Complications following red cell transfusion - Hyperhaemolysis

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Guy’s and St Thomas’ NHS Foundation Trust
Hyperhaemolysis

• Experience from my institution
• Background DHTR and Hyperhaemolysis
• Cases - Local management
• Literature review
• Serious Hazards of Transfusion Reports
Delayed Haemolytic Transfusion Reaction in Sickle Cell Disease

- Severe, uncommon, life threatening complication
- 5-15 days post transfusion
- Immune destruction of transfused red cells by red cell alloantibodies
- Hb decreases to pre-transfusion levels
- Increased haemolysis (bilirubin, LDH, reticulocytes)
- Pain, Fever, Haemoglobinuria
- Positive DAT
- Evidence of new red cell antibody
Delayed Haemolytic Transfusion Reaction in Sickle Cell Disease

- Alloimmunisation does not always lead to DHTR
- Evidence alloimmunisation not always evident in DHTR

**Hyperhaemolysis**

- Severe haemolysis post transfusion affecting transfused red cells and 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
- “Hyperhaemolytic transfusion reaction/ Hyperhaemolysis”
- Life threatening
- Exacerbation or Recurrence

Diamond 1980
Petz 1997
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
- Reticulocytopenia

Hyperhaemolysis
Hyperhaemolysis with alloantibody
Hyperhaemolysis with no new alloantibody
Hyperhaemolysis

• Mechanism
  – Suppression of erythropoiesis
  – Bystander haemolysis
  – Destruction of red cells by activated macrophages
  – Increased red cell exposure of phosphatidylserine, accelerated eryptosis
Suppression of erythropoiesis

The sickle cell hemolytic transfusion reaction syndrome

L.D. Petz, L. Calhoun, I.A. Shulman, C. Johnson, and R.M. Herron

TABLE 1. Components of the sickle cell HTR syndrome

1. Manifestations of an acute or delayed HTR.
2. Symptoms suggestive of a sickle cell pain crisis that develop or are intensified during the HTR.
3. Marked reticulocytopenia (a significant decrease from the patient's usual absolute reticulocyte level).
4. Development of a more severe anemia after transfusion than was present before. A rapid drop in Hb and Hct can occur when hemolysis of donor RBCs is accompanied by suppressed erythropoiesis, as sickle cell RBCs have an intrinsically short survival. In some patients, it is possible that hyperhemolysis of autologous RBCs (bystander immune hemolysis) may play a role in the decrease in Hb and Hct, although more definitive documentation of this phenomenon is necessary.
5. Subsequent transfusions may further exacerbate the anemia and it may become life-threatening or even fatal.  
6. Patients often have multiple RBC alloantibodies and may also have autoantibodies, which makes it difficult or impossible to find compatible units of RBCs. However, in other patients, no alloantibodies are demonstrable, or patients may have alloantibodies for which antigen-negative RBCs are readily obtainable.
7. Serologic studies may not provide an explanation for the HTR. Even RBCs that are phenotypically matched with multiple patient antigens may be hemolyzed.
8. Recovery manifested by reticulocytosis and gradual improvement in Hb may occur only after the withholding of further transfusion. The administration of corticosteroids appears to be an important therapeutic measure in some patients.
9. After a recovery period, similar symptoms may recur following subsequent transfusions, although other patients tolerate further transfusions without incident.

Steady state
RBC Production = Destruction

CONCLUSION: A sickle cell HTR syndrome was defined. A rapid increase in the severity of anemia occurs in patients with sickle cell anemia when all donor red cells are hemolyzed during an HTR and when there is suppression of erythropoiesis, as commonly occurs as a result of transfusion or concomitant illness. Although an increased rate of hemolysis of autologous red cells may also occur, more definitive data are required to document that in these patients.
Bystander Haemolysis

- Destruction of autologous antigen-negative red cells occurs in parallel to that of antigen-positive red cells
  - Auto/Allo antibody sensitisation of autologous red cells
  - Complement activation
  - Other antibodies

Garratty 1997, King 1997, Petz & Garratty 2004

- Defective regulation of complement by the sickle erythrocyte: evidence for a defect in control of the membrane attack complex.

