Hypothetical in Transplantation

Rowan Walker

Any similarity between individuals in this hypothetical and real persons is likely to be entirely deliberate!!!!
“Ulia gets a new Kidney!”

& keeps it ever after
Scenario

- Potential Recipient
- Name: “UJ”
- 49 year old woman,
- Quite a high profile person
- But she has chronic IgA disease.
- Blood Group “B”
- Creatinine 450 umol/l, eGFR ~12 ml/min/1.73m^2
- Easy fatigue-ability, irritability (irrationality)
- Hb = 101 g/L.
Thinking about the Recipient

- Transplant or not to Transplant?
Consultation with Partner

• Wants to consider pre-emptive transplantation.

• What about a period of time on dialysis?
## Waiting Time on Dialysis

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Centre Effect Analysis
Dialysis Choice

What dialysis modality should I recommend?
Patient selection – Encourage patient choice

Data suggest that most patients want to choose their modality and are equally likely to choose PD or HD when fully informed of both options.
Consultation with Partner

• Wants to consider pre-emptive transplantation.

• What about a period of time on dialysis?

• New Private Facility that a couple of your colleagues have bought into and they’re offering extended hour dialysis
How do we help Ulia with her decision?

What negative influences are there about transplantation?
ESRD and life expectancy

Figure 1. Life Expectancy at 45 to 54 and 55 to 64 Years of Age in the U.S. Resident Population and among Persons with Selected Chronic Diseases.

Data for the general population are for 1990, those for colon cancer are for 1983 through 1989, those for end-stage renal disease (ESRD) are for 1992, and those for lung and bronchial cancer are for 1983 through 1989. For cancer and ESRD, the ages shown are at the diagnosis of the disease. Adapted from U.S. Renal Data System,® with the permission of the publisher.

Adjusted Relative Risk of Death:
Deceased-donor Kidney Transplant Recipients compared to Waitlisted candidates

Cardiovascular mortality in CKD patients

Levey et al AJKD 1998;32:853

Transplanted
Dialysis Male
Dialysis Female
Control Male
Control Female
Causes of graft loss

First year

1–5 years

% Losses

HA  AR  PNF  T  CAN  Death

AR  Infection  RD  CAN  Death
Unadjusted 1-Year, 3-Year, and 5-Year Kidney Graft Survival*, by Donor Type: 2000-2005

*Death is included as an event.

- Living Donor
- non-ECD
- ECD

Unadjusted Graft Survival (%)

1-Year: Living Donor 100%, non-ECD 95%, ECD 85%
3-Year: Living Donor 90%, non-ECD 85%, ECD 75%
5-Year: Living Donor 80%, non-ECD 75%, ECD 65%

Data from: 2007 OPTN/SRTR Annual Report, Tables 5.10a, b, c.

5 to 8 %: non-ECD
10 to 20 %: ECD
Thinking about the Recipient

• Transplant or not to Transplant?
• Who is the right donor?
Thinking about the Donor

Partner
Partner

• 58 year old male
• No known history of kidney disease
• Knows his blood group “A1”
• a bit ‘tubby’ (Weight 88 kg; BMI 29.1)— male shaped girth
• Thinks his mother may have had ‘sugar diabetes’ during a pregnancy but she is now on no treatment that he knows of.
• Lived for a long time with his maternal aunt who died of JC disease
• LMO recently placed him on Cipramil for anxiety.

RECOMMENDATION
Thinking about the Donor

• Then you discover ……..
• He is 5 kg heavier than he said he was and his height is 2 cm less!
  (weight 93; Height 1.72 m)
• Then you discover …..
• He has hyperuricaemia and has had a one-off episode of gout
• Then you discover…..
• He has hyperlipidaemia but plans to exercise more and take fish-oil capsules
The Potential Donor

Doc!....

• How long have you been doing living donor transplants in Australia and how long have we been doing living unrelated transplants and are they successful?
Yes!!!
Friendly People!!

- Jeremy Chapman

- Graeme “I don’t believe in evidence-based medicine” Russ
• Graeme Russ on ‘Televideo’
• He gives you not only the traditional South Australian Greeting
• Then he asks you …….
Friendly People

• Scott (WWKIQ – formerly WWTIQ) Campbell
Circa 1963

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Living Donor
Unrelated
“After sequentially testing Pasquale with ‘skin grafts’ from various family members, it was ultimately his father-in-law, Dominic who proved on this basis to be a suitable donor.”
Dominic’s Story

The operation was performed by surgeon Peter Knight ‘almost secretly amid ethical and emotional controversy over whether the risk was justified’.

