HLA Matched Red Cells for Renal Transplant Patients

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Background:

- Average kidney transplant lasts 10-15 yrs;
  - rejection is commonest cause of its failure

- Patients who develop donor-specific HLA Ab’s (DSA) are at ↑ risk of rejection/failure

- “treatment” of DSA graft rejection is poor, so mechanisms to prevent DSA are focus

- Pregnancy, previous renal transplant & transfusion are associated with ↑ HLA Ab’s
  - Only transfusion is modifiable (review factors - Scarnick. Am J Transpl 2011)
Background: ctd

• Association of Tx with ↑DSA
  – Willicombe, abstract Renal Ass’n/BRS, Glasgow 2014;

• Even LD blood still a problem as:
  – Lymphocytes $2 \times 10^5$ class I HLA per cell
  – Rbc $2 \times 10^3$ class I HLA per cell – but $1000\times$ rbc:wbc in unit of red cells (LD);

• (kidney donor transfusion in 1970-80s improved transplant outcome, as 1yr graft survival 60-70%; but now 90% & better IS, so effect not evident)
Factors in HLA Sensitisation

1. Effect of Tx: down-regulatory in naïve patients but stimulatory in previously exposed patients, so HLA Ab’s in transplant candidates is:
   - 10-12% if Tx up to 20 units, if no previous pregnancy/transplant. When produced, were low level & disappeared in months, even if further Tx

2. Age: 35% HLA sensitisation in age 5-20 versus 7.5% in age >20

3. Pregnancy alone: 5-33% HLA sensitisation (∞ technique)
   - Tx & pregnancy: 40% vs 5% with no Tx; & higher titre & broad sensitisation
Debate:

• A) Does Tx cause HLA Ab’s to ag’s from the Tx, which are also on kidney (DSA), so that HLA matched blood would prevent this, **OR**

• B) Does Tx cause general “immune stimulation” so that HLA Ab’s formed (resurged from previous cause) even though Tx did not contain corresponding HLA ag’s – therefore HLA matching of blood, would NOT prevent this

• Need to determine if patients who form HLA Ab’s after Tx, received Tx with the corresponding ag on
Study:
Renal Transplant Team, IC and NHSBT collaboration

• All renal transplant patients who were transfused: selected
  - 164 who developed kidney donor-specific antibodies (DSA) post-transplant
  - 164 controls, who didn't develop DSA

• To identify if donors of components had corresponding ag to HLA (DSA) Ab developed, needed to HLA type all donors

• IC: list of unit nos: of all components transfused - Maggie Przybysiak: looked up identity of all donors on PULSE
  - list of donors to Colin Brown, H&I – previously HLA typed?
  - rest to contact for HLA typing – need consent therefore for extra samples
  - needed ethics, R&D and BSCARE approvals
Flow Diagram for HLA Ab Study

List of Donation Nos: from Imperial, of units transfused to patients

H&I: look up Donor ID on PULSE, to look up on Haematos if already HLA typed

625 donors never HLA typed

MP send pt.info leaflet + SAE to each donor (address from PULSE)

43 (6.4%) donors already HLA typed

No response in 1 month: 1 further chase up letter

Donor consents: MP sends package with saliva kit + form + instructions to donor (sends sample)

Donor declines: enter on spreadsheet

If saliva test fails - donor to Donor Session / GP – sample returned in post to H&I

No sample received in 1 month: letter / email / text to donor to ask if still happy to have sample taken / need another box?

H&I (batch) HLA test: Results to spreadsheet

Transmit-with donation no: to ICHNT Renal Team
Methodology:

• Designed with H&I (Andrea Harmer, Colin Brown), Donor Services (Nicky Anderson, Jane Griffith – Area Nurse Manager, Eileen Bailey – NCC)
  – Estimated up to 10% might fail saliva kit test – so need blood sample

• Before contacting donors – checked all alive (on NHS Spine)
  – If donors suspended/withdrawn - F. Regan & in some cases, CST Drs Colindale – judged on PULSE reasons, if ok to contact

• Letters to donors (batches per week)
  – Info leaflet with consent form and SAE
  – Offer to answer queries
  – Send saliva kit once consent received: prepaid box to post back to F. Regan & PA
  – Chase up letter 1 month, if no reply
Testing

• H&I test in batches of 90
  – Paid for – on basis would get lot of HLA typed red cell donors out of it, in case need to HLA Match in future!

• Donors warned testing up to 6 weeks later, so may get letter to say “need blood sample” after that
  – Very few needed blood sample: 6 of 150 tested (4%)

• Agreed with Donor Teams nationally that if donor wanted sample taken at session, check with Area Manager first (to avoid overload); fully supportive of Study
  – Had letters with instructions and donors post sample

• Comms: Article in Connect and Donor Magazine – for staff and donor awareness
Total Donors = 628

Total donors invited = 603
Active=414; Suspended=18; Withdrawn=171.

Not approached = 25
Unit Nos: incorrect = 3
Not on PULSE / NHS SPINE = 17
Donors died = 4
Previous litigation = 1

Completed: saliva samples tested = 394
Including:

Consent but no sample received = 19

No response: consent = 149

Declined = 41
Blood test needed = 6
Abroad = 4
Medical reason = 5
Unknown = 32

Medically withdrawn = 27
Suspended = 16

WD: DNA / moved / archived = 42
WD: Opted out of Communications = 14
Active = 295
## HLA Typing Renal Study 2015-2017 (Response Rate = 394/625 = 63%)

### Completed

- **6 needed Blood Sample**
  - incl. 27 with ‘Medical Condition’, 16 Suspended/Active (incl. 1 Opt Out of Comms), 12 ‘Opt Out of Comms’, 2 Withdrawn (CLI/ Veins), 1 Withdrawn-Xfer to Wales, 8 Withdrawn for own request (incl. 1 Retired from donating), 32 DNA (incl. 1 Opt Out of Comms), 8 DNA/Archived, 4 Moved.