Test 2009
Macrophage activation

- Serial measurement of HPLC analysis of the urine during hyperhaemolysis confirming both HbA and HbS  
  Win 2001

- Erythroid hyperplasia in association with reticulocytopenia responding to immunoglobulin and steroid  
  Win 2001, Danaee 2014
Increased red cell exposure of phosphatidylserine

• Delayed haemolytic transfusion reaction in sickle cell disease patients: evidence of an emerging syndrome with suicidal red blood cells

Chadebech 2009
Delayed Haemolytic Transfusion Reaction in Sickle Cell Disease

- Increasing blood usage\(^1\)

- 7.7% (17/220) of transfused patients over a 5 year period

- 1.1% transfusion episodes n=2158

Vidler et al 2015\(^2\)

Drasar 2011\(^1\)
Antigen disparity

- Rh and Kell are most common abs
- Matching for C, E and K decreases alloimmunization from 3%-0.5% per unit
- Most common Rh in SCD is D+C-E-c+e+
- Found in <2% of white popn
- If give D- units (D-C-E-c+e+) depletes D- stock

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Yazdanbakhsh 2012³
Antigen disparity

- Other immunogenic, common antigens:
  - Fya, Jkb, S
- Partial variants of Rh antigens
- Lack epitopes on Rh Ags and make Abs to missing epitopes
- Discrepancy phenotype and genotype  

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Chou 2013
Case History 1

- 39 yr old woman from Nigeria
- HbSS: osteomyelitis, leg ulcers, minimal painful crisis, no operations or acute chest syndrome
- Baseline Hb 64g/l
- Previous top up transfusions and 1 exchange transfusion
- Previous Anti D + C
- Recurrent DVT/PE: on warfarin
  - Anti-thrombin deficiency
Further history

- Pregnancy: 2009
- DHTR following automated red cell exchange
- New anti-S alloantibody
- Seven further top up transfusions for symptomatic anaemia during pregnancy without problem
Further history

• Well post-partum and followed up in clinic

• Presented earlier this year for pre-operative evaluation venoplasty and stenting

• Baseline Hb 65g/l

• 2 unit transfusion, post transfusion Hb 88g/l
Further history

• 9/7 later presented to A+E
• Chest pain
• 1/7 later developed worsening chest pain, and marked hypoxia pO2 (7.8kPa) and decreased Hb (58g/l)
Delayed Haemolytic Transfusion Reaction

- **HB (g/L)**
  - Graph showing HB levels from Mon 8 to Mar 1.

- **Bilirubin Level (umol/L)**
  - Graph showing bilirubin levels from Mon 8 to Mar 1.

- **Lactate Dehydrogenase Level (U/L)**
  - Graph showing lactate dehydrogenase levels from Mon 8 to Mar 1.

- **Reticulocyte Count (x10^9)**
  - Graph showing reticulocyte counts from Feb to Sep.
Delayed Haemolytic Transfusion Reaction

A RhD negative

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<th>PS</th>
<th>IgG</th>
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Red Cell Antibody Results

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<td>IAT and enzyme techniques</td>
<td>Plasma</td>
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These alloantibodies are clinically significant.
No antibodies were detected by IAT in an eluate prepared from the patient’s sample.
Select ABO compatible D- C- E- S- K- Jk(b-) HbS- red cell units for crossmatching by IAT.
Management

• Erythropoietin
  – Neorecormon 300 units/kg once daily for 5 days

• (Iron replete, so iv iron therapy not given)

• Intravenous immunoglobulin
  – 1g/kg for 2 days

• Methylprednisolone
  – 500mg iv for 2 days

• 2 units of packed red cells
Delayed Haemolytic Transfusion Reaction

- Typical history and management
- 5-15 days post transfusion
- Drop in Hb with destruction of transfused rbc
- Often mimics VOC or ACS
  - Joint, limb, back & abdominal pain, fever
  - Note rapid increase in S% as HbA cells (transfused cells) are destroyed
- Investigations: Confirmed haemolysis and new alloantibody formation
Case History 2

