**Welcome to the Scottish Exhibition and Conference Centre**

As President of the British Transplantation Society I am delighted to welcome you to Glasgow for the 15th Annual Congress of the BTS. Glasgow may not have the sand and sea of Bournemouth, but I anticipate the weather to be equally bracing. I hope you find the programme this year as stimulating and educational as last year.

We are very grateful to the members of the Programme Committee for putting together an interesting and imaginative programme, drawing together national and international experts as well as providing a forum for presenting new research from within the UK. We hope that there will be something for everyone throughout the congress. We would like to thank BASL for hosting a joint symposium, and also our colleagues from BSHI whose work we have integrated throughout the congress, a reflection of how integral it has become to the practice of transplantation.

We have endeavoured to build on the success of recent meetings. To that end we have continued the early morning workshops that have been so popular in recent years. We have also copied the format of recent years and combined the welcome reception on Wednesday evening with the moderated poster session. This year's Hoffenberg lecture will be given by Professor Margot Brazier, Professor of Law at Manchester, and former chair of the Retained Organs Commission. On Thursday evening the dinner will be followed by a chance to let your hair down at a traditional Celidh.

We would also like to thank our corporate partners and other industry stakeholders whose support will help make our meeting possible. In particular we would like to thank our two gold corporate partners, Bristol Myers Squibb and Astellas, who will also be hosting sponsored symposia on Wednesday and Thursday lunchtimes. Finally we would like to thank the SECC for hosting the meeting and our secretariat, KSAM, for all their work behind the scenes to make the congress a success.

The Annual Congress is always an excellent opportunity to meet with colleagues within an environment that is both educational and enjoyable – this year should be no different.

We hope you have an excellent congress.

With best wishes

Chris Watson
President

| | |
|---|---|
| **Tuesday 21st February 2012** | |
| **Pre-Congress Symposium** | |
| **'HOW TO PLAN GOOD MEDICAL RESEARCH'** | |
| **13.00** | **Registration & coffee** |
| **14:00** | **Promoting excellence in translational research**<br>**Lomond Auditorium**<br>*Anthony Warrens & Anthony Dorling*<br><br>Grant applications – scientific - Robert Lechler<br>Grant applications: clinical - TBA<br>Animals - practicalities and limitations - Andrew Bradley<br>The MHRA – The role of the MHRA in clinical trials - Elaine Godfrey |
| **16:00** | Coffee |
| **16:20** | Ethics applications - Hugh Davies<br>What gets published? - Allan Kirk<br>The clinical trials unit - Richard Haynes<br>Clinical trials workshop - Peter Friend, Chris Watson, Anthony Dorling and Anthony Warrens |
| **18:30** | Symposium closes |

| WEDNESDAY 22ND FEBRUARY 2012 | | | |
|---|---|---|---|
| 09:00 | Registration and coffee | | |
| 10.00 | **Trials in tolerance**<br>**Lomond Auditorium**<br>*Chris Watson & Anthony Warrens*<br>Approaches to, and biomarkers of, clinical transplant tolerance - Robert Lechler<br>Ongoing trials in tolerance - Allan Kirk<br>Tolerance to ABO antigens in infants - Lori West<br>Tolerance protocols in living donors - Joseph Leventhal | | |
| 12:00 | **Preservation & IRI**<br>**Lomond Auditorium**<br>*Rutger Ploeg & Peter Friend*<br>Abstracts x 6 | **Basic Science**<br>**Alsh Suite**<br>*Anthony Dorling & Robert Lechler*<br>Abstract x 6 | **Histocompatibility**<br>**Boisdale Suite**<br>*Craig Taylor & Phil Dyer*<br>Abstracts x 6 |
| 13:00 | Lunch & exhibition | | |
| 13.30 | **Bristol-Myers Squibb sponsored symposium**<br>**NULOJIX (belatacept) – A New Generation of Immunosuppressant in Kidney Transplantation: Sharing the European Experience**<br>**Lomond Auditorium** | | |
| 14.30 | **ABOi transplantation**<br>**Lomond Auditorium**<br>*David Taube &*<br>*Nick Torpey*<br>ABOi cardiac transplantation - Lori West<br>ABOi renal transplantation - Simon Ball<br>ABOi liver transplantation - Andrew Burroughs<br>Abstracts x 3 | **BASL/BTS Joint Session**<br>**Alsh Suite**<br>*Murat Akyol*<br>Controversial decisions in the selection of patients for liver transplantation -<br>Stephen Potts & Ed Day | **Biomarkers in tolerance**<br>**Boisdale Suite**<br>*Iain MacPhee & Nizam Mamode*<br>The molecular signature of tolerance - Maria Hernandez-Fuentes<br>Markers of survival in transplantation -<br>Yohann Foucher<br>Abstracts x 5 |
| 16.00 | Coffee, tea and exhibition | | |
| 16.30 | **Optimising use of the donor pool**<br>**Lomond Auditorium**<br>*Gavin Pettigrew & David Talbot*<br>The Spanish experience - Jose Nunez<br>Optimising the use of paired exchanges - Joseph Leventhal | | **Basic Science**<br>**Boisdale Suite**<br>*Simon Ball &*<br>*Will McKane*<br>What is the significance of endothelitis? -<br>Carmen Lefaucheur<br>Using the molecular microscope - Declan De Freitas |
| 17.10 | **Free communications**<br>**Lomond Auditorium**<br>*Gavin Pettigrew & David Talbot*<br>Abstracts x 6 | **Free communications**<br>**Alsh Suite**<br>*Mark Harber & John Forsythe*<br>Abstracts x 6 | **Free communications**<br>**Boisdale Suite**<br>*Simon Ball & Will McKane*<br>Abstracts x 6 |
| 18.10 | **Moderated Poster Session & Welcome Reception hosted by Glasgow City Council**<br>**Exhibition Hall** | | |

| THURSDAY 23RD FEBRUARY 2012 | | | |
|---|---|---|---|
| 08:00 | **Clinical transplantation workshop – the marginal recipient**<br>**Lomond Auditorium**<br>Vassilios Papalois | **H&I workshop: Definition of unacceptable HLA antigens and patient access to transplantation**<br>**Alsh Suite**<br>Sue Fuggle & Sue Martin | **Animal models in transplantation – What should we be using?**<br>**Boisdale Suite**<br>Allan Kirk & Andrew Bradley |
| 09.30 | **Clinical Controversy: Islets vs Pancreas**<br>**Lomond Auditorium**<br>*Argiris Asderakis & Murat Akyol*<br>Whole pancreas - Peter Friend<br>Islets - Richard Smith<br>Abstracts x 2 | **Recurrent Disease**<br>**Alsh Suite**<br>*Chris Dudley & Sian Griffin*<br>Liver transplantation - TBA<br>Recurrent disease in kidney transplantation - Chas Newstead<br>Abstracts x 2 | **Autoimmunity in Transplantation 1**<br>**Boisdale Suite**<br>*Marlene Rose & Anthony Dorling*<br>Autoimmunity in diabetes - Tim Tree<br>Autoimmunity in renal transplant rejection - Simon Ball<br>Abstracts x 2 |
| 10.30 | Coffee, tea and exhibition | | |
| 11:00 | **MEDAWAR MEDAL COMPETITION - Lomond Auditorium**<br>*Anthony Warrens & Keith Rigg*<br>Abstracts x 8 | | |
| 13:00 | Lunch & exhibition | | |
| 13.30 | **Astellas sponsored symposium**<br>**Assessing the true cost of transplantation**<br>**Lomond Auditorium** | | |
| 14.30 | **State of the art**<br>**Lomond Auditorium**<br>*Hany Riad & Geoff Koffman*<br>What's new in liver transplantation - Derek Manas<br>What's new in heart transplantation - Nick Banner<br>What's new in lung transplantation - John Dark | **Infection and malignancy**<br>**Alsh Suite**<br>*Andrew Bradley*<br>Immunotherapy of PTLD - Tanzina Haque<br>Management of HCV in renal transplantation - David Mutimer<br>Abstracts x 2 | **Autoimmunity in transplantation 2**<br>**Boisdale Suite**<br>*Robert Vaughan*<br>Cardiothoracic - Marlene Rose<br>Non-HLA antigens in renal transplantation - Rudolf Oehler<br>Abstracts x 2 |
| 15.30 | Coffee, tea and exhibition | | |
| 16.00 | **Ethics Symposium**<br>**Lomond Auditorium**<br>How risky is too risky? The ethical landscape of challenging transplants. Interactive discussion around clinical scenarios - Vassilios Papalois | **Clinical renal transplantation**<br>**Alsh Suite**<br>*Adam McLean & Richard Baker*<br>Recognition and treatment of vascular rejection - Carmen Lefaucheur<br>Abstracts x 4 | |
| 17.00 | **Hoffenberg lecture**<br>**Lomond Auditorium**<br>*Chris Watson*<br>Body parts & baleful stars: a short medicolegal history of transplantation - Professor Margaret Brazier | | |
| 19.30 | **Gala dinner**<br>The Glasgow Science Centre | | |

| FRIDAY 24TH FEBRUARY 2012 | | |
|---|---|---|
| 08.00 | **Clinical transplantation - Lomond Auditorium**<br>Adam McLean<br>**ABOi and HLAi transplantation**<br>Rob Higgins, Phil Dyer, Bob Vaughan & Jack Galliford | |
| 09:30 | **NHSBT Symposium - Lomond Auditorium**<br>*Paul Gibbs & John Dark*<br>Are we maximising organ transplantation from the potential donor pool? - Rachel Johnson<br>Can the 2006 National Kidney Allocation Scheme meet the demands of 2012? - Alex Hudson<br>Intestinal transplant activity and outcomes - Kerri Barber<br>The National Organ Retrieval Service (NORS) – 18 months review - David Mayer<br>Chronic kidney disease after adult heart transplantation - Helen Thomas<br>The 2010 National Pancreas Allocation Scheme: A one-year review - Alex Hudson<br>Effect of comorbidities at registration on liver transplant survival - Kerri Barber<br>How long have I got? Up-to-date estimates of patient survival - Dave Collett | **Basic Sciences - Alsh Suite**<br>*Richard Baker & Maria Hernandez-Fuentes*<br>Abstracts x 7 |
| 11.15 | Coffee, tea and exhibition | |
| 11.45 | **Cell therapy: basic science - Lomond Auditorium**<br>*Giovanna Lombardi & Andrew Bushell*<br>Cell therapy in clinical transplantation: A summary of regulatory issues – it's not all bad - Elaine Godfrey<br>Developing a dendritic cell-based therapy for rheumatoid arthritis - Catharien Hilkens<br>Manufacture of a 3-D cellularised bioartificial trachea as a medicine and successful surgical implantation – a first-in-man experience - Mark Lowdell<br>The ONE study: cell therapy prospects in organ transplantation - Ed Geissler | |
| 13:00 | Lunch and exhibition | 13:30 **AGM**<br>**Alsh Suite** |
| 14:00 | **The BTS Non clinical fellowship - Lomond Auditorium**<br>Radhika Chadha<br>**What's hot, what's new?**<br>Science - Alan Salama<br>Clinical - Nick Torpey | |
| 15.15 | Coffee, tea and exhibition | |
| 15.30 | **Meeting of the BTS Chapter of Surgeons - Lomond Auditorium**<br>Welcome and introduction - Derek Manas<br>National transplant unit staffing survey - Neil Parrot<br>Clinical dilemmas in live related renal donors - Chair: Peter Veitch<br>Panellists: Paul Gibbs, Dave Nichol, Nicos Kessaris<br>The selection and allocation of marginal DCD organs - Chair: Derek Manas<br>How best to allocate marginal/DCD organs – liver, kidney and pancreas<br>Panellists: Bimbi Fernando, Martin Drage, Chris Watson, John Issac, Peter Friend<br>Organ resuscitation and reconditioning - Rutger Ploeg | |
| 17.30 | Congress close | |

**Acknowledgements**

We would like to thank the Programme and Congress Organising Committees, comprising Professor Anthony Warrens (chair), Dr Richard Baker, Professor Anthony Dorling (PC only), Dr Chris Dudley and Professor Chris Watson.

The Programme Committee would also like to thank the Abstract Review Panels which comprised:

**Clinical / Ethics**
Dr Richard Baker
Prof Andrew Bradley
Dr Iain MacPhee
Mr Paolo Muiesan
Dr Nick Torpey
Dr Antonia Cronin

**Basic Science**
Prof John Kirby
Ms Lorna Marson
Mr Gavin Pettigrew
Prof Marlene Rose
Prof Andrew George

**H & I**
Dr Sue Fuggle
Dr Paul Sinnott
Dr Craig Taylor
Dr David Turner
Dr Robert Vaughan

**Nursing**
Ms Jane Smith
Ms Lisa Burnapp
Ms Christine Jansen

We would like to thank the following organisations for their contribution to the Congress.

| | |
|---|---|
| Bristol Myers Squibb | Wednesday Lunchtime Symposium |
| Astellas | Thursday Lunchtime Symposium |

**British Transplantation Society**

**Company and Charity Annual General Meeting**

**Friday 24th February 2012 - 13.00 to 14.00 hrs**

**Scottish Exhibition and Conference Centre (SECC), Glasgow**

1. Welcome
2. Apologies
3. Minutes of AGM on 11th March 2011, Tregonwell Hall, Bournemouth International Centre, Bournemouth, (held as BTS registered Charity No 1098584)
4. President's Report
5. Vice President's Report
6. General Secretary's Report
7. Treasurer's Report
8. 16th Annual Congress
9. Any other business
10. Next meeting: Friday 15th March 2013, Bournemouth International Centre, Bournemouth
11. Closure of meeting

By order of the Board of Directors

Date 3rd January 2012

**BRITISH TRANSPLANTATION SOCIETY**
**Minutes of the Annual General Meeting - *Reg. Charity 1098584 & Reg. Company 4691176***
**Friday 11th March 2011 at 12.30**
**The Tregonwell Hall, Bournemouth International Centre, Bournemouth**

**1.** Keith Rigg welcomed the members present to the Annual General Meeting.

**2.** No apologies were received. 41 members were in attendance.

**3.** The minutes from the last AGM of the charity held on 19th March 2010 at Kensington Town Hall, London, were approved and accepted as a true record of the meeting.

**4. President's Report**

i. The president thanked all retiring members of the Council and Executive for their service.

ii. Inward Looking

- The good work of the Executive, Council and sub-committees continues.
- The BTS Education Forum held in December 2010 was a very successful meeting with fifty delegates in attendance. The Council has agreed that this will be a biennial event.
- The travel bursary scheme will continue to provide funding for BTS members to attend meetings. There is surplus money available which enables the Society to continue funding these meetings.
- The BTS is the only organisation that is solely transplantation focused. The President has written to all unit heads asking them to encourage colleagues to join the Society if they are not currently members. The membership database has also been updated enabling target communications to groups as opposed to the entire membership.
- Communication with members is now in the form of the monthly e-bulletin. One of the aims of this is to reduce the number of individual emails sent to members and to encourage use of the website.

iii. Outward Looking

- The number of publications that the BTS and the Standards Committee have produced has increased. Keith Rigg outlined those to the AGM.
- The BTS has wide collaborations and representatives in ten organisations.
- The EU Organ Directive will be implemented in August 2012. The Directive will ensure that the necessary quality and safety structures are put in place across the EU for the donation and transplantation of organs. This will entail that the transplant centres and procurement organisations will need to be licensed to undertake organ transplantation bringing with it a fee.
- Transplant 2013 is a collaboration of clinicians, patients and industry groups. The group was established in December and its aim is to promote leadership of organ donation and transplantation in Parliament and other relevant institutions. Chris Williamson is the chair of the newly established All Party Parliamentary Group on Transplantation; Keith Rigg is chair of the Transplant 2013 executive.
- The BTS has responded to ten consultations over the year and numerous requests from the media.

iv. Challenges facing the BTS

- Professional leadership.
- The need to encourage wider membership and ensure that the Society remains relevant to all groups in the transplant community.
- The impact of the financial environment; the BTS has in the past relied heavily on industry support and in recent years has altered its strategy and become more self sufficient. The Treasurer has ensured this is the case over the last few years.

**5. Vice President's Report**

i. Chris Watson thanked Keith Rigg for all his hard work over the last four years as the President and Vice President of the BTS.

ii. The BTS are hosting ESOT on 4-7 September. Chris Watson talked through the innovative ideas for that meeting and advised that the programme is on the website. Everyone was encouraged to register for the meeting and take advantage of the early bird rates.

iii. The next Congress is scheduled for 22 – 24 February 2012 at the SECC, Glasgow.

iv. Chris Watson has been involved in the marginal donor and consent working party set up by the BTS & NHSBT. He outlined some of the recommendations, and guided members to the website where the guidelines would be published after congress.

**6. Secretary's Report**

i. Prior notification had been made of amendments to the BTS memorandum of Association to comply with the changes to the Company Act. These changes were approved by a majority vote.

ii. Rule 11

An amendment to rule 11 was proposed at the last AGM. A number of the Council positions are only two-year positions and it was proposed to change these to three. This amendment was accepted by a majority vote.

iii. Election Results: 743 online voting codes were circulated, with 228 votes cast (30.7%), this is an increase from last year where only 22.7% voted.

iv. As a result of the above, the following positions have been filled:

- **Vice-President –** Anthony Warrens
- Treasurer – **Richard Baker**
- Councillor representing Transplant Surgery – **Paul Gibbs**
- Councillor representing Transplant Coordination and Nursing – **Nicola Hamilton**
- Councillor without portfolio – **Jacob Akoh**
- Member of the Ethics Committee – **Marlene Rose, Rachel Hilton**

Elected unopposed:

- Councillor representing Donor Coordination – **Jacqui Spencer**
- Member of the Transplant Training and Education Committee – **James Gilbert**

The following positions were unfilled. Therefore a member will be co-opted for each:

- Councillor representing Cardiothoracic Transplantation
- Councillor representing Basic Science
- Member of the Standards Committee

v. A total of 96 members have joined since the last AGM. This brings the total membership to 836 compared to 817 in 2010. There was no opposition to the list presented.

vi. 234 abstracts were submitted for Congress this year. 179 Clinical, 37 Laboratory, 2 Coordinator, 10 Histocompatibility and 6 Ethics, Law and Public Policy. Out of these 228 were accepted; 66 for oral presentation and 162 poster.

vii. The Roy Calne Award was presented jointly to Dr Thet Su Win, Addenbrooke's Hospital and Dr Joanne Hester, Oxford University Hospital. Chris Dudley thanked Andrew George, Anthony Dorling, Marlene Rose and Steve Powis for judging the award.

viii. The Medawar Medals were presented to Matthew Welberry Smith (Clinical), St James' University Hospital, Leeds, and Fadi Issa (Science), Oxford University Hospital.

**7. Treasurer's Report**

i. The Finances of the Society remain healthy and the unrestricted funds remain in a very stable position. Anthony Warrens confirmed there was a surplus of £78,000 up to 31st October 2010 compared to that of £32,000 in 2009. This is due to the success of the Congress in 2010.

ii. Corporate Membership; the Executive and Council have agreed to keep the Corporate membership fee as the same as this year: Senior Corporate member £25,000 and Corporate member £3,000. The Treasurer confirmed that the Society can no longer rely on the continuing support of the sponsors as two senior Corporate Sponsors have been lost this year.

iii. The BTS Annual Congress has run a loss over the years. However, 2010 saw a surplus of £26,000, even though the registration fees were considerably less than Liverpool in 2009. It was confirmed that the Congress for 2011 may make a slight deficit due to reduced sponsorship from Pharma which was not expected in the Congress budget.

iv. Membership rates will not change for the coming year.

**8. 15th Annual Congress**

Scottish Exhibition & Conference Centre (SECC), Glasgow; 22-24 February 2012.

**9. AOB**

The Executive were asked whether the BTS should consider having an external risk assessment undertaken on the financial stability of the Society. The Executive advised that the auditors Mitchell Charlesworth and the secretariat KSAM's parent company provide accounting support and advice on this issue.

**10. Next meeting**

Scheduled for Friday 24 February 2012, Scottish Exhibition & Conference Centre, Glasgow.

**11. The AGM was closed at 13:25.**

# ABSTRACTS

## Preservations & IRI Parallel Session

## Lomond Auditorium

## Wednesday 22nd February 2012

## 12.00 – 13.00

**1**

## Successful transplantation of unusable donor lungs using ex-vivo lung perfusion

John Dark[1,2], Danai Karamanou[1], Stephen Clark[2,1], Henning Pauli[2], Paul Corris[1,2], Andrew Fisher[1,2]

*[1]Newcastle University, Newcastle upon Tyne, UK, [2]Freeman Hospital, Newcastle upon Tyne, UK*

**Introduction:** Lungs from brain dead (DBD) and donation after circulatory death (DCD) donors are very susceptible to acute injury often rendering them unusable. Ex-vivo lung perfusion (EVLP) has been proposed as a way of objectively assessing and reconditioning unusable donor lungs for clinical use. Data on conversion rates and clinical outcomes after EVLP reconditioned donor lungs are transplanted is very limited.

**Methods:** Lungs deemed unusable for lung transplant due to poor or unknown function despite best efforts at donor optimisation were considered for EVLP assessment and reconditioning. Data on changes in functional parameters was collected prospectively and donor lungs reaching pre-defined criteria where transplanted into recipients who had previously provided informed consent to receive EVLP treated donor lungs.

**Results:** Lungs from 18 donors, 4 single and 14 bilateral, deemed unusable for immediate implantation, were treated with EVLP using acellular Steen Solution as perfusate . 4 came from (DCD) donors when macroscopic appearance was unsatisfactory. Mean PaO2 in the 14 DBD donors, with an FIO2 of 1.0, was 34.6kPa, (19.8-70). 7 of the 18 lungs exposed to EVLP (40%) reached criteria with PaO2 increasing to a mean of 68.6kPa (42.3-70.0) There were 3 single and 4 bilateral lung transplants in 3 male and 4 female patients (3CF, 3 COPD and 1 IPF). 4 had PGD 0 at 72 hrs and 2 scored PGD 2 and one PGD3 at 72 hrs. ITU LOS ranged from 1 to 17 days and Hospital LOS ranged from 12 to 43 days. 90 day survival was 100% and all recipients remain alive to date, survival ranging from 4 to 25 months. One patient experienced a minor bronchial dehiscence which settled with conservative management no other complications were identified

**Discussion:** EVLP offers a significant opportunity to increase the availability of donor lungs for transplant. Outcomes in our small series are very encouraging and provide the basis for an adequately powered national study of EVLP in the UK.

**2**

**Online rapid sampling microdialysis (rsMD) for viability assessment, comparing static cold storage versus hypothermic machine perfusion in marginal allografts**

Samir Damji[1], Karim Hamaoui[1, 2], Sally Gowers[1], Nick Bullock[1], Michelle Rogers[1], Agnes Leong[1], George Hanna[1], David Taube[1,2], Martyn Boutelle[1], Ara Darzi[1], Vassilios Papalois[1,2]

*[1]Imperial College London, London, UK, [2]Imperial College Renal and Transplant Centre, London, UK*

Viability assessment of the marginal allograft during the preservation period is imperative to avoid unnecessary discarding of marginal organs and maximising graft survival outcomes. Preservation techniques, static cold storage (SCS) and hypothermic machine perfusion (HMP), aim to ameliorate the effects of ischaemia. To address this need, we have developed a system that allows continuous tissue monitoring with rapid measurements of the metabolic markers of ischaemia, allowing for accurate viability assessment in the preservation period. The system is based on a rapid sampling microdialysis (rsMD) analyser for lactate that has previously been validated in clinical studies monitoring tissue viability in brain injuries and bowel ischaemia.

Two sets of experiments were performed using kidneys retrieved from large Landrace Crossed Breed pigs after termination. The first involved the establishment of a baseline ischaemic profile for unperfused kidneys harvested and then allowed to accumulate ischaemic damage at room temperature for 48hrs (n=12). In the second we aimed to monitor real-time lactate concentrations in kidneys preserved by SCS and HMP, comparing effects of each technique on ischaemic injury. 16 porcine kidneys were retrieved, subjected to 15mins of warm ischaemia and then placed upon clinical models of SCS (n=8) or HMP on a Waters Medical RM3 device (n=8) for 24 or 10hrs respectively. After preservation, kidneys underwent 2hrs of passive warming to room temperature to detect changes in lactate concentration as tissue temperature increases and ischaemic injury accumulates similar to reperfusion. A microdialysis probe was tunnelled superficially into the parenchyma of the renal cortex in each kidney. Probes were perfused with a physiological perfusion fluid. The outlet of each probe was connected directly to the novel analyser producing a real-time, on-line measurement of lactate concentration of the target tissue every 60 seconds.

On commencement of monitoring stable levels were achieved within 10 mins, with quantifiable lactate concentrations. In the baseline group, mean extracellular lactate concentration was 212.2 ± 48.8 microM at 100 min post termination. We successfully identified a subsequent fall in the lactate level to 135.1 ± 47.4 microM at 300 min. In the perfusion group the initial lactate concentration of kidneys in SCS was significantly higher than that of HMP (332.8μM (255.0 - 388.0) and 105.5μM (66.9 - 180.2), P=0.010), dropping to steady state in both groups. During warming, we identified a rapid rise and fall in lactate in the SCS group. In contrast the HMP group exhibited a linear increase in lactate with no observable decrease.

This is the first study utilising rsMD, comparing preservation techniques by examining metabolic activity and ischaemic injury in real time. The differing lactate profiles of kidneys and hence anaerobic metabolic rates, confirms that HMP is more effective than SCS at attenuating ischaemic injury. The contrasting rewarming profile may indicate that HMP has a protective affect on the parenchyma and is more resilient to ischaemia-reperfusion injury.

**3**

## Normothermic Regional Perfusion (NRP) In Organ Donors Following Controlled Circulatory Death: A Single Centre Experience

Andrew J Butler[1], Lucy V Randle[1], David J Gifford[2], Scott Melvin[2], Andrew Nichols[2], Christopher J E Watson[1]

*[1]University of Cambridge Department of Surgery, Cambridge, UK, [2]Cambridge Perfusion Services, Cambridge, UK*

**Background:** There has been a ten-fold increase in the number of donors after circulatory death (DCD) in the UK in the last decade. Organs from such donors suffer warm ischaemic damage during the agonal phase and following circulatory arrest until cold perfusion occurs, damage which is associated with increased rates of delayed graft function in kidney recipients and poor/non function and biliary complications in liver recipients. Evidence from Spain suggests that restoration of a circulation using an extracorporeal pump and membrane oxygenator results in amelioration of the warm ischaemic damage in uncontrolled DCD donors. We established a programme of normothermic regional perfusion (NRP) locally to investigate its benefit in controlled DCD donors.

**Methods:** Following circulatory arrest and confirmation of death in Maastricht category III DCD donors, the patient is transferred into the operating theatre. The chest is opened and arch vessels and aortic root clamped. The right atrium and the ascending aorta are cannulated and normothermic perfusion of the abdominal organs commenced via a Biomedicus® pump, heat exchanger and membrane oxygenator. Perfusion is continued for 2 hours during which time urine output, blood gases and liver function tests are monitored.

**Results:** Kidneys have been retrieved from 3 donors aged 74, 70 and 46. 4 were transplanted as double transplants due to poor scores on pre implantation biopsies (scores 3,4 and 5,5 on Remuzzi scale, NEngJMed 2006;354:343), and 2 were transplanted into separate recipients. Serum creatinine at 28 days were as follows: 74 year old, 110µmol/L; 70 year old (anuric and haemofiltered for 3 days pre donation) 123µmol/L; 46 year old, 128 and 140µmol/L. Mean day 28 creatinine in our unit following a standard DCD kidney retrieval (n=97) is 222µmol/L.
The liver was also retrieved and transplanted from the 46 year old donor; lactate and ALT at the start of NRP were 10mmol/L and 9iu/L (NR<50) respectively, and 4.4mmol/L and 25iu/L following 2 hours of NRP. ALT on day one post transplant was 389 iu/L (median DCD without NRP = 573iu/L).

**Conclusions:** These preliminary data suggest that NRP may have a role in controlled DCD donation to improve both kidney and liver function post operatively.
Many questions remain to be answered, including optimum duration of NRP; thresholds of ALT/AST for safe liver use; optimum flow/pressure during NRP; and optimum NRP circuit design.

We wish to acknowledge the enormous help we have received from our regional Specialist Nurses in Organ Donation with this project.

**4**

**A blinded, randomised pre-clinical study on the effects of Hydrogen sulphide on acute kidney injury**

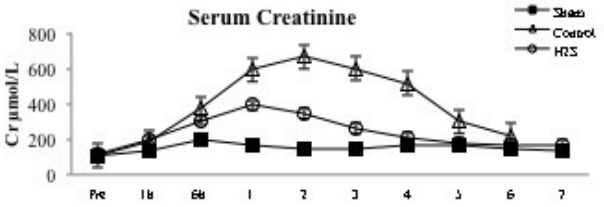
James P Hunter, Sarah Hosgood, Meeta Patel, Michael L Nicholson

*University of Leicester, Leicester, UK*

**Introduction:** Hydrogen sulphide is an endogenously produced gaseous signalling molecule that has shown promise in ameliorating ischaemia-reperfusion injury. However there is little evidence of its role in acute kidney injury. Our aim was to assess the effect of hydrogen sulphide ($H_2S$) on IRI in a large animal model of renal warm ischaemia.

**Methods:** Large white, female pigs were randomised into control (n=6) or treatment with $H_2S$ (n=6) and all veterinary and surgical staff were blinded to the allocation. The left renal pedicle was cross-clamped for 60minutes to induce warm ischaemic injury. $H_2S$ (treatment) or normal saline (control) was infused intravenously. $H_2S$ therapy included a bolus of 100µg/kg given 10 minutes prior to reperfusion, followed by an infusion of 1mg/kg given continuously for 30 minutes after reperfusion. Following clamp release a right nephrectomy was performed and the pigs were recovered for 7days.

**Results:** Renal function improved in the $H_2S$ treated animals on days 1,3 and 5 and recovered more rapidly in comparison with control animals (p=<0.05, figure1.).




| Variable | | $H_2S$ | Control | p-value |
|---|---|---|---|---|
| **Creatinine** | pre | 116+-11 | 107+-7 | 0.097 |
| | Day 1 | 394+-108 | 535+-76 | 0.012 |
| | Day 3 | 245+-45 | 434+-408 | 0.0043 |
| | Day 5 | 187+-26 | 249+-370 | 0.037 |
| | Day 7 | 160+-26 | 186+-109 | 0.39 |
| Area under curve (AUC) | | 2195+-260 | 3009+-1867 | 0.026 |
| Time to Cr <250 (days) | | 3+-1 | 6+-1 | 0.007 |

Tubular function was also protected shown by the protein: creatinine ratio which increased in controls compared with $H_2S$ treated animals (p=0.19 vs. p=0.036). NGAL in the urine demonstrated a significant increase in both groups at 1 and 3 days (p=0.03). TNF-$\alpha$ levels at 6 hours post reperfusion increased in the control animals (57+-15 vs. 109+-51; p = 0.026) but did not in the $H_2S$ treated animals (62+-18 vs. 80+-27; p= 0.46).

**Conclusion**

This is the first large animal study to demonstrate that low-dose hydrogen sulphide significantly ameliorates acute kidney injury. Furthermore, $H_2S$ has an anti-inflammatory effect in the early post-operative period and is protective against tubular damage.

**5**

**The inhibition of the CD40-CD154 signalling pathway protects the liver against ischaemia-reperfusion injury in vitro and in vivo.**

Ricky Bhogal, David Adams, Simon Afford
*University of Birmingham, Birmingham, West Midlands, UK*

**Introduction:** The CD40-CD154 receptor-ligand dyad is known to regulate many cellular signalling pathways. In the liver CD40 is expressed by hepatocytes and can regulate cell death. Furthermore hepatocytes are the main target for ischaemia-reperfusion injury (IRI) after liver transplantation. Whether this signalling pathway plays an important role in cell death during hepatic IRI is not known and is the primary focus of our research.

**Methods & Materials:** Human hepatocytes were isolated from liver tissue using a two-stage collagenase technique and used in a model of in vitro IRI. Human hepatocyte ROS production was determined by intracellular staining with 2,7-dichlorofluorescin. Cell death was assessed by staining with the apoptosis marker Annexin-V and necrosis marker 7-Aminoactinomycin-D (7-AAD). Pro-inflammatory cytokine and chemokine secretion was determined by luminex assay and NMR spectroscopy was used to for metabolomic evaluation. In vivo experiments were conducted using a murine model of partial liver IRI in wild-type mice, CD40 knockout mice and CD154 knockout mice. Liver injury was assessed using serum aminotransferases (AST and ALT) and Haematoxylin & Eosin (H&E) staining. Liver tissue hypoxia was assessed by pimonidazole staining.

**Results:** Human hepatocytes increase intracellular ROS production during in vitro IRI. This increased ROS production induces necro-apoptosis in a p38- and c-Jun N-terminal kinase (JNK)-dependent manner. Moreover increases in ROS during IRI also resulted in up-regulation of the death inducing ligand Fas Ligand (FasL). During in vitro IRI human hepatocytes also increased secretion of the pro-inflammatory cytokines interlukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1). Furthermore abnormal metabolism of leucine was demonstrated within hepatocytes during in vitro IRI with CD154 treatment resulting in reduced leucine levels during in vitro IRI.
Partial IRI of murine liver in wild-type mice resulted in significant more injury than in CD40 knockout mice and CD154 knockout mice as assessed by serum aminotransferases and H&E staining. Moreover CD40 and CD154 knockout mice demonstrated less pimonidazole staining during IRI.

**Conclusion:** IRI results in disordered human hepatocyte metabolism and increased susceptibility to oxidative stress mediated cell death that is augmented by the CD40-CD154 signalling pathway. Hepatocytes and CD40-CD154 further compound the pro-inflammatory process after IRI by increasing the secretion of pro-inflammatory cytokines. Knockout of both CD40 and CD154 protects the liver from IRI in vivo. The manipulation of the CD40-CD154 pathway provides an attractive means by which to limit injury to the liver post-transplantation.

**6**

**Association of the Heme Oxygenase-1 (HO-1) Gene GT(n) microsatellite marker with delayed renal allograft function and long term allograft survival**

Jason Moore[1,2], Aisling Courtney[3], Matthew Simmonds[4], Rajesh Hanvesakul[2], Oliver Brand[4], David Briggs[5], Simon Ball[2], Paul Cockwell[2], Alexander Maxwell[3], Stephen Gough[4], Richard Borrows[2]

*[1]Royal Devon and Exeter NHS Foundation Trust, Exeter, UK, [2]Queen Elizabeth Hospital, Birmingham, UK, [3]Queen's University of Belfast, Belfast, UK, [4]University of Oxford, Oxford, UK, [5]National Blood Service, Birmingham, UK*

**Background**: Heme oxygenase-1 (HO-1) may confer cytoprotection following kidney transplantation. The functional HO-1 GT(n) repeat promoter polymorphism leads to higher expression and activity when the GT(n) repeat length is short ([S], <25 GT repeats) compared with long ([L], ≥25 GT repeats), although previous studies (often underpowered) in transplantation have yielded conflicting Results:

**Study aim**: To investigate whether donor HO-1 genotype influences kidney transplant outcomes.

**Methods:** Genomic DNA was collected from a total of 1295 white kidney transplant donors from two UK sites, Birmingham (n=601) and Belfast (n=694). The outcome measures of interest were delayed graft function, defined as dialysis requirement in the first week following transplantation; and allograft failure, defined as the time from transplantation to dialysis requirement or retransplantation. Time to event associations were interrogated using Kaplan-Meier, Cox and Competing risks (Fine and Grey, 1999) analyses.

**Results:** In the Birmingham population alone, when compared with non-LL genotypes (i.e. SS and SL), LL donors demonstrated a significant increased risk of DGF on both univariate and multivariate logistic regression analysis (adjusted OR: 1.62; 95% CI 1.15-2.28, p=0.006). In addition, in those patients displaying DGF, donor LL genotype was predictive of worse allograft survival (p=0.013). DGF data was not available from the Belfast cohort. In the combined population over a 25 year time period, death censored graft survival was significantly inferior with LL genotype donors in an adjusted Cox model (HR for failure: 1.30; 95% CI 1.01-1.68, p=0.04). Similarly, when death was analysed as a competing risk, a 25% increased risk of graft failure in LL donors was observed. No significant association was seen between donor HO-1 genotype and overall graft loss following Cox analysis.

**Conclusion:** To our knowledge, this is the largest study to investigate the relationship between variation in the HO-1 promoter and kidney transplant outcomes. This "genetic biomarker" may show utility in predicting the risk of DGF and long term allograft survival in individual patients and may prompt future strategies to mitigate risk in this group. In addition it highlights the merits of genetic association studies in transplantation emphasising the need for large patient cohorts over longer study durations.

**Basic science parallel session/free communications**

**Alsh Suite**

**Wednesday 22nd February 2012**

**12.00 – 13.00**

**7**

**Regulatory T cell therapy prolongs cardiac allograft survival in conjunction with low dose co-stimulation blockade in immunocompetent recipients**

Thomas Chan[1], Gang Feng[1], Kieran Clarke[2], Kathryn Wood[1], Carolyn Carr[2], Andrew Bushell[1]

*[1]Transplantation Research Immunology Group, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, [2]Cardiac Metabolism Research Group, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK*

**Introduction**: Numerous experimental studies have shown that when used as a cell therapy, regulatory T cells (Treg) can prevent graft rejection in immunodeficient recipients. Whether Treg delivery can have the same impact in immunocompetent recipients is less clear but represents a question much more relevant to clinical transplantation. Using the mouse cardiac allograft model, we have assessed the impact of in vitro generated adaptive Treg combined with sub-therapeutic co-stimulation blockade in wild type mice. Graft survival was assessed by palpation but in addition, in vivo Magnetic Resonance (MR) Imaging was used to provide an assessment of allograft function.

**Methods:** Donor antigen-experienced Treg were generated in vitro by stimulating naïve CBA (H-$2^k$) $CD4^+$ T cells with modulated C57BL/6 (H-$2^b$) antigen-presenting cells according to an established interferon-γ conditioning protocol. The resulting IFN-γ conditioned T cells (IFN-γ Treg) were validated by expression of Forkhead Box Protein 3 (FoxP3) and were evaluated for their ability to control rejection of fully MHC-mismatched C57BL/6 to CBA heterotopic cardiac transplants (day 0). IFN-γ Treg were administered i.v. on day -1 with or without a sub-optimal regimen of co-stimulation blockade (abatacept, 25μg day 0, 1, 5). Functional MR Imaging was performed 14 and 35 days post transplant using a vertical-bore 500MHz, 11.7 T MR system with a Bruker console. Parameters of cardiac function were calculated from captured cine-MR images.

**Results*:*** Untreated CBA recipients rejected their C57BL/6 cardiac allografts acutely (median survival time, MST, 8 days n=10). Sub-optimal abatacept treatment prolonged graft survival to an MST of 50 days, (n=8). When used alone, $2x10^6$ IFN-□ Treg led to a modest increase in graft survival (MST=20 days, n=2). However, when combined with abatacept, $2x10^6$ IFN-□ Treg led to a striking improvement in graft outcome (MST=95 days, n=6), with 50% graft survival >100days. More importantly, MR Imaging showed that cardiac function of allografts (ejection fraction, stroke volume and cardiac output) were significantly increased (paired t-tests) between days 14 and 35 post transplant in recipients receiving abatacept plus Treg therapy compared to those receiving abatacept alone.

***Conclusions:*** When used as a cellular therapy in conjunction with low-dose immunosuppression, recipient-derived Treg can make a significant contribution to the control of rejection responses in immunocompetent recipients. Combined strategies of this type could offer a potential route to drug-minimisation without compromising transplant outcome.

**8**

## *In vivo* SPECT reporter gene imaging of regulatory T cells in a murine skin transplant model.

Ehsan Sharif-Paghaleh[1,2], Robert Lechler[1], Lesley Smyth[1], Greg Mullen[2], Giovanna Lombardi[1]

*[1]MRC Centre for Transplantation, KCL, London, UK, [2]Imaging Science, KCL, London, UK*

Regulatory T cells (Tregs) were identified several years ago and are key in controlling autoimmune diseases and limiting immune responses to foreign antigens. Imaging of the human sodium/iodide symporter via Single Photon Emission Computed Tomography (SPECT) has been used to image various cell types *in vivo*. It has several advantages over other imaging techniques including high sensitivity, it allows non-invasive whole body studies of viable cell migration and localisation of cells over time and lastly it may offer the possibility to be translated to the clinic. This study addresses whether SPECT/CT imaging can be used to visualise the migratory pattern of Tregs *in vivo*. Treg lines derived from $CD4^+CD25^+FoxP3^+$ cells were retrovirally transduced with a construct encoding for the human Sodium Iodide Symporter (NIS) and the fluorescent protein mCherry and stimulated with autologous DCs. NIS expressing self-specific Tregs were specifically radiolabelled *in vitro* with Technetium-99m pertechnetate ($^{99m}TcO_4^-$) and exposure of these cells to radioactivity did not affect cell viability, phenotype or function. In addition adoptively transferred Treg-NIS cells were imaged *in vivo* in C57BL/6 (BL/6) mice by SPECT/CT using $^{99m}TcO_4^-$. After 24 hours NIS expressing Tregs were observed in the spleen and their localisation was further confirmed by organ biodistribution studies and flow cytometry analysis. The data presented here suggests that SPECT/CT imaging can be utilised in preclinical imaging studies of adoptively transferred Tregs without affecting Treg function and viability thereby allowing longitudinal studies within disease models. Moreover, we have demonstrated the this method of imaging can be utilised to image migration of Tregs with direct-alloantigen specificity to the draining lymph nodes in a skin transplant model.