30 Years Later

Dominic † in 1989 at the age of 90
Live Donor Transplant Rates

- Highest in Tasmania
- Matt Jose
The Potential Donor

• *Doc.*
• *Where would be the best place to get it done?*
• *Do they do ‘key-hole’? (laparoscopic)?*
## Centre Effect Analysis

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<th>time on dialysis</th>
<th>&lt;1.0 years</th>
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**FACTORS INFLUENCING GRAFT OUTCOME**

12 month graft failure and death in adults **HR compared to average for all centres**

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*p<0.05*
Renal transplantation outcome in Australia: is there a centre effect?

Briganti E et al;

This study has shown that the outcomes amongst Australian renal transplant centres were not different from the average outcome for all centres for patients transplanted between 1993 and 1998, after accounting for key outcome predictors and random variability between centres.
Evolution of Laparoscopic Donor Nephrectomy (Australia)
Evolution of Laparoscopic Surgery
Evolution of Laparoscopic Surgery
Potential donor

• Doc!!
What is the risk to me?

Refer to someone else?
May be Refer to a surgeon?
Is “MT” the right Recipient

- Blood Group B
- Anti – A titre is 1:256
1. “Natural” anti-CHO antibodies
   Target
      a) ABH Antigens
      b) Gala 1,3 Gal- containing structures (XenoAg)

2. Primarily IgM - isotype switches do occur

3. Occur in the absence of prior antigenic stimulation. Role in initial defence against various pathogens

4. Polyreactivity - recognise CHO on nucleic acids, proteins & CHO
Antibody Titres - Methods

Method: Mainly looks at:

RT (room temperature)       Cold reacting IgM
37^0                       Warm reacting IgM

IAT (Indirect antiglobulin test) Warm reacting IgG
Different primary titre methodologies

• Test-tubes
• Micro-column technology
  – Diamed gel system
  – Biovue solid phase system
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<th>Different scoring systems for agglutination reactions</th>
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<td>Scoring out of 4&lt;br&gt;usually used with micro-column technology&lt;br&gt;e.g. 0, 1, 2, 3, 4</td>
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<td>Enhancers or not in the Coomb’s method (e.g. RAM)</td>
</tr>
<tr>
<td>Valency of the Coomb’s reagent (e.g. anti-human IgG only)</td>
</tr>
<tr>
<td>Serum vs plasma</td>
</tr>
<tr>
<td>DTT treatment of the serum</td>
</tr>
<tr>
<td>Definition of the titre</td>
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</table>
Different titre methods & Parallels

<table>
<thead>
<tr>
<th>Antibody specificity</th>
<th>Cells Used</th>
<th>Phase</th>
<th>Neat</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>256</th>
<th>512</th>
<th>1024</th>
<th>2048</th>
<th>4096</th>
</tr>
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<tbody>
<tr>
<td><strong>Antibody 1:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>Room-temp. (30 min)</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37°C (30 min)</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IAT</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1024</td>
</tr>
</tbody>
</table>

| Validation           |            |                      |      |     |     |     |     |     |     |     |     |     |      |      |      |

**Is the antibody haemolytic?** YES / NO

**Antibody 2:** parallel: A

|                     |            | Room-temp. (30 min)  | 12   | 12  | 12  | 12  | 10  | 8   | 5   | 3   | 0   | 0   | 0    | 0    | 256  |
|                     |            | 37°C (30 min)        | 12   | 12  | 12  | 12  | 10  | 10  | 5   | 3   | 0   | 0   | 0    | 0    | 128  |
|                     |            | IAT                  | 12   | 12  | 12  | 12  | 12  | 10  | 8   | 5   | 3   | 3   | 0    | 0    | 1024 |

| Validation           |            |                      |      |     |     |     |     |     |     |     |     |     |      |      |      |

**Is the antibody haemolytic?** YES / NO

* Donor cells -
Case Report

ABO Incompatible High-Titer Renal Transplantation without Splenectomy or Anti-CD20 Treatment

Dorry L. Segev^a, Christopher E. Simpkins^a, Daniel S. Warren^a, Karen E. King^b, R. Sue Shirey, Warren R. Maley^a, J. Keith Melancon^a, Matthew Cooper^a, Tomasz Kozlowski^a and Robert A. Montgomery^a,*