### Chasing Sample Boxes (ie: signed Consent Forms)

- **19**
  - incl. 1 with ‘Medical Condition’ (16 chasing since 2016, 3 sent boxes recently), 1 Withdrawn (CLI/Underweight), 1 Opt Out of Comms, 1 Archived.

### Chasing Consent Forms

- **150**
  - incl. 6 with ‘Medical Condition’, 2 Suspended, 60 Withdrawn (38 DNA-incl.1 Opt Out of Comms, 9 DNA/Archived, 3 Moved, 6 Moved/Archived, 4 Withdrawn for own request).

### Did Not Want to Take Part

- **41**
  - incl. 5 with ‘Medical Condition’, 1 Withdrawn (CLI/VV3), 4 Non UK address (incl. 1 Retired, 1 DNA, 1 Withdrawn for own request, 1 Moved/Archived), 2 DNA, 1 DNA/Archived, 2 Withdrawn for own request, 1 Retired due to age, 2 Moved, *2 agreed (sample box sent)/Disagreed*.

### Wrong Address/No E-mail Address

- **17**
  - (incl. 4 that unable to find in NHS Spine)

### Deceased (Identified in NHS Spine: Not Contacted)

- **4**

### Total

- **625**

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**breakdown of donors contacted with medical condition (n = 39)**

- Completed: 27
- Awaiting sample box: 1
- Declined: 5
- No response: 6
  
  (chasing consent forms)
# List of Donors with Medical Conditions – Total 39

<table>
<thead>
<tr>
<th>Completed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pernicious anaemia (gastro)</td>
</tr>
<tr>
<td>Celiac Disease</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Malignancy x3</td>
</tr>
<tr>
<td>Cardiovascular x4</td>
</tr>
<tr>
<td>Vasovagal</td>
</tr>
<tr>
<td>Anaemia x2</td>
</tr>
<tr>
<td>3rd Consecutive Low Hb</td>
</tr>
<tr>
<td>Investigations</td>
</tr>
<tr>
<td>Renal condition</td>
</tr>
<tr>
<td>Drug Induced Hepatitis</td>
</tr>
<tr>
<td>High BP</td>
</tr>
<tr>
<td>TDW Post 1980</td>
</tr>
<tr>
<td>Lymphedema (leg cellulitis)</td>
</tr>
<tr>
<td>Dizzy episode</td>
</tr>
<tr>
<td>Low grade ductal carcinoma in situ</td>
</tr>
<tr>
<td>Colon Polyp – recovered</td>
</tr>
<tr>
<td>Stent fitted – narrow artery</td>
</tr>
<tr>
<td>Lump</td>
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<tr>
<td>Fractured Finger</td>
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<tr>
<td>Shoulder Injury</td>
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<table>
<thead>
<tr>
<th>Chasing Consent Forms:</th>
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<tbody>
<tr>
<td>Drug (Propiramite preventative)</td>
</tr>
<tr>
<td>Faints x2</td>
</tr>
<tr>
<td>Neurological (blackout despite)</td>
</tr>
<tr>
<td>Heart Attack</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>COPD</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Chasing Sample Boxes:</th>
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<tbody>
<tr>
<td>SVT (awaiting cardiac referral)</td>
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</table>

<table>
<thead>
<tr>
<th>Did Not Agree:</th>
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</thead>
<tbody>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes (on Metformin)</td>
</tr>
<tr>
<td>3 Consecutive Low Hb x2</td>
</tr>
</tbody>
</table>
Non-“active” donors on PULSE, who completed study (n=68):

**Suspended/returning to Active – 16 (4% of all who completed)**
(incl. 1 ‘opt out comms’) due to malaria, endoscopy, pregnancy, Low Hb, investigations, own request

**Didn’t attend blood session/Moved/Archived – 42 (10.6%)**
(incl. 3 ‘opt out comms’)

**Withdrawn – 2 (0.5%)**
Clinical conditions (2 no suitable veins)

**Withdrawn for own request – 8 (2.3%)**
(incl. 1 retired from blood donation)
Results (So far 108 donors tested)

- HLA typed 108 blood donors of 36 patients
  - All 36 patients developed de novo DSA post-transfusion
- 54/108 transfusions resulted in a Transfusion Specific Antibody (TSA): this was in 29 patients
- 33/108 transfusions resulted in a TSA which was the same specificity as the DSA: this was in 17 patients
- (completing further HLA typing by end of May: total 394 donors), plus 43 already HLA typed
Censored allograft survival (in TSA+≠DSA+ patients v TSA-DSA+ and TSA+ ≠ DSA+ patients)
AMR free survival (in TSA+=DSA+ patients v TSA-DSA+ and TSA+ ≠ DSA+ patients)
Where next?

- Early results: need further numbers to analyse
  - 316 HLA typed now;
  - total samples received = 394;
- Funding application to extend to larger study, to ascertain whether this is true finding.
- Abstract to BRS Meeting in March 2017