**9**

## Testing the effectiveness of a C5-Specific Inhibitor (Coversin) in a mouse model of renal ischaemia reperfusion injury

Kieran Atkinson, David Talbot, Neil Sheerin

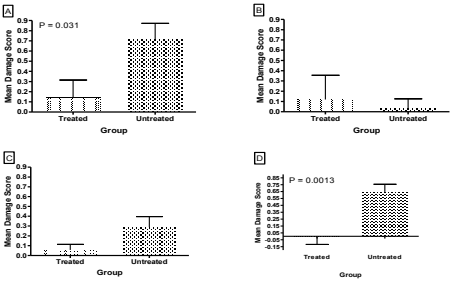
*Institute of Cellular Medicine Newcastle University, Newcastle Upon Tyne, UK*

Ischaemia reperfusion injury (IRI) occurs in donor organs during transplantation. This process causes two distinct injuries: Hypoxic injury - when blood flow to the organ ceases in the donor, and reperfusion injury - when blood flow is re-established in the recipient. These injuries may lead to a clinical syndrome known as delayed graft function (DGF), in which the transplanted organ fails to function normally. DGF is potentially fatal in vital organs and impacts long-term function, through chronic rejection, in non-vital organs such as the kidney. The predominant risk factor for DGF is increased organ ischaemic time. In renal transplantation DGF affects around 23% (Tapiawala et al) of organ recipients with immediate and long term complications.

Coversin is a C5-Specific inhibitor synthesized from a protein found in the salivary gland of the soft tick *Ornithodoros moubata.* A previous study has demonstrated effective inhibition of cell lysis mediated by human, rat and mouse serum in vitro. (Hepburn et al)

In order to test the effectiveness of Coversin we first established a mouse model of renal IRI. Tissue damage in the cortex and cortico-medullary junction (CMJ) was assessed semi-quantitatively for the histological criteria: epithelial necrosis, loss of brush border, tubular dilatation and cast formation. Neutrophils were also counted histologically.

We demonstrated that increasing tissue damage directly correlates to increasing ischaemic time; p=<0.0001. We also demonstrated that neutrophil infiltration followed the same trend; p=<0.0001.




The use of Coversin failed to demonstrate a significant reduction in overall renal IRI; though analysis of the cortex taken in isolation shows a clear reduction in three of the four histological criteria, with two achieving statistical significance (fig). The number of neutrophils infiltrating the CMJ is reduced in the treated group by approximately 40% (p=0.054).

Injury reduction in the cortex is not replicated in the CMJ, suggesting that cortical injury is primarily caused by complement activation in the reperfusion phase of IRI, as the inhibition of the terminal complement pathway greatly reduces cortical tissue damage. This attributes the injury seen in the CMJ to the initial period of hypoxia, as C5 inhibition has no significant effect in reducing injury in the CMJ, advocating the possibility of separate mechanisms being responsible for the injuries seen in each anatomical region.

**10**

## Over-expression of hsp-27 delays the development of cardiac allograft vasculopathy

Borggia Seemampillai, Ann McCormack, Padmini Sarathchandra, Marlene Rose

*NHLI, Imperial College London, London, UK*

Hsp-27 is a constitutively expressed heat shock protein and its expression is further increased during stress. In humans hsp-27 is constitutively expressed in endothelial cells and smooth muscle cells; expression is increased during stress. Clinical studies have suggested that over-expression of hsp-27 protects against atherosclerosis in non-transplant patients and cardiac allograft vasculopathy in cardiac transplant patients. In mice over-expression of hsp-27 has been shown to protect from ischemic injury. We have previously reported that over-expression of hsp-27 delays acute rejection following heterotopic heart transplantation in mice. The purpose of this study was to determine whether over expression of hsp-27 protects the heart from cardiac allograft vasculopathy. B10.A mice, over-expressing Ha-tagged human hsp-27 were used as donors (hsp-27 tg). Western blotting and immunocytochemistry revealed over-expression of Ha-tagged hsp-27 in lung, liver and heart compared to wild-type litter mate controls. Immunocytochemistry demonstrated increased expression of hsp-27 in cardiomyocytes and smooth muscle cells of tg mice. B10.A hearts from hsp-27 tg or wild-type litter mate controls were transplanted into the abdomen of CBA wild-type recipients (n=5/group), representing a class I mismatch and minor mismatch. The recipients were partially depleted of CD4+ T cells with monoclonal antibody prior to transplantation. Cardiac allografts were harvested at 4, 6 and 8 weeks post transplantation to analyze cellular infiltration and intimal thickening. Sections of heart were stained with Van Geesen and antibody to alpha-actin positive smooth muscle cells; quantitative morphometry was used to measure intimal occlusion in arterial vessels (10/section). At 6 weeks, the mean occlusion of vessel was significantly smaller in tg (33.00 ± 4.78) compared to wt allografts (55.00 ± 1.00, p= 0.038). Similar pattern was observed between tg (34.80 ± 3.22) and wt (49.60 ± 5.03, p=0.038) at 8 weeks. Flow cytometric analyses showed no difference in alloantibody levels produced by recipients of wild type or tg hearts. Current studies are analysing presence of effector cells and cytokines by RT-PCR to investigate whether hsp-27 alters Th1/Th2 subsets or monocytes in the allograft.

**11**

## MicroRNA Regulation of Cellular Bio-age Provides a Novel Pre-Transplant Prognostic and Predictive Assessment of Post Transplant Allograft Function

Dagmara McGuiness[1], Marc Gingell-Littlejohn[1,2], Karen Stevenson[1,2], David Kingsmore[2], Marc J Clancy[1,2], Paul G Shiels[1]

*[1]University of Glasgow, Glasgow, UK, [2]Western Infirmary, Glasgow, UK*

**Background:** Pre-transplant prediction of post-transplant renal function and outcome is extremely challenging, particularly when applied to older and marginal donor organs. We and others have demonstrated previously that allograft bio-age, as determined by CDKN2A expression level, is a superior prognostic and predictive marker for post transplant function. The CDKN2 locus is complex, comprising a series of developmentally and epigenetically regulated transcript isoforms. Transcriptional regulation of these isoforms incorporates a broad range of MicroRNAs (miRNA), non-coding, single-stranded RNA molecules that are involved in the regulation of a variety of biological processes, including embryogenesis, differentiation, and senescence. We have sought to investigate whether CDKN2 associated miRNAs expression profile in 'zero hour' pre-transplant renal allograft biopsies are linked to clinico-pathological and functional characteristics post-transplant.

**Methods:** MicroRNA profiles were determined in 'zero hour' allograft biopsies using micro-fluidic TaqMan® MicroRNA arrays (Applied Biosystem) and were analysed in relation to clinical data including serum creatinine (SC), cold ischaemia time (CIT), donor age and acute rejection. Data were analysed using StatMiner® (Integromics). Furthermore, MicroRNA data were validated using individual assays.

**Results:** 19miRNAs showed pre transplant expression levels that correlated with levels of SC at 6 months post-transplantation and CIT. Significantly, linear regression analyses in the cohort (n=43) revealed that pre-transplant expression of five miRNAs (hsa-miR-125b, hsa-miR-505, hsa-miR-125a-5p, hsa-miR-96 and hsa-miR-1275) were associated with acute rejection episodes ($p<0.01$).With the exception of hsa-miR-505, these miRNAs also demonstrated an association with CIT.

**Conclusions:** This data indicates that miRNA profiling has clear potential to be used for pre transplant assessment of post transplant allograft function. It offers the potential for prediction of rejection episodes or other complications. Furthermore, there are also clear links with donor bio-age, which may further enhance the diagnostic possibilities.

**12**

## CDKN2A expression in pre-implantation kidney biopsies is the single, strongest predictive factor for post-transplant renal function at 1 year

Marc Gingell-Littlejohn[1,3], Dagmara McGuiness[1], Karen Stevenson[1,3], David Kingsmore[3], Marc J Clancy[1,3], Christian Koppelstaetter[2], Paul G Shiels[1]

*[1]University of Glasgow, MVLS, Glasgow, UK, [2]Internal Medicine Unit, Innsbruck, Austria, [3]Western Infirmary, Glasgow, UK*

**Introduction:** CDKN2A is a proven and validated biomarker of ageing (McGlynn LM et al, Aging Cell 2009 Feb;8(1):45-51; Koppelstaetter C et al, Aging Cell 2008 Aug;7(4):491-7) . It is responsible for inducing cell cycle arrest and as such can act as a tumour suppressor. In effect, it acts as an off switch for cell proliferation. We have demonstrated previously that CDKN2A is the most robust and the strongest predictor of post transplant renal function when compared to "Gold Standard" clinical factors such as ECD kidney status, DCD vs DBD kidneys and donor chronological age. We have sought to determine if CDKN2A is better than telomere length, the original biomarker of ageing, as predictor of post transplant renal function

**Methods:** The Maxwell® 16 DNA purification robot kits by Promega were used for for DNA isolation and RNA was extracted using the TRIzol® technique. Real time qPCR was used for the expression of CDKN2A and to determine telomere length. Demographic and clinical data was collected prospectively in an electronic database (SERPR) and supplemented by clinical record review. Data was analysed for associations with renal function – MDRD4 eGFR and Urinary Protein/Creatinine Ratio (UPCR) using univariate and multiple linear regression analysis.

**Results:** Univariate linear regression analysis showed that CDKN2A predicts 16.9% of eGFR (n=32, p=0.011) and 15.1% of the UPCR (n=25, p=0.031) at 1 year. ECD kidney status predicted 17.4% of eGFR (n=103, p=<0.001) but only 4.6% of the UPCR (n=85, p=0.027). Univariate linear regression between telomere length and renal function was not significant. A multivariate regression model comprising CDKN2A, ECD kidney status, donor chronological age and cold ischaemic time predicted 35.6% of the eGFR (n=31, p=0.003) and 44.4% of the UPCR (n=24, p=0.004) at 1 year.

**Discussion:** This study confirms that measurement of CDKN2A is the strongest predictor of post transplant function when compared to current organ selection criteria. It indicates that telomere length is inferior to both CDKN2A and ECD kidney status. The model provides a valuable pre-transplant prognostic score on organ quality, allowing improved and objective patient counselling and providing the possibility for targeted intervention strategies to preserve graft function.

**Histocompatibility parallel session/free communications**

**Boisdale Suite**

**Wednesday 22nd February 2012**

**12.00 – 13.00**

**13**

**Retrospective analysis of DSA/MFI in pre-transplant serum and survival after cardiac transplantation; implications for new guidelines**

Anna Danskine[1], Marlene Rose[1,2], John Smith[1]

*[1]Royal Brompton & Harefield NHS Foundation Trust, Harefield, UK, [2]Imperial College, London, UK*

Since the introduction of Luminex beads for the identification of HLA specific antibodies the number of sensitised patients on cardiothoracic transplant waiting lists has increased. Organ Donation and Transplantation and the UK cardiothoracic units have assigned 'risk levels' to aid decisions on patient selection once a donor becomes available. Risk levels would be based on MFI values of donor specific HLA antibodies (DSA) detected in the Luminex Single Antigen Assay. The aim of this preliminary study was to evaluate these protocols.

Sixty-one cardiac patients transplanted between 1991 & 2005 who had pre-transplant Luminex detected DSA were identified. For each patient cumulative MFI values (cMFI) were calculated. MFI values were added together for individual donor mismatched beads; where there was more than one bead present in the single antigen assay the highest MFI value for that antigen was used. Survival at 1 year and treated rejection within 1 year were used to compare the effects of transplanting across the different antibody risk categories.

The guidelines propose cMFI <2000 as low risk (r1), cMFI 2-5000 as significant early rejection with pre-transplant antibody reduction advised (r2) and cMFI >5000 as high risk and therefore a veto to transplant (r3). In our patients there was a trend towards a cMFI >5000 for all loci (HLA-A, B,C,DR,DQ) being detrimental to patient survival. 1yr patient survival was 64.9%, 87.5% and 37.5% for r1 (n=37), r2(n=8) and r3 (n=16) patients respectively (p=0.065). In patients surviving more than 1 year, 66.6% of r2 patients had treated rejection episodes compared to 61.1% of r1 patients (p=1.0). However if cMFI's from only the ABC&DR loci were analysed 1yr survival was 68.3%, 87.5% and 16.7% for the three risk groups respectively (p=0.0009), suggesting that pre-transplant HLA-DQ antibodies have minimal effect on patient survival. Furthermore, 85.7% of r2 patients had rejection within the first year compared to 52.3% of r1 patients, p=0.19. Other cut-off values were investigated and a cMFI of 6300 was selected as the cut off for the upper risk level. Patient survival was 28.6% at 1 year in patients with an ABCDRDQ cMFI >6300, compared to 70.2% for patients with a cMFI <6300 (p=0.0053). When the DQ locus was removed from the analysis one year survival was 72% and 9% for cMFI<6300 and cMFI>6300 respectively, (p<0.0001). In those patients surviving more than 1 year the rate of rejection was identical to that seen with the current risk levels.

This preliminary study suggests that cMFI within r1 and r2 have little effect on patient survival although may impact on rejection rates; r3 should be a veto to transplantation. Further collaborative studies are necessary to corroborate these Results:

**14**

**Comparison between luminex single antigen beads and flow cytometry crossmatching for assessment of hla specific antibodies in renal transplantation**

Judith Worthington, Anna Barker, Amanda Robson, Susan Martin

*Transplantation Laboratory, Manchester Royal Infirmary, Manchester, UK*

**Introduction:** Our laboratory uses microbeads and Luminex X map technology for the detection of HLA specific antibodies both pre-transplant (tpx) for the definition of unacceptable antigens and post-tpx to aid the diagnosis of antibody mediated rejection. Recent literature suggests that these techniques may be too sensitive and that they should be validated in the clinical context. Our preliminary data indicated that the use of flow cytometry crossmatching (FCXM) in addition to antibody detection by Luminex can aid assessment of clinical relevance. The routine use of a post-tpx FCXM is not always possible and so the aim of this study was to investigate the semi quantitative nature of the microbeads with a view to establishing risk stratification according to fluorescent values. This could inform the decision to proceed to tpx in the living donor scenario or modify immunosuppression post-tpx.

**Methods:** FCXMs were performed for 33 patients positive for donor directed antibodies post-tpx and 29 patients with HLA specific antibodies directed against potential living donor antigens. HLA specific antibody definition was performed using LabScreen Single Antigen (One Lambda Inc). In order to improve the quantitative nature of the test the median fluorescent intensity (MFI) value for a bead was expressed as a percentage of the MFI value for the positive control bead. Assuming 100% binding to the positive control, test percentage gave an estimate of relative binding of antibody to a specific bead. The most positive bead corresponding to a donor HLA mismatch was used to determine the MFI and relative binding which were then correlated with the FCXM result. An unpaired t test was used to assess the statistical significance of the Results:

**Results:** Of the 62 FCXM tests performed, 15 gave a negative and 47 a positive result. The median bead MFI for the FCXM negative and positive groups was 1979 and 9033 respectively ($p < 0.0001$). The median relative binding for the FCXM negative group was 15% compared with 83% in the positive group ($p < 0.0001$).

| | Median MFI | MFI Range | Median Relative Binding | Relative Binding Range |
|---|---|---|---|---|
| FCXM NEG (n = 15) | 1979 | 705 - 4306 | 15 | 6.2 - 31 |
| FCXM POS (n = 47) | 9033 | 2937 - 21397 | 83 | 33 -342 |

**Conclusions:** Our data indicate that, for antibodies directed against donor HLA mismatches, relative binding can be stratified into 3 levels. Below 20% consistently equates to a negative FCXM and above 50% equates to a positive FCXM. At these extremes, a FCXM test is not required to aid interpretation of clinical significance. Between 21-49% a FCXM test result would support the interpretation of the bead array result. Adoption of this approach would enable the laboratory to provide an assessment of the clinical relevance of the Luminex data whilst managing increasing workloads.

**15**

## The role of HLA and HLA-reactive antibodies in cytotoxic t-cell immunotherapy of post-transplant lymphoproliferative disease

Victoria Robertson[1], Emily Thompson[1], Paul Dunn[2], Lorraine Syme[1], David Turner[1], Marc Turner[1], Gwen Wilkie[3], David Wilson[4], Phil Dyer[1]

*[1]Scottish National Blood Transfusion Service, Edinburgh, UK, [2]New Zealand Blood Service, Auckland, New Zealand, [3]Scottish National Blood Transfusion Service, Aberdeen, UK, [4]NHS Grampian, Aberdeen, UK*

Epstein-Barr virus (EBV)-specific cytotoxic T-cell (CTL) immunotherapy has been used successfully for the treatment of post-transplant lymphoproliferative disease (PTLD). PTLD occurs in up to 10% of solid organ transplant patients and has a mortality of up to 50%. To ensure recipients worldwide have ready-access to this potentially life-saving immunotherapy, we are currently establishing a GMP EBV-specific CTL bank using lymphocytes from donors resident in areas with low infectious disease risk.

To establish the optimum number of donors required for the bank, low resolution HLA types of 200 apheresis donors were assessed for mismatches against 304 patients on a kidney transplant waiting list. Eleven apheresis donors gave a "low-grade" HLA-A, -B and -DR mismatch for 86.2% of patients. Based on this information, no more than 20 donors will be needed to set up the bank. To date, 15 donors have been selected for the bank on the basis of 1st field (allele group) HLA-A, -B, -DR types determined by PCR-SSOP. To determine the coverage these 15 donors would provide, their HLA types were assessed against 335 patients on a kidney transplant waiting list at a "low-grade" mismatch of 111 or better at HLA-A, -B and -DR. No CTLs with a 2 mismatch at HLA-A, -B and -DR were selected for assessment. Based on 1st field (allele group) HLA types, 191 (57%) of the 335 patients on the waiting list were covered by the current CTL choices at a "low-grade" mismatch. These results indicate further donors are required to achieve the calculated coverage of >80%.

To help investigate future PTLD treatment response rates (currently 52% at 6 months) using *ex vivo* generated CTLs, the impact of patient sensitisation on the coverage provided by the current CTL choices was also assessed. Of 335 patients, 106 had one or more HLA-reactive antibodies (32%). Of these 106 patients, 80 were covered by the current CTL choices at "low-grade" mismatch without taking into account sensitisation. Taking sensitisation into account, 19 patients were no longer covered by the current CTL choices effectively decreasing the proportion of patients covered to 51% from 57%. The overall reduction in the number of patients covered by CTLs due to the presence of HLA-reactive antibodies was significant ($p$ <0.05 using Wilcoxon signed rank test).

Based on this information patient sensitisation should form part of the CTL allocation process to maximise their therapeutic potential, along with the number HLA mismatches and the number of antigens shared at HLA-A, -B and -DR. These parameters will all be considered in conjunction with CTL phenotype. Additional donors must also be identified for the bank to increase the number of patients who can be treated. The availability of such a bank, in conjunction with a robust allocation process, has the potential to offer reliable, effective and targeted treatment for PTLD.

**16**

## Correlation of class I and class II donor specific antibodies (DSA) to occurrence of rejection episodes in renal transplant patients

Joyce Grant, Ray Fernando, Gita Turakhia, Aliyye Karasu, Graham Shirling, Henry Stephens

*Royal Free Hospital NHS Trust, London, UK*

Matching for HLA-DR and B locus antigens has been shown to result in improved transplant outcomes, and be more important than the A locus. Matching for HLA-C, DQ and DP are not currently included in the national kidney allocation scheme (unless recipient C and DQ locus DSA have been reported to ODT). However all donor and recipient pairs are HLA –C and DQ typed. The aim of this study was to analyse and compare HLA-A,B,C,DR and DQ locus DSA and rejection episodes in renal transplant patients at our centre.

We retrospectively studied 587 patients who were transplanted at our centre between 2004 and 2011. This included 204 live donor and 383 cadaver transplants. M:F 347:240; 1st graft:regrafts 500:87. Pre- and regular post-transplant samples were screened for HLA Class I and II antibodies by luminex technology; and positive samples were further investigated with luminex single antigen beads. HLA –A, B,C,DR and DQ typing of donor and recipient pairs was performed and confirmed by the luminex SSO typing technique.

A total of 50 of the 587 transplant patients (8.5%) were found to have DSA to the current graft. Of these 27(54%) included A locus DSA; 12(24%) B locus DSA; 7(14%) C locus DSA; 13(26%) DR locus DSA; and 22(44%) DQ locus DSA. In addition 13(26%) were A locus only, 2(4%) were B locus only, 4(8%) were C locus only, 5(10%) were DR locus only, and 12(24%) were DQ locus only.

Among the patients with A locus only DSA 4 (30%) had rejection episodes post-transplant; and among the patients with DQ only DSA 6(50%) had rejection episodes post-transplant. This was compared to a group of 50 patients who were transplanted between 2004 and 2007 who were sensitised to non-DSA HLA antigens of which 10(20%) had post-transplant rejection episodes.

This study shows that a large proportion of the DSA (54%) in our transplant patients are to HLA-A; which could be explained by the ODT allocation scheme leading to more HLA-A mismatches. There is also a large proportion of DQ-DSA (44%); which may not be explained by the matching algorithm because of linkage with HLA-DR. In addition the highest proportion of rejection episodes were found to occur in the transplant patient group with DQ-only DSA(50%) as compared to A-locus(30%) and non-DSA(20%). This would lead us to propose that DQ matching could be important for renal transplant outcomes.

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## What goes up can come down; donor specific HLA antibody levels undergo dramatic falls after early strong resynthesis response

Rob Higgins[1], John Hattersley[1], Dave Lowe[2], Nithya Krishnan[1], David Briggs[2], Daniel Zehnder[3]

*[1]University Hospital, Coventry, UK, [2]NHS Blood and Transplant, Birmingham, UK, [3]University of Warwick, Coventry, UK*

**Introduction:** The blood level of donor specific HLA antibody DSA after antibody incompatible renal transplantation (AIT) is a complex product of several factors. The aim of this study was to look closely at rates of change of DSA in those who clearly had active synthesis of DSA in response to the transplant.

**Methods:** 151 DSA in 71 patients undergoing AIT were studied. DSA were categorised as 'responders' (peak DSA >20% above pre-treatment level) and 'non-responders'(the others). The doubling time/half life of decay of each DSA level in the 'responder' group was calculated by fitting a logarithmic equation to the most rapid change in DSA. This was verified in a sample of cases using an algorithm modelling single component distribution and non-zero basal production.

**Results:** In responders, median (IQR) pre-treatment DSA measured by microbead was 1992 (930-4507) u, peaked at 8667 (4732-10872) u, and the late DSA was 560 (265-2896) u. In the non-responders, pre-treatment DSA was 4303 (2009-8560), and the late DSA was 1394 (460-4564) u. Assuming a late DSA level of <500 represented effective disappearance, 34/71 (48%) DSA had disappeared in responders, compared to 19/80 (24%) in the non-responders ($p<0.001$). Measurement of doubling time and half life by both mathematical models produced similar results, though in some DSA with slower rates of change the fit to logarithmic equation was poor. Median doubling time during peak DSA synthesis in responders was 1.34 (0.97-2.27) days. The median half life of decay was 8.81 (5.08-18.59) days. The half life of decay was strongly associated with the late DSA level ($p<0.001$) and with the doubling time of DSA ($p<0.01$), but was not associated with the starting level of DSA. In responders with late DSA level <500u, the median rate of decay was 5.56 (4.47-8.12) days. Although rejection was associated with responder status, disappearance of DSA was not associated with any particular therapy, such as plasmapheresis, rituximab, ATG or plasmapheresis.

**Discussion:** Disappearance of DSA was strongly associated with responder status and a rapid fall in DSA, indicating the likelihood of an active immunological mechanism.

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## A composite risk score is highly specific for predicting outcomes in renal transplant recipients with de novo donor-specific antibody

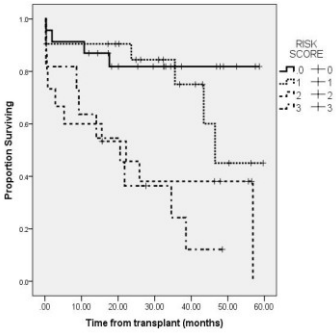
Christopher Lawrence, Michelle Willicombe, Paul Brookes, Eva Santos-Nunez, Candice Roufosse, Terry Cook, Anthony Warrens, David Taube

*West London Renal & Transplant Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK*

**Introduction:** Donor specific antibodies (DSA) are detrimental to renal allograft function and survival. The purpose of this study was to investigate which patients with de novo DSA are at risk of graft loss (GL), antibody mediated rejection (AMR) and Transplant Glomerulopathy (TG).

**Methods:** Between November 2005 and January 2010 469 patients were transplanted at our centre using Alemtuzumab induction, tacrolimus monotherapy and steroid avoidance. Samples for Luminex were taken 3 monthly or for indication. De novo DSA (measured by Luminex) was detected in 70/469 (14.9%, m49:21f, age 46.9± 14.5 years, follow up 29.6± 16.5 months). AMR and TG were diagnosed at indication biopsy according to Banff criteria.

**Results:** During follow up 13 (19%) grafts were lost, 29 (41%) patients have experienced AMR and 11 (16%) patients developed TG. Univariate analysis showed the presence of Class I&II DSA ($p<0.005$), cumulative Mean Fluorescent Intensity (cMFI) >1000 ($p<0.005$) and the presence of complement (C')-activating DSA ($p<0.05$) are predictors of graft loss, AMR and TG (p values for AMR). We developed a composite risk score awarding one point each for the presence of Class I&II DSA, cMFI>1000 and C'-activating DSA so that all patients with de novo DSA scored between 0 and 3 points. A risk score of 3 was highly specific for graft loss (0.91), AMR (0.95) and TG (0.91) but lacks sensitivity (0.46, 0.31, 0.50 respectively). Figure: AMR-free survival according to risk score ($p=0.001$).




| Outcome | | | | |
|---|---|---|---|---|
| Score | N | GL | AMR | TG |
| 0 | 23 | 1(4%) | 4(17%) | 0 |
| 1 | 21 | 3(14%) | 6(29%) | 3(14%) |
| 2 | 15 | 3(20%) | 10(67%) | 3(20%) |
| 3 | 11 | 6(55%) | 9(82%) | 6(55%) |

Table showing the distribution of risk scores and adverse transplant outcomes.

**Discussion:** Patients with de novo DSA are at higher risk of adverse outcome in the presence of both Class I&II DSA, C'-activating DSA and cMFI>1000. This score should be used prospectively to examine whether it allows identification of at risk patients prior to development of tissue injury and whether enhanced immunosuppression alters outcome.

**ABOi Transplantation**

**Lomond Auditorium**

**Wednesday 22nd February 2012**

**14.30 – 16.00**

**19**

## 1-year biopsy data of antibody-incompatible kidney transplantation and correlation with long-term risk of allograft loss – a prospective analysis

Adnan Sharif[1], Nada Alachkar[2], Serena Bagnasco[2], Lois Arend[2], Lorraine Racusen[2], Robert Montgomery[2], Edward Kraus[2]

*[1]Renal Institute of Birmingham, Birmingham, UK, [2]Johns Hopkins Medical Institutions, Baltimore, USA*

**Introduction:** The ability to predict kidney allografts at risk of failure in antibody-incompatible transplant programs would be beneficial. In this study, we investigate the value of 1-year allograft histology by protocol biopsy as a predictive tool for ascertaining long-term risk of allograft loss in incompatible kidney transplant recipients.

**Methods:** We analysed a prospective database maintained on all patients transplanted who were either ABO- and/or HLA-incompatible between 1998 and 2010. 211 incompatible patients had 1-year biopsy data (protocol or for cause) and were grouped as ABO-incompatible patients (n=48), HLA-incompatible patients (n=148) and simultaneous ABO/HLA-incompatible patients (n=15). Biopsies were categorised by Banff 1997 criteria (with 2007 update). Median follow up of all patients was 1078 days (range 0-4232 days).

**Results:** Death-censored graft loss occurred in 3/48 ABO-incompatible, 14/148 HLA-incompatible and 0/15 ABO/HLA-incompatible patients. 36.8% of all incompatible patients had evidence of C4d deposition. Death-censored graft survival in all C4d+ versus C4d- patients was 82.1% versus 96.5% respectively (p=0.001). 17.5% of HLA-incompatible patients were C4d+ and had worse death-censored graft survival compared to C4d- HLA-incompatible patients (61.9% versus 96.0%, p<0.001). By contrast 74.5% and 73.3% of ABO-incompatible and ABO/HLA-incompatible patients respectively were C4d+ with no difference observed in graft survival. Transplant glomerulopathy (TG) was diagnosed in 22.3% of all incompatible patients (25.0% versus 6.8% in HLA- and ABO-incompatible respectively). Compared to no TG, TG was associated with worse death-censored graft survival (72.5% versus 95.7%, p<0.001). TG resulted in worse graft survival in HLA-incompatible (66.7% versus 96.7%, p<0.001) and ABO-incompatible (66.7% versus 92.7%, p=NS) patients compared to having no TG respectively. Death-censored graft survival was worse in all incompatible C4d+ patients with versus without concomitant TG (57.1% versus 93.0%, p=0.001). C4d deposition with or without TG resulted in worse death-censored graft survival in HLA-incompatible (33.3% versus 100.0%, p=0.004) but not for ABO-incompatible (66.7% versus 90.0%, p=NS). Peri-tubular capillaritis was not associated with any difference in death-censored graft survival in any group. Incompatible patients who lost their graft were more likely to have elevated chronicity index scores at 1-year compared to those not lost (5.4 versus 3.4, p<0.001). Chronicity score (cv, ct, ci and cg combined) greater than median of 3.5 was associated with 16.5% risk of subsequent graft loss, compared to 3.3% for those with a chronicity score less than median of 3.5 (p=0.003) in all incompatible patients.

**Conclusion:** 1-year biopsy of incompatible kidney recipients can be utilized to identify high-risk patients at risk for subsequent allograft failure. Translating this data into a predictive risk-scoring tool may be of benefit, but requires clinical validation.

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**Specific removal of HLA antibodies from human sera**

D Lowe[1], C McMurtrey[2], D Zehnder[3], A Duty[3], S Cate[3], N Krishnan[4], R Buchli[5], S Osborn[2], D Mitchell[3], R VanGundy[5], D Briggs[1], W Hildebrand[2], R Higgins[4]

*[1]NHS Blood and Transplant, Birmingham, UK, [2]University of Oklahoma, Oklahoma, USA, [3]University of Warwick, Coventry, UK, [4]University Hospital, Coventry, UK, [5]Pure Protein LLC, Oklahoma, USA*

**Introduction:** The success of antibody-incompatible renal transplantation is heavily reliant upon achieving reduction of donor HLA-specific antibodies (DSA) to manageable levels. Current methods of antibody reduction such as plasmapheresis and immunoglobulin adsorption, or therapeutic agents such as IVIg, rituximab or bortezomib are non-specific and relatively ineffective. We demonstrate here that by using purified HLA molecules produced in mammalian cells it is possible to deplete human sera of HLA antibodies.

**Method:** Milligramme quantities of the soluble HLA molecules were produced in mammalian cells. These were used in soluble phase at a concentration of 0.05µg per 1µl patient sera, and also covalently coupled to a solid support.

**Results:** When patient sera recognizing multiple HLA were passed over DRB1*1101 coupled to a matrix, antibodies specific for DRB1*1101 were removed while antibodies for other class II passed through intact. The bound DRB1*1101 specific antibodies were then recovered, further characterized, and tested as a DRB1*1101 specific reagent. They retained all the expected binding characteristics of the antibody, and also carried the cytotoxic capacity of serum. Soluble HLA-B7 protein inhibited reactivity of antibody directed against the 163E+166E epitope expressed on HLA-B7, B13, B27, B42, B48, B55, B60, B61, B67, B73, B81 and A*66:02. Inhibition with the shared epitope specificity HLA-B13 also showed effective inhibition. Soluble inhibition using HLA-A2 protein did not result in any reduction in reactivity due to lack of the relevant epitope. HLA-A2, A24, B57, and Cw2 proteins were then coupled to separate sepharose columns at a concentration of 100µg protein per 200µl matrix, and all were able to deplete human sera of corresponding antibody reactivity in an epitope specific manner. Anti-HLA reactivity could be reduced by up to 80% in a single pass.

**Discussion:** These data demonstrate that HLA-specific antibody removal can be achieved using whole HLA proteins bound to affinity matrix. Specific anti-HLA antibody reduction may be a plausible strategy in antibody-incompatible transplantation both in the pre and post-transplant phase thus increasing access to transplantation for the highly sensitised patient.

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## Kidney transplantation across simultaneous ABO/HLA-incompatible immunological barriers is similar to either ABO- or HLA-incompatible transplantation for safety and efficacy

Adnan Sharif[1], Nada Alachkar[2], Andrea Zachary[2], Dorry Segev[2], Edward Kraus[2], Niraj Desai[2], Nabil Dagher[2], Andrew Singer[2], Robert Montgomery[2]

*[1]Renal Institute of Birmingham, Birmingham, UK, [2]Johns Hopkins Medical Institutions, Baltimore, USA*

**Introduction:** Transplantation across immunological barriers, either ABO- or HLA-incompatibility, is a successful strategy to provide access to transplantation for patients hitherto deemed immunologically high-risk. However the safety and efficacy of crossing both immunological barriers simultaneously is scarcely reported. In this analysis we compared outcomes between renal transplant recipients transplanted across simultaneous ABO- and HLA-incompatible barriers (n=28) to recipients with ABO-incompatibility (n=68) or HLA-incompatibility (n=221) alone.

**Methods:**We analysed adult incompatible kidney transplant recipients from a prospectively kept database. A total of 317 antibody-incompatible kidney transplant patients were transplanted from 1998 to 2010. 28 patients were transplanted against both immunological barriers and formed the patient cohort for this analysis. Protocol biopsies were performed for all patients on months 1, 3, 6 and 12 post-transplantation and 'per cause'. Outcome data (including patient/graft survival, rejection and graft function) was available for all patients up to a median of 1088 days post-transplantation (range 0 to 4232 days).

**Results:** From the 28 patients 62% were female (14/16 had previous pregnancies) and 57% had previously received a transplant (of whom just under half had received two or more transplants). Median age at transplantation was 45 (range 22 to 74). Total years of renal replacement therapy pre-transplant (dialysis/transplant) were a median of 10 years (range 0-28 years). Prior to any desensitisation, baseline donor-specific antibody strength was; CDC+ (8%), flow+ (61%), Luminex+ (31%). Concomitant baseline AHG isohaemoagglutinin titre was; 256 (21%), 128 (11%), 64 (25%), 32 (18%), 16 (14%) and 8 or under (11%). Patient and graft survival (death-censored) at one-year was 96%% and 93% respectively, with creatinine in surviving kidneys a median of 1.0 mg/dl (range 0.8-4.4 mg.dl). Early (<3 months) biopsy proven cell-mediated and antibody-mediated rejection was observed in 25% and 46% of patients respectively. Late (>3 months) biopsy proven antibody-mediated rejection was observed in 18% of patients. 1-year protocol biopsy data mirrored the ABO-incompatible "accommodation-like" phenotype. After median follow up of 1088 days post-transplant, patient and death-censored graft survival was 93% and 82% respectively, with median creatinine in surviving kidneys 1.2 mg/dl. Contemporaneous HLA-incompatible patient and death-censored graft survival was 88% and 87% respectively, whilst in ABO-incompatible patient and death-censored graft survival was 85% and 79% respectively with comparable median follow up to simultaneous ABO/HLA-incompatible patients.

**Conclusion:** This analysis demonstrates short-to-medium term safety and efficacy of transplanting patients across simultaneous ABO- and HLA-incompatible barriers, when compared to the outcomes of transplantation across either immunological barrier alone.

**Biomarkers in tolerance**

**Boisdale Suite**

**Wednesday 22nd February 2012**

**14.00 – 16.00**

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## Renal function at 2 years in kidney transplant recipients switched from ciclosporin or tacrolimus to belatacept: results from the long-term extension of a phase II study

Josep Grinyó[1], Georgy Nainan[2], Maria del Carmen Rial[3], Steven Steinberg[4], Flavio Vincenti[5], Yuping Dong[6], Dolca Thomas[6], Nassim Kamar[7]

*[1]University Hospital of Bellvitge, Barcelona, Spain, [2]Lakeshore Hospital, Cochin, India, [3]Instituto de Nefrologia, Buenos Aires, Argentina, [4]Sharp Memorial Hospital, San Diego, CA, USA, [5]UCSF Kidney Transplant Service, San Francisco, CA, USA, [6]Bristol-Myers Squibb, Princeton, NJ, USA, [7]Toulouse University Hospital, Toulouse, France*

**Background:** At 1 year, patients who switched from a calcineurin inhibitor (CNI) to belatacept had significant improvements in renal function in a Phase II study. This abstract addresses whether this clinical profile was sustained in the long-term extension (LTE) of this study.

**Methods**: This is a randomised, open-label, Phase II trial in renal transplant patients with stable graft function receiving either a ciclosporin (CsA)- or tacrolimus (TAC)-based regimen. Patients were randomised to either switch to belatacept or continue CNI treatment. After the first year, patients were eligible to enter the LTE.

**Results**: Of 173 randomised patients, 162 (n=81 belatacept; n=81 CNI) entered the LTE. 98% of patients in each group survived with a functioning graft. Two patients (n=1 each group) had graft loss between Years 1 and 2. At Year 2, mean calculated glomerular filtration rate (cGFR) was 62.0 mL/min (belatacept) versus 55.4 mL/min (CNI). The mean change in cGFR from baseline was +8.8 mL/min (belatacept) and +0.3 mL/min (CNI). The relative renal benefit of belatacept was observed in patients switched from either CsA (+7.8 mL/min) or TAC (+8.9 mL/min). The frequency of acute rejection (AR) was 4.9% (belatacept) and 3.7% (CNI) by Year 2. All AR occurred during the first year in the belatacept patients; all AR occurred in the CNI group in the second year. The overall safety profile remained similar between groups, except for more non-serious fungal infections (mostly skin) in patients switched to belatacept. No post-transplant lymphoproliferative disorder was reported.

**Conclusions**: Switching to a belatacept-based regimen from a CNI-based regimen resulted in further improvement in renal function over time, with no new cases of AR. Switching from a CNI to belatacept may be a viable approach, but merits confirmation in a larger controlled trial.

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## Likelihood of improving or sustaining renal function over 3 years with belatacept or ciclosporin: insights from the BENEFIT study

Josep Grinyó[1], Marwan Abouljoud[2], Michael Germain[3], Roberto Manfro[4], José Morales[5], Christophe Legendre[6], Chen-Sheng Lin[7], Mamta Agarwal[7], José Medina Pestana[8]

*[1]University Hospital of Bellvitge, Barcelona, Spain, [2]Henry Ford Hospital, Detroit, MI, USA, [3]Western New England Renal & Transplant Association, Springfield, MA, USA, [4]Hospital De Clinicas De Porto Alegre, Rio Grande do Sul, Brazil, [5]Hospital Universitario 12 de Octubre, Madrid, Spain, [6]Hospital Necker, Paris, France, [7]Bristol-Myers Squibb, Princeton, NJ, USA, [8]Hospital do Rim e Hipertensão, Sao Paulo, Brazil*

**Background:** Patients receiving belatacept had better renal function, similar patient/graft survival, and a higher rate of acute rejection versus ciclosporin (CsA) through 3 years in BENEFIT. We report the likelihood of sustained/improved glomerular filtration rate (GFR) with belatacept versus CsA.

**Methods:** BENEFIT is a randomised, Phase III study in adults receiving a kidney transplant from a living or standard criteria deceased donor. Patients received a more-intensive (MI) or less-intensive (LI) regimen of belatacept, or CsA; basiliximab induction, mycophenolate mofetil and corticosteroids. GFR stage shifts (MDRD formula) from Month 3 to 36 were assessed *post-hoc* (stage 1: ≥90 mL/min, stage 2: 60–89 mL/min, stage 3: 30–59 mL/min, stage 4: 15–29 mL/min, stage 5: <15 mL/min; or return to dialysis, graft loss or death).

**Results:** Data were available for 181 belatacept LI and 162 CsA patients at Months 3 and 36. At Month 3, 59% of belatacept and 30% of CsA patients were GFR stage 1/2 (stage 4/5: 8% versus 11%). Of patients in stage 2, 85% receiving belatacept and 67% receiving CsA had sustained/improved stage at Month 36. Fifty-nine percent of belatacept patients and 17% of CsA patients in stage 3 at Month 3 had improved stage at Month 36; 5/7 belatacept patients (71%) and 3/7 CsA patients (43%) in stage 4 at Month 3 improved by Month 36. Two of seven belatacept patients in stage 5 at Month 3 were stage 2/3 at Month 36; 11/11 CsA patients remained in stage 5. Belatacept LI and MI outcomes were similar.

**Conclusion:** In standard criteria kidney recipients, early renal benefits with belatacept were more likely to be sustained/improved over 3 years versus CsA.

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## Belatacept compared with ciclosporin in renal allograft recipients of extended criteria donor kidneys: 3-year outcomes from the phase III BENEFIT-EXT trial

José Medina Pestana[1], Josep Grinyó[2], Yves Vanrenterghem[3], Thomas Becker[4], Sander Florman[5], Philippe Lang[6], Maria del Carmen Rial[7], Mark A. Schnitzler[8], Tao Duan[9], Alan Block[10], Antoine Durrbach[11]

*[1]Hospital do Rim e Hipertensão, Sao Paolo, Brazil, [2]University Hospital Bellvitge, Barcelona, Spain, [3]University Hospital Leuven, Leuven, Belgium, [4]Medizinische Hochschule Hannover, Hannover, Germany, [5]Recanati/Miller Transplantation Institute, Mount Sinai Medical Center, New York City, NY, USA, [6]Hospital Henri Mondor, Créteil, France, [7]Instituto de Nefrologia, Buenos Aires, Argentina, [8]Center for Outcomes Research, St Louis University, St Louis, MO, USA, [9]Global Biometric Sciences, Bristol-Myers Squibb, Hopewell, NJ, USA, [10]Global Clinical Research, Bristol-Myers Squibb, Princeton, NJ, USA, [11]Bicêtre Hospital, Kremlin Bicêtre, France*

**Background:** Recipients of extended criteria donor (ECD) kidneys have poor long-term outcomes compared with recipients of standard criteria donor kidneys. The efficacy and safety of belatacept in recipients of ECD kidneys were evaluated at 3 years to characterise longer-term outcomes and durability of treatment effect.