Departments of ^aSurgery, ^bPathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
^a Corresponding author: Robert A. Montgomery, rmonty@jhmi.edu

of ABOi renal allografts using protocols that included pre-transplant plasmapheresis (PP), splenectomy, and heavy immunosuppression to control isoagglutinin titers while the recipient was accommodating the incompatible graft (2–6). In two important papers by Alexandre et al., rapid graft loss was universal among the ABOi recipients who did not undergo splenectomy as a part of the pre-conditioning therapy (2,3). Following this report, splenectomy became a standard component of ABOi transplantation protocols.
Summary HLA Typing: A2, 3 ; A*02, *03 ; B51, - ; B*51, *- ; Bw4, - ; Cw1, 15 ; DR8, 11 ; DRB1*08, *11 ; DQB1*0301, *0402 ; DPB1*0401, *0901

Prospective Donor Details:

Donor Name: Matt
Referral Date: 6/10/2009 14:04:00
Date of Birth: 14/02/1943
Relationship: Spouse, PKE Enrolled Pair
Laboratory Reference: LOD 1849
National Reference: 370117038
Summary HLA Typing: A1, 24 ; A*0101, *2402 ; B35, 56 ; B*3501, *5601 ; Bw6, - ; Cw1*0102, *0401 ; DR7, 16 ; DRB1*0701, *1601 ; DRB4*0101, *- ; DRB5*0202, *- ; DQ2, 5 ; DQA1*01, *02 ; DQB1*0202, *0502 ; DPB1*0401, *0402

28/09/2010 HLA Class I IgG antibodies were detected in IgM depleted serum dated 22/9/2010 against the specificities listed in this report using Luminex Single Antigen Beads. Of these antibodies directed against B56 (MFI=2522), A1 (MFI=1453), A24 (ave MFI=977) and B35 (MFI=846) are donor specific for potential kidney donor Matt T.
• Second Flow crossmatch between Ulia and Matt T. The T cell FLOW ALLO crossmatch result was weakly positive with a mean channel shift value of 78. The B cell crossmatch was equivocal with a mean channel shift value of 42. (22/9/2010)

• Sensitisation from pregnancies. ? Any transfusions.
For Ulia, a Solution to Avoiding Dialysis is Still Required

Or

Trying about the Donor

If you don’t like your current donor, try another.

Or

Try again!!
May be a ‘friend’
How many donors do you need?

• Isn’t one enough??!!

Paulo Ferarro
Thinking about the Recipient

• Transplant or not to Transplant?
• Who is the right donor?
• Immunosuppression- what to chose?
Most of the Currently Available Immunosuppressive Agents

- Prednisolone ✓
- Azathioprine
- Cyclosporine
- Tacrolimus ✓
- Mycophenolic Acid ✓
- Sirolimus
- Belatacept
- Daclizumab
- Basiliximab ✓
- OKT3
- Polyclonal Anti-Thymocyte Globulin
- Rituximab†
What to do for Ulia Long-term

- CNI minimisation or withdrawal?
- +/- Switch to an mTOR?
- +/- Steroid withdrawal?
Calculated GFR (Cockcroft-Gault)

- **p < 0.0001**
- **p = 0.0011**

![Bar chart showing GFR (Cockcroft-Gault) over 12 months post-Tx](chart)

- **Normal-dose CsA**
- **Low-dose CsA**
- **Low-dose TAC**
- **Low-dose SRL**

GFR (Cockcroft Gault) (ml/min)

12 months post-Tx
Biopsy Proven Acute Rejection
(ITT, Excluding Borderline)

Probability of acute rejection

Time (months)

0.5
0.4
0.3
0.2
0.1
0.0

0 2 4 6 8 10 12

37.2% Low-dose SRL
25.8% Normal-dose CsA
24.0% Low-dose CsA
12.3% Low-dose TAC
CNI withdrawal of minimisation
RMH transplant patients by era – Tacrolimus exposure

Mean Tac Levels

Days Post Transplant

<30 30 to 90 91 to 180 181 to 365 > 365

ng/mL

2000 to 2003 2004 +
Do we switch

Is there any benefit to me?

