Haemolytic Transfusion Reactions – how many are preventable?

SHOT Launch, July 2004
Sue Knowles
Clare Milkins
Definition of HTR

- Transfusion causing increased red cell destruction
  - usually due to red cell alloantibodies
  - other
    - Autoantibodies
    - Hyperhaemolysis in SCD
Types of HTR

- Immediate/acute –
  - during transfusion or within hours

- Delayed
  - within days
  - following a 2° immune response (anamnestic)
  - Antibody not detectable pre-transfusion
Intravascular vs extravascular haemolysis

- **Intravascular**
  - complement mediated (to C8/C9)
  - always immediate
  - usually severe
  - death in 10%
  - Anti-A, anti-B, anti-A,B, anti-Vel, anti-PP1P^k

- **Extravascular**
  - slower and less severe
  - immediate or delayed
  - phagocytosis of IgG/C3d coated cells (liver & spleen)
Acute or delayed?

- Pre-transfusion tests insensitive
  - Weak antibodies may be missed

- may cause immediate extravascular haemolysis that may or may not be noticed

- or may be present in insufficient amount to cause immediate haemolysis

- Obvious haemolysis as a result of anamnestic response
  - or combination of ATR/DTR
AHTR as a result of IBCT

- All preventable!!

- Figures over the last 7 years:
  - 226 (16%) major ABO incompatibility
    - 32 per year
    - 27% death or major morbidity
  - 77 other red cell incompatibility
    - 11 per year
    - 8% death or major morbidity
What are the errors in non-ABO IBCTs?

- Antibody significance is overlooked
- Antibody detectable but missed
- Antibody not detectable but known

- Similar problems contribute to other preventable HTRs
AHTRs due to platelet transfusions

- With one exception, due to group O platelets being transfused to group A recipients
- Have occurred following the transfusion of both pooled and apheresis platelets
- A negative test for high titre anti-A/B (HTO) does not guarantee the safety of the product
- Potential for haemolysis not restricted to neonates/children
## Platelet AHTRs

<table>
<thead>
<tr>
<th>Year</th>
<th>Number/source</th>
<th>HTO</th>
<th>Patient age</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996/7</td>
<td>1 aph.</td>
<td>Neg</td>
<td>?</td>
<td>Major possibly caused mortality</td>
</tr>
<tr>
<td>1997/8</td>
<td>1 aph</td>
<td>?</td>
<td>55</td>
<td>Minor</td>
</tr>
<tr>
<td>1998/9</td>
<td>1 aph</td>
<td>Neg</td>
<td>36</td>
<td>Minor</td>
</tr>
<tr>
<td>1999/0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000/1</td>
<td>2 pools</td>
<td>NT</td>
<td>?</td>
<td>? Major</td>
</tr>
<tr>
<td></td>
<td>1 aph</td>
<td>Neg</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>2001/2</td>
<td>1 pool</td>
<td>NT</td>
<td>7</td>
<td>Minor (O to B)</td>
</tr>
<tr>
<td>2003</td>
<td>2 aph</td>
<td>Neg</td>
<td>31, 3 mths</td>
<td>Major</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major</td>
</tr>
</tbody>
</table>
Should these be prevented?

- Historical practice to transfuse platelets across ABO groups
- Difficulty of managing a platelet inventory
- Perception that problem confined to “small volume” recipients
- Calculated frequency of 1 in 9000 mismatched platelets (Mair, Benson 1998)
Testing for high titre anti-A/B

- Not universally performed
- ? agreed standard?

- UK – titre 1:100 saline

- 2 cases IAT titres performed; 1 in 8000, 1 in 20000
- 1 case manual saline titre; 1 in 1024
## AHTRs following red cells

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Urgent</th>
<th>AIHA</th>
<th>Difficult</th>
<th>Error</th>
<th>Insens. Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>3</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>4</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>6</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>8</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>4</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>??</td>
</tr>
</tbody>
</table>
Errors resulting in AHTRs

- 1996 – failure to observe recommended sampling intervals in repeatedly transfused patients
- 1999 – patient transfer, anti-Jk^b known
- 2000 – marrow transplant; group O to A recipient, transfused with group A red cells
AIHA and AHTRs

- Disproportionately represented
- 9/31 cases since 1996

How many were necessary?