**Methods:** BENEFIT-EXT was a 3-year, Phase III study in recipients of *de novo* ECD kidneys (n=543) who were randomised to a more-intensive (MI) or less-intensive (LI) belatacept regimen or ciclosporin (CsA).

**Results:** At 3 years, 323 patients remained on therapy (n=109 MI; n=114 LI; n=100 CsA). The proportion of patients surviving with a functioning graft was comparable between groups (80% MI, 82% LI, 80% CsA). Mean calculated glomerular filtration rate (cGFR) at 3 years was 11 mL/min higher among belatacept-treated patients compared with CsA-treated patients (42.7 mL/min MI, 42.2 mL/min LI, vs 31.5 mL/min CsA). Belatacept-treated patients showed less decline of renal function over time (mL/min/year), with slopes of −0.9 (MI), −0.6 (LI), and −1.9 (CsA). More CsA-treated patients (44%) progressed to GFR <30 mL/min (chronic kidney disease stage 4/5) versus those receiving belatacept (27%–30%). Acute rejection (AR) occurred in one additional patient in each group after Year 2; most AR occurred by Month 6. Post-transplant lymphoproliferative disorder risk was highest in the first 18 months (2 MI, 3 LI), with two additional cases (1 LI, 1 CsA) occurring after Month 36. Tuberculosis was reported in two MI patients, four LI patients, and no CsA patients. A risk-prediction model suggested treatment with belatacept would extend graft half-life by 22 months, from 8 years to 10 years.

**Conclusions:** Among recipients of ECD kidneys, treatment with belatacept resulted in comparable patient and graft survival, similar rates of AR, with better renal function compared with CsA at 3 years after transplantation. No new safety issues were observed at 3 years.

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## Donor sub-type analysis of 3-year outcomes from a phase III study of belatacept in recipients of extended criteria donor kidneys (BENEFIT-EXT trial)

Ferdinand Muehlbacher[1], Thomas Becker[2], Josep M. Campistol[3], Deise B. M. Carvalho[4], Sander Florman[5], Philippe Lang[6], Tao Duan[7], Mamta Agarwal[8], Christian P. Larsen[9]

*[1]Medical University of Vienna, Vienna General Hospital, Vienna, Austria, [2]Medizinische Hochschule Hannover, Hannover, Germany, [3]Hospital Clinic I Provincial, University of Barcelona, Barcelona, Spain, [4]Hospital Geral de Bonsucesso, Rio de Janeiro, Brazil, [5]Recanati/Miller Transplantation Institute, Mount Sinai Medical Center, New York, NY, USA, [6]Hospital Henri Mondor, Créteil, France, [7]Global Biometric Sciences, Bristol-Myers Squibb, Hopewell, NJ, USA, [8]Global Clinical Research, Bristol-Myers Squibb, Princeton, NJ, USA, [9]Emory University Transplant Center, Emory University, Atlanta, GA, USA*

**Background:** Belatacept was associated with better renal function and comparable patient/graft survival and acute rejection (AR) rates versus ciclosporin (CsA) through 3 years in recipients of ECD kidneys (BENEFIT-EXT).

**Methods:** BENEFIT-EXT was a 3-year, randomised, Phase III study in recipients of *de novo* ECD kidneys (n=543) randomised to a more-intensive (MI) or less-intensive (LI) belatacept regimen or CsA. ECD was defined as UNOS criteria (UNOS-ECD), CIT ≥24hr, or donation after cardiac death (DCD). This analysis compared patient/graft survival, calculated GFR (cGFR; MDRD), and AR through 3 years in recipients of UNOS-ECD (n=384) and DCD (n=55) kidneys. Because many of those with CIT ≥24hr also met UNOS-ECD, this group was not analysed independently.

**Results:** In UNOS-ECD and DCD recipients, the proportion of patients surviving with a functioning graft was comparable between belatacept and CsA groups, and consistent with outcomes in the overall ITT population (Table). Recipients of DCD kidneys in the belatacept LI group had numerically higher cGFR and patient/graft survival, while those in the belatacept MI group had lower AR rates; however, these outcomes need to be interpreted with caution due to small numbers. One patient in each treatment group had an AR after Year 2. The differential benefit in cGFR of >10 mL/min/1.73m$^2$ observed with belatacept in the ITT population was at least preserved across donor types.

**Conclusions:** In recipients of UNOS-ECD and DCD kidneys, belatacept resulted in better renal function and at least comparable rates of patient/graft survival and AR at 3-years post-transplantation compared with CsA.

| | **Belatacept MI n=184** | **Belatacept LI n=175** | **Ciclosporin n=184** |
|---|---|---|---|
| Patients surviving with functioning graft, % (overall) | 80 | 82 | 80 |
| UNOS-ECD | 80 (n=129) | 80 (n=122) | 77 (n=133) |
| DCD | 78 (n=18) | 100 (n=19) | 72 (n=18) |
| Mean cGFR, mL/min/1.73m$^2$ (overall) | 43 | 42 | 32 |
| UNOS-ECD | 40 (n=107) | 39 (n=108) | 27 (n=100) |
| DCD | 41 (n=13) | 56 (n=17) | 27 (n=14) |
| AR through Year 3, % (overall) | 18 | 19 | 16 |
| UNOS-ECD | 20 (n=129) | 21 (n=122) | 15 (n=133) |
| DCD | 11 (n=18) | 21 (n=19) | 22 (n=18) |

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## Outcomes at 3 years in kidney transplant recipients with pre-transplant diabetes from two phase III belatacept studies

Lionel Rostaing[1], Rafael Reyes-Acevedo[2], Hans-Hellmut Neumayer[3], Stefan Vitko[4], Jun Xing[5], Dolca Thomas[5], Flavio Vincenti[6]
*[1]Toulouse University Hospital, Toulouse, France, [2]Hospital Miguel Hidalgo de Aguascalientes, Aguascalientes, Mexico, [3]University Hospital Charité, Campus Charité Mitte, Humboldt University, Berlin, Germany, [4]Transplant Centre IKEM, Prague, Czech Republic, [5]Bristol-Myers Squibb, Princeton, NJ, USA, [6]UCSF Kidney Transplant Service, San Francisco, CA, USA*

**Background**: Pre-transplant diabetes mellitus is associated with poorer outcomes after kidney transplantation. We report outcomes at 3-years post-transplant in diabetic kidney transplant patients from two Phase III studies (BENEFIT and BENEFIT-EXT), which assessed belatacept-based immunosuppressive regimens versus a ciclosporin (CsA)-based regimen.
**Methods**: Patients in each study were randomised to receive a more-intensive (MI) or less-intensive (LI) regimen of belatacept, or CsA. Patients with a pre-transplant history of diabetes or who were taking anti-diabetic medication at the time of transplantation were included in this analysis.
**Results**: 180 patients in BENEFIT (n=63 MI; n=58 LI; n=59 CsA) and 157 in BENEFIT-EXT (n=52 MI; n=39 LI; n=66 CsA) were classified as having pre-transplant diabetes. Outcomes by Year 3 are listed in Table 1. The type and frequency of serious adverse events were generally reflective of the overall study populations.
**Conclusions**: In kidney transplant recipients who had diabetes mellitus at the time of transplantation, belatacept-based immunosuppression was associated with a numerically higher proportion of patients surviving with a functioning graft versus CsA and better renal function despite higher acute rejection (AR) rates in the BENEFIT trial. AR frequency and overall safety were comparable to the overall intent-to-treat population.

**Table 1. Outcomes at 3-years post-transplant in diabetic kidney transplant patients**

| **BENEFIT** | **Belatacept MI n=63** | **Belatacept LI n=58** | **CsA n=59** |
|---|---|---|---|
| Survived with a functioning graft, % | 94 | 90 | 86 |
| Mean cGFR, mL/min/1.73 $m^2$ | 61 | 65 | 42 |
| AR, % | 27 | 21 | 9 |
| Serious adverse events, % | 67 | 64 | 63 |
| Serious infections, % | 41 | 33 | 32 |
| Serious neoplasms, % | 8 | 7 | 5 |
| **BENEFIT-EXT** | **Belatacept MI n=52** | **Belatacept LI n=39** | **CsA n=66** |
| Survived with a functioning graft, % | 75 | 77 | 67 |
| Mean cGFR, mL/min/1.73 $m^2$ | 41 | 39 | 23 |
| AR, % | 25 | 21 | 21 |
| Serious adverse events, % | 81 | 77 | 88 |
| Serious infections, % | 46 | 41 | 47 |
| Serious neoplasms, % | 12 | 3 | 8 |

**Optimising use of the donor pool**

**Lomond Auditorium**

**Wednesday 22nd February 2012**

**16.30 – 18.00**

**31**

## Are DCD kidneys more susceptible to age-related kidney damage and ischaemic injury?

Dominic Summers[1,2], Lisa Mumford[2], Rachel Johnson[2], Dave Collett[2], Christopher Watson[1], J. Andrew Bradley[1]

*[1]University of Cambridge, Cambridge, UK, [2]NHS Blood and Transplant, Bristol, UK*

**Background:** Many clinicians are reluctant to transplant kidneys from older donation after cardiac-death (DCD) kidney donors and are also concerned that DCD kidneys may be more susceptible to ischaemic injury than donation after brain-death kidneys (DBD). We assessed the evidence for these concerns.

**Methods:** A comprehensive analysis of all adult, first-time, recipients of kidneys from controlled DCD and DBD donors performed in the UK between 2005 and 2010 was undertaken. The variables associated with graft survival were identified and their relative importance for DCD and DBD kidney transplant outcomes described.

**Findings:** Graft survival (all-cause graft loss) was similar for recipients of DCD (n=1826) and DBD (n=4283) kidneys with an unadjusted 3-year survival rate of 82.9% and 85.0%, respectively. A Cox proportional hazards model was built with step-wise variable selection, using one half of DCD kidney data set (n=910), and identified increasing donor age, cold ischaemic time and recipient age as being associated with decreased graft survival. The strength of the associations were tested with the second half of the DCD kidney data set (n=916): increasing donor age (over 60 years vs under 40 years) had a hazard ratio of 2.39 (p= 0.002), increasing cold ischaemic time (over 24 hours versus under 12 hours) HR 2.14 (p=0.044) while recipient age was not significant. Comparison of overall DCD and DBD transplant outcomes, using the Cox model, demonstrated no difference in graft survival between the DCD (n=916) and DBD (n=4283) groups (DCD versus DBD HR 1.15, p=0.17) and no interaction between donor age over 60 years and donor type (p= 0.59). An interaction between cold ischaemic time of over 24 hours and DCD donor kidneys was demonstrated (p=0.042). Further comparison using the Cox model with all the DCD data (n=1826) supported this trend with cold ischaemic times of '12-18 hours' and over '24 hours' having a significant (p= 0.049 and p= 0.005) interaction with DCD donation.

**Conclusion:** Recipients of older DCD donor kidneys are not at higher risk of graft loss than recipients of similarly aged DBD donor kidneys. DCD kidneys are, however, more susceptible to cold ischaemic injury and early transplantation is important to maximise transplant outcome.

**32**

## Individual centre logistics in deceased donor kidney transplantation in the United Kingdom

Sussie Shrestha[1], Rachel Johnson[2], Philip Dyer[3], Craig Taylor[4], Christopher Watson[4], Lorna Marson[1]

*[1]University of Edinburgh, Edinburgh, UK, [2]NHSBT ODT, Bristol, UK, [3]SNBTS, Edinburgh, UK, [4]University of Cambridge, Cambridge, UK*

**Introduction:** A robust support system in each transplant centre is vital to avoid delays and to improve outcomes in deceased donor (DD) kidney transplantation. An insight into the current practices in UK transplant centres is necessary to identify areas for improvement at local level and to ensure better transplant outcomes.

**Methods:**This is an observational study of centres undertaking DD kidney transplantation in the UK. Data were collected for 19 out of the 23 transplant centres. Questionnaires were completed by the lead or senior transplant surgeon in each unit. Information on other organs transplanted in the unit, access to theatre, number of consultant transplant surgeons actively involved in DD kidney transplant, local allocation policy, availability of a dedicated anaesthetic team, number of dedicated ICU, HDU and ward beds available for DD kidney transplants, and factors affecting ability to take the patient to theatre for transplant were recorded.

**Results:** Almost half (9) of the 19 centres are kidney only transplant centres and the rest (10) are multiorgan transplant centres. The majority of the centres (14) have access to emergency theatre only at any time irrespective of whether it is a kidney only or multiorgan transplant centre. Only one centre has access to a dedicated transplant theatre round the clock. Also, only one centre has options for a simultaneous kidney transplant for two kidneys both in and out of hours if required. Five centres said they would cancel an elective transplant for a DD kidney transplant. In the kidney only transplant centres, there is an average of 4 consultant transplant surgeons active in DD kidney transplant and an average of 6 in the multiorgan centres. There is a dedicated anaesthetic team for kidney transplant both in and out of hours in two transplants centres only, both of which are multiorgan transplant centres. There are differences in local allocation policy for donation after circulatory death (DCD) kidneys and donation after brain death (DBD) kidneys not used for first recipient; the majority of the centres contact recipient one at a time. There are dedicated ICU beds for DD transplant in one centre and HDU beds in five centres only. 100% centres said that theatre availability affects their ability to take patients to theatre for transplant. Other factors stated are awaiting crossmatching, surgeon availability and recipient preparation factors. While the median cold ischaemia time was 14 hr for DBD transplants and 10.5 hr for DCD transplants in the centre with a dedicated transplant theatre in 2010, they were between 12 and 19 hr and 12 and 20 hr, respectively, for the centres that have access to emergency theatres only.

**Discussion:** This study provides an insight into the variations of local practices in DD kidney transplants in the UK transplant centres. Majority of the centres lack a dedicated transplant theatre which may cause delays in taking the patient to theatre for transplantation. Most centres also lack a dedicated anaesthetic team and dedicated ICU and HDU beds for kidney transplantation.

**33**

## An audit of discarded deceased donor kidneys: organisational changes are needed to maximise organ usage

Chris Callaghan, Simon Harper, Kourosh Saeb-Parsy, Paul Gibbs, Christopher Watson, Andrew Butler, Gavin Pettigrew, Andrew Bradley

*Department of Surgery, University of Cambridge, Cambridge, UK*

**Introduction:** A small but increasing number of deceased donor kidneys are discarded for a variety of reasons including poor perfusion, retrieval damage, and vascular disease. Anecdote suggests that there is significant inter-surgeon variability in the use of these 'marginal' kidneys. We aimed to determine if discarded kidneys would have been used when assessed by other consultant transplant surgeons, and if current NHSBT offering arrangements are adequate.

**Methods:** From May 2011, discarded deceased donor kidneys were identified by NHSBT and sent to our centre for assessment by one or more consultant surgeons. Assessing surgeons independently classified usability as either 'usable', 'possibly usable (await histological 'Remuzzi' scoring)', or 'not usable'. Donor information, offering sequences, and reasons for non-use were obtained from NHSBT. Kidneys discarded by our unit were included in the study.

**Results:** Over a two-month period, 20 kidneys from 13 donors (five from donation after cardiac death donors, 8 from donation after brain-death donors) were assessed. Donors had a median (range) age of 67 (31-80) years. Kidneys were offered to a median (range) of 3 (1-12) centres before discard; the most common "primary" reasons for declining the organ were donor past medical history (28%), poor perfusion (26%), and donor age (17%). After transport to our centre, discarded kidneys were inspected by a median (range) of 2 (1-3) consultants. Thirteen kidneys (65%) were thought to be usable or possibly usable, and only 7 (35%) were judged unusable. Of the 20 discarded kidneys, five (20%) were initially offered to our centre and declined; three of these five kidneys were subsequently deemed usable or possibly usable when assessed by other consultants from our centre. Assessing consultants agreed in 34 of 36 opinions on usability (94%), indicating a high degree of inter-observer agreement.

**Conclusion:** A significant proportion of discarded deceased donor kidneys are potentially transplantable. The current algorithm for offering declined organs recognises that some centres are prepared to implant kidneys that are considered sub-optimal, but further changes are needed to maximise graft usage.

**34**

**Nitric oxide post-perfusion levels differ in DCD and DBD donor transplants**

Rose Johns[1], Aisha Chaudry[1], Eddie Khanafer[1], Adel Ilham[1], Mike Stephens[1], Aled Philips[2], Argiris Asderakis[1]

*[1]Cardiff Transplant Unit, University Hospital of Wales, Cardiff, UK, [2]Institute of Nephrology, University Hospital of Wales, Cardiff, UK*

**Background:** DCD kidneys graft survival is similar to that of DBD donors. These kidneys have a higher incidence and duration of DGF that does not have the same impact to survival as in DBD kidneys. Nitric oxide is a free radical that plays a role in ischemic reperfusion injury. Following reperfusion with the recipient blood IFN-$\gamma$ increases significantly and induces iNOS synthesis and NO production.

**Aim:** To see if the pattern of change of NO level post reperfusion differs between DBD and DCD kidneys and could explain their different behaviour.

**Methods:** Blood was collected pre and post perfusion (2h) from 32 DCD and 32 DBD kidney recipients. NO was measured with a calorimetric method as NO3. The ratio of the post to the pre-perfusion values (reperfusion ratio-RRt) was recorded and compared between the two groups and also correlated to known risk factors for DGF.

**Results**: The median pre-perfusion value of NO was not correlated with the kidney disease, sex or the recipient age. The median post perfusion NO value was affected by the baseline value and that is why the RRt was considered the best estimate of the change of NO post perfusion. The median RRt was 0.82 (mean 0.86) in DBD kidneys whereas it was 0.89 (mean 1.13) in DCD kidneys (Mann Whitney p=0.05). In univariate analysis the level of RRt was dependent on the type of transplant, CIT, but not the presence of DGF. In addition, in DCD kidneys the NO RRt in recipients with CIT over 12h was 1.29 that was significantly higher than the RRt 0.86 measured in recipients with CIT less than 12h (p=0.005). In DCD kidneys the RRt did not correlate with donor age so that patients with donors under 55 had RRt 0.96 that was no different than the RRt 0.85 in patients with donors over 55 (p=0.3). In DBD kidneys the post/pre Reperfusion Ratio was not correlated with donor age, sex or CIT.

**Conclusion:** The RRt of NO is significantly higher in DCD compared to DBD kidney transplants, perhaps because DCD recipients' NO post reperfusion is significantly affected by long CIT unlike what happens in DBD recipients. In DCD kidneys the level of NO increases post reperfusion with increasing cold ischaemic times.

**35**

## Perceptions and attitudes towards organ transplantation and procurement in junior trainees: nationwide survey of junior doctors

Rajiv Dave[1], Abdul Hakeem[1], Joanne Barwick[1], Hilary Sanfey[2], Andrew Lewington[1], Magdy Attia[1], Lutz Hostert[1], Krishna Menon[1], Niaz Ahmad[1]

*[1]St James University Hospital, Leeds, UK, [2]Southern Illinois University School of Medicine, Chicago, Illinois, USA*

**Aim**: The shortage of organ donors remains a fundamental problem in the United Kingdom. Many recommendations have been put forward to improve this. Improving the understanding and education of clinical personnel, particularly those in training, is vital to the success of campaigns to increase organ donation. In order to do this, one must have an understanding of the attitudes and perceptions of this target group, to identify if they would be receptive to more training in the field of transplantation.

**Methods**: This is one half of a two-part questionnaire. A 36-item anonymous questionnaire exploring attitudes and personal views towards organ donation and transplantation was distributed electronically to 1696 junior doctors (809 FYs and 887 Core trainees). The questionnaire explored some basic perceptions and gathered opinion on some controversial issues.

**Results**: 194 responded (11.4%). Majority of responders were White British (68%) females (65%) aged 25-30 years (57%). Foundation Trainees were more likely to respond (75%) than Core Trainees. Only 27% had previous exposure to transplant surgery, and 9% had a friend or relative who has been a transplant donor or recipient. Most trainees understood brain stem death (69%) but only 78% accepted them as being truly dead. 73% were supportive of an opt-out system, and only 35% felt that it is unreasonable to approach a grieving family to make a decision about organ donation. The majority of responders were happy to donate (85%) a kidney to family/friend and receive an organ in the event of organ failure (89%), and 90% agreed that transplant does improve the quality of life of an individual in organ failure. Only 29% disagreed with liver transplantation for those with liver failure secondary to alcohol or recreation drug abuse. 68% agreed with altruistic donation, and 78% were against paid donation. Most perceived paid donation as a negative process due to exploitation of the poor, rather than the potential mutual gain to both donor and recipient. 86% also disagreed with directed donation.

**Conclusions**: The results reflect a very positive outlook towards organ donation and transplantation, with the majority feeling that transplantation improves the patient's quality of life and the majority being on the organ donor register. Most responders said that they would feel comfortable discussing the issue of organ donation to a patient or a grieving family. The positive attitude amongst junior doctors towards organ donation and transplantation shows that this is a receptive audience for further education and training in donor identification. By understanding the overall attitudes and opinions, we can direct this training in an appropriate manner and at an appropriate level.

**38**

**The impact of body mass index on renal transplantation**

AJ Cockbain, A Hakeem, L Hostert, M Attia, N Ahmad, C Newstead, KV Menon, SG Pollard

*St James' University Hospital, Leeds, UK*

**Introduction:** Large retrospective studies in the United States have demonstrated poorer patient and graft survival in recipients with very high or very low BMI. Smaller studies in other countries have shown own increased postoperative complications and no impact on patient or graft survival. We therefore aimed to assess the impact of BMI on outcome following renal transplantation in the UK population.

**Methods:** Data for all adult renal transplantations between 2000-2011 were collected from a prospectively maintained institutional database. Patients were classified according to WHO criteria as underweight (BMI <18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9) and overweight (BMI >30). BMI was analysed using Kaplan Meier curves and the log rank test of significance for effect on graft survival (GS) and overall survival (OS). The effect of BMI on length of hospital stay (LOS), delayed graft function (DGF) and eGFR at years 1,3 and 5 were analysed as secondary outcome measures. Categorical variables were analysed by $\chi^2$, and continuous variables by one-way ANOVA at 5% significance.

**Results:** Height and weight were available for the calculation of BMI in 1349 of 1443 adult patients transplanted in the study period. Obese recipients had reduced 1yr, 3yr and 5yr OS (93%, 90%, 84% respectively) compared to normal weight recipients (97%, 94%, 91% respectively, p=0.016) and underweight recipients (99%, 96%, 92% respectively, p=0.046). BMI did not affect GS. Obese patients had significantly increased rates of DGF compared to normal weight recipients (26.4% vs. 17.0%, p=0.018) and increased LOS (mean 12.9 days vs. 9.2 days, p=0.014). Overweight and obese patients had significantly worse eGFR at 1yr (eGFR 46.7 and 45.8 respectively) compared to normal weight (eGFR 51.3) and underweight (eGFR 63.8) recipients, and at 3yrs compared to underweight recipients only (all comparisons p<0.02).

**Conclusion:** This is the largest UK series evaluating BMI and outcome following renal transplantation. We have demonstrated poorer outcome in overweight and obese patients, with increased rates of DGF, increased LOS, poorer graft function and reduced patient survival.A more detailed study of postoperative complications may reveal factors contributing to poorer outcome in the overweight and obese.

**Free communications**

**Alsh Suite**

**Wednesday 22nd February 2012**

**16.30 – 18.00**

**22**

**Sequential implementation of a standard and then an extended prophylaxis CMV screening programme in a major renal transplant unit**

Sapna Trivedi, Gill Matthews, Bridget Featherstone, Paul Jones, Sharon Mulroy, Menna Clatworthy, Chris Watson, Andrew Bradley, Afzal Chaudhry

*Addenbrooke's Hospital, Cambridge, UK*

**Background**: Cytomegalovirus (CMV) infection post renal transplantation is associated with significant morbidity, acute rejection, and both reduced allograft and patient survival. Prophylactic anti-viral therapy given during the first year has been shown to result in a statistically significant improvement in preventing disease and in reducing these outcomes. CMV disease may occur either due to a primary infection or due to reactivation of latent infection. The optimum strategy for viraemia and disease prevention remains unclear. A prospective service evaluation of two different screening and anti-viral prophylaxis strategies was conducted to address this.

**Method**: During 2008, an initial screening programme was implemented. All high-risk patients (kidney only donor positive, recipient negative (D+R-), combined kidney pancreas transplants (SPK) either D+ or R+, or recipients receiving T-cell depleting antibodies) were given 100 days of prophylactic oral valganciclovir (VGC). PCR based screening for viraemia was performed for a total of 12 months for high-risk recipients and 6 months for all others. CMV viraemia (based on pre-defined criteria) / disease was treated by a switch to intravenous ganciclovir with secondary oral VGC prophylaxis thereafter. Following the results from this prospective one-year cohort the programme was amended in 2009 to give 100 days of prophylaxis to all recipients (either D+ or R+) regardless of mismatch, except for the high-risk group (as above) who received 200 days of prophylactic therapy. A second one-year cohort was then followed. Immunosuppression protocols remained consistent throughout both cohorts.

**Results**: In the 2008 cohort, 153 transplants were performed (136 kidney, 17 SPK). Fifty patients (32.7%) developed CMV viraemia / disease warranting treatment (14 D+R+, 14 D-R+, 22 D+R-, 0 D-R-) during a 22 month follow up period. Twenty-four of the 26 infections in the first 100 days occurred in the D+R+ and D-R+ groups who had not received prophylaxis. Beyond 100 days the infections were predominantly in the high risk group in whom prophylaxis had now been completed. In the 2009 extended prophylaxis cohort, 146 transplants were performed (120 kidney, 26 SPK). Nineteen patients (13.0%) developed viraemia / infection warranting treatment during the same 22 month follow up period (12 D+R-, 1 D-R+, 6 D+R+) – relative risk (compared to the initial cohort) 0.398, 95%CI 0.247-0.642, $p<0.0001$ Fisher's exact test.

**Discussion**: A successful screening programme for post-transplant CMV infection was implemented at this hospital and then refined following a service evaluation of the initial outcomes. The outcomes for patients were significantly better in the extended prophylaxis cohort and a subsequent cost analysis has shown this to be a cost effective strategy. We recommend an extended prophylaxis strategy in the management of post-transplant CMV.

**23**

## The impact of CMV infection in solid organ pancreas transplantation: a single centre experience.

Otilia-Maria Mitu-Pretorian, Stephen Hughes, David van Dellen, Abbas Ghazanfar, Omar Masood, Melissa Oliveira-Cunha, Gabriele Di Benedetto, Vishnu Venkat, Bence Forgacs, Ravi Pararajasingam, Babatunde Campbell, Neil Parrott, Hany Riad, Declan DeFreitas, Michael Picton, Titus Augustine, Afshin Tavakoli

*Manchester Royal Infirmary, Manchester, UK*

**Background:** Cytomegalovirus (CMV) remains an important opportunistic viral infection in solid organ transplantation and persists despite strict protocols mandating prophylactic treatment regimens. This is often due to a combination of reactivation of latent infection and heightened immunosuppressive load. This has been extensively studied in the context of renal and liver transplantation, but both the rates and sequelae of CMV seroconversion, viral syndrome or tissue-invasive disease, as well as associated complications in solitary or combined solid organ pancreas transplantation have not previously been clearly established. The aim of this study was to establish epidemiology, course and impact of CMV infection and disease in a cohort of patients undergoing solid organ pancreas transplantation.

**Methods:** A retrospective analysis of a contemporaneously maintained database of all pancreas transplants performed in a single unit from the programme's inception in 2001 until 2011 was performed. Primary CMV infection rates were assessed as a primary endpoint. Potential confounding factors including the use of CMV prophylaxis, donor (D) and recipient (R) pre-transplant CMV status, age and time post-transplant to onset of infection were also assessed. In addition, infection rates were also compared between patients receiving Alemtuzumab or Basiliximab induction therapy for transplantation. All D+/R- patients received 100 days CMV prophylaxis (oral Valganciclovir was adjusted to the Creatinine clearance) as per published and established guidelines. Maintenance Immunosuppression was given as a standard therapy (calcineurin inhibitor, anti-proliferative agent with or without steroid).

**Results:** 230 pancreas transplants were performed over the study period (183 SPK, 13 PTA and 34 PAK). The overall CMV disease incidence was 22% (51/230; median age 54, range 26-60). Patients receiving Alemtuzumab induction (14/28; 50%) showed a much higher CMV disease rate than the Basiliximab group (44/202; p=0.002; Fisher's exact test). 1 year patient and graft survival were worse for those who acquired CMV disease.(86% and 75% respectively) compared to patients who did not acquired CMV ( 95% and 81% respectively).

**Summary:** The rate of CMV disease in pancreas allograft recipients demonstrates equivalence to previously published data for other solid organ recipients. Recipient status and induction therapy appear to the determining factors of potential susceptibility to post-transplant disease. This finding's significance is however limited partially by the low numbers of patients receiving Alemtuzamab in the studied group, reflecting a recent change in unit immunosuppressive policy. CMV infection remains a devastating complication of solid allograft transplantation, due to both the direct and indirect effects of the disease on patient and graft outcome and survival in addition to the significant financial implications in the current NHS. Adequate prophylactic measures and stringent vigilance are mandated to prevent unwanted adverse events.

**24**

**Real impact of the IMPACT study-cost effectiveness of extended CMV prophylaxis post kidney transplantation**

Maria Langdon, Michelle Morgan, Chris Dudley, Uday Udayaraj

*Richard Bright Renal Unit, Bristol, UK*

**Background:** The IMPACT Study has shown that extending cytomegalo virus (CMV) prophylaxis from 3 to 6 months in CMV donor positive (D+) to recipient negative (R-) kidney transplant recipients reduced incidence of CMV disease from 36.8 % to16.1% in the first year. In our centre CMV prophylaxis is given only for 3 months post kidney transplantation with valganciclovir for D+/R- recipients. All patients receive IL-2 receptor antibody as part of induction immunosuppression.

**Aims and objectives:** To establish the incidence and pattern of CMV disease in kidney only transplant recipients and examine the cost effectiveness of extended CMV prophylaxis for up to 6 months.

**Methods:** Retrospective study of all adult renal transplant recipients between August 2008 and July 2009 with 2 year follow up. CMV disease was defined as blood CMV PCR positive with or without clinical/ laboratory manifestations that resulted in initiation of therapy with treatment dose valganciclovir or ganciclovir.

**Results**: 94 patients (D+/R- =14,D+/R+= 26,D-/R+= 23, D-/R- = 31) were included. There were six cases (6.3 %) of CMV disease in the first 2 years with a higher incidence (N=3, 21%) in the in D+/R- group. All cases had received appropriate CMV prophylaxis as per centre protocol. Time to CMV diagnosis post transplantation was < 3 months (n=1), between 3-6 months (n=2) and > 6 months (n=3). All 6 patients with CMV disease were on Mycophenolate mofetil at time of diagnosis of CMV disease. Three of these patients had previous treatment for acute rejection with methylprednisolone and none received Antithymocyte globulin).Three patients were treated with intravenous ganciclovir and the remaining three received oral valganciclovir. There were no deaths or grafts lost from CMV disease. Five out of the 6 cases were CMV PCR negative at the end of treatment and one patient had asymptomatic persistent low grade viraemia.

**Discussion:** The incidence of CMV disease in the D+/R- group was 21 %, lower than reported in the IMPACT study (36.8 %), probably due to the high usage of antilymphocyte antibody (30%) during induction therapy in the IMPACT study. Only one out of the 14 D+/R- patients developed CMV disease between 3-6 months and would have potentially benefitted from extended CMV prophylaxis up to 6 months as suggested by IMPACT study. The cost of treating all 14 high risk patients with additional 3 months prophylaxis of valganciclovir (900mg daily) would be approximately £54,600 compared to the cost of £11,500.treating one patient with CMV disease (including 7 hospital days and IV ganciclovir for 3 weeks).

**Conclusions:** Routine extended CMV prophylaxis up to 6 months post kidney transplantation in the CMV high risk group (D+/R-) may not be a cost effective approach in centres with low usage of antilymphocyte antibody for induction therapy and low incidence of CMV disease.

**25**

## Messenger RNA levels in peripheral blood and urine can potentially stratify risk of rejection following renal transplantation

Manohursingh Runglall[1,4], Irene Rebollo-Mesa[1], Yogesh Kamra[1,4], Sui Phin Kon[5], Chris Farmer[6], Terry Strom[3], Graham M. Lord[4,1], Steven Sacks[1,4], Maria Hernandez-Fuentes[1,4], Paramit Chowdhury[1,2]

*[1]King's College London, London, UK, [2]Guy's and St Thomas' NHS Foundation Trust, London, UK, [3]Harvard Medical School, Boston, USA, [4]NIHR Comprehensive Biomedical Research Centre at Guy's and St Thomas's Hospital NHS Foundation Trust in partnership with King's College London and King's College Hospital, London, UK, [5]King's College Hospital NHS Foundation Trust, London, UK, [6]East Kent Hospitals University NHS Foundation Trust, Canterbury, UK*

Identification of genetic biomarkers in non-invasive peripheral samples has the potential to revolutionise post transplantation management. Such biomarkers could help risk stratify patients and reduce the need for invasive testing with biopsies to diagnose acute rejection. Furthermore, changes at a molecular level are likely to precede both graft dysfunction and histological findings, allowing earlier diagnosis and treatment to limit graft damage.

Our study aims to analyse messenger RNA (mRNA) levels in peripheral blood and urine samples from renal transplant recipients to identify those that could distinguish patients who underwent acute rejection from those that did not.

**Methods:** Serial blood and urine samples were collected from adults undergoing renal or combined renal/pancreas transplants over the first year post-transplant. Samples were collected at 26 routine time-points and during episodes of graft dysfunction. Blood samples were collected into "Tempus" tubes from which mRNA was extracted and stored. Urine samples were processed within 4 hours of collection. Urine was centrifuged and mRNA was extracted from cell pellets before extraction of mRNA. Preliminary analysis was carried out by identifying patients with biopsy proven acute rejection (BPAR) within the first year post transplant. Using creatinine plots, controls were identified using patients with less than 15% fluctuation in creatinine blood levels from baseline.

Analysis of mRNA levels in blood for 20 target and 4 control genes at 8 time points between 2 and 28 weeks post transplant was carried out using quantitative real time PCR in a total of 21 patients, 8 with BPAR and 13 with stable function. Gene expression levels were normalized to the control gene HPRT, and expressed as dCt values. Wilcoxon rank sum test was used to compare expression levels between stable and BPAR patients at each time point, and multiple testing corrected using False Discovery Rate below 10%. Statistically significant genes at week 2 were combined into a multivariate prediction model, and a ROC curve used to evaluate performance.

**Results:** Five genes were significantly up-regulated in BPAR patients at week 2 compared to stable patients; one gene at week 4, and three genes at week 12. The combination of the expression levels of the 5 genes at week two into a multivariate prediction model returned a probability score that predicted BPAR with a sensitivity of 0.85 and specificity of 0.93, with an AUC of 0.93.

**Conclusion:** This pilot study suggests that measurement of mRNA levels in peripheral blood could help risk-stratify patients for AR at 2 weeks post transplantation, allowing potential individualisation of anti-rejection therapy. Validation of these findings in a larger cohort is clearly needed.

**36**

**A prospective randomised trial of standard vs extended-release Tacrolimus monotherapy after Alemtuzumab induction in kidney transplantation: Initial outcomes - DGF and initial Tacrolimus levels**

K K Edmond Chan, Gary Chusney, Janet Lee, Jack Galliford, Rania Betmouni, David Taube, Adam McLean

*Imperial Kidney & Transplant Centre, London, UK*

**Introduction:** We have undertaken a prospective investigator-led RCT comparing standard release twice daily Tacrolimus (Prograf) with once-daily extended-release Tacrolimus (Advagraf) as maintenance monotherapy after Alemtuzumab induction with rapid (7-day) steroid withdrawal in kidney transplantation. Aggressive *de novo* dosing of extended release Tacrolimus has been reported to be associated with prolonged high Tacrolimus levels with associated delayed graft function (DGF). Following completion of trial recruitment, we report the incidence of DGF and initial Tacrolimus levels in our trial cohort.

**Methods**: 102 patients undergoing renal transplantation received 30mg Alemtuzumab induction, followed by 7 days steroids with Tacrolimus at total daily dose 0.1mg/kg either as 2 divided doses of standard-release Tacrolimus (50 patients, 23 live and 27 deceased donors) or as a single dose of extended-release Tacrolimus (52 patients, 25 live and 27 deceased donors). Randomisation was stratified for live vs deceased donors, and extended criteria and DCD donor organ recipients were included in the trial. Tacrolimus levels were measured by LC-MSMS (tandem mass-spectrometry) with target range 6-9ng/ml . DGF was defined as the need for dialysis within 7 days of transplantation.

**Results:**

**Delayed Graft Function**

| | | | |
|---|---|---|---|
| Standard release | 11/50 | 22% | |
| Extended release | 12/52 | 23% | p=0.91 vs standard release ($X^2$) |

**Mean Tacrolimus level in first 10 days (ng/ml)**

| | | |
|---|---|---|
| Standard release | 8.6 | |
| Extended release | 7.6 | p=0.22 (mixed effect model) |

**Time to stable Tacrolimus level in target range (days)**

| | | |
|---|---|---|
| Standard release | 9.4 | |
| Extended release | 7.7 | p=0.34 (binomial model) |

**Summary:** We found no significant differences in the incidence of delayed graft function, or the achievement of target drug levels between standard and extended-release Tacrolimus used as *de novo* maintenance monotherapy after Alemtuzumab induction with rapid steroid withdrawal.

**37**

## HbA1c is comparable to postprandial glucose for diagnostic probability of NODAT at both 12- or 52 weeks post kidney transplantation compared to fasting glucose alone

Shazia Shabir[1], Seema Jham[1], Baksho Kaul[2], Helen Smith[2], Richard Borrows[1], Adnan Sharif[1]
*[1]Renal Institute of Birmingham, Birmingham, UK, [2]Centre for Inflammation and Translational Research, Birmingham, UK*

**Introduction:** Glycated haemoglobin (HbA1c) can be utilised to diagnose diabetes mellitus in the general population, but guidance regarding its utility in the transplant population is limited and lacks validation. Beyond 3-months post-transplantation HbA1c may be useful to diagnose NODAT and easier to perform than an oral glucose tolerance test (OGTT). We analysed the sensitivity of three diagnostic markers for diabetes (fasting glucose, postprandial glucose and HbA1c) for their probability of diagnosis of NODAT at 12- or 52-weeks post kidney transplantation.

**Methods:** In this prospective analysis, 72 non-diabetic kidney transplant recipients received an OGTT at weeks 12 and 52 post-transplantation with concomitant HbA1c analysis. All patients received standard immunosuppression of basiliximab induction with maintenance tacrolimus, MMF and corticosteroids. Patients were classed with NODAT in accordance to American Diabetes Association guidelines; fasting blood glucose ≥ 7.0 mmol/L, postprandial blood glucose ≥ 11.1 mmol/L or HbA1c ≥ 6.5%. Correlation between continuous variables was by Pearson's or Spearman's rank test for parametric and non-parametric data respectively. Receiver operator characteristics (ROC curve analyses) were performed to determine the probability of having NODAT. All statistics were performed using SPSS software, with a p value $< 0.05$ considered significant.

**Results:** NODAT was diagnosed in 22.9% and 19.6% of recipients at 12- and 52 weeks post-transplant respectively. 25% of NODAT was diagnosed by HbA1c alone. ROC curve analyses for probability of NODAT at 12-weeks were; 12-week fasting glucose (AUC=0.713, p=NS), 12-week HbA1c (AUC=0.991, p<0.001) and 12-week postprandial glucose (AUC=0.984, p=0.001). ROC curve analyses for probability of NODAT at 52-weeks were; 52-week fasting glucose (AUC=0.599. p=NS), 52-week HbA1c (AUC=0.935, p=0.001) and 52-week postprandial glucose (AUC=0.796, p=0.023). Analysing both time points together HbA1c had the greatest probability of predicting NODAT with an AUC 0.967 (p<0.001) compared to postprandial glucose (AUC=0.871, p<0.001), whilst fasting glucose had poor probability (AUC=0.651, p=NS). Excluding patients diagnosed with NODAT by HbA1c alone at 12- or 52-weeks, HbA1c still demonstrated excellent sensitivity for probability of NODAT in the remaining patients with an AUC of 0.926 (p<0.001). 12-week OGTT showed HbA1c correlated strongly with postprandial glucose (r=0.700, P<0.001), but had only moderate correlation with fasting glucose (r=0.475, p=0.002). 52-week OGTT showed moderate correlation between HbA1c and fasting glucose (r=0.338, p=0.041) with only a trend towards correlation between HbA1c and postprandial glucose (r=0.307, p=0.064).

**Conclusion:** HbA1c is comparable to postprandial glucose for diagnosis of NODAT beyond 3-months post-transplantation and merits clinical utilisation.