Evi-

dence

Bx

CNIs

switch

switch
+/− Switch or not to Switch

Key toxicities of mTOR’s

• Cytopaenias
• Mouth sores, poor wound healing
• Hyperlipidaemia
• Enhancement of CNI nephrotoxicity
• Pneumonitis
• Apparent association with proteinuria
+- Switch or not to Switch

- ‘Clean’ biopsy
- Uncertainty about long-term outcomes
- Side-effects
- Proteinuria
- CAN already present
- CNI toxicity already present
- Level of HLA matching
- Prevention of Cancer – is it a panacea?
RATE OF NEW BCC AND SCC PER PATIENT YEAR: ITT

<table>
<thead>
<tr>
<th></th>
<th>BCC</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL (n=39)</td>
<td>0.43</td>
<td>0.88</td>
</tr>
<tr>
<td>CNI (n=47)</td>
<td>0.77</td>
<td>1.71</td>
</tr>
</tbody>
</table>

p=0.104  p=0.038
PROPORTION OF PATIENTS WITH NEW NMSC: ITT

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with NMSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRL (n=39)</td>
<td>56.4%</td>
</tr>
<tr>
<td>CNI (n=47)</td>
<td>80.9%</td>
</tr>
</tbody>
</table>

*p = 0.015*
PROPORTION OF PATIENTS WITH NEW BCC AND SCC: ITT

% patients with ≥1 BCC or SCC

- SCC
  - SRL (n=39): 41.0
  - CNI (n=47): 70.2
  - p=0.006

- BCC
  - SRL (n=39): 35.9
  - CNI (n=47): 51.1
  - p=0.163
Complications

- Protocol Biopsy??

Patient not keen!!!
Westmead Nephropathy
Complications

- Protocol Biopsy??

  When to do?

  How often to do?
Switch or not to Switch?

- Costimulation blockade: Belatacept
  - Engineered monoclonal antibody directed against CD80/CD86
  - Prevents costimulation by blocking interaction between CD28 and CD80/CD86

Renal function and histology

- Measured GFR significantly better in Belatacept groups than CsA
- Lesser degree of tubular atrophy and interstitial fibrosis with Belatacept
Thinking about the Recipient

- Transplant or not to Transplant?
- Who is the right donor?
- Immunosuppression- what to chose?
- Complications along the way
What the hell is this?

BK virus
BK virus-associated nephropathy

- Double-stranded DNA polyoma virus
- Affects ~8% of renal transplant recipients
- 30-60% of affected allografts fail of BKVAN within 1 year

Chapter 13 (BKV)

• **13.1:** BK POLYOMA VIRUS

• **13.1.1:** We suggest screening all KTRs for BKV with quantitative plasma NAT (2C) at least:

  - monthly for the first 3–6 months after transplantation (2D);
  - then every 3 months until the end of the first post-transplant year (2D);
  - whenever there is an unexplained rise in serum creatinine (2D);
  - after treatment for acute rejection. (2D)

• **13.1.2:** We suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10000 copies/mL (2D)
Clinical manifestations

• Risk factors:
  – Older, male, white, diabetic recipient
  – More HLA mm, ACR, DGF
  – Net state of immune suppression

• Asymptomatic allograft dysfunction

• Suspect BK when rejection does not resolve with usual therapy
Diagnosis

• Viruria precedes viremia and nephropathy
  – Urine cytology
  – Urine PCR
• Viremia
  – More specific for nephropathy
• Screening protocols increasingly used
• Renal biopsy is gold standard
Treatment

• Reduce immune suppression
  – Stop antiproliferative
  – Stop steroids
  – Cut CNI and antiproliferative doses by 50%

• Noteworthy that all other treatments for BKVAN include reducing IS…
  – Cidofovir
  – Leflunomide
Ulia finally has her Say!

Everyone should have a transplant!

• Important that everyone has access to transplantation that needs it

• Need to think of
  – Regional differences
  – Unit differences

  – And reduce Variability!!!
Geographic Disparity

Table 1: Mean annual transplantation rates (%): [number of transplants/number of patients on dialysis]