- Transfusion exacerbating haemolysis due to autoantibody?
- Insufficient pre-transfusion testing to detect underlying alloantibody?
Does transfusion increase the rate of haemolysis in AIHA?

- Salama et al 1992
- 53 patients studied
- Transfusions all well tolerated
- Hb increments frequently less than predicted
- No evidence that increased the rate of haemolysis
Incidence of alloantibodies in AIHA

- Divergent figures
- 15 to 40%

- Dependent on number and nature of adsorptions performed
- Likely that some alloantibodies were autoantibodies with mimicking specificities
## Pre-transfusion testing in AIHA

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
<th>Ref. lab</th>
<th>Alloantibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>1</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>1997</td>
<td>2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>1999</td>
<td>1</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>2000</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2001</td>
<td>3</td>
<td>Yes</td>
<td>Anti-Vel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>2002</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Why might other HTRs be preventable?

- If antibody not detectable but known
- If antibody detectable but missed or misidentified
- Unnecessary transfusion
Not detectable but known

- No longer detectable
  - Anamnestic response
  - True DHTR

- Are these DHTRs preventable?
  - Perhaps if antibody has been previously identified
    - 61/488 (13%) lab errors (6 yrs) were failure to check historical records
    - Antibody cards?
    - National database?
Detectable but missed

- Pre-transfusion tests incomplete
  - Emergencies
  - Omission of ID panel in presence of known antibody (IBCT and DHTR reports)
    - Preventable? Probably
- Sample too old
- Pre-transfusion tests insensitive
- Antibody misidentified (and/or masked)
Omission of ID panel – e.g.

- Non-urgent tx requested on-call
- Transfused 9 weeks previously
  - identified anti-K + non-spec cold antibody
- No ID panel performed
- Xmatch was ‘sticky’ but transfusion given
- 3 days later anti-Jk^a was identified
  - Retrospective ID panel still not performed (sample available)
Sample too old

- **99/00**
  - Patient with anti-D tx x2 in one week
  - Tx again 6 days later with >4 day-old sample
  - DHTR (?when) due to anti-Jk\(^a\)

- **01/02**
  - One 4 week old pre-admission sample used with intervening tx
    - Lack of communication between hospitals (SCD)
    - Mulitple antibodies, severe DHTR
  - 48 hr sample used with tx 5 days previously
    - c+E, fatal DHTR
    - ? emergency
Insensitive techniques

- Anti-Jk\textsuperscript{a} x2 missed in xm vs Jk(a+b+) cells
  - ID omitted in emergency
- Anti-c+E+Jk\textsuperscript{a} missed by DiaMed & ignored by CRRS
- Anti-Jk\textsuperscript{a} x2 not detected by automated techniques
  - Detected retrospectively by manual techs
Insensitive techniques

- Anti-s not detected by CAT using non-validated cell suspension
  - Detected retrospectively by CAT and solid phase
- Anti-Jk\(^a\) missed by LISS IAT
  - Detected retrospectively by solid phase
Antibody misidentified

- Anti-Jk$^a$ + E masked by anti-Kn$^a$
- anti-Jk$^a$ misidentified as Ab to low frequency antigen
- Anti-Jk$^a$ misinterpreted
- Anti-M+UI (later -M+E+C+S)
- Anti-Do$^a$ not identified
  - ? HLA related, ?HTLA
- IBCTs
Evidence that antibodies may be missed

- Often difficult to tell from SHOT data
  - DHTRs may be unrecognised
  - Unreported
  - Under-investigated
- UK NEQAS data
Evidence from UK NEQAS data

- Antibody screening:
  - 0.2 to 0.3% missed antibodies
  - 47 errors in 18,600 tests
  - 40% transcription/transposition errors

- Causes:
  - Non-validated cell suspensions
  - Lack of homozygous cells for screening
  - Aspiration failures in automated systems
Evidence from UK NEQAS data

- Antibody identification:
  - Single specificity error rate = 0.3% error rate
    - 15% transcription/transposition error
    - 27 out of 7800 tests
  - Mixture of two antibodies = 2.4% error rate
    - 129 out of 5400 tests
    - 9% transcription/transposition error
  - Theoretical exercise (03E5) suggests proficiency is potentially much worse
Evidence from UK NEQAS data