**Basic Science**

**Boisdale Suite**

**Wednesday 22nd February 2012**

**16.30 – 18.00**

**40**

**Accommodation in ABO blood group incompatible renal transplantation: monitoring of post-transplant antibody titres**

Nicholas Barnett[1,3], Irene Rebollo Mesa[2,3], Myura Nagendran[4], Nizam Mamode[1,3]

*[1]Renal and Transplant Department, Guy's and St Thomas' NHS Foundation Trust, London, UK, [2]MRC Centre for Transplantation, London, UK, [3]King's College London, London, UK, [4]University of Oxford, Oxford, UK*

**Introduction:** ABO blood group incompatible (ABOi) renal transplantation, using desensitisation procedures to reduce pre-transplant antibody titres, is an effective strategy to increase the number of living donors. To date, little research has been undertaken examining changes in ABO isoagglutinin titres post-transplantation.

**Methods:** Within a single centre's ABOi renal transplant programme, 54 consecutive patients were transplanted between 05/07/2005 and 04/03/2011. All patients underwent routine monitoring of antibody titres pre- and post-transplant. Desensitisation involved rituximab, with or without antibody removal, aiming for a target antibody titre of 8 or lower on the day of transplant. Patients were prospectively followed-up, and clinical outcomes noted. Anti-A and anti-B antibody titres (total immunoglobulin load) were measured using DiaMed gel cards.

**Results:** As has been previously described, clinical outcomes are excellent in this cohort of patients. Desensitisation strategies (antibody removal, including Double Filtration Plasmapheresis (DFPP) and immunoadsorption (IA)) were effective in achieving a target pre-transplant antibody titre of 8 or lower. Post-transplant, antibody levels remained stable, at a mean titre between 2 and 8 with no significant evidence of a rebound in antibody levels. Patients with higher initial antibody titres tended to have higher post-transplant titres (correlation coefficient of 0.48 between titre on referral to the programme and the most recently measured titre post-transplant). No Antibody Mediated Rejection (AMR) episodes were associated with a contemporaneous rise in anti-blood group antibody titres: all episodes were attributed to anti-HLA antibody. The antibody titre on first referral to the programme appeared independent of age (correlation coefficient 0.058). Men had lower anti-blood group antibody levels than women (Wilcoxon rank sum test, $p<0.001$). The levels of anti-A antibodies were higher than the levels of anti-B antibodies (Wilcoxon rank sum test, $p<0.001$). The blood group of the recipient affected antibody levels: blood group O patients had higher levels of antibodies than both blood group B and blood group A. (Generalised linear model: B v A $p<0.05$ at all measured time points, O v A $p<0.01$ at 1 week post-transplant and $<0.001$ at initial and most recently measured titres.)

**Conclusions:** This study provides information for risk stratification in ABOi renal transplantation: knowledge of which patients are more likely to have high antibody levels will aid counselling of potential donors and recipients during initial assessment. Moreover, it may explain why ABOi renal transplantation leads to excellent outcomes: once the transplant is performed, antibody levels remain stable with no evidence of rebound, possibly indicating the onset of accommodation.

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## Class I HLA-specific antibody quantification

Dave Lowe[1, 2], Daniel Zehnder[2], Rob Higgins[3], A Mulder[4], Frans Claas[4], David Briggs[1]

*[1]NHS Blood and Transplant, Birmingham, UK, [2]University of Warwick, Coventry, UK, [3]University Hospital, Coventry, UK, [4]Leiden University Medical Centre, Leiden, The Netherlands*

**Introduction:** Recent advances in anti-HLA antibody detection methodologies has provided the clinical laboratory with a valuable tool to rapidly and accurately monitor the changes in antibody levels through the course of a kidney transplant. This is of particular importance in HLA antibody incompatible transplantation (HLAiTx) where daily monitoring of antibody status is often necessary and clinical intervention can be heavily influenced by these Results: However antibody data is given only as units of detectable fluorescence and no insight into the serum concentration of HLA specific antibody can be inferred. We describe a simple method for estimating serum concentration of HLA specific antibody using standard curves derived from human monoclonal HLA specific antibody.

**Methods:** HLA epitope specific monoclonal antibodies of IgG isoform were quantified and 'spiked' into HLA antibody negative AB serum and standard curves for single antigen bead binding were constructed in the dynamic range of 0.1-200µg/ml. Patient sera with the same single epitope reactivity as determined by inhibition analysis were then analysed using the concentration curve as reference.

**Results:** Standard curves using monoclonal antibodies showed a linear relationship between antibody concentrations of up to 25µg/ml and MFI up to 6000-8000units, and complete saturation of binding at antibody concentrations of 100 µg/ml and MFI at 12000-15000units. One transplant waiting list patient demonstrated a 142T epitope specific antibody (HLA-A2,28) at a consistent concentration of between 30-40µg/ml between three-monthly samples. The second patient underwent HLAiTX at our centre and had a pre-treatment serum antibody concentration of 12.8µg/ml which rose to a peak of 185µg/ml at day 17 post-transplant during a period of antibody mediated rejection. The base/peak ration of absolute concentration was 14.5, compared to base/peak ration of microbead MFI of 2984 and 12000, giving a ration of 4.1.

**Discussion:** This pilot study provides a valuable insight into the concentrations at which anti-HLA antibody is found in the general circulation and the dynamic ranges of antibody concentration that can be observed during the early post-transplant period in HLAiTx. Knowledge of circulating HLA-specific antibody levels is of fundamental importance if designing more specific antibody reduction strategies.

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**No effect of HLA antibodies detected by luminex based single antigen tests only, on kidney survival, graft function or acute rejection**

Argiris Asderakis[1], Deborah Singleton[2], Dina Asprou[1], Amy De'Ath[2], Mike Stephens[1], Sian Griffin[1], Tracey Rees[2]

*[1]Cardiff Transplant Unit, University Hospital of Wales, Cardiff, UK, [2]Welsh Transplantation and Immunogenetics Laboratory, Cardiff, UK*

**Background:** There are conflicting reports about the risk of kidney transplants performed in the presence of donor specific HLA Antibodies (Abs) that are only identified with Luminex single antigen testing. Furthermore there are reports that other non-DSA HLA Abs might also carry some additional risk. Our experience has shown in the past that such transplants can be performed safely.

**Aim and methods:** This was a prospective study to investigate in a series of consecutive kidney transplant patients performed in the knowledge of a negative crossmatch if the presence of HLA Abs that were Donor specific or otherwise resulted to an increased incidence of graft failure, acute rejection or to a worse kidney function as measured by creatinine and eGFR. Pre-transplant sera from 343 adult renal transplant recipients transplanted during a 45 month period were investigated for the presence of antibodies to HLA using Luminex LABScreen Mixed. Mixed positive sera were further tested by LABScreen Single Antigen for determination of HLA specificity. There was a minimum follow up of three years. A significant number of those patients did not receive any antibody induction.

**Results:** There were 213 patients with Luminex only Abs with a level over 500 out of which 85 had DSAs. There were 28 patients with DSA level over 2000 (9 class I and 19 class II) and 9 with level over 5000 all class II. There was no impact of the Ab presence (DSA or not) or the antibody level (as measured by the Single Antigen beads) on the kidney graft survival up to 3 years. Furthermore the rejection rate including borderline rejection was no different between the positive and the negative DSA groups either class I or class II and at any antibody level. The 6 months, 1 year and 2 years creatinine and creatinine clearance were similar between the positive and negative groups again at any level of sensitisation.

**Conclusion:** *Transplantation in the presence of Luminex only HLA Abs*, in the absence of a positive crossmatch, *is safe*, resulting in equivalent graft survival, kidney function and rejection rates up to 3 years post transplant. This is the largest prospective study of single antigen testing in kidney transplantation with a complete 3 year follow up

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## ABO incompatible living donor kidney transplantation in a single centre are associated with favourable medium term outcomes

Jack Galliford, Kakit Ed Chan, Rawya Charif, Christopher Lawrence, Candice Roufosse, Michelle Willicombe, Nadey Hakim, H Terence Cook, Adam McLean, Vassilios Papalois, David Taube

*Imperial College Kidney and Transplant Centre, London, UK*

Although there are reports that ABO incompatible living donor renal transplantation [ABOiLDT] has similar patient and allograft survival to ABO compatible living donor transplantation [ABOcLDT] in the US and Japan, there are data suggesting that this is not the case in the UK, and that outcomes may be more comparable with ABO compatible deceased donor transplantation [ABOcDDT]. The purpose of this study was to examine the outcomes of our ABOiLDT programme and compare them with our ABO compatible programme. 60 ABOiLDT [24f, 36m; mean age 46.8±11.7yrs] were compared with 454 ABOcDDT patients [158f, 296m; mean age 48.7±13.4yrs] and 434 ABOcLDT patients [166f, 268m; mean age 46.2±14.2yrs] performed at the same time. ABOiLDT patients received plasma exchange to achieve a pre-transplant anti-blood group antibody IgG titre of ≤1/4, preconditioning with either Rituximab or Campath and then a Tacrolimus based, steroid sparing immunosuppressive regime. All patients had a negative CDC and FXM crossmatch at the time of transplantation. Mean follow up is 37.5±21.0 months. The table below shows similar patient and allograft survival in all groups. Rejection free survival is significantly reduced in ABOiLDT but this is not different on allograft function which is at 12, 24, 36, 48 and 60 months [MDRD eGFR 50.2±3.3, 49.0±4.0, 50.7±5.4, 55.7±6.7 and 50.7±10.3 mls/min/1.73m$^2$] and only marginally lower that ABOcDDT and ABOcLDT function [-0.5 and -3.8mls/min/1.73m$^2$ ; p=0.85 and 0.17 respectively].

| | Months | ABOiLDT | ABOcDDT | ABOcLDT | ABOiLDT compared with ABOcDDT | ABOiLDT compared with ABOcLDT |
|---|---|---|---|---|---|---|
| **Patient survival** | 6 | 100.0% | 98.9% | 99.5% | HR 0.6 95%CI:0.15,2.72 p=0.546 | HR 1.2 95%CI:0.26,5.10 p=0.846 |
| | 12 | 100.0% | 98.2% | 99.3% | | |
| | 24 | 100.0% | 96.2% | 99.0% | | |
| | 36 | 97.6% | 94.4% | 98.3% | | |
| | 48 | 93.3% | 94.4% | 95.9% | | |
| | 60 | 93.3% | 92.6% | 94.7% | | |
| **Censored allograft** | 6 | 98.3% | 95.6% | 96.5% | HR 1.0 95%CI:0.42,2.34 p=0.992 | HR 1.0 95%CI:0.43,2.34 p=0.997 |
| **survival** | 12 | 96.6% | 94.2% | 96.5% | | |
| | 24 | 94.5% | 92.8% | 94.9% | | |
| | 36 | 89.0% | 92.0% | 91.3% | | |
| | 48 | 89.0% | 90.4% | 87.1% | | |
| | 60 | 83.8% | 87.7% | 85.4% | | |
| **Rejection free survival** | 6 | 73.3% | 86.3% | 86.1% | **12 months** | **12 months** |
| | 12 | 69.8% | 79.6% | 81.4% | HR 1.7 95%CI:1.02,2.83 p=0.04 | HR 1.9 95%CI:1.12,3.12 p=0.017 |
| | 24 | 60.3% | 77.1% | 79.2% | **Overall** | **Overall** |
| | 36 | 57.1% | 75.6% | 75.9% | HR 2.1 95%CI:1.34,3.22 p=0.001 | HR 2.3 95%CI:1.46,3.51 p=0 |
| | 48 | 53.3% | 74.5% | 74.5% | | |
| | 60 | 53.3% | 73.8% | 74.5% | | |

This study shows that outcomes of ABOiLDT at our centre are similar to ABOcLDT living donor transplantation at our centre. This technique to expand the donor pool produces excellent Results:

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**Rituximab treatment affects T-cell homeostasis in ABO-incompatible live donor kidney transplant patients.**

Giovanni Povoleri[1], Behdad Afzali[1,3], Nicholas Barnett[3], Peter Mitchell[1], Simon Ball[2], Giovanna Lombardi[1], Nizam Mamode[3]

*[1]King's College London, London, UK, [2]Renal Medicine - University Hospitals Birmingham NHS Foundation Trust Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Birmingham, UK, [3]Guy's and St Thomas' NHS Foundation Trust, London, UK*

**Introduction:** Most transplantation studies have focussed on the role of T cells in rejection; however, it is increasingly evident that B-cells also play an essential role in the immune response to a foreign graft. Rituximab (chimeric anti-CD20) is a B-cell-depleting monoclonal antibody used clinically to limit B cell-mediated allograft injury. B-cells are known to have a role in humoral immunity, but also function as antigen presenting cells (APCs) in the indirect pathway of allorecognition. We hypothesise that the removal of B-cells by Rituximab in the context of renal transplantation has significant effects on T-cell subsets, both numerically and functionally, as well as on antigen presentation to T-cells.

**Methods:** Subjects recruited for this study were adult recipients of ABO-incompatible live donor kidney transplants who were undergoing isohaemagglutinin modulation, including Rituximab. Blood was taken at different time points: day of rituximab treatment (D-30), pre-immunosuppression (D-7), day of transplant (D0), one week (D7), three months (D90) and one year post-transplant (D360). Peripheral blood mononuclear cells (PBMCs) from these patients were isolated using standard separation protocols and stored in liquid nitrogen before analysis. These cells were thawed and then a series of staining for B, T and leukocyte cell markers were performed by flow cytometric analysis.

**Results:** Preliminary data from a cohort of patients (n=16) at different time points of treatment confirmed the depletion of $CD20^+$ B-cells after rituximab was administered and transplant performed (D0; 0.96% ± 0.58%) and at three months (D90; 0.83% ± 0.35%); however, after one year of treatment (D360), percentage of single positive B-cells, $CD19^+CD20^-$, increased (79.94% ± 5.74%; $p<0.05$) whilst double positive $CD19^+CD20^+$ cells was still low (20.06% ± 5.74%; $p<0.05$), compared to pre-treatment samples (53.10% ± 12.47%). It also appeared that depletion of B-cells had an impact on $CD4^+$ T-cells. In particular, the mean percentage of $CD4^+CD45RA^+CD45RO^-$ naïve T cells decreased at both D0 (40.79% ± 3.22%; $p<0.05$) and D90 (42.04% ± 4.17%) in comparison to blood taken prior to Rituximab treatment (52.62% ± 4.54%) and compared to healthy controls (52.51% ± 6.07%). However, percentage of $CD4^+CD45RA^-CD45RO^+$ memory cells appeared to be unaffected by treatment of rituximab at the same time points (pNS).

**Discussion:** The clinical benefits of Rituximab have been shown in ABO-incompatible renal transplantation; however, very few studies in transplantation have been performed examining the mechanisms of action of B-cell depletion on T-cell count and activity. The results obtained so far showed a significant decrease in the number of naïve $CD4^+$ T-cells, whilst leaving other subsets fairly unaffected. The evaluation of B-cell depletion and reconstitution, and the effect on T-cell phenotype and functions, will provide a translational platform to enhance understanding of the mechanisms of effectiveness of Rituximab, which would be a key component of tailored and combination immunotherapy for future programmes of transplantation.

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## BK virus allograft nephropathy: Enhanced risk for ABO-compared to HLA-incompatible kidney transplantation

Adnan Sharif[1], Serena Bagnasco[2], Nada Alachkar[2], Duvuru Geetha[2], Gaurav Gupta[2], Karl Womer[2], Lois Arend[2], Lorraine Racusen[2], Robert Montgomery[2], Edward Kraus[2]

*[1]Renal Institute of Birmingham, Birmingham, UK, [2]Johns Hopkins Medical Institutions, Baltimore, USA*

**Introduction:** It has been observed in some studies that ABO-incompatible kidney transplant recipients have a higher incidence of BK virus allograft nephropathy (BKVAN) compared to ABO-compatible recipients. This could be related to desensitisation and induction protocols or a greater risk for rejection treatment. It is unclear whether HLA-incompatible kidney recipients, who share similar treatment protocols, share this risk or whether this phenomenon is unique to ABO-incompatible patients.

**Methods:** We analysed adult incompatible kidney transplant recipients from a prospectively kept database. 68 ABO-incompatible and 221 HLA-incompatible, transplanted between 1998 and 2010, formed the patient cohort. Patients transplanted against both immunological barriers were excluded from analysis. Protocol biopsies were performed for all incompatible patients on months 1, 3, 6 and 12 post-transplantation and 'per cause' biopsies in the context of transplant dysfunction (creatinine rise greater than 20% from baseline). All incompatible patients diagnosed with BKVAN on biopsy (protocol or for cause) were identified. Multivariable logistic regression analysis was used to identify independent risk factors for development of BKVAN.

**Results:** Risk of BKVAN was greater amongst ABO-incompatible compared to HLA-incompatible patients (17.7% versus 5.9%, p=0.008). This compared to the BKVAN rate of 3.0% observed amongst all kidney transplant recipients, compatible or not, at this transplant centre. 42% of BKVAN cases were subclinical and diagnosed on protocol biopsy. ABO-incompatibility, male sex and age were independent predictors for development of BKVAN on multivariable logistic regression. C4d deposition without histologic features of capillaritis (the typical ABO-incompatible graft 'accommodation' phenotype) on 1-year protocol biopsies of ABO-incompatible patients, with and without BKVAN, was 40% versus 75.8% respectively (p=0.040), a putative pathophysiological mechanism. At median follow up of 1399 days post-transplantation, ABO-incompatible patients with BKVAN had death-censored graft survival of 91% and serum creatinine of 1.8 mg/dl amongst surviving kidneys. For HLA-incompatible patients, at median of 1017 days post-transplant death-censored graft survival was also 91% and serum creatinine 1.8 mg/dl amongst surviving kidneys. In contrast compatible kidney recipients, at a median of 1117 days post-transplantation, death-censored graft survival were 69% and serum creatinine 2.6 mg/dl amongst surviving kidneys.

**Conclusion:** This study suggests that ABO-incompatible patients have an elevated risk of developing BKVAN unrelated to desensitisation, intensity of immunosuppression or risk of antibody-mediated rejection. However risk of BKVAN related graft loss is negligible, contrary to compatible kidney transplant recipients. Thus ABO-incompatible patients may have unique risk profiles and mechanisms for development and progression of BKVAN.

**Clinical controversy: Islets versus Pancreas**

**Lomond Auditorium**

**Thursday 23rd February 2012**

**09.30 – 10.30**

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**Comparable outcomes for simultaneous pancreas-kidney transplantation from brain-dead and controlled cardiac-death donors**

Saeed Qureshi, Chris Callaghan, Andrew Bradley, Christopher Watson, Gavin Pettigrew

*Department of Surgery, University of Cambridge, Cambridge, UK*

**Introduction:** Organ scarcity has prompted increased utilization of organs from donation after cardiac death (DCD) donors. However, reports on outcomes after simultaneous pancreas-kidney (SPK) transplantation from DCD donors are limited, and, in controlled DCD donors, there is uncertainty regarding the acceptable duration from withdrawal of life-sustaining treatment to cold perfusion (warm ischaemia time - WIT). We describe our early experience of SPK transplantation from controlled DCD donors, including those with a prolonged WIT.

**Methods:** Outcomes of patients receiving SPK transplants from DCD and donation after brain death (DBD) donors between August 2008 and January 2011 were reviewed. Donor and recipient information was obtained from a prospectively-collected database and retrospective case-note review. Estimated GFR (eGFR) was calculated using the 6-variable MDRD formula. Patient and graft survivals were calculated by Kaplan-Meier analysis.

**Results:** SPKs from 20 DCD and 40 DBD donors were implanted. Median (range) follow-up was 14 (3-32) months, with no cases lost to follow-up. Donor and recipient characteristics were similar for both groups, though median (range) pancreas cold ischaemic times (CIT) were shorter in DCD recipients (8.2 (5.9-10.5) vs 9.5 (3.8-12.5) hours, $p<0.01$). For DCD donors, the median (range) WIT was 24 (16-110) minutes. Six DCD donors (30%) had WIT >30 minutes; these donors had a median (range) age of 28 (15-53) years with BMIs of 22.7 (17.2-24.2) $kg/m^2$. There were no cases of pancreatic delayed graft function (DGF) or primary non-function (PNF) in the DBD or DCD groups; the graft thrombosis rate was the same (one DCD (5%) vs two DBD (5%)). Renal DGF rates were higher in DCD donors but did not reach significance (7 (35%) vs 6 (15%); $p=0.10$). There were no episodes of renal PNF in the DCD group, but one occurred in the DBD group (2.5%; $p=1.00$) due to venous thrombosis. Rates of re-operation within 30 days and acute rejection were similar between DCD and DBD recipients, as was the length of stay. Similarly, there were no differences in median (range) 12 month HbA1c% (DCD 5.4 (4.9-7.7) vs DBD 5.4 (4.1-6.2); $p=0.91$) and eGFR (DCD 48.5 (30.1-81.4) vs DBD 53.5 (32.6-100.2) $mL/min/1.73\ m^2$; $p=0.58$). Pancreas graft survival was not significantly different ($p=0.18$) with Kaplan-Meier one-year survival estimates of 84% (DCD) and 95% (DBD). Of the 6 recipients of organs from DCD donors with WIT >30 minutes, five have functioning pancreas and renal grafts, while one died with functioning grafts. Overall, only one patient died.

**Conclusions:** DCD SPK grafts have comparable short-term outcomes to DBD grafts, even when procured from selected donors with a prolonged WIT. DCD donors are an important source for expanding the pancreas donor pool.

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## Clinical and metabolic outcomes following islet transplantation in subjects with Type 1 diabetes in Scotland

John Casey[2,3], Kirsty Duncan[2], Debbie Anderson[1], Janet Barclay[1], Christine Jansen[2], Tammie McGilvray[2], Janice Davidson[2], Neil McGowan[4], Shareen Forbes[1,3]

*[1]Diabetes and Endocrinology Unit, Royal Infirmary Edinburgh, Edinburgh, UK, [2]Transplant Unit, Royal Infirmary Edinburgh, Edinburgh, UK, [3]University of Edinburgh, Edinburgh, UK, [4]Scottish National Blood Transfusion Service, Edinburgh, UK*

**Introduction:** Subjects with Type 1 diabetes, who have recurrent hypoglycaemia are at risk of impaired awareness of hypoglycaemia (IAH). Those with IAH may be eligible for islet transplantation. A Scotland-wide Islet Transplant Programme has been established at the Royal Infirmary, Edinburgh. We summarise the clinical and metabolic outcomes to date.

**Methods:** Subjects were assessed by our multidisciplinary team pre-and post-transplant. Hypoglycemic and detailed dietary histories, weight and continuous glucose monitoring (CGM) were recorded pre and post transplantation. Post transplant (range 1-6 months) all subjects had a meal tolerance test (MTT). Graft function was defined as stimulated 90 minute C-peptide (MMT90) >30pmol/l. Post-transplant outcome data was derived from the patient's most recent assessment.

**Results:** 4 C-peptide negative patients (1 male, 3 females) all with IAH, received 6 islet transplants (3 recipients single, 2 recipient two grafts). Mean recipient age was (mean±SEM) 47±7years. Graft mass was 3952±295 IEQ/kg, purity 79±5%. Primary graft function was attained in all recipients (stimulated 90 minute C peptide 509±109 pmol/l). Following transplantation all subjects reported a restoration in awareness in hypoglycaemia and on CGM, glucose variability and frequency of hypoglycaemia decreased (all $p<0.01$). Glycosylated HbA1c decreased from 67±0.9 mmol/mol (8.3±0.08%) to 46±5 mmol/mol (6.3±0.4%) ($p=0.04$) and mean daily dose of insulin decreased: 0.49±0.07 units/kg vs. 0.24±0.06 units/kg ($p<0.001$); one subject was insulin independent one month following second engraftment. The weight of the recipients decreased significantly pre vs. post transplant (Δ-4.4±0.9 kg; $p<0.01$) secondary to a seven fold reduction in carbohydrate required to treat episodes of hypoglycaemia (237±120 kcals vs. 34±17 kcals ($p <0.01$)).

**Conclusions:** The Islet transplantation Programme for Scotland has achieved the main primary outcome goal of restoration of hypoglycaemic awareness in subjects transplanted to date. All metabolic data has improved in this short term follow-up period, in association with a decrease in body weight secondary to a reduced requirement for rescue carbohydrate. Long term follow up of these patients is important and underway.

**Acknowledgements:** UK Islet Transplant Consortium. Diabetes UK.

**Recurrent disease**

**Alsh Suite**

**Thursday 23rd February 2012**

**09.30 – 10.30**

**47**

**The impact of living donor nephrectomy on life cover and health insurance**

Sarah Richards, Justin Morgan, Najib Kadi

*Southmead Hospital, Bristol, UK*

**Aims:** Increasing numers of living related and unrelated donors are coming forward to offer organs. Whilst there has been extensive research on long-term health effects of nephrectomy, some of the wider socio-economic implications to the donor are less well known. One such area is the ability to obtain Life Cover and Health Insurance. We seek to establish a consensus of opinion amongst the major Life and Health Insurers in the United Kingdom.

**Methods:** Twenty major insurance underwriters in the United Kingdom were contacted by email or letter. They were asked to provide quotes for Life Cover of £100,000 for a fixed term of 15 years or their standard Health Care Cover in the following individuals:

1. 45 year old male non-smoker. BMI <25. No significant past medical history. No current illnesses or medications. No family history.

2. 45 year old male non-smoker BMI <25. Donated kidney to brother 1 year ago. No subsequent complications. No current illnesses or medications. No family history.

**Results:** Nine out of ten Life Cover Insurance underwriters responded. Whilst there was a range of quotes provided (£15.5 to £33.5 per month) all were prepared to offer standard rates to the donor provided there had been no post-operative complications and pending medical reports. Only six out of ten Health Insurance underwriters responded with half stating they felt the request for information covered an area of commercial sensitivity they did not wish to comment on. Of the three underwriters responding- one was not prepared to offer cover to the donor on any terms, the remaining two were prepared to offer standard rates of cover but one requested regular nephrologist follow up.

**Conclusions:** The rigorous screening involved in donor work up ensures that donors are fit and have no occult co-morbidity. Life Cover quotes provided reflected this with all underwriters offering standard premium rates for live donors. Establishing a consensus of opinion on the impact of donor nephrectomy on Health Insurance Cover was far more difficult to elucidate and potential donors should be advised accordingly during the consent process.

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## Placebo controlled double blind randomised clinical trial of transversus abdominis plane block in live donor nephrectomy

Sarah Hosgood, Umasankar Thiyagarajan, Michael Nicholson

*University of Leicester, Leicester, UK*

**Introduction:** Post operative pain may be reduced after laparoscopic donor nephrectomy (LDN) by using a technique which introduces a local anaesthetic into the transverse abdominal plane (TAP) at the suprapubic retrieval incision. This study assessed the safety and efficacy of using a TAP block in a randomised double blinded placebo controlled trial.

**Methods:** 46 patients participated in the trial and were randomised to undergo the TAP block procedure with either Bupivacaine (Bupivacaine n=24) or saline placebo (Control n=22) injected into the muscle plain. After surgery the amount of morphine, level of pain and measures of recovery were recorded. Pre-filled syringes were dispensed with the group allocation concealed to maintain blinding.

**Results:** The amount of morphine used 6 hours after surgery was significantly lower in patients receiving TAP block with bupivacaine compared to the control (12.4 ± 8.4 vs 21.2 ±14.0mg; P=0.016). However, the total amount thereafter was similar in both groups (40.4 ± 29.8 vs 44.7 ± 27.8mg; P = 0.527). Patients in the bupivacaine group experienced significantly lower levels of pain with a lower visual analogue score on post operative days 1 and 2 ($P < 0.05$) and less intermittent pain at rest on day 1 compared to the control group (P = 0.045). The amount of oral analgesics required was also significantly lower in the bupivacaine group (P = 0.001). Recovery and post operative hospital stay were similar in both groups ($P < 0.05$). There were no complications associated with the procedure.

**Conclusion:** The TAP block procedure is a safe method of pain relief that reduces the amount of morphine required in the early phase after LDN. Although, the requirement was similar thereafter, patients experienced less pain up to 2 days after surgery and required less oral analgesia during their hospital stay.

**Autoimmunity in Transplantation 1**

**Boisdale Suite**

**Thursday 23rd February 2012**

**09.30 – 10.30**

**49**

**Autoimmune responses that develop following transplantation exacerbate conventional cellular and humoral alloimmunity**

Ines Harper, Kourosh Saeb Parsy, Thomas Conlon, Eleanor Bradley, J Andrew Bradley, Gavin Pettigrew

*Department of Surgery, Cambridge, UK*

**Introduction:** The development of autoimmunity after transplantation is increasingly described, but its role in graft rejection remains controversial. Aside from a direct effector role, autoimmunity may cause graft damage indirectly, by augmenting conventional alloimmunity. This has not been addressed experimentally, but the recent description that autoantibody is initiated by passenger donor CD4 T cells within heart allografts now permits a definitive examination.

**Methods:** Donor CD4 T cells within bm12 cardiac allografts trigger autoantibody production when transplanted into MHC class II-disparate B6 recipients. To examine possible augmentation of conventional cellular and humoral alloimmunity, the model was refined by inter-crossing bm12 mice to create a new donor strain (bm12.$K^d$.IE) that incorporated additional MHC class I (H-2$K^d$) and class II (I-E) target alloantigens. IgG allo- and auto-antibody responses in C57Bl/6 (B6) recipients of bm12.$K^d$.IE heart allografts were assayed by performing anti-$K^d$ ELISA and indirect immunofluorescence labelling of nuclear-antigen-expressing HEp-2 cells. Indirect-pathway CD4 T cell responses were assessed by transfer of CFSE-labelled, I-$A^b$-restricted, $K^d$-peptide specific, TCR75 T cells. Donor CD4 T cell depletion was achieved by administration of 1mg of anti-CD4 antibody (YTS) 6 and 1 day prior to heart graft retrieval. Allograft vasculopathy was assessed morphometrically

**Results:** Analysis of weekly serum following transplantation confirmed that challenge of B6 mice with bm12.$K^d$.IE heart allografts provoked strong and long-lasting antinuclear autoantibody responses. Autoantibody did not develop if donors were treated with depleting anti-CD4 antibody prior to heart graft removal, demonstrating the essential role for donor CD4 T cells in initiating humoral autoimmunity in the recipient after transplantation. In recipients of hearts from untreated donors, strong anti-$K^d$ alloantibody responses developed and $K^d$-peptide specific TCR75 CD4 T cells divided robustly when transferred into recipients five weeks after transplant, In contrast, anti-$K^d$ alloantibody was much lower in recipients of hearts from donors depleted of CD4 T cells, and similarly division of the TCR75 indirect-pathway CD4 T cells was markedly attenuated. This effect was not due to carry-over of residual donor anti-CD4 antibody, because there was no discernible impact on recipient CD4 T cell numbers. Unsurprisingly, the reduction in cellular alloimmunity and humoral allo- and auto-immunity associated with transplantation from CD4 T cell-depleted donors impacted beneficially upon graft rejection.

**Conclusions:** The contribution of autoimmunity to graft rejection is unclear, but these results highlighting augmentation of alloimmunity by a concurrent autoantibody response provide strong support for a destructive role.

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## The relative effectiveness of donor- and recipient-derived regulatory T cells in preventing autoantibody-mediated allograft vasculopathy

Ines Harper, Simon Harper, Chris Callaghan, Eleanor Bolton, J Andrew Bradley, Gavin Pettigrew

*Department of Surgery, Cambridge, UK*

**Introduction:** We have recently reported that autoantibody responses following MHC class II-mismatched mouse heart transplantation contributed to the progression of allograft vasculopathy and were surprisingly triggered by graft-versus-host (GVH) recognition by passenger donor CD4 T cells. Regulatory T cells (T-regs) can both prevent allograft rejection and inhibit autoimmune disease, and we thus sought to examine the role of donor and recipient-derived T-regs in preventing allograft vasculopathy in our model.

**Methods:** The potential of T-regs to abrogate transplant-induced autoantibody and allograft vasculopathy in the MHC-class II mismatched (bm12 to B6) heart transplant model was examined by treating recipients or donors with anti-CD25 (PC61) antibody and by adoptive transfer of naturally-occurring $CD25^{+ve}$ CD4 T-regs (nTregs) of donor or recipient origin. Graft survival was assessed by daily palpation and autoantibody production assayed by indirect immunofluorscence of nuclear-antigen-expressing HEp-2 cells.

**Results:** Whereas unmodified B6 recipients reject bm12 heart allografts very slowly (MST 95 days), recipients depleted of T-regs at time of transplant rejected their grafts rapidly (MST 20 days). That this rapid rejection was a consequence of more aggressive humoral autoimmunity response was suggested by marked augmentation of the autoantibody response in the T-reg depleted recipients and by indefinite graft survival and absence of autoantibody production when hearts from CD4 T cell deficient donors were transplanted into T-reg depleted recipients. Surprisingly, heart grafts retrieved from T-reg-depleted donors were also rejected rapidly (MST 14 days), with similar augmentation in autoantibody. The ability of donor T-regs to prevent humoral autoimmunity was confirmed by subsequent adoptive transfer experiments; whereas transfer of bm12 nTregs inhibited autoantibody production, reduced the severity of allograft vasculopathy (mean luminal stenosis 41,3% vs. 80% in WT) and prolonged allograft survival, transfer of recipient (B6) nTregs had no impact.

**Conclusions:** Our results demonstrate a previously-unrealised mechanism whereby T-regs contribute to graft survival by preventing effector autoantibody responses. We hypothesise that donor nTregs are more effective that recipient nTregs at preventing GVH mediated autoimmunity because they recognise the same target ligand (MHC class II on host autoreactive B cells) as is recognised by the population of donor, helper $CD25^{-ve}$ CD4 T cells contained within the heart graft. Because the recognition of allogeneic MHC class II by donor CD4 T-regs is unlikely to be peptide-specific, theoretically MHC class II on all B cells will be targeted. Allogeneic T-reg adoptive transfer may thus have wider potential for preventing T-dependent humoral immunity against a diverse spectrum of target antigens.

**Medawar Medal Competition**

**Lomond Auditorium**

**Thursday 23rd February 2012**

**11.00 – 13.00**

**51**

## The importance of cytomegalovirus super-infection following renal transplantation

Shazia Shabir[1,2], Baksho Kaul[2,3], Annette Pachnio[3], Gemma Banham[1], Helen J Smith[2], Simon Ball[1,2], Lorraine Harper[1,2], Paul Moss[3], Richard Borrows[1,2]

*[1]Department of Nephrology and Renal Transplantation, University Hospitals Birmingham NHS foundation Trust, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, B15 2WB, Birmingham, UK, [2]Renal Research Laboratories, Centre for Inflammation and Translational Research, University of Birmingham Research Laboratories, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, B15 2WB, Birmingham, UK, [3]School of Cancer Sciences, University of Birmingham, Vincent Drive, Edgbaston, B15 2TT, Birmingham, UK*

**Introduction:** Despite improvements in antiviral regimens, cytomegalovirus (CMV) reactivation and disease remains a significant complication in solid organ transplantation. In a study by Kliem (AJT 2008) increased CMV infection was demonstrated in the $D^+/R^+$ group (indicating super-infection) compared with the $D^-/R^+$ group. However, there was limited data on clinical disease. The purpose of our study was to:

1. Assess risk of clinical CMV in the different serotype combinations $D^-/R^+$, $D^+/R^+$, $D^+/R^-$) in renal transplant recipients
2. Compare CMV-specific cell mediated immune response in the $D^-/R^+$ and $D^+/R^+$ groups
3. Evaluate the prognostic utility of cell mediated immunity assays in the above two groups

**Methods:** In an audit of 569 patients transplanted at University Hospital Birmingham between 01/08/2007-30/06/2011 the incidence of CMV viraemia, syndrome and disease was evaluated. In a separate prospective study of 85 patients' serial assessment of CMV viral load, CD4 and CD8 T cell immune responses to CMV were performed. All patients received standard immunosuppression of basiliximab induction with maintenance tacrolimus, mycophenolate mofetil and corticosteroids.

**Results:** Audit results revealed an increased incidence of CMV disease in the $D^+/R^+$ group (hazard ratio 2.6, 95% CI 1.36, 5.01) compared to $D^-/R^+$ group (hazard ratio 0.2, 95% CI 0.05, 0.7), suggesting super-infection with CMV increases risk of clinical disease. In recipients of kidneys from seropositive donors, we could not demonstrate the development of a cell mediated immune response to CMV presented in the context of donor HLA class I, when assessed using CMV peptides bound to major histocompatibility complex-tetramers. However, a CMV immune response in the context of recipient HLA was found in 60% of seropositive recipients and also developed in one seronegative recipient of a seropositive kidney. Baseline cell mediated immunity to CMV was moderately predictive for subsequent CMV disease, with area under the ROC curve of 0.6-0.7 depending on the assay used (either CMV lysate or peptide pools). In the $D^-/R^+$ group, the CD8 response was more predictive than the CD4 response with the reverse in the $D^+/R^+$ group. Higher percentages of CMV specific T cells were required in the $D^+/R^+$ group to protect against CMV compared to the $D^-/R^+$ group.

**Discussion:**

1. CMV super-infection is clinically relevant.
2. The donor organ may act as an "immune privileged" reservoir for CMV latency.
3. There is a difference in the strength and nature of the cell mediated immune response to control CMV in the $D^+/R^+$ group compared with the $D^-/R^+$ group in renal transplantation.

**52**

## A novel pathway for CD8$^+$ T cell activation by donor derived non-haematopoietic cells leading to acute allograft rejection

Simon Harper, Marg Negus, Ines Harper, Tom Conlon, Eleanor Bolton, Andrew Bradley, Gavin Pettigrew

*University of Cambridge, Cambridgeshire, UK*

**Introduction:** Although seminal studies have shown that CD8$^+$ T cells can reject cardiac allografts that lack donor haematopoietic cells (HPCs) through a direct cognate interaction with graft parenchymal cells, the observation from other studies that secondary lymphoid tissue (SLT) is essential for graft rejection creates a paradox yet to be resolved. Here we examine the hypothesis that CD8$^+$ T cell activation by graft parenchymal cells requires acquisition and re-presentation of intact MHC class I alloantigen by recipient antigen presenting cells (APCs) within SLT. If proven, this hypothesis would not only resolve this paradox, but would also represent the first definitive demonstration of the contribution of the semi-direct pathway to graft rejection.

**Methods:** CD8$^+$ T cell-mediated allograft rejection following activation by donor parenchymal cells was examined using a transgenic heterotopic murine heart transplant model. Balb/c cardiac donors were lethally irradiated and treated with depleting antibodies ensuring complete eradication of HPCs, such that parenchymal cells in these grafts were the only source of alloantigen presentation. These HPC-depleted Balb/c (Balb/c$^{HPC-}$) cardiac allografts were transplanted into: 1) 2C transgenic mice (monoclonal population of CD8$^+$ T cells against Ld MHC class I); 2) Splenectomised aly/aly (aly/aly$^{spl}$) mice (complete absence of SLT) with adoptive transfer of 2C CD8$^+$ T cells, to investigate the importance of SLT in this pathway; 3) CD11c-DTR transgenic mice, in which host dendritic cells (DCs) are selectively depleted by diphtheria toxin, allowing delineation of the role of these cells in parenchymal alloantigen presentation to CD8$^+$ T cells.

**Results:** 2C transgenic mice rejected Balb/c$^{HPC-}$ grafts as rapidly as non-depleted Balb/c grafts (MST = 5d vs. 4d respectively; p=0.4) suggesting an effective mechanism for parenchymal cell driven CD8$^+$ T cell mediated rejection. Balb/c$^{HPC-}$ allografts showed prolonged survival (>50d) in aly/aly$^{spl}$ mice given 2C CD8$^+$ T cells, whereas in non-splenectomised controls all grafts rejected (MST = 17d; p=0.01) suggesting an essential role for SLT in this pathway. In addition, when aly/aly$^{spl}$ mice were given activated 2C CD8$^+$ T cells (from a 2C recipient of a Balb/c cardiac graft) they rapidly rejected Balb/c$^{HPC-}$ allografts (MST = 7d; p=0.01) indicating that SLT plays a fundamental role in the activation of CD8$^+$ T cells. To examine, therefore, whether recipient DCs were required to present to CD8$^+$ T cells within SLT, CD4$^+$-depleted CD11c-DTR mice given 2C CD8$^+$ T cells were transplanted with Balb/c$^{HPC-}$ allografts. When these mice were also treated with diphtheria toxin to deplete host DCs they demonstrated significantly delayed rejection kinetics when compared with untreated controls (MST = 26d vs. 16d; p=0.02) highlighting a key role for these cells.

**Conclusion:** These results indicate that allorecognition of graft parenchymal cells represents an important mechanism of CD8$^+$ T cell mediated rejection. They support the role of a novel pathway in which recipient DCs acquire intact MHC class I from donor parenchymal cells and present to CD8$^+$ T cells in SLT leading to their activation.

**53**

## Outcomes of kidney transplants from donation after cardiac death donors aged 70 years or older

Georgina Riddiough, Chris Callaghan, Mark Salji, Andrew Bradley, Gavin Pettigrew

*Department of Surgery, University of Cambridge, Cambridge, UK*

**Introduction:** The ongoing expansion of the donation after cardiac death (DCD) donor pool raises questions as to the suitability of using kidneys from very old donors. Double kidney transplantation (DKT) may enable utilisation of a proportion of these kidneys that would otherwise have been discarded. Here we report a single-centre experience of DCD kidney transplants from donors aged 70 years and older, comparing outcomes of single kidney transplants (SKT) and DKT.

**Methods:** Outcomes were assessed for SKT and DKT from DCD donors aged ≥70 years old between 1 January 2009 and 31 August 2011, with follow-up ceasing on 1 November 2011. The decision to implant a double or single kidney was based on donor and recipient characteristics, macroscopic appearance, and pre-implantation histological score (Remuzzi G *et al*, NEJM 2006). Estimated GFR (eGFR, mL/min/1.73 $m^2$) was calculated using the 4-variable MDRD equation; delayed graft function (DGF) was defined as the need for dialysis within a week post-transplantation. Continuous variables were described using median (range).