- 32 year old man with HbSS
- Severe phenotype
  - previously on hydroxycarbamide
- Admitted with chest pain, left knee pain and swelling
- Hb 80g/l, CRP 129
- Treated with iv antibiotics
- Progressively hypoxic
  - Diagnosis Acute Chest Syndrome
  - Exchange blood transfusion
Case History

• 6/7 post transfusion
• Clinically very well apart from noticed dark urine and pyrexia
• Hb 57g/l (87g/l post transfusion)
• Haemoglobinuria
Hyperhaemolysis

HB (g/L)

Bilirubin Level (μmol/L)

Lactate Dehydrogenase Level (U/L)
Hyperhaemolysis

A RhD positive

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Red Cell Antibody Results

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<th>Specificity</th>
<th>Technique</th>
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<td>Allo</td>
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<td>IAT and enzyme IAT</td>
<td>Plasma</td>
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No alloantibodies were identified in the modified plasma by the following technique:
Bio-Rad IAT
This antibody is unlikely to be clinically significant but may cause problems cross-matching by IAT.
No antibodies were detected by IAT and enzyme IAT in an eluate prepared from the patient's sample.
Select ABO and D compatible C- E- K- HbS- red cell units for crossmatching by IAT and select those least incompatible.
Management

- Erythropoietin
  - Neorecormen 300 units/kg once daily for 5 days

- Iv Iron (1g ferrinject)

- Intravenous immunoglobulins
  - 1g/kg for 2 days

- Methylprednisolone
  - 500mg iv for 2 days

- 1 unit of blood due to hypoxia
Hyperhaemolysis

- Diagnosis is not always straightforward
- Early identification DHTR
- Treatment to abate haemolysis
- Supportive measures
- Optimisation of erythropoiesis
- Immune suppression
- Identification alloantibodies
- Avoidance of further transfusion where possible
- Consider Eculizumab to halt MAC formation
Hyperhemolysis in Patients With Hemoglobinopathies: A Single-Center Experience and Review of the Literature

Anicee Danaee a,*, Baba Inusa b, Jo Howard a, Susan Robinson a

a Department of Hematology, Guys Hospital, London, UK
b Evelina Children's Hospital, St Thomas' Hospital, London, UK
GSTT Cases

• 15 HbSS/ 2 HbSC/ 1 HbH
• 15/18 female, age range 7-65 years
• 2 paediatric patients (siblings)

• 11/18 had allo-antibodies prior to event
• 7/18 new allo-antibodies detected

• 10/18 presented acutely <7 days
  – 3 of these had a new allo-antibody

• Nadir Hb 56-31g/l
• Mean Hb 32g/l below pre-transfusion Hb
# GSTT Cases

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No relationship timing reaction, DAT positivity and detection new allo-antibody
### GSTT Cases

Chest Crisis post cholecystectomy
Transfusion (Ig’s & steroids)
D7 Hyperhaemolysis

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*Planned if further haemolysis to transfuse and give eculizumab

Elective exchange or top up prior to surgery n=6

3 further transfusions (ig’s and steroids) - no recurrence
Literature review 1980-2016 n=95

- 88 Haemoglobinopathy
- Age 1-80
- Female 56(58%)
- Known Abs 49(52%)
- New Abs 40(42%)
- Ig 49(52%)
- Steroids 63(66%)
- Erythropoietin 33(35%)
- Rituximab 5(5%)
- Eculizumab 6(6%)
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<td>Ibanez 2016</td>
<td>F†</td>
<td>30</td>
<td>SS</td>
<td>Fy, E, C, S, JK, HI, M</td>
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<td>-</td>
<td>Yes</td>
<td>-</td>
<td>Epo</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>29</td>
<td>SCD</td>
<td>M, Jk, Le</td>
<td>-</td>
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<td>M†</td>
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<td>Epo</td>
</tr>
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<td>Boonyasampant 2015</td>
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<td>SCD</td>
<td>C, E, K, S, Fy, Jk, Sd</td>
<td>IH</td>
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<td></td>
<td></td>
<td>Eculizumab 1200mg D1, 8, 15, 22, Rituximab 375mg/m²D3, D10, D17, D24</td>
</tr>
<tr>
<td>Eberly 2015</td>
<td>M</td>
<td>55</td>
<td></td>
<td></td>
<td>Jk</td>
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</tr>
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<td>Santos 2015</td>
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<td>17</td>
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<td>Yes</td>
<td>-</td>
<td>Epo</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>16</td>
<td>SCD</td>
<td>Di</td>
<td>S</td>
<td>Yes</td>
<td>Yes</td>
<td>-</td>
<td>Epo</td>
</tr>
</tbody>
</table>