<table>
<thead>
<tr>
<th></th>
<th>2003–2008 All transplants</th>
<th></th>
<th></th>
<th>Deceased donors</th>
<th></th>
<th></th>
<th>Living donors</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean (%)</td>
<td>Lower CI (%)</td>
<td>Upper CI (%)</td>
<td>Mean (%)</td>
<td>Lower CI (%)</td>
<td>Upper CI (%)</td>
<td>Mean (%)</td>
<td>Lower CI (%)</td>
<td>Upper CI (%)</td>
</tr>
<tr>
<td>Unit 1</td>
<td>7.6</td>
<td>4.6</td>
<td>10.5</td>
<td>5.3</td>
<td>3.2</td>
<td>7.4</td>
<td>2.3</td>
<td>1.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Unit 2</td>
<td>4.4</td>
<td>2.7</td>
<td>6.1</td>
<td>2.3</td>
<td>1.4</td>
<td>4.2</td>
<td>1.6</td>
<td>0.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Unit 3</td>
<td>9.1</td>
<td>7.2</td>
<td>10.9</td>
<td>4.1</td>
<td>3.6</td>
<td>4.4</td>
<td>5.0</td>
<td>3.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Unit 4</td>
<td>5.6</td>
<td>4.6</td>
<td>6.7</td>
<td>3.1</td>
<td>3.0</td>
<td>3.3</td>
<td>2.5</td>
<td>1.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Unit 5</td>
<td>4.2</td>
<td>3.4</td>
<td>4.9</td>
<td>2.9</td>
<td>2.1</td>
<td>3.7</td>
<td>1.2</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Australia</td>
<td>7.5</td>
<td>6.5</td>
<td>8.4</td>
<td>4.5</td>
<td>3.8</td>
<td>5.2</td>
<td>3.0</td>
<td>2.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

All transplants: Pearson $\chi^2 = 14.44$, $P = 0.013$. Deceased donor transplants: Pearson $\chi^2 = 6.06$, $P = 0.301$. Living donor transplants: Pearson $\chi^2 = 19.56$, 0.02. CI, confidence interval.
Summary

• Transplantation remains the treatment of choice for patients with ESKD
• Increasing numbers of options for pre-emptive live-donor transplantation include
  – ABO incompatible
  – PKD
  – Other immunosuppression directed at AbMR
• The optimal long-term immunosuppression therapy is unclear- there are a number of options
  – Minimising CNIs
  – mTOR’s
  – Co-stimulatory Blockade?
• BK virus is a relatively new concern, and is an important source of morbidity
What message do we want to get across?
Take Home Message

• Transplantation is a bit more complicated now
• Think laterally about transplant options
• You do have friends that you can talk to
  – Communicate & ask
  – Communicate & ask
• Consider the evidence – but every patient really needs his/her therapy individualised
  – Communicate & ask
  – Communicate & ask
• For those in Transplanting hospitals, remember a lot of the care of patients long term is being provided by very competent nephrologists – for good long term outcomes ..
  – Communicate & ask
  – Communicate & ask
Levels of Evidence for Eminence-based medicine

- Level I: Bearded old gentleman with a bow-tie & from Royal Australasian College of Physicians
- Level II: Doctor with air of credibility and honest face
- Level III: Academic with mad stare
- Level IV: Network Health CEO with trust only in financial crises
Opinions on the content and effects of clinical practice guidelines for CKD: a survey of nephrologists in Australia and New Zealand

Seven questions were repeated from a similar survey in 2002. A total of 211 nephrologists (70% of practising nephrologists) responded.

- More than 90% agreed that the CARI guidelines were a useful summary of evidence,
- Nearly 60% reported that the guidelines had significantly influenced their practice,
- The proportion of nephrologists reporting that the guidelines had improved patient outcomes increased from 14% in 2002 to 38% in 2006.
Everybody’s Happy!

• Ulia has a kidney that will last!
• Non-home based dialysis is completely abolished in the region!
• Federation is abolished & New Zealand becomes the 7th & 8th States of the ‘Greater Australasia’
• An Evidence based medicine module becomes a mandatory requirement for *kidney transplant physicians*
• Greater Australasia wins 14 successive World Rugby Cups and State of Origin football becomes relegated to an historical dinner party conversation point.
• Furphy loses a bit on ESAs but cleverly tenders for Tacrolimus, mycophenolate and every other immunosuppressant and makes an absolute killing
• Most importantly………no more palpably under-talented New South Welshmen selected in the national Cricket Team!!
• South Parkville Bush Nursing Hospital becomes recognised by the College of Physicians, the TSANZ & a whole lot of other people with discernment as a place where a trainee registrar can have exposure to 11 acute transplants in 1 year!
&

This Hypothetical comes to end!

Thank You
The After Party

Shit Bevan! Is that you??