**Results:** Forty-three kidneys were implanted (27 SKT and 8 DKT), with a median follow-up of 13 months. Donor ages were similar in both groups (SKT 73 (70-78) years vs DKT 74.5 (70-79) years; p=0.20). Although median donor terminal creatinine was lower in the SKT group, it did not reach significance (66 (41-88) µmol/L vs 81 (40-235) µmol/L; p=0.08); likewise, there was no difference in donor terminal eGFR (SKT 90 (62-140) mL/min/1.73 $m^2$ vs DKT 74 (25-144) mL/min/1.73 $m^2$; p=0.22). As expected, kidneys subsequently used as DKT had significantly higher pre-implantation biopsy scores (DKT 5 (3-6) vs SKT 3 (2-6); p<0.01). Recipients were generally elderly, but median ages were similar between the two groups (SKT 65 (47-74) years vs DKT 64 (57-70) years; p=0.40), as were the cold ischaemic times (SKT 13h24m (9h59m-20h57m) vs DKT 15h23m (11h27m-23h27m); p=0.24), and DGF rates (37.5% (n=3) for DKT and 33% (n=9) for SKT; p=1.00). Graft function (eGFR) was better in recipients of DKT, though this did not reach significance at either one month (SKT 36.7 (19.3-63) mL/min/1.73 $m^2$ vs DKT 43.3 (26.5-67.7) mL/min/1.73 $m^2$; p=0.46) or 6 months (SKT 34.5 (26.8-58.9) vs DKT 50.8 (28.3-72.7); p=0.26). There were 2 primary non-functions and 3 deaths in the SKT group (heart failure, sepsis, invasive aspergillosis), but none of either in the DKT group. Actuarial one-year graft and patient survivals were 92.6% and 88.6% SKT vs 100% and 100% DKT (p=0.44, p=0.37, respectively).

**Discussion:** These early results demonstrate that the DCD donor pool can be expanded through careful selection of donors and recipients. Recipients of DKT from elderly DCD donors had similar outcomes to those receiving SKT, implying that our selection algorithms are adequate. Utilisation of organs from this source is an acceptable strategy to reduce the growing number of older patients waiting for renal transplantation.

**54**

**Memory CD4 T cells that recognise additional mismatched alloantigen provide CD40-independent help for effector anti-MHC class I alloantibody responses.**

Jennifer Cole, Kourosh Saeb-Parsy, Eleanor M Bolton, J Andrew Bradley, Thomas M Conlon, Gavin J Pettigrew

*University of Cambridge, Cambridge, UK*

**Introduction:** Although antibody specificity is classically thought to be restricted by the requirement for T cell help to be delivered through 'linked cognate' recognition of the target antigen following BCR-mediated internalisation, processing and presentation, we have recently demonstrated that help for anti-MHC class I alloantibody responses can also be provided by CD4 T cells that recognise additional graft alloantigens. Here we examine the potential for memory CD4 T cell responses against these additional graft alloantigens to dominate the helper component of an anti-MHC class I alloantibody response.

**Methods:** The ability of helper T cell recognition of additional graft alloantigen to provide help for anti MHC class I alloantibody responses was compared to that of conventional recognition of target class I antigen by reconstituting T cell deficient (TCR KO) recipients of male BALB/c heart grafts with monoclonal populations of either Mar (specific for I-$A^{b}$-restricted H-Y antigen) or TCR75 (specific for I-$A^{b}$-restricted H-$2K^{d}$-peptide) CD4 T cells. Anti-$K^{d}$ antibody responses were assessed by ELISA and germinal centre (GC) activity by immunohistochemical staining of splenic sections and by demonstration of long-lived plasma cell (LLPC) migration to bone marrow by day 50. Memory Mar responses were generated by challenge with male B6 skin grafts 6 weeks before heart transplantation and the dependence on CD40 / CD40L signalling for antibody production tested by administration of anti-CD154 antibody (MR1).

**Results**: When reconstituted with TCR75 CD4 T cells, female B6 TCR KO recipients of male BALB/c heart grafts mounted strong and durable anti-$K^{d}$ alloantibody responses, with splenic GC activity and migration of LLPC to bone marrow evident at day 50. Anti-$K^{d}$ alloantibody also developed upon reconstitution with Mar CD4 T cells, but this response was short-lived (<21 days), without demonstrable GC activity. In contrast, Mar-reconstituted recipients, when first challenged with male B6 skin grafts (to generate memory Mar CD4 T cells but not memory $K^{d}$-specific B cells), developed, upon subsequent challenge with a male BALB/c heart graft, anti-$K^{d}$ GC and long-lasting alloantibody responses comparable to the TCR-75 reconstituted group. Notably, CD40 blockade abrogated the $K^{d}$ alloantibody response in unprimed TCR75 or Mar recipients, but had no impact on primed Mar recipients. This inability to block alloantibody impacted upon the severity of allograft vasculopathy, in that vasculopathy was significantly reduced by CD40 blockade in unprimed Mar (22% vs 62%) recipients, but not in memory Mar mice (75% vs 90%).

**Conclusions:** These results demonstrate that memory CD4 T cell responses against additional alloantigen can provide CD40-independent help for long-lived anti MHC class I alloantibody production. They suggest that in the presence of concurrent immunosuppressant administration in the clinic, helper T cell reactivation from recognition of additional, previously encountered alloantigens may be the dominant mechanism for providing help for developing alloantibody against 'new' graft HLA antigens.

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## Risk-adjusted outcomes of liver transplantation from donation after cardiac death donors in the UK: a national registry analysis

Chris Callaghan[1], Susan Charman[2], Paolo Muiesan[3], James Powell[4], Wayel Jassem[5], Alex Gimson[1], Jan van der Meulen[2]

*[1]Liver Transplant Unit, Addenbrooke's Hospital, Cambridge, UK, [2]Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK, [3]Department of Liver Transplantation and HPB Surgery, Queen Elizabeth Hospital, Birmingham, UK, [4]Department of Surgery, Royal Infirmary of Edinburgh, Edinburgh, UK, [5]Division of Liver Transplantation and HPB Surgery, King's College Hospital, London, UK*

**Introduction:** The major challenge facing liver transplantation (LT) is the increasing disparity between the demand and supply of donor organs. Livers from donation after cardiac death (DCD) donors are a significant source of grafts, and DCD LT has been actively adopted by most UK centres. However, US registry analyses have identified poorer risk-adjusted outcomes with DCD livers, perhaps contributing to a recent drop in DCD LT in the US. We sought to determine if similar outcomes were apparent in the UK.

**Methods:** Using data submitted to the UK Liver Transplant Audit, we identified adults receiving a first elective liver transplant between 1 January 2005 and 31 December 2010. Follow-up ceased on 31 March 2011. Graft and patient survival of livers from DCD and donation after brain death (DBD) donors was compared. Risk-adjustment was achieved using a multivariable Cox regression model incorporating 8 donor and 19 recipient factors, including centre and era of transplantation. In order to confirm the robustness of our risk-adjustment we also used propensity score matching (PSM), utilising a further one donor and 16 recipient variables, with a subsequent Cox regression analysis. Hazard ratios (HR) with 95% confidence intervals (CI) were generated.

**Results:** We identified 2572 first elective liver transplants; 352 (14%) from DCD donors. Annual use of DCD livers increased almost four-fold over the study period (7% to 26%); in 2010, usage between UK centres varied from 0% to 36%. DCD donors were significantly more likely to be male, younger, and have lower BMI and serum sodium compared to DBD donors. Recipients of DCD livers were significantly more likely to be older, male, have lower serum bilirubin, and have cancer as the primary liver disease. As expected, cold ischaemic times for DCD liver were lower than those for DBD livers (median (IQR) 404 (335-480) mins vs 569 (465-668) mins, respectively; $p<0.01$). Three-year graft loss (95% CI) was higher in recipients of DCD livers (27.3% (21.8-33.9) vs 18.2% (16.4-20.2); HR (95% CI) 1.6 (1.2-2.0)). After adjustment using the multivariable model the HR (95% CI) for DCD graft use was 2.3 (1.7-3.0). Similarly, three-year mortality (95% CI) was raised in DCD recipients (19.4% (14.5-25.6) vs 14.1% (12.5-16.0); unadjusted HR (95% CI) 1.4 (1.1-2.0), adjusted 2.0 (1.4-2.8)). Reassuringly, the PSM approach gave similar results; DCD LT had adjusted HR (95% CI) for three-year graft loss and mortality of 2.3 (1.3-4.1) and 2.0 (1.0-4.2), respectively.

**Conclusions:** After adjustment for donor and recipient factors, three-year graft losses and deaths in recipients of DCD donor livers are approximately double that of DBD grafts. Further analyses are required to identify DCD donor factors associated with particularly poor outcomes, and which recipients are most likely to benefit from DCD grafts. These studies are essential in order to inform proposed liver allocation schemes.

This abstract is submitted on behalf of the Royal College of Surgeons of England/UK Liver Transplant Audit.

**56**

**The role of donor and recipient CD4 T cells in the initiation and maintenance of autoantibody after heart transplantation.**

M Saeed Qureshi, Thomas C Conlon, Reza Motallebzadeh, Sylvia Rehakova, Margarett Negus, Eleanor Bolton, AJ Bradley, Gavin J Pettigrew

*University of Cambridge, Department of Surgery, Cambridge, UK*

**Introduction**: Autoantibody responses described following solid organ transplantation are generally class-switched and long-lasting, suggesting germinal centre (GC) output and a requirement for autoreactive T follicular helper ($T_{FH}$) cells. Graft-versus-host recognition by donor CD4 T cells has been recently highlighted as the trigger for humoral autoimmunity, raising questions as to whether maintenance of the autoantibody response and GC development requires continued survival of donor lymphocytes.

**Methods**: The role of recipient CD4 T cells in the maintenance of donor-CD4 T cell-mediated autoantibody was investigated by transplanting MHC class II-disparate bm12 heart grafts into either wild-type or T cell deficient ($TCR^{-/-}$) B6 mice. In certain experiments, bm12 and / or B6 CD4 T cells (purified by MACS bead separation) were additionally transferred. Germinal centres were identified on immunofluorescence staining of splenic sections as peanut agglutinin (PNA) and Ly77 (GL7) positive B cell follicles and quantified by calculating percentage of secondary follicles to total follicles. Serum autoantibody levels were measured using Hep-2 indirect immunofluorescence staining.

**Results**: When transplanted into B6 recipients, bm12 heart allografts provoked production of long lasting antinuclear autoantibody (>100 days). In keeping, 72 ± 2.8% of the splenic B cell follicles at week 7 exhibited $PNA^{+ve}/GL7^{+ve}$ germinal centre morphology. Similar responses were induced by adoptive transfer of purified bm12 CD4 T cells alone, highlighting the critical role of passenger CD4 T cells within the heart graft as initiators of recipient humoral autoimmunity. Surprisingly, although adoptive transfer of bm12 CD4 T cells into $TCR^{-/-}$ mice also provoked autoantibody, the response was short-lived, without differentiation of the B cell follicles into activated GCs. In support, flow cytometric analysis of donor CD4 T cells after bm12 heart transplantation into $TCR^{-/-}$ mice revealed differentiation into helper T cells with extra-follicular phenotype ($CXCR4^{hi}$, $ICOS^{hi}$) only; no $CXCR5^{hi}$ $T_{FH}$ subset could be identified. Finally, adoptive transfer of both bm12 and B6 CD4 T cells into $TCR^{-/-}$ mice resulted in long-lasting autoantibody production and restoration of GC reactions (57.8 ± 2.8 % of follicles, vs 2.07 ± 1.25% in $TCR^{-/-}$ mice with bm12 CD4 T cells alone, $p=0.02$), confirming the requirement for recipient CD4 T cells to maintain autoantibody responses triggered by donor CD4 T cells.

**Conclusions:** These results highlight that, following transplantation, donor CD4 T cells need survive only long enough to initiate recipient humoral autoimmunity; thereafter host CD4 T cells are responsible for development of GC reactions and production of long-lasting autoantibody.

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## The first clinical series of normothermic perfusion in marginal donor kidney transplantation

Sarah Hosgood, Michael Nicholson

*University of Leicester, Leicester, UK*

**Introduction:** Delayed Graft Function (DGF) is a common problem in kidneys from donation after cardiac death (DCD) and extended criteria donors (ECD). A period of *ex-vivo* circulatory support prior to transplantation may allow the reversal of some of the detrimental effects of hypothermic storage and improve early graft function. Here we report the first clinical series of normothermic perfusion in marginal kidneys.

**Methods:** A total of 15 kidneys from ECD donors and 1 donation after cardiac death (DCD) donor underwent normothermic perfusion (NP) after a period of static cold storage (CS). Kidneys were perfused on an isolated perfusion system adapted from paediatric cardiopulmonary bypass technology with one unit of compatible cross matched packed red blood cells. This was supplemented with a priming solution, nutrients, multivitamins and a vasodilator. Kidneys were perfused for an average of 65.4 ± 15.3 minutes (range 35 – 100 minutes) at 34.1 ± 1.1ºC. After NP kidneys were flushed with preservation solution and transplanted.

**Results:** The mean donor age was 59 ± 9.7 years, cold ischaemic time 12.2 ± 4.7 hours and total preservation time 13.3 ± 4.7 hours (range 6.11 – 21.10 hours). Renal function was restored in all kidneys during perfusion and they produced an average of 210 ± 119 ml of urine (range 50 – 450 ml). There were no complications during NP and all kidneys were transplanted successfully. The mean recipient age was 57 ± 10.3 years and anastomosis time 26.4 ± 6.1 minutes. One patient had delayed graft function (6.3%) requiring dialysis within the first week of transplantation. Four patients were treated for acute rejection within the first month (25%). The mean serum creatinine levels at day 7, 1 and 3 month post transplant were 223 ± 168µmol/L,163 ± 62µmol/L and 141 ± 28µmol/L respectively. Graft and patient survival at 3 months was 100%.

**Conclusion:** The novel application of cardiac bypass technology to restore circulation to the kidney after a period of hypothermic storage and before implantation appears to be a safe and feasible method of preservation. Furthermore, the high rate of initial graft function in this series of marginal kidneys is notable but further comparative studies are required to assess the effects on DGF. The technique also has potential in the delivery of pre transplant *ex-vivo* therapies such as stem cells or gene transfer.

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## Assessment of longevity of the direct and indirect CD4 T cell allorecognition response

Jason Ali, Kathleen Elliott, Ines Harper, Marg Negus, Thomas Conlon, Eleanor Bolton, Andrew Bradley, Kourosh Saeb-Parsy, Gavin Pettigrew

*Department of Surgery, University of Cambridge, Cambridge, UK*

**Introduction:** Recipient CD4 T cells can recognise alloantigen 'directly', intact on donor antigen presenting cells (APCs), and 'indirectly', as self-restricted processed allopeptide. The relative duration of each pathway remains unclear, and further complicated by our recent description that the longevity of indirect responses differed according to target alloantigen. This work however examined different CD4 T cell responses in different murine models, and to control for differences in the immunogenicity of each, we developed a new model of chronic allograft vasculopathy that would allow definitive examination of all CD4 T cell allorecognition pathways operating in each recipient.

**Methods:** Several mouse strains were intercrossed to generate a novel strain, bm12.$K^d$.IE, which differs from wild-type B6 by possessing additional MHC cIass I (H-2$K^d$) and MHC class II ($IA^{bm12}$ and IE) molecules, but lacks the $IA^b$ MHC class II antigen. Heterotopic cardiac allografts were performed using bm12.$K^d$.IE donors into B6 recipients, and the model characterised by measuring rejection kinetics, degree of allograft vasculopathy, and production of alloantibody and autoantibody. The relative duration of direct and indirect allorecognition of different alloantigens was assessed by comparing division of monoclonal populations of alloreactive, CFSE-labelled TCR-transgenic CD4 T cells that were adoptively transferred either on day 0 or 28 post transplantation. Indirect allorecognition of MHC I was assessed using TCR75 CD4 T cells (I-$A^b$-restricted, H2-$K^d$ peptide-specific); class II using TEa CD4 T cells (I-$A^b$-restricted, I-E peptide-specific) and minor antigen using Mar CD4 T cells (I-$A^b$-restricted, H-Y peptide-specific). Direct allorecognition of I-$A^{bm12}$ MHC II was assessed using ABM CD4 T cells.

**Results:** Bm12.$K^d$.IE hearts survived >50 days in B6 recipients, with histological evidence of chronic allograft vasculopathy and production of anti-$K^d$ and anti-I-E alloantibody. Autoantibody, assessed by indirect immunfluosrescent binding to nuclear-antigen-expressing HEp-2 cells, also developed. Flow cytometric analysis of CFSE labelled transgenic CD4 T cells confirmed that direct pathway responses were robust immediately after transplant, with extensive division of the transferred ABM CD4 T cells, but were minimal four weeks later. Similarly, strong indirect pathway responses against MHC II alloantigen occurred immediately after transplant, but were surprisingly undetectable at later time points. In contrast, indirect alloresponses against MHC I alloantigen were equally strong at early and late times after transplant. Comparable results were obtained when indirect alloresponses against minor H-Y antigen were studied, although division at five weeks was less marked than immediately after transplant.

**Conclusions:** Our results provide experimental evidence to support the paradigm that direct pathway CD4 T cells responses are short-lived, but also highlight that the duration of indirect pathway responses varies according to target alloantigen. The transient nature of anti-class II responses presumably reflects rapid loss of donor APC after transplantation.

**Infection and malignancy**

**Alsh Suite**

**Thursday 23rd February 2012**

**14.30 – 15.30**

**59**

**PTLD presentation in adult kidney transplant recipients**

Muir Morton[1,2], Paul Klapper[1], Stephen Roberts[1,2], Pamela Vallely[1,2], Beatrice Coupes[1], Kate Ryan[1], Michael Picton[1]

*[1]Manchester Royal Infirmary, Manchester, UK, [2]University of Manchester, Manchester, UK*

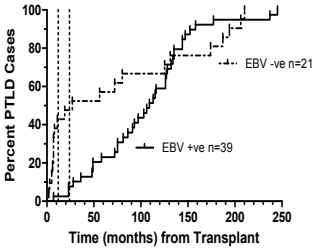
**Introduction**: EBV donor positive recipient negative kidney transplant recipients have increased risk of developing PTLD in the first year after transplant. Changes in PTLD incidence and data on presentations in EBV seropositive and negative recipients in the late post transplant period is more limited.

**Methods:** All adult renal transplantations performed in our unit 28th March 1968 to 31st December 2010 (n=3888) were reviewed. Procedure date and graft and patient outcomes were obtained from our regional tissue typing laboratory database. PTLD cases were identified from pathology databases and incidence rates calculated. Pre-transplant frozen serum samples were retrospectively analysed for IgG antibodies to EBV VCA and EBNA. Timing of PTLD was analysed in relation to recipient EBV serostatus.

**Results:** PTLD occurred in 70/3888 (1.8%) adult kidney transplant recipients, an incidence rate of 2.47 cases per 1000 patient years (95%CI 1.93-3.12). The rate for non-Hodgkin's lymphoma (NHL; monomorphic PTLD) was 1.69 cases/1000 patient years (95% CI 1.25-2.25) and 0.18 cases/1000 patient years (95% CI 0.057-0.41) for Hodgkin's lymphoma (HL). Rate ratio versus the general population in England (2008) was 7.45 (95% CI 5.21-10.33) for NHL and 5.37 (95% CI 1.74-12.55) for HL. Incidence rates of PTLD were high in the first year and highest during the 10th to 14th post transplant years (Table 1). No significant increase in incidence rates was seen for more recent transplant cohorts (Table 1). PTLD occurred in EBV seronegative recipients in 9/21 (43%) during the first transplant year compared to 1/39 (3%) seropositive recipients (relative risk 2.6 95% CI 1.72-3.84 p=0.0015) (Figure 1). Median time to presentation for the seropositive was 109 months (IQR 72-135 months) and 27 months (IQR 7-153) for the seronegative. PTLD occurred in approximately 19% of all our adult EBV seronegative recipients and 1.4% of the seropositive, a 14 fold difference.

| Transplant Year | PTLD Cases per 1000 patient years (95% CI) | | | |
|---|---|---|---|---|
| | 1968-2010 | 1990-1999 | 2000-2004 | 2005-2009 |
| 1st | 3.6 (1.9-6.3) | 4.6 (1.5-10.7) | 5.0 (1.0-14.7) | 4.1 (0.9-12.1) |
| 2nd-4th | 1.6 (0.9-2.7) | 1.0 (0.2-3) | 1.8 (0.4-5.3) | 1.4 (0.2-5) |
| 5th-9th | 2.3 (1.4-3.5) | 2.6 (1.3-4.8) | 3.1 (1.1-6.7) | |
| 10th-14th | 4.4 (2.7-6.8) | 5.5 (3.1-8.9) | | |
| | | | | |

**Conclusions:** The highest rates of PTLD occur 10-14 years post transplant. Recipient EBV serostatus influences time to presentation of PTLD. There is no evidence of increasing incidence of PTLD in more recent transplant cohorts



**60**

## Encapsulating peritoneal sclerosis and transplantation: mortality and risk prediction

David van Dellen, Linda Birtles, Michael Picton, Angela Summers, Bence Forgacs, Ravi Pararajasingam, Afshin Tavakoli, Titus Augustine

*Manchester Royal Infirmary, Manchester, UK*

**Background**: Encapsulating peritoneal sclerosis (EPS), a serious complication of long-term peritoneal dialysis (PD) commonly presents as bowel obstruction due to peritoneal sclerosis with characteristic appearances at laparotomy, requiring enterolysis and peritoneal resection (peritonectomy). It requires multidisciplinary approaches with specialist referral centre input mandatory, due to elective and emergency mortality approaching 15% and 50% respectively. Transplantation's temporal relationship with EPS onset has been studied as immunosuppression and the '2nd hit hypothesis' of peritoneal injury has been recognised as an integral aetiological component of disease development. We aimed to establish mortality and identify potential predictive risk factors for this patient cohort.

**Methods:** Retrospective analysis was completed of EPS cases at a national referral centre over an 11 year period (173 referrals, 133 operated (53 semi-elective; 80 emergencies; Feb 2000-Nov 2011) Post-transplant EPS patients were assessed, with patient and graft survival as primary endpoints. Potential predictive factors for EPS initiation and outcome, including duration from transplant to disease, duration of PD, immunosuppression, pre-operative C reactive protein (CRP) and Albumin were analysed as secondary endpoints.

**Results:** 24 of the operated group had EPS related to transplantation (12M, 12F; median age 49, range 7-69). The overall mortality in this group was 26% (5/24, total mortality 31%, non-transplant mortality 36.8% (p=0.05, Fisher's exact test); elective mortality15%, emergency mortality 56%) All patients had Calcineurin (Tacrolimus) based immunosuppression in the period leading up to EPS diagnosis. 22 had functioning grafts (1 each lost to venous thrombosis and recurrent FSGS) with a median eGFR of 43ml/min (range 3-144) at diagnosis. There were no predictive differences in the surviving and mortality groups for the following parameters (median values): eGFR at time of diagnosis (45±8.1 vs. 35±14.2 ml/min respectively; p=0.08, unpaired t-test); time from transplant to EPS onset (295±57 vs. 344±149.6 days; p=0.37; total group mean time 318±52.5 days); pre-operative CRP (44±28.6 vs. 95±26.5; p=0.9); or length of time on PD (96±14.6 vs. 120±1.6; p=0.46). There was however a tendency towards prognostic differences for age at surgery (45±3.8 vs. 59±4.9; p=0.08) and pre-operative albumin (28±1.4 vs. 22±1.4; p=0.05) EPS surgery does not appear to have an impact on transplant function in surviving patients (median change in GFR 3ml/min; range -14 to 49; p=0.44)

**Conclusion:** EPS can be exacerbated by transplantation and is potentially catastrophic. This is the largest series worldwide of post-transplant EPS and demonstrates improved mortality rates compared to patients with co-existing renal disease. This may reflect a distinct pathophysiological phenomenon but may be due to a reduction in co-morbidities associated with successful transplant. There also appear to be no adverse renal function effects for patients undergoing surgery. Reliable models or methods to predict both disease and outcome of treatment are required, but data suggest that younger age and pre-operative nutritional status are important. Management should undoubtedly focus on dedicated specialised centres providing treatment to improve outcomes.

**Autoimmunity in transplantation 2**

**Boisdale Suite**

**Thursday 23rd February 2012**

**14.30 – 15.30**

**61**

## Interferon-gamma production to non-polymorphic HLA class 2 derived peptides correlates with those to HLA class 1 derived peptides in long-term renal transplant patients

Seema Jham[1,2], Helen Smith[2], Shazia Shabir[1,2], Andrew Bentall[1,2], Simon Ball[1,2]

*[1]Department of Nephrology and Renal Transplantation, Queen Elizabeth Hospital Birmingham, Birmingham, UK, [2]Centre for Inflammation and Translational Research, University of Birmingham, Birmingham, UK*

**Introduction:** In long-term renal transplant patients we have shown a response to non-polymorphic peptides derived from the HLA Class 1 α3-domain: cryptic self-epitopes (AJT 2007). These responses were more common in patients with evidence of deteriorating graft function suggesting that measures of immune function based on responses to these peptides may be used as a basis for an assay of T cell responses to HLA that can be standardized across the population. We hypothesized that long-term renal transplant recipients would also respond to non-polymorphic HLA class 2 derived peptides and these responses would provide an opportunity to refine an assay that could be tested prospectively.

**Methods:** An 'in silico' approach was used to design potential peptide epitopes (13-19 amino acids long) derived from the distal β1 and β2 domain of HLA-DR (sequences with significant homology to other HLA class 2 molecules). This used an EpiMatrix algorithm for epitope prediction and calculated the grand average of hydropathicity index to exclude peptides that were extremely insoluble. In contrast to our approach with class 1 peptides we did not then test for binding of these peptides to class 2 molecules in vitro but used them directly to test PBMC responses in transplant recipients. Peptides were synthesized using Fmoc Chemistry (GL Biochem, Shanghai, China). Recruits were at least 18 months post transplantation, recruited as previously described; interferon $\gamma$ ELISPOT was performed and positive responses defined as previously described. The responses to class 2 peptides were compared to those previously documented against single or multiple class 1 peptides (Transplantation 2011).

**Results:** The mean values for responses to HLA class 1 and class 2 peptides in healthy controls was 2.86 ± 0.35 (n=23) and 2.30 ± 0.13 (n=19) respectively but for transplant patients was 5.54 ± 0.288 ($p<10^{-3}$) and 4.45 ± 0.19 (p=0.02) respectively. The response to HLA class 2 derived peptides correlated with responses to class 1 derived peptides, tested singly or as mixes ($p<10^{-4}$). The numbers discordant between the two groups however, preclude any meaningful interpretation of clinical correlates of differential responses.

| | Response to class 1 peptide | No response to class 1 peptide |
|---|---|---|
| Response to Class 2 peptide | 25 | 7 |
| No response to Class 2 peptide | 2 | 20 |

**Discussion:** These data demonstrate a significant correlation between responses to non-polymorphic HLA class 1 and class 2 peptides. They imply that indirect alloresponses most frequently arise to both class 1 and class 2 peptides, although it cannot be proved that these particular responses are pathogenic. They suggest that a limited peptide set is likely to be sufficient to identify patients who response to such peptides; the clinical significance of which requires testing in a prospective manner.

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**Do reports of randomised controlled trials in solid organ transplantation adhere to the 2010 consort statement? a 3-year overview**

Liang Qin Liu, Liset Pengel, Peter Morris

*Centre for Evidence in Transplantation, The Royal College of Surgeons of England, London, UK*

**Introduction:** The CONSORT statement, which was developed in 1996 and last updated in 2010, was developed with the aim to improve the reporting of randomised controlled trials (RCTs). We assessed to what extent RCTs in solid organ transplantation adhered to the CONSORT statement.

**Methods:** All primary reports of RCTs published between 2007-2009 were included. Two independent reviewers assessed the adherence of the reports to 27 items of the 2010 CONSORT statement.

**Results:** In total, 290 trials were included in the analysis. Most reports were on kidney transplantation (56%), followed by liver (23%), heart (10%) and lung (4%) transplantation. There were 142 single centre and 97 multicentre trials however the number of centres was unclear for a further 51 trials. On average, trial reports described 13 out of 27 CONSORT items. Only 38% of trials described the trial as randomized in the title. CONSORT items relating to the Introduction showed that most reports provided an adequate description of the scientific background (98%) and included specific objectives and hypotheses (97%). CONSORT items relating to the Methods were on average poorly reported. For example, only 35% of trials described how the randomisation sequence was generated. While most reports (94%) provided an adequate description of the statistical analysis, only 33% pre-specified additional analyses and 8% described how they dealt with missing data. Other poorly reported items included specification of primary (52%) and secondary outcomes (42%), and description of sample size calculation (40%). CONSORT items relating to the Results were also poorly reported. A flow chart of participants at each study stage was included in only 32% of reports. In those 151 reports specifying a primary outcome only 17% reported the estimated effect size and its precision. Thirty-six percent of trials analysed the data according to the original assigned groups but only 13 trials (4%) presented this analysis together with a per protocol analysis. The CONSORT item relating to the Discussion indicated that only half of trials (53%) discussed trial limitations. Mandatory trial registration was only included in 17% of reports. RCTs published in journals that endorse the CONSORT statement in their author instructions reported on average 15 out of 27 CONSORT items whilst only 10 out of 27 items were reported for those trials published in journals without CONSORT endorsement.

**Discussion:** Despite the development of guidelines to improve the reporting of RCTs and the endorsement of the CONSORT statement by many medical journals, the reporting of RCTs in solid organ transplantation is still inadequate. Both journal editors and authors show insufficient commitment to use these guidelines when reporting RCTs.

**Clinical renal transplantation**

**Lomond Auditorium**

**Thursday 23rd February 2012**

**16.00 – 17.00**

**63**

## Microcirculation injury in renal transplant patients with *de novo* donor-specific antibodies is predictive of graft loss

Hanneke de Kort, Michelle Willicombe, Paul Brookes, Katherine M Dominy, Jack W Galliford, David Taube, Adam G McLean, Terence H Cook, Candice Roufosse

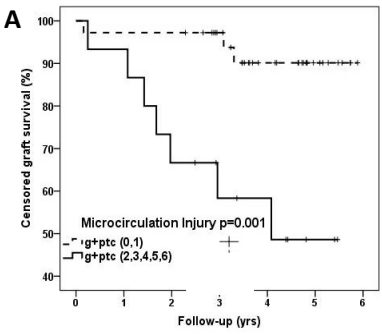
*Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK*

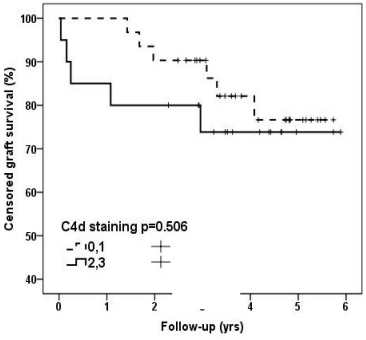
Renal transplant patients who develop *de novo* donor-specific antibodies (DSA) are likely to have worse graft survival; however we can't predict which individual patients are at risk as histological parameters are not well-defined. Microcirculation injury (MI), defined by the combination of glomerulitis (g) and peritubular capillaritis (ptc), is proposed to predict those at risk for graft failure. In renal transplant patients with *de novo* DSA we assessed the value of MI to predict development of transplant glomerulopathy (TG) and long term renal graft survival.

The first indication biopsy after *de novo* DSA development (defined by Luminex single antigen beads, MFI>500) was classified according to Banff '09 (n=51). MI was defined as a g+ptc score ≥2 (n=15) and MI was negative when the g+ptc score did not exceed 1 (n=36). These were compared with g (0,1 vs 2,3) or ptc (0,1 vs 2,3) alone. Median time to *de novo* DSA development was 7.1 (IQR 1.9-17.7) months. Median time to biopsy after DSA development was 1.25 (IQR 0-5.91) months. The Kaplan-Meier product limit method was used to estimate time to transplant glomerulopathy (TG) and renal graft survival, with log-rank test to detect differences between the two groups.

The two g+ptc groups did not differ significantly in clinical donor and recipient parameters pre-and post-transplantation, except that post-transplantation MI+ patients were more likely to have both HLA class I&II *de novo* DSA (40%) than the MI- (11%) ($p<0.05$). The g+ptc score did not correlate with C4d staining pattern ($p=1.00$) and C4d staining was not predictive for graft survival ($p=0.506$) (figure A). MI+ group had worse graft survival ($p=0.001$) (figure B) and were more likely to develop TG ($p<0.001$). The g score alone predicted for the development of TG ($p=0.004$), but not graft survival ($p=0.645$). The ptc score alone did however show the same results as the g+ptc score with worse graft survival ($p=0.001$), and development of TG ($p=0.023$).

In renal transplant patients with *de novo* DSA, microcirculation injury, defined by g+ptc, predicts for worse graft survival, however the ptc score alone is as predictive.




A B

**64**

## B-cell dependent alloreactive IFNγ-producing CD4+ T cells in patients with deteriorating function and antibody-mediated rejection (AMR) on biopsy: correlations with graft outcome and response to therapy

Kin Yee Shiu[1,2], Irene Rebollo-Mesa[1,2], Esperanza Perucha[1,2], Pervinder Sagoo[1,2], Elvira Jimenez-Vera[1,2], H Terence Cook[3], Candice Roufosse[4], Paul Brookes[5], Helen Clarke[3], Sakura Hingley[3], Gagori Bandopadhyay[3], Rob Bowers[6], Jack Galliford[6], David Taube[6], Robert I Lechler[1,2], Maria Hernandez-Fuentes[1,2], Anthony Dorling[1,2]

*[1]MRC Centre of Transplantation, King's College London, London, UK, [2]NIHR Biomedical Research Centre, Guy's & St Thomas' Hospital and King's College London, London, UK, [3]Division of Immunology & Inflammation, Imperial College London, Hammersmith Hospital, London, UK, [4]Dept of Histopathology, Hammersmith Hospital, London, UK, [5]Clinical Immunology Laboratory, Hammersmith Hospital, London, UK, [6]West London Renal and Transplant Centre, Hammersmith Hospital, London, UK*

**Background:** Chronic graft deterioration is a major cause of graft loss. HLA-specific antibodies (HLA Ab) are strongly associated with premature graft loss, and are thought to cause chronic AMR. We hypothesised that interactions between allospecific B and CD4+ T cells, driving cellular effector mechanisms may also play an important role.

**Methods:** 46 patients with chronically deteriorating graft function (defined by linear regression analysis of serial 1/creatinines and/or uPCR>50) had indication biopsy. 33/46 had histological features of AMR e.g. transplant glomerulitis (g)/glomerulopathy (TGP) or peritubular capillaritis, without evidence of acute cellular rejection (ACR) by Banff criteria. The other patients had concomitant AMR/ACR (n=5), or no evidence of AMR or ACR (n=8). Detailed clinical and histopathological data will be presented. Serial blood samples (n=95) were obtained from all patients and PBMC were analysed using a modified ELISPOT assay utilising allogeneic membrane proteins. Donor-specific reactivity (DSR) was defined by the frequency of IFNγ-producing CD4+ T cells, including pre- and post-depletion of CD19+ B-cells and/or CD25+ Tregs. The 33 patients with histological features of AMR yielded 58 viable PBMC samples and this report is focused on these patients.

**Results**: Evidence of DSR (>25 IFNγ-producing cells/million CD4+ cells (spot-forming cells, SFCs) over background) was demonstrated in 22/58 (38%) of samples. B cell depletion significantly reduced the number of SFCs in 16/22 (73%) of the samples with DSR. 18 of the 33 patients with CAMR and deteriorating creatinines were treated with a protocolized 'optimised' immunosuppression protocol comprising FK/MMF followed by Rituximab. Plasma exchange / IVIG and steroids were not part of the protocol. Of these 18, 12 were DSA+, 2 HLA Ab+ only, 9 had TGP, 10 had g and 13 had focal or diffuse C4d positivity. The other 15, who will also be presented in detail, had features of AMR on indication biopsy but had proteinuria only or did not have optimised immunosuppression. Patients were followed up for a median (IQR) of 39.3 (17.6-48.4) months post-biopsy: graft function stabilized in 11/18 (61%), 8/18 (44%) and 7/18 (39%) at 1, 2 and 3 years. Viable PBMC samples were obtained from 14/18 patients at 0.4 (0.3-0.9) months post-biopsy: 4/5 patients with DSR at time of biopsy remained stable at 3 year follow-up, following treatment with FK/MMF/Rituximab. All 4 of these patients were no longer donor reactive on ELISPOT assay after therapy. In contrast, only 2/9 patients without DSR remained stable at 3 years. However, 3/18 (16%) patients experienced serious infections during follow-up.

**Discussion:** These results support our hypotheses that patients with histological evidence of AMR have B cell dependent IFNγ-producing CD4+ T cells, and that these cells play an important role in the progression of CAMR. This study also suggests that in these cases, targeting cellular immunity rather than alloantibody may be an effective treatment for graft deterioration. This assay may be able to help risk-stratify patients into those most likely to benefit from this treatment strategy, and such individualised treatment could reduce the number of patients exposed to adverse effects.

**65**

## Rituximab use in HLA-incompatible transplantation for prevention and/or treatment of antibody mediated rejection – a single centre analysis of 246 patients

Adnan Sharif[1], Nada Alachkar[2], Andrea Zachary[2], Dorry Segev[2], Edward Kraus[2], Niraj Desai[2], Nabil Dagher[2], Andrew Singer[2], Robert Montgomery[2]

*[1]Renal Institute of Birmingham, Birmingham, UK, [2]Johns Hopkins Medical Institutions, Baltimore, USA*

**Introduction:** Anti-CD20 antibody rituximab use has been omitted from some ABO-incompatible programs (including this centre) but its use continues in HLA-incompatible transplantation protocols. However its use in our HLA-incompatible program is not ubiquitous and administration likely reflects clinical perception of perceived immunological risk. It is therefore difficult to ascertain a clear role for rituximab in this specific context. The aim of this study was to review our experience of rituximab utilisation, either pre-emptively pre-transplantation or as rescue therapy for severe antibody-mediated rejection post-transplantation, in HLA-incompatible patients.

**Methods:** We analysed 246 prospectively monitored HLA-incompatible patients from 1998 to 2010 (3 additional HLA-incompatible patients had no documentation regarding use of rituximab and were excluded from further analysis). Protocol biopsies were performed for all patients on months 1, 3, 6 and 12 post-transplantation and 'per cause' biopsies in the context of transplant dysfunction (creatinine rise greater than 20% from baseline). Outcome data (including patient/graft survival, rejection and graft function) was available for all patients with median follow up of 1066 days post-transplantation (range 0 – 4232 days).

**Results:** 45.5% of patients did not receive rituximab pre- or post-transplant, 30.5% received rituximab pre-transplant alone, 16.3% received rituximab post-transplant alone and 7.7% received rituximab pre- and post-transplantation. From patients not receiving rituximab pre-emptively (n=152), 26.3% required it as rescue treatment of severe antibody-mediated rejection post-transplant. Although 94 patients did receive rituximab pre-emptively, 20.2% still required rescue rituximab for severe antibody-mediated rejection. Factors influencing pre-transplant rituximab use included presence of donor-specific antibody to class I and II antigens in conjunction, multiple transplants and concomitant ABO-incompatibility (all $p<0.05$). Patients receiving pre-transplant rituximab were also more likely to receive thymoglobulin induction ($p=0.024$). Patients requiring rescue rituximab had more transplant glomerulopathy at 1-year biopsy compared to other groups (48.3% versus 25.5% respectively, $p=0.004$). Patients requiring rituximab both pre- and post-transplantation had detectable donor-specific antibodies at 12-months post-transplantation. At median of 1063 days post-transplant patients requiring rescue rituximab had worse death-censored graft survival than those not needing rituximab post-transplant (64.7% versus 84.5% respectively, $p=0.012$). Graft function of surviving kidneys was equivalent in all groups.

**Conclusion:** This study highlights our experience of differential rituximab use in positive cross-match patients, identifying factors we perceive as immunologically high risk and confirming the adverse graft survival associated with severe AMR that necessitates need for rescue rituximab treatment.