*2014 Paper, Hom homozygous, Epo Erythropoietin
Rituximab in SCD

- Rituximab for prevention of delayed haemolytic transfusion reaction in sickle cell disease *Noizat-Pirenne 2007*
- Rituximab as an effective treatment of hyperhemolysis in sickle cell anemia *Bachmeyer 2010*
- An attempt to induce transient immunosuppression pre-erythrocytapheresis in a girl with sickle cell disease, a history of severe delayed hemolytic transfusion reaction and need for hip prosthesis *Cattoni 2013*
- Immunoglobulin-resistant delayed hemolytic transfusion reaction treated with rituximab in an adult with sickle cell disease n=1 *Delmonte 2013*
- Successful treatment of recurrent hyperhaemolysis syndrome with immunosuppression and plasma to red blood cell exchange n=1 *Uhlmann 2014*
- The use of rituximab to prevent severe delayed haemolytic transfusion reaction in immunized patients with sickle cell disease n=8 *Noizat-Pirenne 2015*
Rituximab in SCD

- Prevents occurrence of new antibodies
- Minimises severity of DHTR
- Risk - benefit
- Reactivation hepatitis B
- Progressive multifocal leucoencephalopathy
- Vaccines
- Dose variable
Eculizumab in SCD

• Hyperhemolysis syndrome in a patient without haemoglobinopathy, unresponsive to treatment with eculizumab Gupta 2015
• Life threatening delayed hyperhaemolytic transfusion reaction in a patient with sickle cell disease: effective treatment with eculizumab followed by rituximab Boonyasampant 2015
• Etiopathological mechanisms and clinical characteristics of hyperhaemolysis syndrome in Spanish patients with thalassemia Vagace 2016
• Eculizumab salvage therapy for delayed haemolysis transfusion reaction in sickle cell disease n=3 Dumas 2016
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
• One of:
  – New red cell ab
  – Haemoglobinuria
  – Accelerated HbS% increase post transfusion
  – Increase x2 in LDH
Results

• 220 patients had at least one transfusion
  – 2158 transfusion episodes

• 23 DHTR episodes in 17 patients

• 11 episodes occurred in context of previous allo-antibodies

• 7 episodes associated with new allo-antibody

• 21 episodes had a Hb nadir lower than the pre-transfusion Hb
Delayed haemolytic transfusion reaction in adults with sickle cell disease: a 5-year experience

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)
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

- Risk of exacerbation/ recurrence

- HDU setting – clinical and laboratory parameters

- GSTT series
  - 4/18 needed immediate transfusion
  - 2/18 needed transfusion at later date

- Literature review n=95 including only published GSTT cases n=9
  - 44/95 needed immediate transfusion
  - 7 deaths
SHARED CARE

“I need Special Blood”

Please Contact:
Blood Transfusion Laboratory
Guy’s & St Thomas’ Hospital
Tel: 020 7188 4774
Previous Hyperhaemolysis

Decision made Future Transfusion necessary

Apply for Rituximab
Hepatitis B status
Vaccines
Rituximab D-14 & D-7

Transfuse with Iv immunoglobulin & methyprednisolone

Recurrence Hyperhaemolysis: Supportive management ivig, methylprednisolone, erythropoietin & haematinics +/- Eculizumab

Emergency transfusion required
SHOT 2016 - Haemolytic transfusion reactions in Sickle Cell Disease  n=8