- Anti-S+Fya
  - Same reaction pattern as anti-M
  - 35% reported anti-M
    - 20% of these missed anti-S
    - = 7% overall

- Causes:
  - Lack of understanding
  - Lack of resources
Is it possible to quantify?
DHTRs – 7 years (excl IBCT)

- 213 cases (completed questionnaires)
  - 8 deaths (4%)
  - 21 major morbidity (10%)
- At least 24 potentially preventable
  - Antibody misidentified pre-tx (7)
  - Historical Ab known but not to lab involved (6)
  - Antibodies missed (11 in 3 years)
AHTRs - 7 years (excl IBCTs)

- 233 cases
  - 10 deaths (4%)
  - 5 major morbidity (2%)
- At least 13 *potentially* preventable
  - 9 group O plts to group A recipient
  - 4 errors (? should be IBCT)
DHTR – Potentially missed antibodies

- Every year DHTRs are reported within 72 hours of transfusion
  - 10 in last 2 years
  - Many are likely to have been detectable pre-tx
- Retrospective testing is carried out in only 24% to 62% cases
- No evidence that retrospective testing is confirmed by a reference lab or a different technique
Ideal retrospective testing

Retest pre-tx sample by:
- Same technique
- Different technique (e.g. tube)
- More sensitive technique (e.g. enz/enzIAT)
- Different BMS
- Include DAT
- Reference centre
Ideal post-tx testing

- Careful appraisal of antibody identification results
  - More sensitive techniques
  - More cells
  - ? Reference lab
- DAT (eluate if positive)
- To prevent further DHTR
<table>
<thead>
<tr>
<th>Day 1</th>
<th>Resection Ca colon and post-operative evacuation haematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1-3</td>
<td>Multiple transfusions</td>
</tr>
<tr>
<td>Day 6</td>
<td>Antibody screen neg</td>
</tr>
</tbody>
</table>
| Day 8 | Hb 4g/dl; fever, jaundice, red urine  
Third laparotomy for presumed bleed  
5 units red cells issued; IS, day 6 sample |
| Day 9 | Acute renal failure requiring dialysis  
Antibody screen; anti-c+E |
| Day 12 | Died |
Is the patient morbidity/mortality preventable? (Case 13 DTR 2001)

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Vaginal bleeding requiring transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 4</td>
<td>Further transfusion</td>
</tr>
<tr>
<td>Day 6</td>
<td>Pre-op sample for hysterectomy; incorrect computer entry in lab, not tested</td>
</tr>
<tr>
<td>Day 7</td>
<td>Screen pos, anti-c and ? Cold autoantibody/anti-(P_1) (\text{DAT} ) pos. Further samples requested at 37°C</td>
</tr>
<tr>
<td>Day 8</td>
<td>Repeat testing at 37°C, further sample requested for referral to reference laboratory</td>
</tr>
<tr>
<td></td>
<td>Hb 4g/dl  Shocked</td>
</tr>
<tr>
<td></td>
<td>? Bleeding/?haemolysis – transferred to ICU</td>
</tr>
<tr>
<td></td>
<td>2 hours later agreement that ABO/RhD identical units should be transfused – patient died in interim</td>
</tr>
</tbody>
</table>
Conclusions

- IBCTs are all preventable and are the most frequent cause of HTRs

- Difficult to know from the SHOT data the percentage of preventable non-IBCT HTRs!
AHTRs due to platelets

- AHTRs due to ABO mismatched platelets are in theory all preventable

- Transfusion services should be encouraged to produce more group A platelets for neonates

- Hospitals holding a stock of platelets should be encouraged to include group A
HTRs and alloantibodies

- Historical data must be checked
- Antibodies missed due to insensitive testing
- Inappropriate intervals between sampling and transfusion
- Non-systematic approach to antibody ID
HTRs and autoantibodies

- Disproportionately represented
- Not all are investigated for underlying alloantibodies
- Not confident that all the reactions reported are due to an exacerbation of underlying autohaemolysis
Clinical features of HTRs

- HTRs can be mis-diagnosed or completely overlooked

- Lack of communication between all parties at an early enough stage leads to delays in providing necessary transfusion support
In answer to the question!!

- If insufficient investigation is performed we may never know!

- SHOT is working towards making earlier contact with the reporters in order that cases are better understood