**66**

## Efficacy of antibody reduction therapies in cardiac transplant recipients treated for antibody mediated rejection

John Smith[1], Priya Siddhanathi[2], Nicholas Banner[1,2], Marlene Rose[1,2]

*[1]Royal Brompton & Harefield NHS Foundation Trust, Harefield, UK, [2]Imperial College, London, UK*

Antibody mediated rejection (AMR) following cardiac transplantation is characterised by clinical evidence of allograft dysfunction, presence of donor specific HLA antibodies (DSA) and changes in the endomyocardial biopsy. The objective of this analysis was to determine the effectiveness of antibody removal therapies in reducing levels of HLA and non-HLA antibodies. 17 patients with 2 weeks to 21 years after cardiac transplantation have been studied. Antibody removal therapy was either plasma exchange (PE, N=5 ), plasma exchange followed by immunoabsorption (PE + IA, N=3) or IA N=9 . Patients were also treated with IvIg and rituximab, and 2 received Bortezomib. HLA antibodies and anti-vimentin abs (AVA) were tested before and after treatment; HLA abs with Labscreen single antigen assays (One Lambda) and AVA with ELISA. HLA ab levels were measured using the cumulative MFI for the mismatched donor antigens. Of patients receiving PE alone, there was a 56.5% reduction in HLA DSA MFI (range -15% - 98.48); 4 patients exhibiting antibody reduction whilst 1 patient showed a slight increase in MFI levels. The mean DSA MFI pre-treatment was 10848 (1509-20728) compared to 7041 (23-20610) post treatment, p=0.213. Patients receiving IA alone showed a significant reduction (77%) in HLA DSA MFI (range 49.4%n – 99.38%). The mean MFI pre-treatment was 15410 (1287-32850) compared to 4648 (8-13341) post treatment p=0.0014. Patients receiving PE+IA showed a 75.8% reduction in HLA DSA MFI (range 64.1%-93.3%), p=0.027. The mean MFI pre-treatment was 8818 (5871-12371) compared to 2353 (392-3717). The two patients receiving bortezomib treatment showed reductions of 87% and 64%. AVA were detected in 9 patients prior to treatment (6 IgM, 2 IgM & IgG, 1 IgG). There was a 87% reduction in IgM AVA titres after treatment and 74% reduction in IgG titres. The mean titre of IgM AVA pre-treatment was 371 (range 166-748) compared with 42 (4-108) after treatment, p=0.0028. The mean titre of IgG AVA was 1100 (range 190-2782) prior to treatment compared to 105 (3-242) after treatment, p-0.36. The time from antibody detection to treatment was 5.4 days (range 0-14) for those patients undergoing PE, compared to 275 (range 4-693) for those undergoing IA treatment, p=0.052. There was also a trend for patients receiving IA treatment to have undergo more cycles of treatment (14 cycles, range 4-34) compared to those patients undergoing PE (5 cycles, range 3-7), p=0.063.

**Conclusion:** All treatments reduce HLA and non-HLA ab levels although for some patients repeated cycles of treatment are necessary. Plasma exchange is less successful but is often used as an emergency treatment.

**Basic science parallel session/free communications**

**Alsh Suite**

**Friday 24th February 2012**

**09.30 – 11.15**

**67**

**Regulatory B cells promote long-term allograft survival**

Mekhola Mallik, Chris J Callaghan, Margaret C Negus, Eleanor M Bolton, J Andrew Bradley, Gavin J Pettigrew

*University Department of Surgery, NIHR Comprehensive Biomedical Research Centre, Cambridge, UK*

**Introduction:** Despite improvements in preventing acute allograft rejection, late graft loss remains the major problem in clinical transplantation. IL-10 secreting B regulatory cells (Bregs) have been described recently that ameliorate autoimmune disease progression. Here, we study whether Bregs can prevent chronic rejection using a well-characterised murine model of cardiac allograft vasculopathy.

**Methods:** Bregs were generated in vitro by culturing naive C57Bl/6 (B6) B cells with anti-CD40 monoclonal antibody for 3 days. IL-10 within culture supernatant was assayed by ELISA. Cultured B cells from IL-10 deficient B6 mice were used as controls. The ability of Bregs to ameliorate allograft vasculopathy was tested by adoptive transfer into B6 recipients of MHC class II-mismatched heart allografts the day after transplantation. Graft rejection kinetics, effector autoantibody responses, and the development of allograft vasculopathy were then monitored.

**Results:** Bm12 heart allografts provoke long-lasting autoantibody responses in naïve B6 recipients, are rejected slowly (median survival time (MST), 57 days (n=5), and develop severe allograft vasculopathy. Administration of control cultured B cells from IL-10-deficient mice (n=4) at time of transplant hastened heart graft rejection (MST 28 days, p=0.03). In contrast, culture of naïve B6 B cells with anti-CD40 induced release of IL-10 into culture supernatant and their transfer into B6 recipients of bm12 heart grafts (n=4) abrogated the autoantibody response, and prolonged allograft survival until experimental termination at day 100 (p=0.08). Histological assessment of explanted allografts at day 100 confirmed a marked reduction in severity of allograft vasculopathy (luminal stenosis = 4.3%, p=0.00).

**Conclusion:** This is the first demonstration of Breg-mediated inhibition of solid allograft rejection, and highlights the potential for using B lymphocytes as a cellular therapy to prolong clinical allograft survival.

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**Elevated BAFF correlates with deteriorating renal graft function**

Louise Onions[1], Arun Gupta[2], Raj Thuraisingham[3], Anthony Warrens[1, 3]

*[1]Centre of Translational Medicine and Therapeutics, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, UK, [2]Clinical Transplantation Laboratory, Royal London Hospital, London, UK, [3]Department of Nephrology, Royal London Hospital, London, UK*

**Introduction:** The B cell activating factor (BAFF) of the tumour necrosis family is essential for B cell selection, differentiation and survival[1] and therefore an important regulator of B cell immunity. In animal models, it has been shown that excess BAFF can lead to the development of autoimmune disorders[2] and that BAFF is upregulated in patients with SLE[3]. In renal transplant patients, increased levels of BAFF were detected in those treated with Campath-1H[4]. However, a key question remains as to whether the dysregulation of B cell activation could be a contributing factor in alloantibody production and if aberrant expression of BAFF correlates with allograft function. Given this and the association of B cells in renal allograft rejection, we investigated if BAFF and its receptor are differentially expressed depending on the level of function of the allograft.

**Method:** Peripheral whole blood was collected from renal transplant recipients with deteriorating (gp 1), stably impaired (gp 2) and well-functioning (gp 3) grafts a minimum of one year post-transplant. $CD19^+$ cells were isolated by positive selection, stained with anti-human CD19 & BAFF-R (BD Biosciences) and analysed by flow cytometry. Serum BAFF levels were measured by ELISA (R&D Biosysytems). The presence of HLA antibodies were assessed using Luminex technology and HLA Single Antigen beads (One Lambda).

**Results**: Patients in gp1 (n=23) had significantly higher serum BAFF levels than those in gp 2 (n=8) and gp 3 (n=14) (mean values 1706pg/ml, 675pg/ml, 774pg/ml respectively; gp 1 vs. gp 2 p=0.04, gp 1 vs. gp 3 p=0.02). In addition, expression of BAFF-R on $CD19^+$ cells is downregulated significantly in gp 1 patients (60%) compared to gp 3 patients (73.7%; p=0.02) but not gp 2 patients (69.8%; p=0.27). Stratified by HLA antibody status of study patients, donor-specific antibodies (DSA) were only detected in gp 1 patients (DSA, 41%, non-DSA 27%, negative 32%) compared to gp 2 (non-DSA 14%; negative 86%) and gp 3 patients (non-DSA 21%; negative 79%). However, no correlation was found between the presence of HLA antibody (DSA or non-DSA) and high expression BAFF (>1223pg/ml, the overall mean) or downregulation of BAFF-R (<68.3%, the overall mean).

**Conclusion**: B cells are increasingly recognised as key mediators in allograft injury. These data show that expression of BAFF and its receptor significantly correlate with renal graft function, suggesting that measurement of BAFF could act as a biomarker of deteriorating graft function. However, it does not appear that BAFF is a mediator in enhanced alloantibody production. Further research into B cell regulation and their dependence on BAFF expression could provide important information as to whether B cell survival factors should be utilised as potential markers of humoral rejection.

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## FcγRIIb-mediated inhibition of mouse cardiac allograft rejection is determined by the magnitude of T cell help

Chris Callaghan[1], Thet Su Win[1], Reza Motallebzadeh[1], Tom Conlon[1], Ines Harper[1], Siva Sivaganesh[1], Eleanor Bolton[1], Andrew Bradley[1], Rebecca Brownlie[2], Ken Smith[2], Gavin Pettigrew[1]

*[1]Department of Surgery, University of Cambridge, Cambridge, UK, [2]Department of Medicine, University of Cambridge, Cambridge, UK*

**Introduction:** By modulating the response to immune complexes, activatory and inhibitory Fc receptors are critical components of humoral immunity. Mice lacking the only inhibitory Fc receptor, FcγRIIb, have augmented autoimmune and antibacterial responses, but the role of FcγRIIb in allograft rejection has yet to be determined.

**Methods:** FcγRIIb signalling in cardiac allograft rejection was examined in murine models of acute (MHC-disparate) or chronic (selective MHC-mismatch) rejection and survival compared in WT Bl/6 (H-$2^b$), FcγRIIb$^{-/-}$ Bl/6, and transgenic Bl/6 recipients with increased macrophage (MPTG) or B cell (BTG) FcγRIIb expression. MHC class II-mismatched bm12 heart graft rejection is characterised by progressive allograft vasculopathy associated with development of anti-nuclear autoantibody (quantified by indirect immunofluorescent staining of HEp-2 cells). Humoral responses to BALB/c (H-$2^d$) or MHC class I-mismatched B6.$K^d$ hearts were assessed by anti-$K^d$ IgG ELISA; serum IgG responses to CBA/Ca (H-$2^k$) hearts were assayed using flow cytometry. Additional T cell help for alloantibody production was provided in some experiments by the transfer of I-$A^b$-restricted, $K^d$ peptide-specific, TCR75 CD4 T cells.

**Results:** FcγRIIb$^{-/-}$ mice rejected either BALB/c hearts or CBA/Ca hearts acutely, at the same tempo as WT B6 and BTG recipients, and with similar IgG alloantibody responses. In contrast, chronic rejection of bm12 cardiac allografts was accelerated in FcγRIIb$^{-/-}$ mice (MST 28d vs MST >50d in WT recipients, $p<0.01$), with more severe graft vasculopathy and stronger autoantibody responses. Conversely, overexpression of FcγRIIb in MPTG and BTG recipient mice delayed bm12 heart graft rejection and inhibited autoantibody production, albeit the differences did not reach statistical significance. Similarly, whereas B6.$K^d$ hearts survived indefinitely in B6 mice (MST >100d), these hearts developed vasculopathy and rejected when transplanted into FcγRIIb$^{-/-}$ mice (MST 88d; $p<0.01$), with much stronger alloantibody responses. To test the hypothesis that the different impact of FcγRIIb signalling in acute and chronic rejection related to differences in alloantigen stimuli and the magnitude of available T cell help, FcγRIIb$^{-/-}$ and B6 recipients of B6.$K^d$ grafts received $10^3$, $10^4$, or $10^5$ TCR75 CD4 T cells iv. As T cell help increased, the discrepancy in IgG anti-$K^d$ responses and B6.$K^d$ allograft survival between B6 and FcγRIIb$^{-/-}$ recipients decreased, until no difference was apparent when $10^5$ cells were transferred.

**Discussion:** FcγRIIb signalling modulates chronic but not acute rejection, most likely reflecting differences in inhibition of effector antibody responses that become apparent when T cell help is limited. Polymorphisms in FcγRIIb gene expression exist in humans and are thus likely to influence allograft survival.

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## Ischaemia-reperfusion injury accelerates human antibody-mediated transplant arteriosclerosis

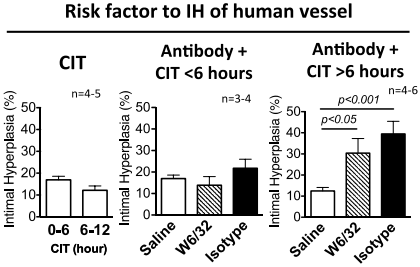
Ryoichi Goto[1], Fadi Issa[1], Sebastiaan Heidt[1], David Taggart[2], Kathryn Wood[1]

*[1]Transplantation Research Immunology Group, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK, [2]Department of Cardiovascular Surgery, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK*

**Background:** Transplant arteriosclerosis (TA) is the hallmark lesion of chronic allograft dysfunction (CAD). The pathogenesis of TA is multifactorial, and occurs even in situations where alloimmune responses are inhibited. TA-associated intimal hyperplasia (IH) may develop and contribute to CAD. To investigate the ***hypothesis*** that ischaemia-reperfusion injury and antibody-mediated damage contribute to the development of TA, we have used *in vivo* humanised mouse model where the adaptive immune response is deficient.

**Materials and methods:** Branches of the human internal mammary artery were procured, with informed consent, from live human donors undergoing cardiac surgery. These were stored in4.0% phenoxybenzamine saline solution on ice and used within 12 hours. Balb/c $Rag2^{-/-}c\gamma^{-/-}$ mice, deficient in T, B and NK cells, were each transplanted with a human infrarenal aortic interposition vessel graft. Groups of mice were divided into those transplanted within 6 hours of vessel procurement or between 6-12 hours of procurement. Transplanted mice received weekly intravenous injections of purified anti HLA class I antibody (w6/32), isotype control antibody, or saline, from 7 to 42 days weekly after transplantation. On day 42, human vessels were harvested and assessed for the degree of intimal expansion as a measure of IH by histological analysis.

**Results:** First, we assessed the influence of prolonged cold ischaemia time (CIT, >6 hours) on the development of IH in mice not receiving antibody, and found that this was not sufficient to induce IH (*Figure below*, left panel). Moreover, in mice that received antibody where vessels were transplanted within 6 hours of procurement, no effect of antibody on IH was observed (*Figure below*, middle panel). In contrast, in vessels exposed to >6 hours cold ischaemia, both w6/32 and isotype control antibodies promoted increased IH (*Figure below*, right panel). Importantly, we confirmed by histological analysis that the isotype control antibody did not cross-react with human vessels. Interestingly, the number of mouse Fc-receptor positive cells was significantly increased in human vessels exposed to >6 hours cold ischaemia, but only in the presence of antibody.




**Conclusion:** These data suggest that that antibody, regardless of its specificity, may promote IH in human vessels that are injured through cold ischaemia, via innate immune mechanisms involving Fc-receptor positive cells. This highlights the importance of controlling the degree of cold ischaemia in clinical transplantation in an effort to reduce the risk of TA development.

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**A novel method to detect HLA-specific B cells In renal transplant recipients**

Louise Onions[1], Paul Brookes[2], David Taube[3], Anthony Warrens[1]

*[1]Centre of Translational Medicine and Therapeutics, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, UK, [2]Department of Clinical Immunology, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK, [3]Imperial College Kidney & Transplant Centre, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK*

**Introduction:** The presence of donor-specific HLA antibodies is associated with acute and chronic renal allograft rejection. In an effort to minimise their damaging effects, highly sensitive and specific solid-phase assays have been developed to aid their detection in patient serum. However, investigating HLA antibodies in serum alone will only reflect the presence of B cells actively secreting antibody and may not reflect the overall B cell sensitisation status, such as the potential presence of memory B cells. Although such cells are very rare in the circulation; a more sensitive approach would be to identify circulating HLA-specific B cells as a method of assessing B cell alloreactivity between recipient–donor pairs.

**Method:** Peripheral whole blood was collected from HLA-A*0201 sensitised renal transplant recipients a minimum of one year post-transplant. Non-sensitised healthy males served as controls. PBMCs were prepared by Ficoll-Hypaque separation and $CD19^+$ cells isolated by positive selection. A minimum of $10^6$ $CD19^+$ cells were stained with anti-human CD19 followed by Luminex Single HLA Antigen HLA-A*0201 beads (One Lambda) and analysed by flow cytometry. All cells with a staining intensity higher than the upper limit obtained using the non-sensitised control were considered positive.

**Results:** Sensitised renal transplant recipients known to have HLA-A*0201 antibody (MFI >1000) as previously defined by Luminex technology were tested for the presence of HLA-A2 specific B cells. Using beads coated with HLA-A*0201 it is possible to show the presence of a small population of B cells capable of binding to the beads as assessed by flow cytometry. The data shows a significantly higher proportion of $CD19^+$ cells which bind HLA-A2 beads in sensitised (n=5) compared to non-sensitised subjects (n=5; 0.124 ± 0.049% and 0.042 ± 0.008%; p=0.007 sensitised patients and non-sensitised controls respectively).

**Conclusion:** This preliminary data shows differences in B cell reactivity in sensitised patients compared to controls which can be effectively demonstrated using a simple technique. This method can detect and quantify HLA-specific B cells which could provide useful information for predicating the B cell response to donor antigens and be a valuable tool in both the pre- and post-transplant setting.

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## Complement (C1q)-fixing de novo donor-specific antibodies predict renal allograft loss, antibody mediated rejection and transplant glomerulopathy

Christopher Lawrence, Michelle Willicombe, Paul Brookes, Eva Santos-Nunez, Canidce Roufosse, Terry Cook, Anthony Warrens, David Taube

*West London Renal & Transplant Centre, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK*

**Introduction:** Donor specific antibodies (DSA) are detrimental to renal allograft function and survival. The purpose of this study was to investigate the complement activating properties of de novo DSA occurring after renal transplantation.

**Methods:** Between November 2005 and January 2010 469 patients were transplanted at our centre using Alemtuzumab induction, tacrolimus monotherapy and steroid avoidance. De novo DSA (measured by Luminex) were detected in 70/469 (14.9%, m49:21f, age 46.9± 14.5 years, follow up 29.6± 16.5 months). Stored serum samples from patients with de novo DSA were retrospectively analysed to determine complement (C')-activation by detection of C1q deposition on the surface of Luminex beads. Briefly 0.5µL of C1q is mixed with 2.5µL heat inactivated serum and 2µL antibody detection beads. After incubation phycoerythrin-labelled anti C1q is added, after washing the beads are analysed by Luminex.

**Results:** Of the 70 patients with de novo DSA 43 (61%) patients had DSA with cumulative Mean Flourescent Intensity (MFI) >1000. 40 (57%) had Class I DSA (C I, MFI 2393± 2599), 48 (69%) patients Class II DSA (C II 2619± 3098), 18 (26%) patients had both Class I&II DSA (C I&II). In 23(32.9%) patients the C'-fixing DSA was positive (C' Pos).

| | Graft Survival (%) | | | AMR-Free Survival (%) | | | TG-Free Survival (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| ***DSA*** | **1Yr** | **3Yr** | **p** | **1Yr** | **3Yr** | **p** | **1Yr** | **3Yr** | **p** |
| C I | 95.5 | 95.5 | | 86.4 | 80.2 | | 100 | 100 | |
| CII | 90 | 79.6 | | 69.6 | 64.6 | | 100 | 85 | |
| CI&II | 83.3 | 67.3 | <0.05 | 27.8 | 20.8 | <0.001 | 61.3 | 42.9 | <0.001 |
| ***MFI*** | | | | | | | | | |
| <1000 | 96.3 | 86.7 | | 84.7 | 76.2 | | 100 | 90.5 | |
| >1000 | 86 | 76 | 0.06 | 71.7 | 49 | <0.005 | 84.5 | 71.7 | <0.05 |
| ***C'DSA*** | | | | | | | | | |
| C' Neg | 93.6 | 90.4 | | 93.6 | 90.4 | | 97.7 | 91.3 | |
| C' Pos | 82.6 | 71.2 | <0.005 | 82.6 | 63.3 | <0.005 | 75.4 | 54 | <0.001 |

C1q-fixing de novo DSA has a sensitivity of 0.52 and specificity of 0.80 for predicting antibody mediated rejection (AMR), this compares favourably with CI&II DSA (0.77 and 0.6) and with MFI>1000 (0.82 and 0.54 respectively).

**Discussion:** C1q-fixing de novo DSA have previously been shown to predict late graft loss and transplant glomerulopathy but this is the first study to our knowledge to show that the presence of C1q-fixing DSA results in early graft loss and AMR, in addition to transplant glomerulopathy (TG). Patients with graft dysfunction, de novo DSA and evidence of C'-activation (C4d staining on biopsy or C1q-fixing DSA by Luminex) may benefit from novel treatments such as the monoclonal antibody directed against C5a, Eculizumab.

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**Changes in echocardiographic abnormalities following kidney transplantation**

Tuan Ismail[1], Sofia Rocha[1], Nihil Chitalia[1], Nicos Kessaris[1], Mysore Phanish[2], Juan Carlos Kaski[1], Rajan Sharma[1], Debasish Banerjee[1]

*[1]St. George's Healthcare NHS Trust, London, UK, [2]Epsom and St. Helier University Hospital, London, UK*

**Background**: Echocardiographic abnormalities are predictors of cardiovascular (CV) morbidity and mortality in patients with chronic kidney disease. CV events in patients with chronic kidney disease significantly improve following kidney transplantation. The reason for this improvement remains unclear and the data on long-term effects of kidney transplantation on echocardiographic progression and changes is limited. This study aimed to assess the evolution of echocardiographic variables in kidney transplant patients compared to patients who remain on the waiting list.

**Methods:** The study cohort include patients from one kidney transplantation centre(St George's and St Helier Hospitals) with two echocardiograms at least one year apart between the period of January 2004 to December 2010. Transplant patients were included if they had the second echo at least one year post transplantation.

**Results**: We assessed 223 patients (males: 52.2 % females: 47.5%); of these, 191 patients remained on the waiting list (83% on dialysis; 62% on HD, 21% on PD, and 17% Predialysis) and 32 patients underwent kidney transplantation.

| Variables | **Waiting-list patients n=191** | | | **Transplanted patients n=32** | | |
|---|---|---|---|---|---|---|
| | Baseline ECHO | Follow up ECHO | p value | Baseline ECHO | Follow up ECHO | p value |
| **IVS (cm)** | 1.12±0.24 | 1.15±0.24 | 0.06 | 1.15±0.26 | 1.13±0.23 | 0.546 |
| **PWT (cm)** | 1.06±0.24 | 1.09±0.23 | 0.051 | 1.1±0.26 | 1.05±0.23 | 0.283 |
| **LVDD (cm)** | 4.8±0.56 | 4.76±0.62 | 0.37 | 5.0±0.76 | 4.87±0.67 | 0.377 |
| **LVMI (g/m)** | 139±51 | 144±50 | 0.165 | 153±53 | 140±51 | 0.102 |

On follow up echocardiograms for waiting-list patients the mean interval between two echocardiogram was 30±15 months. There was slight increase in LVMI (139±51 to 144±50; p=0.16). In the transplant patient there was mild decrease in LVMI (153±53 to 140; p=0.10). The mean LVMI change in the waitlist group was 4.79 g/m and the mean LVMI change for the transplant group was -13.84 g/m. The mean change in LVMI between the wait list compared to the transplant patients was significant (p=0.039).

**Discussion**: This study suggests there is an improvement in Left Ventricular Mass in transplant patients compared to the waiting-list patients. This could at least partly explain the improvement in post-transplant patient cardiovascular morbidity and mortality.

**Posters**

**Exhibition Hall**

# Basic Science

**1**

**Strategies for inhibition of chemokine (CCL2) mediated monocyte migration**

Mahsa Saleki

*Newcastle University, Newcastle upon Tyne, UK*

**Introduction:** CCL2 mediated migration of monocytes has been shown to play an integral role in the pathogenesis of lethal reperfusion injury (LRI) following cardiopulmonary bypass operation. The study aims are the *in vitro* analysis of the properties of synthetic CCL2 inhibitors and GAG binding peptides in inhibiting CCL2 mediated monocyte migration, as potential therapeutics for the treatment of LRI.

**Methods:** THP-1 cells were used as a model of human monocytes. Chemotaxis assays were used in initial screening of the inhibitory effects of synthetic CCL2 inhibitor compounds (C1-8) and GAG binding peptides (P1-5) on (10nM) CCL2 mediated monocyte migration. In the next stage of experiments the most potent compounds and peptides were tested using activated trans-endothelial chemotaxis (*in vitro* model of inflamed capillary wall) in the presence of 30nM of CCL2.

The inhibitory effects of the most potent compound on monocyte adhesion to V-CAM1 under flow and shear stress conditions was analysed using the Cellix system. Western blotting was used to analyse CCL2 mediated monocyte expression of p-ERK1/2, following stimulation with 10nM of CCL2 in the presence of synthetic compounds.

**Results:** P1-5, C1 and C5 were most potent CCL2 inhibitors. C5 mediated statistically significant reduction ($p<0.05$) in the number of adherent monocytes to VCAM-1 coated channels in the presence of 10nM of CCL2 and 50μM of C5. Western blotting showed no inhibitory effects on CCL2 mediated monocyte expression of p-ERK1/2, following 5 minute stimulation with 10nM of CCL2 in the presence of C1 or C5.

**Discussion:** The *in vitro* analysis of synthetic CCL2 inhibitors and GAG binding peptides has shown these strategies to be effective in blocking CCL2 mediated migration of monocytes. Further studies are needed to define the mechanism of action of these compounds and will aid their development as therapeutics for the prevention of lethal reperfusion injury in both transplantation and cardiac operations.

**2**

## The role of anti-HLA class I antibodies in chemokines mediated leukocytes migration post transplantation

Fatmah Naemi[1], Vaughan Carter[2], John Kirby[1], Simi Ali[1]

*[1]Newcastle University, Newcastle Upon Tyne, UK, [2]National Blood Service, Newcastle upon Tyne, UK*

**Background**: The development of donor specific HLA class I antibody after organ transplantation has been associated with acute rejection and is a risk factor for chronic rejection. The infiltration of circulating leukocytes into transplanted allograft is associated with antibody mediated rejection. However, the potential of anti-HLA class I antibodies in mediating this process is not fully understood. The aim of this study was to examine the role of anti-HLA class I antibody in modulating endothelium-leukocyte interaction focusing on endothelial transduction pathways, adhesion molecule up-regulation and inflammatory cytokines-chemokines expression.

**Methods**: Human microvascular endothelial cells (HMEC-1) were typed for the classical HLA class I molecules by using PCR-SSP method. Cells stimulated with anti-HLA class I antibody (W6/32, 12µg/ml) or allospecific antibodies from sensitized patients (n=6) were examined for the upregulation of endothelial adhesion molecules (VCAM-1, ICAM-1) by flow cytometry and induction of cytokines and chemokines by q-PCR. Using *in vitro* flow based adhesion assay (Cellix platform), the potential of HLA class I antibodies in enhancing leukocytes adhesion was assessed.

**Results**: HMEC-1 cells treated with W6/32 antibodies resulted in the activation of various cell signalling kinases, including transcription factor; CREB in PKA dependent pathway as verified by using PKA inhibitor (H89). Moreover, treatment of cells with W6/32 antibodies significantly induced the expression of cell surface VCAM-1 and ICAM-1 which peaked at 12 and 8 hours respectively, compared to isotype treated group ($p<0.01$ & 0.001). Allospecific antibodies from sensitized patients (A1, A28, B35, B58, CW4, CW6) also induced significant expression of these adhesion molecules after 24 hours treatment. In addition, exposure to W6/32 antibodies upregulated the expression of endothelial cytokines such as IL-6 and various chemokines; CXCL8, CXCL1, CXCL10 and CCL5. The expression of CXCL8 appeared to be dependent on antibody concentration. Allospecific antibodies induced significant expression of CXCL8 (2-11 fold, $p<0.001$). Chemotaxis assay demonstrated that the conditioned media from W6/32 treated endothelial cells stimulated a significant monocyte migration ($p=0.011$) compared to isotype treated group. Under flow based adhesion condition, endothelial cells treated with W6/32 antibodies significantly increased the adhesion of monocytes compared to isotype treated group at 0.5 dyne/cm$^2$ within 5 minutes ($p<0.0001$).

**Conclusion**: These findings suggest the ability of anti-HLA antibodies in modulating the chemokine mediated adhesive interactions between endothelium and circulating leukocytes. Work is ongoing to evaluate the potential of heparinoids in blocking this interaction as a novel approach to improve allograft survival.

**3**

**Accelerated renal senescent phenotype in the AS/AGU Rat – a novel in-vivo model**

Marc Gingell-Littlejohn, Paul G Shiels, Marc J Clancy

*University of Glasgow, Glasgow, UK*

**Introduction:** The mutant rat sub-strain (AS/AGU) arose spontaneously as a result of a specific single gene mutation (PKCγ) in a colony of Albino Swiss (AS) rats. It was initially characterised as giving rise to a parkinsonian movement disorder (Craig NJ et al, Nat Neurosci 2001 Nov;4(11):1061-2). PKCγ is a member of an important family of cell signalling molecules with a wide range of functions in various cell types. This knowledge enhances the importance of this strain, as it provides a defined molecular change from which all subsequent physiological and pathological changes derive. The strain was demonstrated to display accelerated bio-ageing in the kidney (Wright et al: unpublished data) and we have subsequently performed glomerular filtration (GFR) and biochemical studies to phenotypically characterise this model.

**Methods:** 0.2% w/v Flourescein Isothiocyanate Inulin (FITC-Inulin) was used for GFR experiments by constant infusion through a central vein under general anaesthesia. Measurements of fluorescence in the urine of each kidney and plasma at equilibrium provided quantitative data on the filtration process across the glomerulus. Laboratory biochemical analysis was performed on separated plasma and urinary samples.

**Results:** Biochemical analysis showed a significant difference in both sodium and urea concentrations between the strains (n=61), with mutant AS/AGU having higher mean urea concentrations (8.67mmol/L vs 7.23mmol/L, p=0.009) and lower mean sodium concentrations (144.7mmol/L vs 146.9mmol/L, p=0.023). There was a proportional increase in GFR with increasing weight of the animal (n=24, p=<0.001) and a significant difference in GFR/100gr body weight between AS and AS/AGU rats in female rats (n=11, p=0.028). The GFR difference between AS and AS/AGU in the total experimental cohort approached significance (n=24, p=0.065)

**Conclusions:** This strain is a unique and useful model of human diseases of ageing and organ dysfunction in particular, for renal dysfunction and transplant related pathologies. It is postulated that the PKCγ mutation impairs the sodium-urea counter transporter in the rat inner-medullary collecting duct and in conjunction with the difference in GFR between both strains, confirms the premature senescent genotype of the mutant AS/AGU strain. This provides promising ground for future transplant-related scientific research.

**4**

**Contribution of MHC disparity to development of chronic allograft vasculopathy**

Paula Blair[1,2], R Motallebzadeh[1], T Conlon[1], M Negus[1], S Rehakova[1], J A Bradley[1], G J Pettigrew[1], E M Bolton[1]

*[1]Dept of Surgery, University of Cambridge, Cambridge, UK, [2]University of Glasgow, Glasgow, UK*

**Introduction:** Chronic allograft vasculopathy (CAV) is characterised by inexorable loss of transplant function that is unresponsive to immunosuppression. There is a strong association between the presence of circulating alloantibodies and CAV, but recent studies also imply an important role for autoantibody in CAV. Here we examined the contribution of MHC disparities to development of CAV and their ability to provoke a post-transplant antibody response, using selected mouse strain combinations that represent a class I, class II or combined class I and class II MHC incompatibility, together with priming for invoking a memory response.

**Methods:** The relative contribution of MHC disparities was compared by histological assessment of vessel luminal occlusion in vascularised heart grafts removed at ≥day 50 post-transplant. Circulating levels of alloantibody were measured by ELISA (anti-$K^d$) or FACS in consecutive serum samples from C57Bl/6 (B6) recipients. HEp-2 slides were used to analyse autoantibody production.

**Results:** B6 recipients of B6.$K^d$ heart grafts (MHC class I mismatch) had low levels of CAV (25% luminal occlusion, n=11) while a class II mismatch resulted in 38% occlusion (bm12 to B6, n=5); neither was associated with alloantibody production but bm12 hearts elicited moderate levels of autoantibody. A combined class I and II mismatch caused only a slightly higher degree of CAV and was again associated with no alloantibody but moderately high levels of circulating autoantibody (bm12.$K^d$ to B6, n=8, 42% occlusion). Memory responses were induced by priming with bm12 CD4 T cells, known to induce preformed autoantibody and to enhance CAV and graft rejection in class II-disparate recipients (*Win et al, Circ Heart Fail 2009;2:361*), or with $K^d$ peptide to enhance alloantibody in class I disparate recipients, or with both. Class I-disparate graft recipients primed with $K^d$ peptide (n=6) had initially high alloantibody but low autoantibody, and developed moderately severe CAV although heart grafts survived >50d. When primed for high autoantibody (with bm12 CD4s, n=3) a similarly severe CAV developed and interestingly, was accompanied by increasing anti-$K^d$ but no graft loss. Dual priming (n=4) caused the most severe CAV with one graft lost by d50.

**Conclusions:** In non-primed mice, severity of CAV was associated with increasing MHC disparity, but also with increasing auto- but not allo-antibody levels; however, priming for either auto- or alloantibodies masked any relative contribution of MHC disparity to the development of CAV. Overall, these findings imply that both auto- and allo-antibodies contribute to CAV.

**5**

## Correlation between endothelial gene expression and histological findings in renal transplant biopsies in patients with *De Novo* DSA

Katherine M Dominy, Candice Roufosse, Hanneke De Kort, Michelle Willicombe, Paul Brookes, Jacques Behmoaras, Jack Galliford, Peter Choi, Tom Cairns, David Taube, Terence Cook, Adam Mclean

*Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK*

Current diagnosis of antibody mediated rejection (AbMR) requires the presence of donor specific antibody (DSA), positive staining for C4d and histological evidence of tissue damage, but recent identification of AbMR cases that are negative for C4d staining indicate a need for additional methods of diagnosis.

Microarray analysis of endothelial associated transcripts has identified a panel of genes with increased expression in individuals with AbMR. In many centres it is not practical to carry out diagnostic microarray analysis of individual patients, and it has been proposed that quantitative real time PCR of selected genes, with the most highly elevated expression, would provide the same sensitivity and specificity for AbMR.

To investigate this hypothesis, RNA was extracted from 31 renal transplant biopsies for cause from 24 patients with previously detected *de novo* DSA (Luminex detection). RNA was reverse transcribed prior to quantitative real time PCR using 10ng cDNA per reaction. Gene expression of 5 genes – *CDH5*, *DARC*, *PECAM1*, *SOX7* and *vWF,* was normalised to the reference gene *HPRT1* and measured relative to Stratagene QPCR Reference RNA.

Microcirculation inflammation, as shown by the presence of glomerulitis (g) and peritubular capillaritis (ptc), is known to be associated with AbMR. Higher PTC scores correlated with increased expression of *PECAM1* (p=0.017) and *DARC* (p=0.017, Jonckheere-Terpstra test for ordered alternatives). Higher g scores correlated with *vWF* expression (p=0.045). A combined PTC and G score grouped into 0-2 or 3-6, correlated with expression of *vWF* (p=0.025), *SOX7* (p=0.023) and *PECAM1* (p=0.018, Mann-Whitney U test, figure 1).

No significant correlation was found between C4d staining and gene expression.

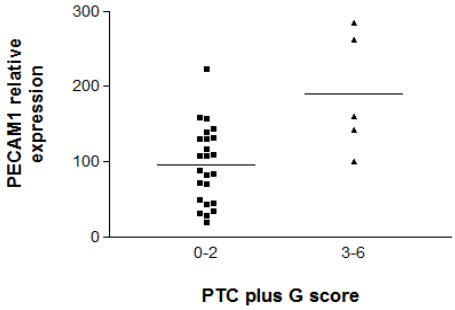


Figure 1: *PECAM1* expression compared to histology score for microcirculation injury.

These data show that microcirculation injury, as detected by histological lesions, correlates with gene expression. This initial finding supports the hypothesis that gene expression could be a useful additional parameter to indicate AbMR but further analysis of a larger data set is required to show any diagnostic benefit of this type of assay.

# Ethics 1

**6**

**Changing opinions to organ transplantation?**

CHD Lawrence[1], Patrick Ward[2], Isobel Chen[3]

*[1]NHS Forth Valley, Scotland, UK, [2]Imperial College Healthcare NHS Trust, London, UK, [3]University of Edinburgh, Scotland, UK*

**Background:** Increasing numbers of people in the UK await organ transplantation despite the shortage of donor organs. Various schemes have been proposed to improve donation rates, ranging from donor incentives to changes in consent, and most recently the provision of funeral costs to donor families. Our study compares attitudes towards transplantation in 2004 with 2010, to establish whether the introduction of the organ donation taskforce, the high profile media coverage and the legal adjustments implemented during that period, have resulted in any significant changes in opinion.

**Method:** A questionnaire examining attitudes towards organ transplantation was distributed to 40 lawyers, 40 medical students, 40 transplant team members and 40 members of the general public, once in 2004 and again in 2010. The questionnaire comprised sixteen questions exploring the ethics of organ transplantation, each with yes or no responses. The 2004 and 2010 answers were compared to identify significant changes in opinion towards transplantation. Results were analysed using the chi square test.

**Results:** Comparison of question responses, with all groups included, between 2004 and 2010 showed no statistically significant differences in 15 of the 16 questions. There was a significant ($p < 0.05$) increase in the number of people supporting the statement "It is unethical to sell or buy organs even if all other alternatives to increase donor organs have not been sufficient to meet the demand". Concerning the most recent organ donation proposal, there was no significant increase (16.9% in 2004 versus 17.9% in 2011) in the number of people in favour of payments to the "family of an individual who is going to die, who agrees to donate".

**Discussion and Conclusions:** Our study shows that amongst the groups tested opinion towards organ transplantation has not changed significantly over the last seven years. The most recent suggestion of providing funeral costs to donors' families was not viewed any more favourably than in 2004. The modifications to consent already implemented and the possibility of introducing donation incentives does not appear to have been related to any significant shift in public or professional opinion regarding transplantation. We feel that further investigation of the reasons for the concerns about the ethics of organ transplant incentives are warranted.

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## Need for more emphasis on organ donation and transplantation in medical education: results of a nationwide junior doctor survey

Abdul Hakeem[1], Rajiv Dave[1], Kate Brady[1], Andrew Lewington[1], Lutz Hostert[1], Magdy Attia[1], Krishna Menon[1], Hilary Sanfey[2], Niaz Ahmad[1]

*[1]Department of Renal Transplantation, St James's University Hospital NHS Trust, Leeds, West Yorkshire, UK, [2]Department of Transplantation, Southern Illinois University School of Medicine, Illinois, Chicago, USA*

**Aim:** The shortage of donor organs is a worldwide problem. We believe that lack of understanding of ethical and practical issues surrounding organ donation and transplantation prevails within the medical community, particularly medical students and junior doctors. Educating medical students and junior doctors might positively influence the decision of families of potential donors. The purpose of this study is to survey the knowledge of organ donation and transplantation among junior doctors and to identify their educational needs.

**Methods:** The authors conducted a cross-sectional online survey among 1696 junior doctors (809 Foundation Year Trainees and 887 Core Trainees) in the UK. We used a 36-point questionnaire, exploring knowledge on transplantable organs/tissues, basic transplant terminologies, transplant waiting list, consent, complications and insight of medical student transplant curriculum.

**Results:** There were 193 respondents (11.4% response rate, 73.8% Foundation Year trainees and 26.2% were Core Medical/Surgical Trainees). Reassuringly, more than 90% of respondents recognised kidney, liver, heart, lung, bone marrow and cornea as being transplantable organs. Pancreas (56.3%), small intestine (34.1%) and islet of Langerhans (39.8%) were poorly recognised as transplantable organs. We also noted that retina (27.8%) and face (29.5%) were wrongly answered as previous successful transplantation in the UK. Only 43.0% could correctly approximate the number of patients on the UK Kidney Transplant waiting list and majority of them correctly answered the average waiting time as 3 years (76.3%). The knowledge level was considerably poor for liver transplant list with only 19.8% and 24.9% answering the approximate patients waiting and average waiting time respectively. Whilst 69.7% of the respondents were aware of live liver donation, only 12.0% were aware of live lung donors. There was also poor understanding (25.0% of respondents) of the terms commonly used in transplantation like DBD (HBD) and DCD (NHBD). 30.7% of them were unaware of Brain Stem Death (BSD) and criteria used to test BSD. On the subject of consent, 49.7% felt that final word rested on the next of kin, but 46.3% answered patient signing the donor card as the final word for donation. Following a rejection episode, 40.9% felt that organs failed completely and needed to be removed.

86.9% of respondents felt that junior doctors were poorly exposed to organ donation and transplantation during their training. Only 25.1% of the junior doctors were happy with their knowledge of organ donation and transplantation and 57.7% felt their knowledge level was inadequate. In keeping with above responses, 98.3% of respondents felt that organ donation and transplantation should be part of medical student curriculum.

**Conclusions:** Junior doctors in UK have limited knowledge about organ donation and transplantation. Majority of them felt that their knowledge level was inadequate and considered need to change medical student curriculum. Educating medical students and junior doctors about organ donation might be an important factor in maximising the benefits from the limited organ donor pool.

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**What are the patients' views on the current kidney allocation system in UK?**

Amy Vowler[1,3], Talya Kobrin[1,3], Aryeh Greenberg[1,3], Zoe Melrose[2], Natasha Reed[2], Helen Gregson[3], Sarah Heap[3], Iain MacPhee[1], Mysore Phanish[4], Nizam Mamode[6], Bimbi Fernando[2], Nicos Kessaris[3,1]

*[1]St Georges University, London, UK, [2]Royal Free Hospital, London, UK, [3]St Georges Hospital, London, UK, [4]St Heliers Hospital, London, UK, [5]Royal Sussex County Hospital, Brighton, UK, [6]Guys Hospital, London, UK*

**Introduction:** The aim of this study was to assess patients' understanding and views on how kidneys are allocated on the waiting list in UK as there are no studies in the current literature assessing this. Further aims included the assessment of what patients think the priorities should be and to find out whether patients are in favour of the current allocation system.

**Methods:** A two-part questionnaire was sent to all patients awaiting kidney transplantation at three transplant centres and two associated renal units after ethics approval (REC Reference 10/H083/61). Part-1 assessed patients' knowledge and priorities. Part-2 assessed patients' understanding and agreement after reading the UK kidney allocation guidelines.

**Results:** The response rate was 318/780 (41%). 18 responded that they did not want to participate. The key issues patients think should be taken into consideration are the degree of tissue matching between recipient and kidney (86%), the time spent on the waiting list (76%), the likelihood the patient will die soon (74%) and whether the patient will take their medication after transplantation (76%).
Ability to pay (78%), contribution to society (55%) ethnic origin (54%) and whether the recipient smokes (35%) were issues that most did not think should be part of the guidelines. 7.5% thought the ability to pay for a kidney is part of the allocation system. Moreover, 31% thought that patient contribution to kidney failure is part of the allocation system and 51% thought that it should be part of it.
After reading the enclosed guidelines, there was an increase in understanding of the system from 42% to 86% saying that they mostly or completely understand the guidelines now. Finally, 83% said they mostly or completely agree with the current guidelines.