<table>
<thead>
<tr>
<th>Case</th>
<th>Serology</th>
<th>Clinical &amp; laboratory signs</th>
<th>Morbidity</th>
<th>No. days post transfusion</th>
<th>Additional comments</th>
<th>Imputability of reaction to the transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH1</td>
<td>No antibodies; DAT positive (IgG+C3d); eluate negative</td>
<td>Fever; haemoglobinuria; bilirubin↑; Hb↓↓</td>
<td>Major: impaired renal function (creatinine 63 to 184 micromol/L) Hb fell to 41g/L</td>
<td>6</td>
<td>Treated with steroids and IVlg</td>
<td>Probable</td>
</tr>
<tr>
<td>HH2</td>
<td>Anti-E+S+c and positive DAT pre transfusion; anti-N in eluate</td>
<td>Fever; jaundice; pain; nausea; bilirubin↑↑; Hb↓↓; LDH↑↑</td>
<td>Major: Hb fell to 33g/L</td>
<td>6</td>
<td>Treated with steroids</td>
<td>Possible</td>
</tr>
<tr>
<td>HH3</td>
<td>No new antibodies; anti-C+Jkα pre transfusion; probable anti-N between transfusions</td>
<td>bilirubin↑↑; Hb↓↓</td>
<td>Major: Hb fell to 42g/L</td>
<td>2 - 14</td>
<td>Transfused on 3 occasions within 3 weeks; treated with steroids</td>
<td>Probable</td>
</tr>
<tr>
<td>HH4</td>
<td>Known anti-Jkα+; no new antibodies</td>
<td>Chest pain; dark urine, jaundice; bilirubin↑↑; Hb↓↓; LDH↑↑↑ (8180U/L)</td>
<td>Major: Hb fell to 41g/L</td>
<td>5</td>
<td>Treated with IVlg and steroids; death not related to transfusion</td>
<td>Certain</td>
</tr>
<tr>
<td>HH5</td>
<td>No antibodies</td>
<td>Tachycardia; hypoxia; haemoglobinuria;</td>
<td>Death probably related to HH; Hb fell to 31g/L</td>
<td>7</td>
<td>Treated with IVlg and steroids</td>
<td>Certain</td>
</tr>
<tr>
<td>HH6</td>
<td>Known anti-E+Jkα+Kpα, DAT1+; no new antibodies</td>
<td>Fever, jaundice, dark urine; Hb↓; LDH↑</td>
<td>Moderate: Hb fell to 58g/L</td>
<td>6</td>
<td>3 unit transfusion; treated with IVlg and steroids</td>
<td>Probable</td>
</tr>
</tbody>
</table>
SHOT 2016- Haemolytic transfusion reactions in Sickle Cell Disease  n=8

- Classic DHTR n=2
- 1 could have been prevented, the patient had a history of red cell antibodies, undetectable pre-transfusion.
Patients with sickle cell disease are particularly vulnerable to severe haemolytic transfusion reactions. Laboratory staff should not assume that it is safe to give only Rh/K-matched blood, as antibodies are prone to evanescence and historical antibodies may no longer be detectable serologically. The laboratory should take active steps to seek a transfusion history, and an antibody history if previous transfusion has occurred. For patients in England, Sp-ICE (Specialist Services Electronic Reporting using Sunquest ICE) should also be checked before selecting appropriately phenotyped units and similar shared databases should be checked where available in devolved countries.
Acknowledgments

Jo Howard
Anicee Danaee
Rachel Kesse Adu
Baba Inusa
Nay Win
Tim Maggs
Brian Robertson
Paula Bolton-Maggs
Results

