HLA Sensitisation in Renal Transplantation

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- on behalf of the National Working Group on HLA sensitisation in renal transplantation
Background

1. Transplantation is the treatment of choice for patients with end-stage renal disease (ESRD)

2. HLA sensitisation is a major barrier to a successful outcome
   - **PRE-TRANSPLANT** - increased difficulty in finding a compatible donor (long wait times and for some prevention of transplantation)
   - **POST-TRANSPLANT** - inferior allograft outcomes (graft failure)

3. Blood transfusions are a recognised cause of HLA antibody sensitisation

4. Anti-HLA antibody development is not prevented by leucodepletion or red cell washing
   - Depleted unit contains $<5 \times 10^6$ leucocytes
   - HLA Class I molecules expressed on *red cells* at low levels (100-2000/cell), but $10^9$ in a unit
Background

Post-transplant blood transfusions (PTBT) - shown to be associated with de novo *kidney donor specific HLA antibodies* (DSA) and HLA antibody mediated rejection (AMR)

*DSA and AMR are associated with reduced allograft survival*

<table>
<thead>
<tr>
<th>Study</th>
<th>Time Period</th>
<th>PTBT (Leucodepleted; Y/N)</th>
<th>DSA Development/ Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scornik et al. <em>Transplantation, 2009</em></td>
<td>2000 - 2005</td>
<td>746 patients; 45% transfused (No LD)</td>
<td>20% of patients who produced a NDSA were transfused, as opposed to 57% who produced a DSA, p=0.005</td>
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<tr>
<td>Fidler et al. <em>Human Immunology, 2013</em></td>
<td>2003 - 2007</td>
<td>111/258 (43%) (Yes)</td>
<td>Pre + PTBT: greater risk of developing AMR (HR 13.9) and graft loss (HR7.1)</td>
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<tr>
<td>Ferrandiz et al. * AJT, 2016*</td>
<td>2008 - 2012</td>
<td>250/390 (64.1%) (Yes)</td>
<td>Transfused group: de novo anti-HLA antibodies and de novo DSA (p&lt;0.0001)</td>
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<tr>
<td>Verghese et al. <em>Pediatr Transplantation, 2016</em></td>
<td>1984 – 2013</td>
<td>208/482 (44%) (Yes)</td>
<td>Sub-analysis (n=82) transfused &lt;1/12: no increase in DSA [HR 0.9, 95% CI 0.6-1.4, p=0.65]</td>
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<tr>
<td>Bynum et al. <em>Transfusion, 2018</em></td>
<td>2004 - 2015</td>
<td>182/244 (74.6%) (Yes)</td>
<td>HLAi transplant: transfusions were not associated with increased risk of AMR</td>
</tr>
</tbody>
</table>
**Q:** Are HLA Ab’s made to HLA antigens on blood transfused? Or does transfusion “stir up” immune system, resurging previous HLA Ab’s? Difference: would HLA matched red cells prevent this, or not.

HLA typed the blood donors of transplant recipients transfused post-transplant (PTBT).

**Aims:**

1. Determine whether an HLA Ab is made against a blood donor post-transplant (=development of a de novo transfusion specific antibody [TSA])
2. Explore relationships between the development of HLA Abs common to both a blood donor and the kidney donor (ie: TSAs and DSAs of shared HLA specificities: TSA=DSA)
3. Analyse the effect of HLA Abs on clinical outcomes

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**Background:** Hassan et al, AJT, 2019
Hassan et al, AJT, 2019 - Results

• HLA sensitisation from PTBT associated with inferior allograft outcomes

• When blood transfusions share HLA antigens with the kidney donor, de novo HLA antibody formation is common (& outcomes worse).

• Highlights importance of:
  • Avoiding/minimising transfusions
  • Avoiding shared donor antigens - Role for HLA selected blood for some?
HLA Matched red cell working group

↑ requests from clinicians for HLA matched red cells

+ The results of our study/debate in the literature

= Formation of the HLA matched red cell Working Group

**NHSBT H&I** – Andrea Harmer, Colin Brown;

**Clinical** – Fiona Regan, Mike Murphy, Edwin Massey;

**Renal** – Michelle Willicombe, Sevda Hassan, Nick Torpey (BTS rep);

**Statistics** – Lisa Mumford (Head of ODT Studies)

**MAIN OBJECTIVE:** address question whether or not HLA matched red cells for transplant patients is justified (& how could do it).
Multi-centre study of the incidence of blood product transfusion & impact on transplant outcomes
Aims

Unclear how PTBT impacts our renal transplant population - as transfusion rates in UK transplant units are not known.

Collaborative study (NHSBT, BTS and the National Working Group):
• Aim: review incidence of blood transfusion and impact on 1-year allograft outcomes.

Methods:
1. 4 UK transplant centres participated - Cambridge; Guys; Imperial; Oxford.
2. Patients transplanted between April 2016-2017 were analysed.
3. The Hospital Tx Lab at each hospital identified transfusions received for each individual (one month before, to 1 year post transplant)
4. NHSBT statistical department collated the data and analysed the outcomes
Post-transplant transfusions

- 723 kidney only transplants were included
- 221/723 (31%) were transfused
  - 189 (26%) blood alone
  - 7 (1%) platelets alone
  - 25 (3%) both blood and platelets
- The median time to transfusion was 4 (0-12) days
- Of those transfused, the median number of blood and platelets transfused was 2 (2-5) units and 1 (1-3) pools respectively
- Of note – on survey just before, most centres underestimated their Tx rates (10-30%)
Conclusions

1. The current transfusion rates are comparable amongst the four units
2. Blood alone is most commonly transfused
3. The time to transfusion is acute (0-12 days) and associated with DGF
4. Transfusions are associated with inferior patient and allograft outcomes.
   At 1 year, transfusions are independently associated with:
   a. Inferior patient survival
   b. Inferior allograft survival
   c. Inferior allograft function
Plan:

1. **Transfusion Rates** –
   a) Publications on survey (estimated Tx rates) of all renal transplant units; & of 4 Pilot Sites’ actual Tx rates (& outcomes) – to raise awareness (months);
   b) Offer audit tool of actual Tx to all sites beyond 4 pilot sites;
   c) Repeat in:
      i. Paediatric transplants;
      ii. Pancreatic transplants; (leads for both nominated)
   d) Review guidelines – strengthen EPO advice.

2. **HLA matched blood question:**
   a) Repeat HLA sensitisation study in patients on Wait List for renal transplants (? more Ab formation)
   b) Working with DH Health Economics Analyst – on modelling of size of donor panel for HLA matched blood / HLA antigen avoidance (for future 2nd transplants etc); timing; other requirements (ABO & D matched as well).
   c) In liaison with Australia re: studies; panel logistics / practicalities and Health Economics.