**Conclusions:** Patients were aware of some aspects of the current UK allocation system but lacked information regarding other aspects. When they are provided with the appropriate information the majority agree with the prioritization criteria. We conclude from these responses that provision of more information alongside greater patient involvement increase understanding of the system and help with management of expectations for patients on the transplant waiting list.

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**Anonymity and live donor transplantation: an ELPAT view**

Nizam Mamode[1], Annette Lennerling[2], Sigrid Sterckx[3], Mihaela Frunza[4], Harald Jung[5], Assya Pascalev[6], Willij Zuidema[7], Frank Dor[7]

*[1]Guys and St Thomas Hospital, London, UK, [2]Sahlgrenska University Hospital, Gothenberg, Sweden, [3]Ghent University, Ghent, Belgium, [4]University Babes-Bolyai, Cluj, Romania, [5]Tg-Mures University, Tirgu Mures, Romania, [6]Bulgarian centre for Bioethics, Sofia, Bulgaria, [7]Erasmus Medical Centre, Rotterdam, The Netherlands*

**Introduction:** Anonymity is a fundamental part of renal transplantation; recipients are not given information regarding their donor when receiving a deceased donor transplant. In living donor transplantation in the UK, anonymity is routinely preserved for both donor and recipient in unspecified donation (altruistic donors) and specified indirect donation (paired exchange schemes). However, this practice is not always followed in other countries. Current European practice was assessed and recommendations regarding anonymity formulated by ELPAT.

**Methods:** A working group of ELPAT (Ethical, Legal and Psychosocial Aspects of Transplantation), a subsection of ESOT convened in Berlin in 2011 and collected examples of practice from 8 countries across Europe. Views were sought from transplant surgeons and physicians, ethicists and philosophers, donor co-ordinators, lawyers and psychologists and arguments for and against anonymity considered.

**Results:** Requirements for anonymity ranged from absolute anonymity in perpetuity to no requirements for anonymity. The main arguments against absolute anonymity were paternalism and the difficulty in enforcement. Potential problems that could arise from loss of anonymity were identified, including commercialisation or reward, withdrawal from the process and selection of pairings, and loss of idealisation of either donor or recipient, with resultant psychological harm. A distinction was made between the possibility of harm before and after the transplant.

**Conclusions:** The working group recommended that anonymity be maintained prior to either unspecified or specified indirect transplantation. After transplantation, a permissive approach to loss of anonymity was considered possible if the following requirements were met: both donor and recipient wished to identify each other, both had been counselled thoroughly regarding potential risks and adequate support services were available (due to the real risk of psychological harm, for example when a donor discovers her recipient has a failed transplant).

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## Transplant listing using audiovisual adjuncts: survey of patient education and satisfaction

Hussein Khambalia[1], David van Dellen[1], Agimol Pradeep[1], Hannah Wilkin-Crowe[1,2], Nicos Kessaris[1,2], Afshin Tavakoli[1]

*[1]Manchester Royal Infirmary, Manchester, UK, [2]St. George's Hospital, London, UK*

**Background:** Informed consent, via both patient education and pre-operative counselling, is associated with both best medical practice and a reduction in patient anxiety, ultimately improving outcomes. This is especially relevant in the context of transplant surgery, with the complexities of organ variability, complexities of surgery and peri-operative care, as well as the importance long term immunosuppression. Recent national guidelines have also highlighted the importance of rigorous informed consent for transplantation. This process can however be lengthy and is therefore prone to the omission of relevant information coupled with a lack of long term information retention for potential recipients, which can be vital with prolonged waits for organs. It is therefore vital to be able to clearly and concisely educate patients in the out-patient department via reproducible Methods:We aimed to assess patient satisfaction of a 10-15 minute from a PowerPoint presentation highlighting issues pertinent to transplant listing and establish the validity of this method as an educational forum for medical students, and trainee medical and nursing staff.

**Methods:** Patients and relatives including potential live donors attending the renal or pancreas transplant and live donor assessment clinics of two consultant surgeons in two transplant units, were given a 10-15 minute PowerPoint presentation (Microsoft®, Redmond, Washington, United States) comprehensively related to aspects of transplant listing and procedure, types of donor organs, peri-operative care, immunosuppression and follow up, prior to consideration for listing. All attendants were then asked to complete a questionnaire under direct guidance by a transplant specialist nurse immediately following the clinic attendance (5 grades of response to each question: strongly disagree (1), disagree (2), neither agree nor disagree (3), agree (4), strongly agree (5).

**Results:** 88 questionnaires were completed (June to October 2011) by 51 patients (58%), 26 relatives (29%) and 11 students & staff (13%), mean age 49.4 (range 21-77); 43 males with a wide spread of ethnic and socio-economic backgrounds. 99% agreed or strongly agreed (4-5/5) that the content level was appropriately targeted whilst all felt (4-5/5) that the experience was usefully complemented by the presentation. The majority (96.1%) appreciated the interactive process and (94.7%) found the slides useful to reinforce the educational components of the talk.

**Conclusion:** This study represents the first reported use of innovative adjuncts allowing interaction between surgeons and potential donor/ recipients and their families. It allows a reproducible technique to be employed thereby ensuring that all relevant information is reliably disseminated in a form which is easily accepted across a range of social and ethnic groups. In addition, it has proven to be well received in 2 distinct transplant units enhancing the method's reliability. This represents a novel method of ensuring and improving patient education whilst also potentially decreasing pre-operative anxieties. Further prospective study is required to corroborate findings across larger groups as well as increase the number of transplant procedures incorporated into this approach.

**11**

**Are patients well informed about their renal transplant procedure? – An audit of transplant procedure Patient Information Leaflet (PIL)**

Abdul Hakeem, Andrew Cockbain, Kate Brady, Joanne Barwick, Clare Ecuyer, Georgina Speak

*Department of Renal Transplantation, St James's University Hospital NHS Trust, Leeds, West Yorkshire, UK*

**Aim:** Patient Information Leaflet (PIL) is an important part of patients journey through the surgical procedure and is central to the overall quality of patient's experience with the multidisciplinary team. There are no consensus on the ideal content of a good quality PIL prior and after renal transplant procedure. Our aim is to assess the written information given to patients when undergoing donor or recipient renal transplant procedures.

**Methods:** Cross-sectional observational study design was used. Specifically designed questionnaire to evaluate the pre-operative and post-operative information leaflets used within the department.

**Results:** Over a period of 4 months in 2011, 152 responses were gathered (33 donors and 119 recipients). Majority of them who responded were in the age group of 51-65 years (31.0%) and were males (53.3%). Majority of the respondents confirmed receiving PILs before their operation (72.4%), whereas 9.2% did not receive the leaflet and rest of them were unsure of such leaflets. 78.9% of respondents were satisfied with the information provided in the PILs and only 1.9% rated the information as poor. More than $1/4^{th}$ of our respondents (25.6%) would have liked to have more information on their procedure, which they felt was not provided by the PIL. The additional information patients would have liked were –a) transplant waiting list and how it works (5.9%), b) what will happen when I come in to hospital (3.3%), c) details of operation (7.9%), d) what to expect whilst in hospital after operation (7.2%), e) immunosuppression (5.9%), f) what I can or cannot do when I go home after the operation (3.3%) and g) all above (3.9%). 80.9% of patients confirmed that they received written information during their discharge from the hospital. Discussion with doctors and nurses (46.7%) and PILs (33.5%) were the two sources of information that patients found very useful. Respondents felt the discussion with the nurses to be most useful than doctors (22.4% versus 18.4% respectively).

**Conclusions:** PILs used before and after donor/recipient transplant procedure were well received by most patients. 27.6% and 19.1% of our patients reported not receiving the pre-procedure and post-procedure information leaflet respectively, which needs to be addressed in future. The audit highlighted areas of information patient's deemed important and identified omissions in the current leaflets. It is imperative to maximise the information on these leaflets, as they form second major source of information for the patients following an effective doctor/nurse-patient communication.

# Ethics 2

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**Gender disparity and ethnicity in living donation renal transplantation: a single centre 30 years experience**

Tameem Arab, Abbas Ghazanfar, Muneer Junejo, Susan Martin, Michael Picton, Titus Augustine, Hany Riad, Afshin Tavakoli

*Department of Transplantation, Manchester Royal Infirmary, Manchester, UK*

**Introduction:** Living donation (LD) in kidney transplantation provides the best form of therapy for end-stage renal disease offering an opportunity to avoid a long period on the waiting list and benefit from a better quality of life. The majority of these donations are from related donors, followed by spousal donation and a minority from unrelated donors. When gender is taken into consideration we find that donation from women outnumber those from men. The hypothesis of an interplay of factors socioeconomic, psychological, immunological and physiological has been proposed to explain this disparity. Our study sets out to investigate another important factor; ethnicity. Research has shown ethnic minorities (8%) are under-represented among donors (2%) and over-represented among patients awaiting transplant (22%). To reduce this ethnic disparity LD has been encouraged in minorities. This study specifically looks at the relationship between ethnicity and gender bias in LD renal transplantation in a modern multicultural society of the United Kingdom.

**Methods:** A retrospective analysis of data recorded on all LD renal transplantations in our centre (a tertiary care facility and specialist centre in kidney and pancreas transplantation) between 1971 and 2011 was carried out. Statistical analyses were carried out using non-parametric, Chi-square test with Fisher's exact probability.

**Results:** Of 705 Living donor kidney recipients males received more of the transplants: 451(64%) males and 254 (36%) females ($P<0.0001$). Among the donors however, there were 395 (56%) females who donated their kidney compared to 310 (44%) males($P=0.002$). 593 (84.2%) were biologically related, 82 (11.6%) spousal, and 30 (4.2%) unrelated non-spousal donors. In the spousal group 62% of donors were female. The ethnic make up of the recipients were (90%) Caucasian, (9%) Asian, and (1%) other. Overall there were more female donors than male donors in all ethnic groups, Caucasians (55.6%) and Asians (57.3%). Both ethnic groups showed a significant predominance of female donors in spousal donations 6/7 vs 45/75 ($P<0.0001$). Spousal female to male donor ratio was Caucasian (3:2) and Asians (6:1) although this did not prove to be a significant difference.

**Conclusion:** This study provides evidence that gender bias and disparity in LD renal transplantation is prevalent across all ethnic groups. The disparity was equally observed in British Caucasians and Asians, which is contrary to the common belief that gender bias is a "minority issue". The greatest discrepancy appears in spousal donation where women significantly donate more to their male counterparts. Again Ethnicity does not seem to influence this but the trend in Asian spouses suggests women may be donating alone.

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**Non–directed altruistic living donation: journey from intent to donation**

Hemant Sharma, Chang Wong, Adham El-Bakry, Ajay Sharma, Abdul Hammad, Sanjay Mehra

*Royal Liverpool University Hospital, Liverpool, UK*

**Background:** Although Living organ donation from family members is most common, altruistic donation is also gaining popularity. Liverpool Regional Living Organ Donation Program incorporates support to altruistic donation.

**Aim:** Assessment of all altruistic organ donation offers to our unit over past 5 years and to identify the causes of fruition/non-fruition.

**Methods:** The Living Donor Coordinator (LDC) carried out the program operation and provided the general support. The donation process was divided into 10 phases

| Stage | Activity |
|---|---|
| Phase I | Call /letter of intent to offer |
| Phase II | Telephonic interview/ Information posted |
| Phase III | Personal Interview |
| Phase IV | Laboratory Tests |
| Phase V | Psychiatric Evaluation |
| Phase VI | Transplant team review |
| Phase VII | HTA Referral/ selection |
| Phase VIII | HLA match/ Recipient Selection |
| Phase IX | Donor Operation |
| Phase X | Follow up |

**Results:**

| | |
|---|---|
| Total Offers of Intent | N=41 |
| M: F Ratio | 3:1 |
| Average Age | 44 (19 -73) year |
| Total Donations | N=3 |
| Average age of donors | 62.5 (62-63) year |

N= 20/41 candidates did not respond to the telephonic calls. N=8/21 had abnormal laboratory results and were deemed unsuitable. N= 3/13 had family reasons not proceed. After Psychiatric evaluation 6/10 were considered fit to proceed. N=1/6 had renal artery stenosis thus only N=5/6 were considered fit for donation. N=3/5 have successfully donated and N= 2/5 are awaiting surgery.

There was no mortality in the operated patients. The median hospital stay was 03 (2-4) days. 46% (N=19/41) of candidates proposed donation after reading articles or posters on organ donation and 20% (N=9/41 proposed donation due to a relative/friend history of donation/transplant.

**Conclusions:** An early review by the transplant team and psychiatrists will save costs by assessing the candidate at early stages and expedite the donation. Our data suggests that an individual is more likely to donate a kidney after reading articles or posters than a psychosocial aspiration. A media drive and promotional social programs may help to promote more interest in the local population.

**15**

**Pattern of internet use and satisfaction with the quality of information on renal transplantation: donor versus recipient survey**

Abdul Hakeem, Andrew Cockbain, Georgina Speak, Joanne Barwick, Charles Newstead, Lutz Hostert, Magdy Attia, Niaz Ahmad, Krishna Menon

*Department of Renal Transplantation, St James's University Hospital NHS Trust, Leeds, West Yorkshire, UK*

**Aim:** Use of the internet has transformed communication and improved access to health-related information for patients and physicians. The purpose of this study was to identify the frequency of internet use by the living renal donors and live/cadaveric renal recipients for the purpose of seeking information regarding their transplant procedure. We also want to assess their satisfaction towards the quality and usefulness of information provided by currently available web sources.

**Methods:** This is a cross-sectional observational study. A specifically designed questionnaire with 22 questions (6 demographics, 5 related to information given before the operation and 11 related to the information accessed via the internet and other sources) was used to survey information from renal donors and recipients attending the outpatient clinics over a period of 4 months in 2011. Comparison was made between the renal donor and recipient responses. SPSS 19.0 was used for statistical analysis.

**Results:** There were 152 responses. Among the respondents there were 33 Donors (open nephrectomy-51.5%, laparoscopic nephrectomy-48.5%) and 119 Recipients (live donor recipient-28.6%, cadaveric recipient-63.8%). 7.6% of our recipients were unsure of where the kidney came from. Majority of the respondents were in the age group of 51-65 years (31.0%), were males (53.3%) and were educated above O level (64.7%). Age, gender, level of education, access to internet and average hours of internet used per week did not differ among the cohorts. 48.5% of donors and 49.6% of recipients used internet to access more information regarding their transplant procedure ($p=0.1057$). As expected, donors used the internet more frequently to access transplant related information than the recipients (mean 8.0 hours Vs 6.4 hours), which was statistically significant ($p=0.006$). 24.2% of donors preferred to use British Kidney Patient Association website and 15.9% of recipient favoured National Kidney Foundation website to get more information on their surgical procedure. Overall, only 2.6% of respondents mentioned difficulty in finding and understanding the information on the internet regarding the transplant procedure. 7.2% of our respondents felt the web information to be confusing and 0.6% of them characterised the information as poor. 42.7% of the respondents felt the information they acquired from 'other patients' to be particularly more useful than GP, internet or book sources.

**Conclusions:** Less than half of our respondents used internet to find transplant procedure related information and majority of them were satisfied with the information available on the websites. Donors were significantly more likely to use internet frequently than the recipients. A significant number also acquired information from other patients and donors who had undergone the process. Physicians and surgeons should enquire patients about internet use and counsel them on where they can find reliable, accurate and quality information regarding their transplant procedure.

**16**

**Timely listing for renal transplantation: an ongoing quality improvement initiative**

Partha Das, Donal O'Donoghue, Beverley Matthews

*NHS Kidney Care, England, UK*

**Background:** Renal transplantation is the "Gold Standard" modality of renal replacement therapy (RRT) in suitable patents and has been associated with improved patient and graft survival. Significant barriers exist preventing patient access to transplantation including demographic and geographical variations in practice, delays in prompt work-up and financial constraints. Furthermore pre-emptive transplantation, which offers the best patient outcomes with regard to morbidity and mortality, is only performed in a minority of incident patients commencing RRT (7.3%, UK Renal Registry Report 2009.) NHS Kidney Care report here on the progress of a nationally funded and locally led program to improve access to renal transplantation and increase the uptake of pre-emptive transplantation.

**Methods:** In July 2011 all renal units in England were invited to submit a project work profile detailing the barriers impeding listing for transplantation in their practice and an outline of strategies to address these including specifics of methodology to assess quality improvement. The successful bids were provided with a grant to assist their projects for the recruitment of a band 6/7 nurse to act as local problem solvers and facilitators. Projects began in September 2011 with a six month timescale. Project evaluation will be an ongoing process and the results of the project will be published in 2012. Units will develop their own set of benchmarks and quality metrics to assess their service improvement. NHS Kidney Care will support the transplant facilitators in each of the units and to further improve and refine their local projects as they progress.

**Results:** 20 out of 52 renal units have successfully applied for and received funding with which to launch their projects. The majority of units have completed month 1 of their programs and have been self-reporting progress through the use of a web-based customised reporting tool. At present all units are meeting their milestones. Identified difficulties encountered at this early stage have been related to the recruitment of new staff secondary to austerity measures at local NHS Trust level though it is predicted that all units will have overcome this by month 2 with minimal impact on their long term goals. NHS Kidney Care has been providing a regular e-seminar programme to which all local project leads are invited. In addition to providing education, these also serve as an opportunity for units to network and share experiences. An online dedicated discussion forum on the NHS Networks website, which units can access at any time, provides another dynamic and evolving environment through which ideas can be exchanged. It is anticipated that this virtual portal will become integral in assisting units to develop their projects, troubleshoot any problems and ultimately meet their deliverables.

**Conclusions:** This quality improvement project will enable renal units to offer the best modality of renal replacement therapy to their patients with advanced kidney disease. Although individual units run their own projects, the novel use of several online media throughout the duration of the program will serve as a means of improving quality between networks. The effectiveness of this program will be assessed in April 2012. DN so the 16 vs 36 is a great natural experiment.

**17**

## Is it unethical for doctors to encourage a healthy adult to donate a kidney to a stranger?

Antonia Cronin

*MRC Centre for Transplantation, King's College, London, London, UK*

**Introduction:** In the UK the Human Tissue Act 2004 provides the legal framework for living non-directed altruistic kidney donation (NDAD), or 'stranger kidney donation'. Since 2007, when the first such donation took place in the UK, there has been a year-on-year increase in the number of individuals who have come forward to donate a kidney to a stranger. NDAD now contributes 3% of the total UK living-donor kidney transplant activity. Kidneys donated through the NDAD programme are currently allocated to individuals waiting on the national transplant list using deceased donor criteria. Excellent transplant outcomes have been reported.

This paper reviews the current NDAD programme and examines whether it is unethical for doctors to encourage a healthy adult to donate a kidney to a stranger. The ethical acceptability of different forms of encouragement for donating bodily material are discussed.

**Method:** Up to date review of NDAD data available from NHSBT and theoretical ethical analysis.

**Results:** Between July 2007 and July 2011, 80 NDADs took place in the UK. The mean age of the donors was 52 years (range 25-82 years), and 59% of donors were male. The mean age of the kidney transplant recipients was 46 years (range 3-76 years) and 57% of recipients were male. The average recipient waiting time for a kidney transplant was over 3 years. Excellent transplant outcomes have been reported.

**Discussion:** Doctors do not have a moral obligation to encourage stranger kidney donations. However, encouraging a healthy competent adult to voluntarily donate one of their kidneys for the benefit of another by providing them with adequate information about the 'process' involved, and recognising the value of their donation, is consistent with the ethos of the NHS, which exists for the common good. Whether or not it is ethical for doctors to encourage a healthy adult to donate a kidney to a stranger is also a question of how far society can, or perhaps should go in trying to encourage people to donate their bodily material for the benefit of others. Whilst the ethical acceptability of different forms of encouragement for donating bodily material is likely to vary in different circumstances, the key point is that if something is not only not wrong to do but actually a good thing to do, then it cannot be wrong to encourage the doing of it.

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## Patients' views on generic substitution in the United Arab Emirates (UAE): Focus on renal patients

Mubarak Al Ameri[1, 2], Clare Whittaker[4], Walaa Mohamed[2], Emad Makramalla[2], Bassam Shalhoub[3], Magdi Yaqoob[1,4], Arthur Tucker[1], Atholl Johnston[1]

*[1]William Harvey Research Institute, London, UK, [2]The UAE General Hospital, Abu Dhabi, United Arab Emirates, [3]The University Hospital, Al Ain, United Arab Emirates, [4]Royal London Hospital, London, UK*

**Introduction:** In the last two decades healthcare cost has been rising globally. As a consequence, many countries, including the UK, were encouraged to limit their healthcare expenditures. A major strategy for lowering the cost of medications is with accepting generic equivalents of branded drugs into the global market. However, patients might suspect that substitution is based only on economic grounds and may compromise their quality of care. The aim of this survey was to examine the renal patients' awareness and understanding of generic drugs and substitution in the United Arab Emirates (UAE).

**Method:** A total of 188 renal patients treated at the renal clinic of two Hospitals in the UAE were surveyed using a questionnaire containing 36 questions. Renal patients over 18 years, able to read and write Arabic and willing to fill in the questionnaire were included in the survey.

**Results:** Majority of patients (78%) were taking between 1 and 6 medications, 80% were on kidney dialysis and More than half were highly educated. Overall the key findings conclude that 70% of patients were aware of the availability of generic medicines, 60% understood the term "generic" and "branded" in relation to medicines and 73% were conscious of generic substitution practice. However, 72% did not know if they were taking generics and 68% felt that generics are not equivalent or only equivalent sometimes, and they were uncertain that generics had the same quality as branded medicines. Nevertheless, 87% of patients stated that they were not monitored after switching their medicine. Therefore, 47% of patients admitted that they would refuse the generic substitution of ciclosporin. According to the result of this survey, healthcare professionals could have a significant role in educating patients related to generic prescribing and medication management. 69% of patients stated that they would accept generic substitution if their physician agreed to do so.

**Discussion:** This survey demonstrates that the lack of transparency related to generic substitution is of concern and might lead to confusion for patients. Appropriate patient education and involvement in decision making related to medication management may ensure safety and reduce the number of patients dissatisfied with generic drugs and substitution.

# Histocompatibility Science

**19**

**Measurement of donor specific antibodies by serial serum dilution: a guide to desensitization**

Sian Griffin[1], Frances Boyns[2], Emma Burrows[2], Sandra Lloyd[2], Argiris Asderakis[1], Tracey Rees[2]

*[1]University Hospital of Wales, Cardiff, UK, [2]Welsh Transplantation and Immunogenetics Laboratory, Pontyclun, UK*

**Introduction:** The presence of HLA donor specific antibodies (DSA) can be detected with increasing sensitivity by cytotoxicity, flow cytometry and Luminex analysis. There is generally a correlation between the degree of positivity of these assays, with a high Luminex mean fluorescent intensity (MFI) being associated with a greater linear channel shift by flow cytometry and increased cytotoxicity. When planning antibody removal, the initial Luminex MFI is often used to predict the frequency and intensity of treatments required to deplete antibodies sufficiently to allow transplantation to proceed.

**Methods:** Ten patients have undergone desensitization to enable removal of HLA antibodies prior to kidney transplantation from a living donor. Two patients had a positive pre-treatment complement dependent cytotoxic (CDC) crossmatch (XM) and eight patients were flow cytometric (FC) XM positive but CDC negative, due to the presence of both class I and class II HLA antibodies (5 patients), class I (one patient) or class II (4 patients) alone. Five recipients were also ABO incompatible with their donors. Four weeks prior to transplantation, all recipients received rituximab ($375mg/m^2$). A schedule for antibody removal using with double filtration plasmapheresis (DFPP) was planned according to the initial antibody level detected by Luminex using neat serum. After failure of one patient to respond to DFPP with falling Luminex MFI, we proceeded to repeat the assay following serial serum dilution.

**Results:** The strength of the initial XM as determined by CDC or FC XM was a better predictor of subsequent effectiveness of antibody removal (assessed by fall in Luminex MFI) than the starting Luminex MFI value *per se*. In 2/4 patients, Luminex testing of serum in serial dilution revealed both static and increasing MFI values, suggesting possible bead saturation and/or steric hindrance of binding when testing neat serum. The number of DFPP sessions required to achieve antibody depletion was adjusted accordingly, and all patients have subsequently undergone transplantation.

**Discussion:** Luminex testing of serial serum dilutions in selected patients is a useful adjunct when planning desensitization. We have subsequently applied this approach when considering de-listing apparently relatively low level DSAs in potential recipients undergoing assessment for paired exchange and cadaveric transplantation.

**20**

**Does virtual cross matching affect outcomes of renal transplant? preliminary report at 6-month follow up**

Matthew Wickham[1], Emma Aitken[1], Julie Glen[1], Ann-Margaret Little[2], David Kingsmore[1], Marc Clancy[1]

*[1]RenalTransplant Unit, Glasgow, UK, [2]Histocompatibility and Immunogenetics Service, Glasgow, UK*

**Introduction:** The advancing capabilities of virtual cross matching (1) and its ability to reduce cold ischaemic time prior to renal transplantation is desirable for the long-term outcome of any graft (2). The aim of this report is to assess graft outcomes at 6-months, following the introduction of a virtual cross match database at our unit.

**Method:** A retrospective review of emergency kidney transplant recipients from Jan 2007 to Sept 2011 was conducted. Primary outcome measures were Creatinine level and graft survival at 6-months. Virtual cross matching was introduced in May 2010 and comparison of outcomes pre and post virtual cross matching is presented. All live donor transplants were excluded. Results are presented as a mean and students t-tests performed for statistical analysis ($p<0.05$).

**Results:** 287 patients received an emergency renal transplant between Jan 2007 – Sept 2011; ten had incomplete data and were excluded from analysis. 186 transplants were undertaken prior to, and 91 post virtual cross match Introduction: A total of 45 transplants had a virtual cross match (49.5%) and to date, 62 transplants post virtual cross match had 6-month follow up data available. There was no difference in the demographic data between the two groups.

A significant decreasein CIT from 16.46 to 12.51 hrs was seen following the introduction of virtual cross matching ($p<0.001$).

6-month graft survival was 92.5% (172/186) pre and 100% (62/62) post virtual cross matching ($p = 0.22$).

6-month mean Creatinine was 151 pre and 120 post virtual cross matching ($p = 0.09$).

**Conclusion:** Virtual cross matching does significantly reduce the CIT, however this does not have an identifiable impact upon 6 month graft survival. Creatinine levels at 6-months show a trend to improvement with virtual cross matching. Increased numbers and longer follow up will be required to confirm any beneficial effect on long term graft/patient survival.

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**21**

**HLA-C compatibility affects outcome in renal transplantation**

Hoey Koh[1], Claire Burt[2], Marc Littlejohn[1], Ann-Margaret Little[2], Marc Clancy[1]

*[1]Western Infirmary, Glasgow, UK, [2]Histocompatibility & Immunogenetics Service, Glasgow, UK*

**Background:** Emerging evidence is showing that HLA-C has an impact on outcome of renal transplantation through modulation of natural killer cells. HLA-A, -B and DR compatibility has long been considered pivotal to successful outcomes in kidney transplantation. There is however a difference of 21% in 10-year survival between best and worst match categories, which would suggest other immunological differences such as HLA-C, may contribute. This study assesses the effect of HLA-C on clinical outcomes in renal transplantation.

**Methods:** Demographic, clinical and biochemical data for kidney transplant recipients from January 2007 to March 2009, were collected prospectively in an electronic database supplemented by clinical record review. HLA-C matched grafts were compared with matched controls for outcome measures alongside other potential confounding demographic factors using linear regression analysis (SPSS).

**Results:** 149 renal transplantations occurred during the study period. Mean time from transplant was 34 months (16-49 months). No significant difference in graft/patient survival was evident for HLA-C mismatched grafts, However HLA-C matched grafts had better creatinine/eGFR levels at 1-year post-transplant than their mismatched counterparts [mean creatinine 111 vs 131 ($p<0.003$), eGFR 55 vs 47 ($p<0.001$)]. HLA-C matched patients also have less rates of acute rejection (8.2% vs 17.6% mismatched grafts; $p<0.08$).

**Conclusion:** These results suggest HLA-C mismatch has a direct effect on short-term graft function and acute rejection incidence. Modern immunosuppressive regimens may dampen any clinical effect within the early years post-transplant but given the expanding evidence linking antibodies to donor HLA to long-term outcomes, further studies with expanded patient numbers and longer follow-up are required to assess the magnitude of HLA-C effect on emergent anti-HLA antibody and longer term outcomes.

**22**

**HLA specific antibody production and patient course following islet after pancreas transplant**

Symon Lockhart[1], Neil McGowan[1], Kirsty Duncan[2], Shareen Forbes[3], John Casey[2], David Turner[1]

*[1]SNBTS, Edinburgh, UK, [2]Transplant Unit, RIE, Edinburgh, UK, [3]QMRI, Edinburgh, UK*

Recipients of HLA mismatched islet transplants are known to have a comparable risk of HLA sensitisation as those receiving solid organ transplants. HLA donor specific antibodies at the time of islet transplant have also been associated with reduced graft survival, especially in the presence a positive Flow Cytometry XM. In the presented case, HLA sensitisation following islet after pancreas transplantation was assessed and related to clinical outcome.

A 32yr old female patient with hypoglycaemic unawareness underwent an islet transplant in 2011 after a previous pancreas only Tx in 2006. The islet isolation gave 226,000 IEs with 90% purity and 96% viability. Immunosuppression consisted of induction with Alemtuzumab and maintenance with Tacrolimus and MMF. The 211 MM pancreas transplant had sensitised the patient to both HLA class I and II. The 121 MM islet transplant did not repeat any HLA antigen mismatches with the 2006 pancreas transplant although the public epitope Bw6 represented a repeat mismatch.

At the time of islet transplant the HLA DSA (A3, B65, B60, Cw10, Cw8, DR15, DR51, DQ6) levels were low (<1000 MFI) as measured by One Lambda Luminex single antigen bead testing. The T & B cell CDC XM was negative and the Flow XM was T cell positive, B cell negative. The transplant proceeded as a low immunological risk. At d+7, HLA antibody testing showed a similar pattern to the day of transplant sample, with only low titre DSA. However, by d+17 the patient had developed strong DSA (e.g. A3: MFI = 8036, B65: 13,529, DR7: 8720).

Immediately post islet transplant the patient's insulin requirements were reduced by 50% and glucose control was excellent. When the HLA DSA levels were shown to be raised at d+17 post-transplant the patient had a transient increase in insulin requirement. However no treatment was given to reduce the HLA DSAs and by d100 insulin requirement was at 40% of pre-transplant level with good glucose control.

This case illustrates the immunogenic capacity of mismatched islet transplantation, especially when following a previous pancreas transplant. Class I and II HLA DSA levels were elevated by d+17, but in the absence of any intervention the function of the islets is considered good, as measured by the patient's insulin requirement and general glucose control. In this case the development of HLA DSA at d+17 post islet transplant has not compromised the function of the transplanted islets up to d+100. The patient is now listed for a second islet transplant.

**23**

## Does virtual cross matching reduce cold ischaemic time in renal transplantation performed on a mixed emergency theatre list?

Matthew Wickham[1], Emma Aitken[1], Julie Glen[1], Ann-Margaret Little[2], David Kingsmore[1], Marc Clancy[1]

*[1]Renal Transplant Unit, Glasgow, UK, [2]Histocompatibility & Immunogenetics Service, Glasgow, UK*

**Introduction:** Cold Ischaemic Time (CIT) is well established as a key risk factor for Delayed Graft Function (DGF) [1] which is an important predictor of short and long-term graft outcomes [2]. Virtual cross matching (VC) may avoid a delay of several hours for performance of a cross match but most studies of VC are from large transplant units with dedicated theatres for implantation. When implantation occurs on a mixed emergency theatre list, external delays such as general or vascular surgical emergencies may erode this benefit. The aim of this study was to assess the impact of the introduction of virtual cross matching on the length of CIT in a renal transplant unit in which deceased donor transplants are performed as part of the workload of a mixed emergency theatre.

**Method:** Deceased donor kidney transplants from three-monthly (July – Sept) sample groups from 2009 and 2011 were included. The 2009 sample was pre virtual cross match and the 2011 sample followed the established introduction of a virtual cross match database in 2010. Clinical demographic and outcome data were prospectively compiled in a database and associations with CIT and DGF analysed with the students t-test. DGF was defined as either dialysis required beyond day 1 or failure of Creatinine to fall by 50% in the first week post transplant.

**Results:** There was no difference in the number of DCD kidney transplants between the groups and demographic parameters were otherwise equivalent. 40 deceased transplants were undertaken within the total study period. Three were excluded due to incomplete data availability. A significant decrease in the CIT was seen following the introduction of a virtual cross matching ($p=0.017$) with the average CIT reduced from 16.09 hrs (range 8.4 – 24) to 12.59 hrs (range 5 – 18.5). Statistical analysis showed there was no significant difference ($p=0.49$) found for DGF between the two groups (41% in 2009 and 30% in 2011). Six patients (30%) underwent transplantation following virtual cross-match, one of whom received DCD kidney and subsequently developed DGF. Virtual cross matching significantly reduced the time from arrival of kidney on the ward to the start of operation from 8.61hrs to 3.28 hrs ($p=0.002$).

**Conclusion:** Virtual cross matching of transplant recipients does reduce CIT even within the limitations of a mixed emergency case load in the theatre used. In this small study, no improvement in the rate of DGF was evident suggesting additional factors such as kidney biological age and post operative perfusion may be equally or more important than CIT in the genesis of DGF.

**References:**

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**24**

## A novel and effective technique of risk stratification of renal allografts using the presence of HLA antibody

Hannah Kilbride, Colin Forman, Kathie Wong, Martin Drage, Robert Vaughan, Rachel Hilton, Anthony Dorling, Paramit Chowdhury

*Guy's and St Thomas's, London, UK*

In 2010 Guy's Hospital moved to a novel risk stratification policy for immune suppression in adult renal transplant recipients. Recipients are stratified into 3 groups, using HLA antibody status and risk of repeat mismatch:

Low (LR) Risk: Never had HLA antibodies or first transplant from HLA identical sibling.

Standard (SR) Risk: 3rd party HLA antibodies, husband to wife, child to mother, previous transplant or black recipient.

High (HR) Risk: Xmatch negative, but current or historical DSA.

Excluded: On HAART, ABOi/HLAi, in immune suppression trial.

The aim of the study was to assess compliance with the protocol, and compare rejection rates, NODAT and viral infections with our 2008 cohort.

**Protocol:**

LR: Basiliximab (Bas) induction, Tacrolimus (Tac) 3-7, 2g MMF, Prednisolone (Pred) weaning to 5mg .

SR: Bas induction, Tac 10-12 for 2 months, then 8-10, 2g MMF, Pred weaning to 5mg.

HR: Campath induction, Tac 10-12, 2g MMF, Pred weaning to 5mg.

**Results:** 91 Patients over an 8 months period were stratified, 46 were live donors (1H, 25S, 20L), 45 were deceased (1H, 21S, 23L). Follow-up was a median of 6 months (2-11 months).

Pt/Graft survival: 1 patient death at 5/12 from lung cancer, 2 graft losses to rejection.

Tac levels: at 7 days levels were not significantly different between the groups, reflecting similar loading. At 30 days there was significant separation between the groups ($p<0.001$). Mean levels in the LR group were 7.4 for both live and deceased (i.e. slightly above range). For the S/HR group, mean levels were 11.3 for live and 10.4 for deceased (i.e. within target). The difference was maintained at 3 and 6 months ($p<0.01$).

Biopsy proven rejection: 14% TCMR or AAMR (with a trend to a higher rate in the LR group), 10% borderline change.

NODAT: 6.6% representing 5 patients in SR, 4 of whom were afrocaribbean, and 1 in LR

CMV: 35% viraemia, 1 case (1.1%) of CMV syndrome who was inappropriately not given prophylaxis.

BK nephropathy: 6.6%, aggressive in 1 case.

**Conclusion:** We are adhering to our protocol, although tacrolimus levels in the LR group tend to be slightly above target. Compared to our 2008 cohort, rejection and viral infection rates are both on course to be lower, even allowing for shorter follow-up.

**25**

## HLA incompatible live donor transplantation is associated with a high incidence of transplant glomerulopathy

Jack Galliford, Kakit Edmond Chan, Candice Roufosse, Christopher Lawrence, Rawya Charif, Paul Brookes, Michelle Willicombe, Nadey Hakim, Vassilios Papalois, H Terence Cook, Adam McLean, David Taube

*Imperial College Kidney and Transplant Centre, London, UK*

Although HLA incompatible live donor renal transplantation [HLAiT] is reported as having acceptable short term outcomes, there are few published medium or long term data.

In this study we report the medium outcomes of our HLAiT programme.

Since 2006, we have performed 20 HLA incompatible transplants [15f, 5m; mean age 49.0±12.26 yrs] and have compared them with 309 DD transplants [102f, 207m; mean age 49.5±13.7 yrs] and 258 LD transplants [97f, 161m; mean age 46.7±14.3 yrs] performed over the same period.

17/20 patients were FXM+ prior to antibody removal, 2 of whom were also CDC B cell positive. 3 other patients had high titres of donor specific antibodies but were FXM-.

All patients received plasma exchange, preconditioning with either Rituximab or Campath and then a Tacrolimus based, steroid sparing immunosuppressive regime. All patients had a negative CDC and FXM crossmatch at the time of transplantation. The 2 CDC B+ patients also received Eculizumab post transplant [600mgs weekly x 6].

Mean follow up is 28.5±15.4 months.

The table below shows similar patient survival in all groups but reduced allograft survival in the HLAiT group at 3 years. 5/20 [25%] HLAiT patients experienced AMR and 4 of these patients have subsequently developed transplant glomerulopathy [TG] with 1 graft loss.

Allograft function is comparable between groups with mean MDRD eGFR at 6, 12, 24 and 36 months in HLAiT group of 55.9±21.1,54.5±13.9, 48.7±16.1 and 49.9±11.9 mls/min/1.73m$^2$.

| | Months | HLAi | DD | LD | HR HLAi vs DD | HLA vs LD |
|---|---|---|---|---|---|---|
| Patient survival | 6 | 100.00% | 98.35% | 100.00% | 1.2 95%CI: 0.15,8.93;p=0.881 | 2.8 95%CI: 0.33,23.93;p=0.348 |
| | 12 | 95.00% | 97.63% | 99.59% | | |
| | 24 | 95.00% | 96.30% | 99.59% | | |
| | 36 | 95.00% | 93.36% | 97.95% | | |
| Censored graft survival | 6 | 100.00% | 95.11% | 95.73% | 1.2 95%CI: 0.28,4.89;p=0.839 | 1.1 95%CI: 0.25,4.54;p=0.921 |
| | 12 | 100.00% | 94.10% | 95.73% | | |
| | 24 | 91.67% | 92.29% | 93.82% | | |
| | 36 | 80.21% | 90.82% | 91.73% | | |
| Graft survival | 6 | 100.00% | 93.53% | 95.73% | 1.2 95%CI: 0.36,3.76;p=0.802 | 1.4 95%CI: 0.41,4.44;p=0.617 |
| | 12 | 95.00% | 91.86% | 95.34% | | |
| | 24 | 87.08% | 88.87% | 93.44% | | |
| | 36 | 76.20% | 84.77% | 89.85% | | |
| Rejection free survival | 6 | 65.00% | 83.81% | 82.13% | * at 12 months | |
| | 12 | 65.00% | 75.46% | 78.87% | 1.7 95%CI: 0.78,3.70;p=0.18 | 1.9 95%CI: 0.88,4.27;p=0.099 |
| | 24 | 65.00% | 73.85% | 77.36% | | |
| | 36 | 65.00% | 73.85% | 75.25% | | |

This study shows that although initial outcomes of HLAiT may be good, medium term allograft survival is not as good as in the HLA compatible group of patients, with transplant glomerulopathy occurring in 20% of patients within 3 years.

# Immunosuppression 1

**26**

**Eculizumab prevents allograft loss from acute antibody mediated rejection in the short and medium term**

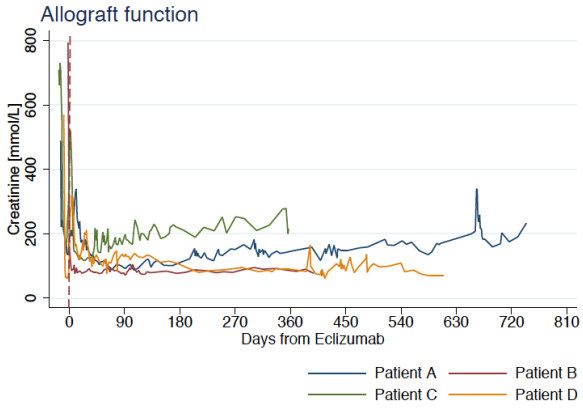
Jack Galliford, Kakit Ed Chan, Candice Roufosse, Rawya Charif, Christopher Lawrence, Paul Brookes, Nadey Hakim, Vassilios Papalois, Adam McLean, H. Terence Cook, David Taube

*Imperial College Kidney and Transplant Centre, London, UK*

Acute antibody mediated rejection [aAMR] is a common cause of renal allograft failure. Eculizumab [Ez] has emerged as a therapeutic option when allograft loss seems inevitable, either as a substitute for conventional treatment with poly or monoclonal antibodies, ivIg, plasma exchange and splenectomy, or when these therapies have failed.