- Table (2) Summarises trend in Hb in each case, whether the episode of hyperhaemolysis was Acute (A) or Delayed (D). Also demonstrated are historical antibodies, new antibodies formed and transfusion history.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood Group</th>
<th>A vs D</th>
<th>DAT</th>
<th>Pre-Tx Hb g/l</th>
<th>Post Tx Hb g/l</th>
<th>Nadir Hb g/l</th>
<th>Historical Abs</th>
<th>New Antibodies</th>
<th>Total units transfused prior to Hyperhaemolysis</th>
<th>Emergency vs elective transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O +ve</td>
<td>D</td>
<td>-ve</td>
<td>81</td>
<td>91</td>
<td>56</td>
<td>Anti C, Anti Fya, Auto e</td>
<td>Nil</td>
<td>29 units</td>
<td>Elective ( Prior to hip replacement)</td>
</tr>
<tr>
<td>2</td>
<td>O +ve</td>
<td>A</td>
<td>-ve</td>
<td>59</td>
<td>73</td>
<td>33</td>
<td>Nil</td>
<td>Nil</td>
<td>5 units</td>
<td>Emergency ( Acute chest syndrome)</td>
</tr>
<tr>
<td>3</td>
<td>O +ve</td>
<td>D</td>
<td>+ve</td>
<td>64</td>
<td>82</td>
<td>31</td>
<td>Nil</td>
<td>Nil</td>
<td>11 units</td>
<td>Emergency ( Acute chest syndrome)</td>
</tr>
<tr>
<td>4</td>
<td>O +ve</td>
<td>D</td>
<td>-ve</td>
<td>70</td>
<td>75</td>
<td>46</td>
<td>Anti E , Anti CW</td>
<td>Anti-C Anti-JKb, Anti-Lua</td>
<td>2 units *</td>
<td>Emergency ( Transfusion following myomectomy)</td>
</tr>
<tr>
<td>5</td>
<td>AB +ve</td>
<td>D</td>
<td>+ve</td>
<td>74</td>
<td>115</td>
<td>44</td>
<td>Anti E</td>
<td>Anti-jkb, Anti-Lua</td>
<td>3 units</td>
<td>Emergency ( exacerbation of asthma and low Hb)</td>
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<tr>
<td>6</td>
<td>O +ve</td>
<td>A</td>
<td>+ve</td>
<td>110</td>
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<td>35</td>
<td>Nil</td>
<td>Anti-S, Anti-Fya, Anti-Fyb</td>
<td>16 units</td>
<td>Elective ( pre-operative)</td>
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<tr>
<td>7</td>
<td>B +ve</td>
<td>D</td>
<td>+ve</td>
<td>57</td>
<td>114</td>
<td>44</td>
<td>Nil</td>
<td>Nil</td>
<td>10 units</td>
<td>Emergency( Acute chest syndrome)</td>
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<td>8</td>
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<td>A</td>
<td>-ve</td>
<td>69</td>
<td>99</td>
<td>38</td>
<td>Nil</td>
<td>Nil</td>
<td>2 units</td>
<td>Emergency ( Acute chest syndrome)</td>
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<tr>
<td>9</td>
<td>A +ve</td>
<td>A</td>
<td>+ve</td>
<td>51</td>
<td>86</td>
<td>41</td>
<td>Anti M, Anti S</td>
<td>Nil</td>
<td>2 units</td>
<td>Emergency ( Splenic sequestration)</td>
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</table>
Results

- Table (3); summarises treatment received by each patient

<table>
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<tr>
<th>Patient</th>
<th>IVIG</th>
<th>Steroids</th>
<th>Folic acid</th>
<th>iron</th>
<th>EPO</th>
<th>Vitamin B12</th>
<th>Further red cells acutely</th>
<th>Further challenge with red cells Following the acute episode</th>
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<td>Yes</td>
<td>Yes</td>
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</tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes (with further IVIG, steroids and EPO)</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>9</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes (further IVIG, steroids)</td>
</tr>
<tr>
<td>A vs D</td>
<td>DAT</td>
<td>Pre-Tx Hb (g/L)</td>
<td>Post-Tx Hb (g/L)</td>
<td>Nadir Hb (g/L)</td>
<td>Historical Abs</td>
<td>New antibodies</td>
<td></td>
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</tr>
<tr>
<td>D</td>
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<td>81</td>
<td>91</td>
<td>56</td>
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</tr>
<tr>
<td>A</td>
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<td>73</td>
<td>33</td>
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<td>Nil</td>
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<td></td>
</tr>
<tr>
<td>D</td>
<td>+ve</td>
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<td>82</td>
<td>31</td>
<td>Nil</td>
<td>Nil</td>
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</tr>
<tr>
<td>D</td>
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<td>46</td>
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<td>Anti-C anti-JKb, anti-Lua</td>
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</tr>
<tr>
<td>D</td>
<td>+ve</td>
<td>74</td>
<td>115</td>
<td>44</td>
<td>Anti-E</td>
<td>Anti-jkb, anti-Lua</td>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>+ve</td>
<td>110</td>
<td>102</td>
<td>35</td>
<td>Nil</td>
<td>Anti-S, anti-Fya, anti-Fyb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>+ve</td>
<td>57</td>
<td>114</td>
<td>44</td>
<td>Nil</td>
<td>Nil</td>
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<td></td>
</tr>
<tr>
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<td>−ve</td>
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<td>99</td>
<td>38</td>
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</tr>
<tr>
<td>A</td>
<td>+ve</td>
<td>51</td>
<td>86</td>
<td>41</td>
<td>Anti-M, anti-S</td>
<td>Nil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Additional treatment in Thalassaemia n=19

