticulocytes) and haemoglobinuria
  – Positive DAT
  – Evidence of new red cell antibody
Delayed haemolytic transfusion reaction (DHTR) in Sickle Cell Disease

- Hyperhaemolysis
  - More severe haemolysis than DHTR with haemolysis affecting the transfused red cells but also the patient’s own red cells
  - Hb decreases to below pre-transfusion levels
  - May be associated with a reticulocytopenia
  - May or may not be associated with a new red cell alloantibody
  - Mechanism unclear (bystander haemolysis, suppression of erythropoiesis, rbc destruction)
Hyperhaemolysis

- Antibody mediated red cell destruction
  - Decreased Hb
  - Haemolysis
  - Positive DAT
  - New allo ab

Hyperhaemolysis

- Hb decreases below pre-transfusion Hb
- Patients own rbc are destroyed

Hyperhaemolysis with alloantibody

Hyperhaemolysis with no new alloantibody
Delayed haemolytic transfusion reaction in adults with sickle cell disease: a 5-year experience

- Retrospective review of all red cell transfusions in adults with SCD: 2008-2013
- DHTR defined as
  - Significant drop >25% in Hb between 24h and 21/7 post transfusion
- Incidence: 7.7% of transfused patients over a 5 year period
  - 1.1% of transfusion episodes
23 DHTR episodes

4 episodes
Conservative Management
- All showed slow Hb increment

5 episodes
Immunosuppression +/- RBC transfusion
- 3 patients responded to first line immunosuppression
  - 2 required critical care
- 2 patients required multiple doses immunosuppression
  - Both required critical care, one died (ICH)

14 episodes
RBC transfusion only
- 4 appropriate Hb response
- 9 inappropriate Hb response
- 1 unable to assess Hb response (died one day after presentation (ALI) and transfer to critical care)

Vidler et al 2015
• 9 cases of hyperhaemolysis identified from review of database 2009-2013

• Review of literature: 69 cases over 34 years
  • 71% SCD, 18% thalassaemia
  • 42% developed new allo antibody
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<th>EPO</th>
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- Avoid transfusion unless patient is haemodynamically compromised
- Monitor Hb twice daily – If Hb continues to drop or in the interim patient cardiovascularly compromised:
  - Commence IVIG (1g/kg daily for two days) or (0.4g/kg if renal impairment present +/- concerns with regards to thrombosis) and methylprednisolone (500mg daily for 2 days)
- High dependency unit is the ideal setting for patient management
- Optimise any haematinc deficiency
- Generally: folic acid 5mg should be commenced in all patient
  - Hydroxycobalamin if active B12 < 70pg/ml or serum B12 < 200pg/ml
  - Ferritin in these patients is generally elevated and not a good marker of iron deficiency (however, if iron saturations < 20% or ferritin < 100) then correct with one dose ferric carboxymaltose 1g or 500mg depending on weight
- Commence EPO at dose of: NeoRecormon® 300units/kg once daily for 5 days.
- Then 300units/kg once daily alternate days (i.e. 3 times per week)
When to transfuse in DHTR

• DHTR with evidence of new allo-ab
  – Transfuse with compatible blood for new ab

• Hyperhaemolysis
  – Transfuse as per clinical need

• High risk of recurrence with transfusion

• GSTT series
  – 2/9 needed immediate transfusion
  – 2/9 needed transfusion at later date

• King’s series
  – 14/23 transfused (4 with good response, 10 with poor response)
Subsequent management

• Additional immunosuppression
  – Rituximab, Eculizumab

• Alert on transfusion records
• Antibody negative blood
• Patient awareness
  – ‘I need special blood card’

• Notify SHOT
• ? International registry
Thank you to the Sickle/Transfusion Team at Guy’s and St Thomas’ Hospital

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Dr Anicee Danaee