• Cyclophosphamide n=3
• Azathioprine n=2
• Ciclosporin n=2
• Rituximab n=2
• Eculizumab n=1
• Splenectomy n=6
  - 2 continued to haemolyse
• 3 Patients went on to receive a BMT
Serious Hazards of Transfusion 2015

- 9 cases (2 confirmed, 5 probable, 2 possible)
- 5 no new alloantibody
  - n=4: 4-7 days
  - n=4: 7-10 days
  - n=1: 18 days
- 4 new red cell antibody
Macrophage activation

Autologous red cell (Hb SS) → Phosphatidylyserine

Sickle reticulocyte

α4β1 → VCAM-1

Allogeneic transfused red cell (Hb AA)
Case 19.1: Death probably related to hyperhaemolysis

A young male patient with sickle cell anaemia received a red cell transfusion in the intensive therapy unit (ITU) in view of hepatic sequestration. Seven days later he had a sudden reduction in his Hb from 85g/L to 45g/L and then a further drop to 31g/L. He had haemoglobinuria, chest pain and had a tachycardia. He was treated with methylprednisolone and intravenous immunoglobulin (IVIg) and further red cell transfusion. While he was being transfused with his first unit he deteriorated, developed chest infiltrates and acidosis. He died of circulatory collapse and respiratory failure some 12 hours later despite maximum support. The coroner’s report is awaited.
Case 19.9: Avoidable DHTR following transfusion of antigen-positive red cells

The patient received an eight unit red cell exchange transfusion at hospital A (prior to surgery at hospital B) with red cells matched only for Rh and K. She was admitted to hospital B 6 days later, very unwell, with fever, jaundice, black urine and a falling Hb. Hospital B had a historical record of anti-E+S+Fy\textsuperscript{a}+Fy\textsuperscript{b}+Fy3 for this patient and confirmed that several of the units used in the exchange were antigen positive; anti-Fy\textsuperscript{a}+Fy3 were identified in the plasma and eluate.

There were two opportunities for the patient history to be available to hospital A: the laboratory in hospital A could have requested the history from either hospital B or from Sp-ICE; the laboratory in hospital B could have actively informed the laboratory in hospital A as they were aware that the exchange transfusion would take place there.
Local protocol

In a patient with sickle cell disease presenting with:
- pain, fevers, dark urine
  - Inquire about recent transfusions if a transfusion reaction is likely
  - Liaise with transfusion lab and establish transfusion history

Remember that haemolytic transfusion reaction/hyperhaemolysis often presents with symptoms similar to painful crisis. Ensure patient is haemodynamically stable: treat with analgesia, hydration and low threshold for commencing antibiotics.

Send following investigations:
- FBC/Reticulocyte count and blood film
- U&E/LFT/CRP/LDH
- Ferritin/haematocrits
- DAT/ Hb5%
- G&G
- Urine dip
- Cultures in event of underlying sepsis

Do your investigation results and patient's clinical status support the diagnosis of haemolytic transfusion reaction?

- 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 (0.4 g/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 haematric 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)

- Report case to SHOT/MHRA (Medicines and Healthcare Regulatory agency)
- Ensure an alert exists on patients transfusion records
- Patient education with regards to potential risk of subsequent transfusions is paramount and patients should be provided with an alert card

Fig. Flowchart demonstrating investigation and management of hyperhemolysis full blood count (FBC), urea and electrolytes (U&E), lactate dehydrogenase (LDH), liver function test (LFT), and C-reactive protein (CRP).