In this study we describe our experience of Ez therapy in 4 patients [1m, 3f; mean age 49.2 ± 13.9 years] who had refractory aAMR. All 4 received Campath induction and Tacrolimus monotherapy. 2 patients received antibody incompatible transplants and underwent pre-transplant plasma exchange [ABOi (Patient A) and 1 FXM+ (Patient D)]. All had negative CDC and FXM crossmatches at the time of transplantation although one [Patient B] had low level Class I DSAbs [Cw6 (MFI 50) and B50 (MFI 220)] and the FXM+ transplant had Class II DSAbs [DQ7 (MFI 2760)].

Mean time to aAMR was 6.5 ± 4.8 days. All patients received methyl prednisolone, ivIg and a mean number of 5.0 ± 5.5 plasma exchanges, but creatinine continued to rise [see figure below] with high and rising de novo DSAbs [3/4 Class II alone and 1/4 with Class I + II]. 600mg of Ez was administered to each patient at weekly intervals for a total of 6 doses. At this time plasma exchange was stopped.




Mean follow up is 16.9 ± 5.7months. Patient and allograft survival is 100%. No patients have developed proteinuria. All patients have undergone re-biopsy. DSAbs have persisted in patients B and D.

Patient A has ongoing chronic antibody mediated injury without C4d. Patient B had TMA on a surveillance biopsy, responding to plasma exchange and ivIg. Patient C, without evidence of alloimmune injury, has BK viral nephropathy. Patient D had a surveillance biopsy at 1 year showing Banff 2a rejection treated successfully with oral steroids No other infective complications have occurred.

This is the largest study to show that Ez is highly effective at preventing allograft loss from aAMR in the short term. All patients have reasonable allograft function up to 2 years post Ez treatment. However 3 patients have had continuing alloimmune injury requiring further intervention and long-term prognosis is therefore guarded.

**27**

**Acute rejection is not increased in Afro-Caribbean renal transplant recipients receiving a steroid sparing immunosuppressive regime**

Ka Kit Edmond Chan, Jack Galliford, Rawya Charif, Dawn Goodall, Terence Cook, Candice Roufosse, Neill Duncan, Nadey Hakim, Vassilios Papalois, David Taube

*Imperial College Kidney and Transplant Centre, London, UK*

Steroid sparing regimes are increasingly used in renal transplantation because there is a lower risk of diabetes mellitus and cardiovascular co morbidities although there is a higher incidence of acute rejection, particularly in African Americans.

This issue has not been addressed in UK Afro Caribs and in this study we examine the outcomes of a steroid sparing immunosuppressive regime in a large, inner city, ethnically diverse population.

920 [103 Afro Caribs (AC), 283 South Asians (SA), 473 Caucasians (CA), 61 Others (OT); 339m, 581f; 478 dd, 442 ld; mean age: 47.4 yrs] consecutive renal allograft recipients transplanted between Sept 2002 and Sept 2011 were included in this study. 236 received induction with IL2R monoclonal antibodies [mabs] and 684 received Campath. All patients received methylprednisolone 500mg on induction, prednisolone 30mg bd, d0 – d3, 30mg od, d4 - d7, and then stopped. All patients were on tacrolimus maintenance and patients with IL2R mab induction also received Mycophenolate Mofetil.

Steroids were reintroduced to treat rejection.

Overall cumulative 1, 3, 5 and 9 year patient survival was 98.5%, 96.3%, 93.6% and 91.8% respectively. After adjustment for age and time lapsed, AC [HR1.5, 95%CI 0.6, 3.7; p=0.412] and AS patients [HR1.0, 95%CI 0.4, 2.1; p=0.951] did not associate with an increased risk of death compared to CA.

Cumulative 1, 3, 5 and 9 year censored allograft survival was 95.6%, 91.7%, 86.8% and 83.3%. AC [HR0.9, 95%CI 0.5, 1,8; p=0.809] and SA [HR0.9, 95%CI 0.5,1.5;p=0.639] graft survival was similar to CAs.

Cumulative 1, 3, 5 and 9 year rejection free survival was 80.1%, 76.1%, 74.9% and 73.3%. There were no evidence suggesting ethnicity increases risk of rejection [AC HR1.1, p=0.709; AS HR0.8, p=0.311] nor risk of late rejection.

MDRD eGFR at 1, 3, 5 and 9 years was 54.7+18.6, 51.6+17.7, 50.8+17.2 and 47.8+15.5 mL/min/1.73m2. After adjustment for donor type and individual patient measurements variation over time, data suggested a change of eGFR -0.7 mL/min/1.73m2 per year [95%CI -1.1, 0.5; p<0.001] There was no difference in trajectory in the AC [p=0.552] and AS [p=0.06] patients.

The incidence of new onset diabetes after transplantation [NODAT], defined as the de novo need for oral hypoglycaemics or insulin was low, 7.2%, 12.5%, 14.0% and 14.0%, at 1, 3, 5 and 9 years respectively. However, when compared with CA patients, both AC and AS patients have a 2.6 [95%CI 1.3, 5.1; 0=0.006] and 2.9 [1.7, 5.0;p<0.001] fold increased risk of NODAT, respectively.

This study shows that AC patients do not have a higher risk of rejection using our steroid sparing regime although there is a higher risk of NODAT.

**28**

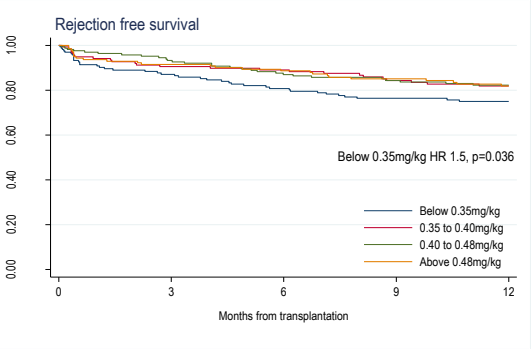
**Induction with Campath should be weight adjusted to achieve optimal outcomes in renal transplant recipients.**

Ka Kit Edmond Chan, Rawya Charif, Dawn Goodall, JacK Galliford, Adam McLean, Nadey Hakim, Neill Duncan, Andy Palmer, Vassilios Papalois, David Taube

*Imperial College Kidney and Transplant Centre, London, UK*

Although Campath induction in renal transplantation has been shown to be safe and efficacious, its optimal dose has not been determined. In this retrospective study we examine the effect of body weight adjusted dosage on outcomes.

Between Nov 2005 and May 2011, 608 consecutive renal transplants were performed at our centre and included in this study. ABO incompatible and HLA FxM + patients were excluded. All patients received induction with 30mg iv Campath, tacrolimus monotherapy and steroid-sparing [30mg bd between d0 and d3, 30mg od between d4 and d7 then stopped]. This cohort was divided into the following quartiles according to Campath dosage per body weight [<0.35mg/kg, 0.35-0.40mg/kg, 0.40-0.48mg/kg and >0.48mg/kg to maximise the power of the model].




Cumulative patient survival was similar between the groups, 98.1, 100, 98.1 & 99.3% and 86.2, 98.1, 93.6 and 83.4% respectively at 1 and 5 years. Cumulative censored allograft survival was similar between groups, 95.2, 97.7, 96.3 and 98.6% and 86.9, 89.9, 82.3 and 91.7% respectively at 1 and 5 years.

Figure 1 shows that 12 month rejection free survival in the <0.35mg/kg group was lower [75.0% vs 82.0%] with a 50% increased risk of acute rejection [HR1.5, 95%CI 1.02, 2.21; Weibull model. p=0.036] compared to the rest of the cohort. Patients receiving >0.48mg/kg had a 2.4 fold increased risk of infection [95%CI 1.5,3.7; Neg Binomial model p<0.001], with a 70% higher risk of urinary tract infection [95%CI 1.2, 2.5; p=0.002] and 97% increased risk of bacteraemia [95%CI1.2,3.4; p=0.015].

This study, the first of its kind, shows that Campath dosage by weight is importantly related to rejection and infective complications and our model suggests a target of 0.40mg/kg.

**29**

## Adoport® trough blood concentration is a reliable surrogate measure for the area under the concentration-time curve in the immediate post-transplant period.

Andrew Connor[1], Andrew Prowse[1], Iain MacPhee[2], Peter Rowe[1]

*[1]South West Transplant Centre, Derriford Hospital, Plymouth, UK, [2]Division of Clinical Sciences: Renal Medicine, St George's, University of London, London, UK*

**Introduction:** Adoport® is a recently introduced immediate-release, twice-daily, oral tacrolimus preparation. Most centres measure trough concentrations (C0) as a surrogate for the area under the concentration-time curve (AUC), which predicts efficacy. Recent guidance from the European Society for Organ Transplantation Advisory Committee has drawn further attention to the possibility that the relationship between the exposure of a drug and the surrogate marker may vary between formulations. For cost reasons the South West Transplant Centre switched from administering Prograf® to Adoport® for *de novo* transplant recipients in November 2010.

**Aim:** In the absence of publically available data, and in order to satisfy local governance requirements, we sought to evaluate the relationship between C0 and AUC for Adoport® in patients who had undergone recent renal transplantation.

**Methods:** Adoport® was commenced at a dose of 0.10 mg/kg in two divided doses on the day of transplantation in 16 sequential patients (11 male, 5 female) with a mean age of 54.6 years (range 31-72). Whole blood tacrolimus concentrations were measured on day 4 or day 5 post-transplantation by LC mass spectrometry before the dose and at 0.5, 1, 2, 4, 8 and 12 hours after administration of Adoport®. The AUC was calculated using the linear trapezoid rule in an Excel spreadsheet. Further pharmacokinetic data are reported below.

**Results**

| | **Dose** mg/kg/day | **AUC** ng h/mL | | **C0** ng/mL | **$T_{max}$** h | **$C_{max}$** ng/mL |
|---|---|---|---|---|---|---|
| **Mean (+/- SD)** | 0.09 +/- 0.03 | 136.0 78.2 | +/- | 7.9 +/- 4.8 | 2.2 +/- 1.7 | 18.3 +/- 9.0 |
| **Dose-normalised mean (+/- SD)** | | 3327 2389 | +/- | 196 +/- 146 | | 460 +/- 276 |
| **AUC C0 $r^2$** | | 0.92 | | | | |

**Conclusion:** These results suggest that in normal clinical practice, for patients in the acute phase after transplantation receiving Adoport®, the C0 is a reliable surrogate measure of the AUC. The coefficient of determination (0.92) calculated for the relationship between C0 and AUC is comparable to the best available data (in stable transplant patients) for this relationship for Prograf®. We will report longer term outcome measures for patients receiving Adoport®.

**30**

**Alemtuzemab induction and sirolimus maintenance therapy in renal transplantation: 5-year follow-up Results:**

Andrew Sutherland, Peter Friend

*University of Oxford, Oxford, UK*

The avoidance of long-term maintenance therapy with calcineurin-inhibitors is attractive as a means of reducing the development of chronic allograft dysfunction. Sirolimus may provide the means to achieve this, but the drug is difficult to use from the time of transplantation because of side-effects and higher rejection rates. In this study we investigated a modified strategy by using alemtuzemab induction therapy, followed by an initial six month period of tacrolimus and MMF; then switching to low-dose sirolimus and MMF and finally reducing to sirolimus monotherapy at 12 months. Here we report the 5-year follow-up Results:

30 renal transplant patients were prospectively recruited to this single arm, open label trial. Outcome measures, including patient and graft survival, renal function, episodes of rejection, infection, and malignancy were recorded for 5 years. Outcomes for this study were then compared in a retrospective contemporaneous-controlled manner to 30 patients who received conventional basiliximab induction and tacrolimus based therapy according to the unit protocol.

Five-year patient survival was similar in the study group (87% ) compared to the control group (83%). Graft survival (censored for death) was 100% in the study group compared to (90%) in the control group. Early rejection rates were similar in both groups (6.6% vs. 10% respectively). However, the incidence of late rejection (greater than one year post-transplant) was higher in the study group (10%) compared to the control group (0%). These episodes of late rejection corresponded to reduction to sirolomus monontherapy and therefore patients recruited in the latter part of the study were continued on half-dose MMF and there were no further rejections.

There were no significant differences between the groups in terms of infections or total numbers of malignancies. However, there was a higher incidence of PTLD (10%) in the alemtuzemab group compared to the control group.

A 6-month initial treatment with tacrolimus facilitates conversion to low dose sirolimus and MMF without the side effects and acute rejection seen in earlier protocols. Withdrawal of MMF at 12 months was associated with late rejection, a problem which was avoided by maintaining very low-dose MMF in conjunction with sirolimus. The 5 year results of this study compare favourably with conventional calcineurin inhibitor based immunoppression. A randomised trial will provide further information on the medium and long-term benefits of this protocol.

**31**

## Effects of immunosuppression on renal tumours after transplantation: a rodent tumour transplant model

Muhammad A Khurram[1,2], Colin H Wilson[1], Susan Stamp[3], Neil Sherrin[1,3], David Rix[1], Anne Cunningham[2], Noel Carter[2], David Talbot[1,2]

*[1]Freeman hospital Newcastle upon Tyne Hospitals NHS trust, Newcastle uponTyne, UK, [2]University of Sunderland, Sunderland, UK, [3]Newcastle University, Newcastle upon Tyne*

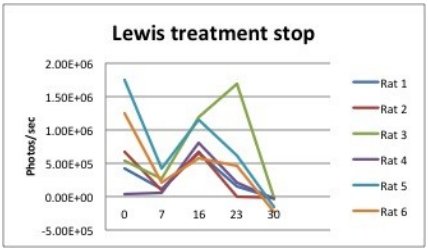
**Introduction:** Recently kidneys from patients with small renal cell carcinoma (RCC) have been used for transplantation after ex vivo tumour resection with excellent Results: Such an approach can have great potential but there are concerns regarding tumour behaviour in immunosuppressed host. This study looks at the tumour dynamics under cyclosporine immunosuppression and role of rejection in a well matched and poorly matched group.

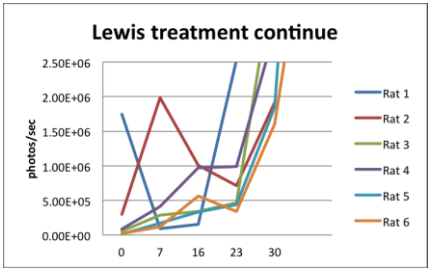
**Methods:** Wistar rat kidney tumour cells were stably transfected with GFP and Luciferase to enable real time in vivo imagining of tumours. A total of 35 rats (Wistar and Lewis strians) were divided into Controls with no immunosuppression, Cyclosporine (C) arm with 4 weeks of treatment and Cyclosporine withdrawal arm with 2 weeks of immunosuppression followed by treatment withdrawal. Wistar rats were well matched with the tumour cell line while Lewis rats made poorly matched group. Cells were injected subcutaneously and animals scanned every week to detect the photons emitted by the bioluminescent tumour cells. Flow cytometric analysis is being performs for T cells subsets as well.

**Results:** Results are summarised in the following table.

| Groups Rats | Control-Wistar (6) | Control-Lewis (6) | C Treatment-Wistar (4) | C Withdrawal-Wistar (7) | C Treatment-Lewis (6) | C Withdrawal-Lewis (6) |
|---|---|---|---|---|---|---|
| Result | Complete rejection within **two** weeks | Complete rejection within **one** week | Continued growth of tumour in all rats | Rejection in **57%** (4/7) rats within 2 weeks | Continued growth of tumour in all rats | Rejection in all rats within 2 weeks |

**Conclusions:** 1) Rejection of tumour is significantly stronger in poorly matched animals. 2) Under cyclosporine tumour continues to grow in both groups. 3) Tumour was rejected in all poorly matched animals while only 57% rejected the same tumour load in well matched group within two weeks of drug withdrawal. 4) Clinically, recipients of "restored" organs should perhaps be less well matched to aid rejection should a tumour develops. 5) Immunosuppressives with anti-neoplastic properties may be a better option than cyclosporine in these recipients.



**32**

**Post transplant tacrolimus variability but not pre-transplant phosphate variability predicts worse post transplant outcomes.**

Julie Glen, Henry Whalen, Kathryn Stevens, Alan Jardine, Colin Geddes, Marc Clancy

*NHS Greater Glasgow and Clyde, Glasgow, UK*

**Introduction:** Tacrolimus shows substantial intrapatient variability in pharmacokinetics requiring therapeutic drug monitoring and frequent dose adjustments. Borra et. al. (NDT Vol 25 2010) described an association between high intrapatient variability and worse clinical outcomes. Covariation with poor patient compliance has been postulated as an explanation of these Results: We hypothesised that high phosphate variability pre transplant may identify poorly compliant patients post transplantation and shed light on whether poor compliance is the major contributor to this association.

**Methods:** Data was collected from the prospective electronic patient record for 250 adult kidney recipients performed between 01/01/07 and 31/03/2009. 6 cases were excluded due to parathyroidectomy during the year preceding transplantation and a further 22 patients were excluded as there was no phosphate level data. Median variability was calculated from all Tacrolimus trough levels in 6-12 months post transplant and all pre dialysis phosphate levels in the year preceding transplantation. High variability (HV) was defined as variability > observed median group and low variability (LV) as < observed median group. Groups were compared for AR, LAR, and creatinine 1 year post transplant in univariate analysis . A P value of 0.05 was considered as statistically significant.

**Results**: Median variability of tacrolimus trough levels was 17% (Range 0-81%). HV tac patients showed an AR rate of 20.6% (21/102) compared with 8.2% (8/97) for LV tac patients (P=0.01). HV and LV PO4 groups showed no significant difference in rates of AR.Average Creatinines at 1 year, were shown to be significantly lower (P=0.02) when comparing LV tac (117, N= 97) and HV tac (137, N=102). There was no significant difference in creatinines at 1 year when comparing the phosphate groups. When tacrolimus and phosphate variability patient groups were compared it was shown that there was no significant association between the groups.

**Discussion**: This data supports the assertion that high intrapatient variability in Tacrolimus clearance is associated with inferior clinical outcomes and is consistent with the observations of Borra et.al. The relationship with phosphate pre transplant and tacrolimus levels is difficult to interpret however the putative poor compliance group of high pretransplant phosphate variability did not show an association with acute rejection or worse renal function. This suggests other factors beyond simple compliance may contribute to tacrolimus variability and worse clinical outcomes.

**33**

**Rodent tumour transplant model: to assess the effects of immunosuppressive agents on tumour growth after transplantation**

Muhammad A Khurram[1, 2], Colin H Wilson[1], Susan Stamp[3], Neil Sheerin[1,3], David Rix[1], Anne Cunningham[2], Noel Carter[2], David Talbot[1,2]

*[1]Freeman hospital Newcastle upon Tyne Hospitals NHS trust, Newcastle upon Tyne, UK, [2]Universityof Sunderland, Sunderland, UK, [3]Newcastle University, Newcastle upon Tyne, UK*

**Introduction:** Transplantation has immense benefits for the recipients, but there can be some serious risks associated both in short and long terms. One such risk factor is either the development of a de-novo tumour or transmission of a tumour from the donor inadvertently. Immune system, one of the major defences against cancer cells is suppressed in transplant recipients and thus the behaviour of tumours in the presence of immunosuppression can be unpredictable. We describe a tumour transplant model to assess the behaviour of transplanted tumour in host under experimental conditions.

**Methods:** Rat kidney tumour cells (BP36B) were co-transfected with Green florescent Protein (GFP) and Luciferase (used as a bioluminescent marker based on the principle of light emitted from firefly) to enable real time imaging of the tumour cells. Transfection was achieved with Lentivirus also carrying the genes for Puromycin resistance and stably labelled cells were selected and expanded by culturing in medium supplemented with Puromycin. Fixed number of tumour cells of Wistar origin ($1.8* 10^7$) were injected subcutaneously into two different strains of rats – Wistar and Lewis; to mimic Well-matched (Wistar) and poorly-matched (Lewis) groups. Animals were further divided into treatment group receiving cyclosporine and a control group with no immunosuppression. Tumour behaviour was monitored in real time with IVIS spectrum in vivo imaging system. 10-15 minutes before imaging, the animals were injected with Luciferin (substrate for Luciferase) and the anaesthetised animals were placed in a heated dark chamber and photons emitted from the labelled tumour cells were detected on an ultra sensitive CCD camera. Animals were scanned once weekly for 4-6 weeks and tumour behaviour was monitored in different experimental conditions. Cyclosporine treatment in half of the animals from both strains was stopped midway to further determine the role of rejection on transplanted tumour cells. Tumour depth was determined in some animals with 3D reconstruction and was reconfirmed after post mortem examination in palpable tumours.

**Results:** All the animals displayed good bioluminescent signals apart from one batch which was injected with cells grown in medium without puromycin. Due to the high sensitivity of the imaging system, we were able to monitor the tumour cells even in the absence of palpable tumour lumps. Significantly varied tumour behaviour under different experimental conditions was observed using this model.

**Conclusions:** This model provides a highly sensitive approach of monitoring tumour behaviour under different experimental conditions even in the absence of palpable tumours. Accurate measurements for local and distant spread can be made in live animals. Furthermore post mortem analysis of the tumour cells can be done with florescent microscopy for tissue invasion and flow cytometry for hematopoietic metastasis.

# Immunosuppression 2

**34**

## Switching Prograf ® to generic tacrolimus (Adoport®) is safe and cost effective in renal and pancreas transplants

Rania Betmouni[1,2], Rachna Bedi[1,2], Neill Duncan[1], Jack Galliford[1], Dawn Goodall[1], Jane Owen[1], Vassillios Papalois[1], David Taube[1]

*[1]Imperial Renal and Transplant Centre, Imperial College Healthcare NHS Trust, London, UK, [2]Pharmacy Department Imperial College Healthcare NHS Trust, London, UK*

The use of generic drugs offers an opportunity for significant cost savings in the face of increasing health costs.

Generic tacrolimus (Adoport®) has been commercially available in the UK since 2010. The bioequivalence assessment for Adoport® for EMEA licensing and early US data suggested that trough tacrolimus levels could vary by up to 20%, raising patient safety concerns particularly relating to rejection and nephrotoxicity.

The aim of this study was to evaluate the safety and efficacy of generic tacrolimus substitution in a group of stable renal and pancreas transplant recipients.

109 patients [70m, 39f, mean age 53 yrs and 8 yrs post transplant] were switched from Prograf to Adoport at an equivalent dose and were instructed to return 7 – 10 days post switch for a 12-hour trough tacrolimus level and repeat plasma creatinine.

8 patients were excluded from the final analysis (4 were on interacting medicines and 3 patients switched back to Prograf® and one was non compliant).

The average number of days patients presented for their first trough tacrolimus level and repeat plasma creatinine post switch was 12.8 days. The patients were subsequently followed for a period of 1.6 months to 6.5 months.

The data for 101 patients, pre and post switch are shown below:

| | Mean tacrolimus level (ng /ml) | Mean daily tacrolimus dose (mg) | Mean Serum Creatinine (µmol/l) |
|---|---|---|---|
| Baseline data - Prograf® | 6.4 | 5.6 | 150 |
| Range | 2.5 – 17.1 | 1 – 16 | 72 – 374 |
| Median | 6.2 | 4 | 135 |
| Post switch data - Adoport® | 6.9 | 5.7 | 152 |
| Range | 2.8 -14.2 | 1 -16 | 69 -423 |
| Median | 6.5 | 4 | 137 |

12 patients [12%] had an increase in tacrolimus level > 2 ng/ml and 9 [9%] had a decrease in levels by < 2 ng/ml. Of these 21 patients, 14 had levels that fell outside our target range [5 – 8ng/ml]. Of the original 109 patients switched, 3 (3%) reported side effects and were switched back to Prograf. The side effects included a rash, headache and flu like symptoms.

This study demonstrates that switching to generic tacrolimus is safe, producing similar dose requirements and trough levels and maintaining graft function. The saving to the health economy for these patients is estimated to be £63,000 annually.

**35**

**Experience with Rapamycin in the north west of england. an immunosuppressive agent still in search of an optimum role**

Gabriele Di Benedetto[1], David van Dellen[1], Abbas Ghazanfar[1], Clare Griffin[1], Margaret Delargy[2], Bence Forgacs[1], Ravi Pararajasingam[1], Hany Riad[1], Neil Parrott[1], Alexander Woywodt[2], Michael Picton[1], Grahame Wood[3], Tunde Campbell[1], Afshin Tavakoli[1], Titus Augustine[1]

*[1]Manchester Royal Infirmary, Manchester, UK, [2]Royal Preston Hospital, Preston, UK, [3]Salford Royal Hospital, Salford, UK*

**Background:** Rapamycin, an mTor inhibitor, is a potent immunosuppressant agent in solid organ transplantation. Initial enthusiasm on its efficacy and reduced nephrotoxcity was tempered by unacceptable side effects leading to sporadic usage by transplant centres. It appears to have a niche for specific and varied indications, particularly as 'rescue therapy' and in situations where its anti-neoplastic or anti-fibrotic properties are advantageous rather than as primary maintenance immunosuppression. We aimed to assess the frequency and pattern of Rapamycin use focusing on indications, usage length, outcomes and complications, in three large North of England centres since its introduction in 1997.

**Methods:** All Patients who have had Rapamycin at any point after transplantation were identified through laboratory records of assays done at 3 follow up centres. A retrospective analysis was then done of a database of 1412 patients receiving either a kidney or pancreas transplant between 1997 and 2011. 123 patients received Rapamycin with data on the indications, pattern and length of usage available in 91 patients (8.7%). These comprised 2 distinct groups: Rapamycin as *de novo* immunosuppression (primarily in clinical trials with Mycophenolae Mofetil and steroid) or as a modification of therapy at a later date. End points including Biopsy proven acute rejection (BPAR), complication rates, proteinuria (>1g/24hr) and mortality were reviewed in this cohort of patients.

**Results:** 36 patients received *de novo* Rapamycin treatment (Trial 35/36; non trial 1/36 – previous PTLD) 13 (36%) of these patients required immunosuppression change (recurrent BPAR, 38%; 10 single episodes of BPAR), impaired wound healing (23%), interstitial pneumonitis (15%) and mouth ulcers (7.6% each). Complications which did not require immunosuppressive changes included hyperlipidaemia (>6mmol/l, 83%), mouth ulceration (19%), and lymphocoele (22%). The incidence of neoplasia was 5% and mortality 14%. Rapamycin associated significant proteinurian was 5%. 53 patients were converted to Rapamycin as 'rescue therapy' (median interval 6 years post-transplant (range 1/12 to 42 years); indications including: allograft nephropathy 17/53 (32%), anti-neoplastic 14/53 (11 skin cancer, 1 PTLD, 1 small bowel lymphoma, 1 renal cell Ca; 26%), and intolerance of other drugs 9/53 (17%). 19/53 (36%) had changes due to intolerance (infection (11%); mouth ulcers (17%); BPAR (5%), or chest infections (interstitial pneumonitis or PCP pneumonia; 4%.) Other adverse effects included hyperlipidaemia (22%) and mouth ulcers (15%). The incidence of significant proteinuria was 20% with a mortality rate of 13%

**Conclusion** Rapamycin has been sparingly used in the last decade due to severe adverse outcomes associated with *de novo* usage. Trends have developed for its use for allied benefits including anti-fibrotic and neoplastic properties and as rescue therapy for toxicity rather than as defined maintenance immunosuppression. This study highlights that despite not fulfilling original indications, it has a role for both maintenance and rescue therapy. Its side effect profile ensures that it is better tolerated than originally perceived.

**36**

## Withdrawal of calcineurin inhibitors for managing chronic allograft nephropathy is associated with improvement in fasting plasma glucose

Pramod Nagaraja, Vinod Ravindran, Kesh Baboolal

*University Hospital of Wales, Cardiff, UK*

**Introduction:** Chronic allograft dysfunction (CAD) due to interstitial fibrosis / tubular atrophy (IF/TA) is a leading cause of graft failure after renal transplantation. When no specific cause is identified for CAD, minimisation or elimination of calcineurin inhibitors (CNI) is one of the strategies in its management in immunologically low risk patients. Here, we report our centre's experience of managing progressive CAD with a CNI-free regimen of mycophenolate mofetil (MMF) and prednisolone.

**Methods:** We conducted a retrospective analysis of patients in whom a CNI had been withdrawn completely, and MMF and prednisolone continued for the management of CAD between January 1999 and June 2011. Allograft function (MDRD eGFR) and cardiovascular risk factor data were recorded at the time of CNI withdrawal (baseline) and later time-points until November 2011 (follow-up). Allograft biopsy was performed only if indicated. Paired t-tests were used to compare means.

**Results:** A CNI was withdrawn in 31 patients after a median of 11 years (range 1.5–28) from transplantation (ciclosporin n=19, tacrolimus n=12). Median length of follow-up after CNI withdrawal was 2.5 years (range 0.5–5.3), during which time 3 patients died with functioning grafts and 1 patient returned to dialysis. Nine patients (30%) had experienced an episode of acute rejection prior to CNI withdrawal, the majority within 1 year after transplantation. Allograft biopsy had been undertaken in 25 patients (87%) prior to CNI withdrawal (10 patients in the year before withdrawal), of which 14 patients had at least mild IF/TA or CNI toxicity reported. None of the 31 patients experienced acute rejection after CNI withdrawal (none had a biopsy performed). Mean serum creatinine and eGFR at the time of CNI withdrawal (baseline) were 200±68 μmol/l and 35±17 ml/min respectively. Mean eGFR was significantly higher than baseline at 1, 6, 12 and 24 months (38.6, 40.4, 41.5 and 42.3 ml/min respectively, $p<0.05$ at all time-points). In the 26 non-diabetic patients, mean fasting plasma glucose decreased from 5.9 mmol/l at baseline to 5.2 mmol/l at 6 months ($p<0.001$) and 5.3 mmol/l at follow-up ($p=0.01$). Mean prednisolone dose increased from 3.2 mg/day to 5.5 mg/day ($p=0.001$) from baseline to 6 months, with no significant change in body mass index (26.9 vs. 26.6). Urine protein:creatinine ratio, blood pressure, S. total cholesterol and triglycerides remained unchanged.

**Conclusion:** In our centre, in carefully selected patients with CAD, switching to a CNI- and sirolimus-free immunosuppression regimen of MMF and steroids was safe and effective in stabilising allograft function. There were no episodes of acute rejection after CNI withdrawal. Fasting plasma glucose decreased after CNI withdrawal despite a concomitant increase in steroid dose, possibly conferring an additional cardiovascular benefit.

**37**

## Myfortic versus MMF as first line MPA in renal transplantation – A Gastro-intestinal side-effects perspective

Omar Masood, Stephen Hughes, Afshin Tavakoli, Hany Riad

*Manchester Royal Infirmary, Manchseter, UK*

Mycophenolate Mofetil (MMF; Cellcept, Roche Pharmaceuticals) was introduced in 1995 and in combination with a calcineurin inhibitor (CNI) it improved graft survival and reduced rejection rates in kidney transplant recipients (Knoll et al 2003). This antiproliferative agent was associated with upto 70% of pts experiencing GI side effects and led to development of enteric coated Mycophenolate Sodium (Myfortic, Novartis). The literature claims that "Dose reductions in MMF due to GI side effects can lead to an increased risk of acute rejections (after renal transplantation) particularly during the first year post transplant. (Bolin et al 2007)

Optimal MPA levels are increasingly important as we move towards CNI sparing. Other side effects of MPA's include: leukopaenia, anaemia, thrombocytopaenia, viral, bacterial and fungal infections. This study looked at whether patients tolerated higher doses of myfortic as compared to MMF and if this translates to greater efficacy.

**Methods:** On the basis of the literature Myfortic was made first line for MPA in May 2010 in all first renal transplants in this centre. A retrospective study was then carried out to a collect and analyse the data of transplant outcomes and complications seen in all first renal allograft transplants in 2010 (cadaveric and live related transplants). All patients selected were on the standard regime of MPA + CNI (Tacrolimus) +/- Steroid only.

Data included: biopsy proven rejection as a marker of efficacy, CMV infection, neutropaenia and GI side effects that required a dose change (loose stools, abdominal cramps +/- vomiting)

**Results:** The study group included 193 Kidney transplants: 59.6% were cadaveric donors with a mean age of 47.6 (80 DBD, 35 DCD). 40.6% were live related transplants (75 ABO compatible, 3 incompatible). 102 patients were on MMF as first line whilst 91 were on myfortic. 53.9% of patients on MMF versus 27.5 % on myfortic patients required dose amendments to manage GI side effects ($p<0.0001$). 1 year results for biopsy proven rejection reveals 9.8% and 8.7% for MMF ($p=0.495$) and myfortic respectively. There was no significant differences in CMV prevalence and neutropaenia between the two groups

**Conclusion:** Myfortic is associated with a significant reduction in GI side-effects and therefore greater patient tolerance of the optimal MPA dose as compared with MMF. This did not translate as a significant reduction in biopsy proven organ rejection in this study group.

Myfortic being therapeutically equivalent to MMF but better tolerated is justified as first line MPA in renal transplantation.

**38**

## Pilot study of the reversal of acute cellular rejection [ACR] in renal transplant recipients with a single dose of campath

Rosa Maria Montero, Kakit Edmond Chan, Paul Brookes, Adam McLean, Candice Roufosse, Terry Cook, Jack Galliford, David Taube

*Imperial College Kidney and Transplant Centre, London, UK*

ACR occurs in 8 -15% of renal transplant programmes and is conventionally treated by high dose corticosteroids, which are associated with significant co-morbidity.

Campath, an anti cd 52 monoclonal antibody, rapidly depletes lymphocytes from the circulation and is now widely used as an induction agent. This agent has also been used to reverse ACR but the reports are unclear due to differing induction and immunosuppressive protocols, dosing of Campath, and severity of rejection.

In this study we describe the use of a single 20 mg iv dose of Campath to reverse Banff 1a and 1b [Banff 2007] rejection in patients who had undergone kidney transplantation with Campath induction [30mg iv perioperatively], a 7-day steroid sparing regime and Tacrolimus monotherapy without the use of MMF.

11 [6m, 5f] patients [mean age 52.3yrs] received 1 x 500mg methyl prednisolone [mp] iv and 20mg Campath iv after the diagnosis of ACR [Campath group]. These were compared with a control group of 28 [19m 9f] matched historical patients [mean age 55.6 yrs] who were treated with our conventional protocol of 3 x 500mg mp, 30mg prednisolone po (reduced to 10mg at 3 months and continued for 9 months) and the addition of MMF (12 hour trough MPA levels of 1.2-2.4mg/L[LCMS]). All patients received CMV and PCP prophylaxis. No donor specific antibodies were detected at the time of diagnosis and all biopsies were C4d negative. Results were analysed at 12 months.

Patient survival was 100% in the Campath group but 96% in the Control group. In the Campath group allograft survival was 100% and in the control group was 96%, 92% and 89%at 3, 6 and 12 months [p=0.565].

Allograft function was similar in both groups.

3/11 of the Campath group had further allograft dysfunction and had continuing ACR on rebiopsy treated with our conventional steroid and MMF regime. 6/28 in the control group had repeat biopsies for dysfunction which showed ongoing ACR.

Although there was no difference in weight gain between the 2 groups, none of the Campath group developed NODAT, whereas NODAT free survival in the control group was 88%, 78% and 72% at 3, 6 and 12 months respectively.

There were fewer admissions for infection in Campath group [0 vs. 5.5 per 100 patient months in the control group], and there was 1 death from infection and 1 graft loss from BK nephropathy in the control group. There have been no fungal infections, CMV, malignancy or PTLD in either group.

This pilot study shows that a single 20 mg dose of Campath reverses Banff 1 ACR in 70% of patients without the need for additional steroids or MMF. The incidence of NODAT and serious infection was also minimal when compared with a conventionally treated control group. This promising approach needs more patients and longer follow up.

**39**

**High intrapatient tacrolimus variability is associated with worse renal transplant function at 1 year**

Henry Whalen, Kathryn Stevens, Julie Glen, Colin Geddes, Alan Jardine, Marc Clancy

*Transplant Unit, Western Infirmary, Glasgow, UK*

**Introduction:** High intrapatient tacrolimus level variability 6 -12 months post renal transplantation has been shown to be associated with increased rates of graft loss and incidence of chronic rejection. (Borra et.al. NDT Vol 25 2010). Studies in our unit have found increased rates of acute rejection and graft loss in patients with high tacrolimus variability in the first post transplant year but many external factors such as acute rejection episodes may increase variability in this early post transplant period. We investigated the effect of tacrolimus variability in the 6 – 12 month period post transplant on clinical outcomes of renal transplantation in our unit.

**Methods:** Data was collected from the prospectively-compiled electronic patient record for 239 adult kidney transplants performed between 01/01/07 and 01/03/09. All patients received Basiliximab induction and tacrolimus targeted to 5-8ng/dl trough level. Median variability was calculated from all recorded Tacrolimus trough levels 6 – 12 month post transplantation. High variability (HV) was defined as variability > observed median and low variability (LV) as </= observed median. HV patients were compared with LV for acute rejection (AR), graft survival, development of new onset of diabetes after transplantation (NODAT) and eGFR at one year.

**Results:** Median tacrolimus variability between 6 – 12 months was 16%. (Range 1% - 81%). Patients with HV had an AR risk of 21% (25/119), compared with an 8% risk (9/120) for LV patients. (P= 0.0049)

Acute rejection was more frequent in the HV group but 26 of 34 episodes occurred less than 3 months after transplantation prior to calculation of variability. 33 of 34 episodes of AR occurred before 6 months. eGFR at one year was found to be significantly worse in the HV group (mean 54 µMol/L, SD 21.2) compared to the LV group. (Mean 64 µMol/L, SD 20.0) P = 0.0008.

There was no significant difference in graft survival and NODAT between the LV and HV groups examined in our study.

**Discussion:** Our findings are consistent with previous observations that HV is associated with worse clinical outcomes. The majority of AR episodes occurred early post transplant, and it might be that AR itself increases susceptibility to tacrolimus variability. We speculate that our follow up time is not long enough to show a significant association between HV and shorter graft survival. However, we find a substantially reduced eGFR in the HV group that is likely to predict shorter graft survival in the long term.

**40**

**Does a patient's weight and age affect tolerance to Mycophenolate treatment post-kidney transplantation?**

Stephen Hughes, Omar Mahsood, Marc Vincent, Afshin Tavakoli, Declan de Freitas,

Hani Riad

*CMFT, Manchester, UK*

**Background:** Immunosuppressive agents are required following kidney transplantion to prevent graft rejection and improve graft survival. Current practice recommends the use of mycophenolate (MPA), either myocephenolate mofetil 1g BD or mycophenolate sodium 720mg BD, and tacrolimus with an optional course of prednisolone. The standardised dosing of MPA does not address the wide variation in total body weight (TBW) of this population. A disproportionately higher MPA dose per kilogram may expose the low weight patient to an increased risk of immunosuppressive complications, such as gastro-intestinal (GI) intolerance, neutropenia, anaemia and infections. Older patients (>60yrs old) receiving MPA are an understudied population and little is known on their tolerance to full dose treatment. Local practice suggests intolerance is high in this group.

**Objective:** The objective of this study was to identify if patients with low TBW or of age >60yrs were at an increased risk of developing adverse effects requiring dose reduction or withdrawal with the standard MPA dose.

**Method:** All adult patients initiated on MPA following a kidney transplant from 01/2009-12/2010 were investigated. The patients age, dry body weight and MPA dose on day 1 was recorded. Any dose reduction within the first six months of transplantation was followed up and the indication for adjustment was recorded.

**Results:** At 180days post-transplant, patients with low body weight (<60kg) required more dose reductions in comparison to the transplant population with a higher baseline body weight (RR=2.48 [95% CI=1.13 – 5.41]). A higher incidence of GI adverse effects was seen among the patients <60kg and, to a lesser degree the patients of TBW 60-79kg (RR=1.3 [95% CI=1.09-1.54]). 75% of the low weight group (<60kg) had at least one dose reduction and a lower average MPA dose at 180days in comparison to patients with TBW >80kg. Older patients (>60yrs) had an increased number of dose reductions required in older patient group was evident(R=2.02 [95% CI=0.9-4.54]) and GI side-effects were higher in this group (RR=1.91 [95%CI=0.92-3.96]). No difference was seen in baseline TBW between the older group (mean 75.6kg) and its younger control (mean 74.4kg).

**Discussion:** Patients with a low body weight, represented in this study as TBW <60kg, had a higher incidence of adverse effects requiring dose reduction. GI side-effects were more problematic in the low weight patients. Over-immunosuppression in the low TBW groups, represented as bone marrow suppression and increased immune related virology, such as CMV, HSV and BK virus, was not pronounced at 180 days. This is possibly due to the enforced dose reductions early in the treatment due to intolerance with GI effects, reducing the MPA burden. A trend of increased dose reductions was seen in the older population group but with no statistical significance. The increased GI side-effects confirmed what is seen in practice. A limitation of this study is the short follow-up period that is unlikely to detect long-term complications of immunosupression. Long term follow-up is required to determine if graft function is affected by MPA dose reductions.

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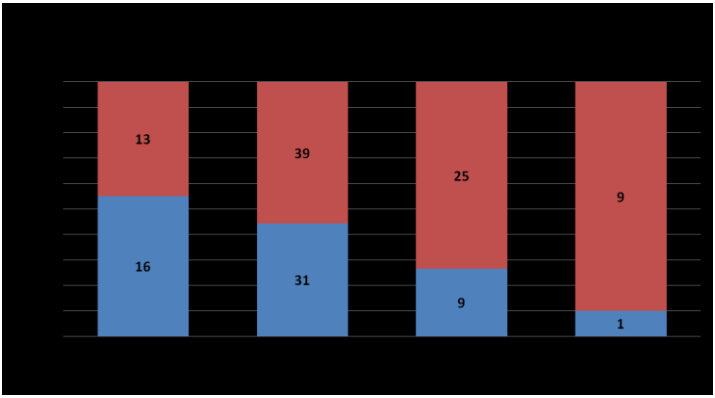


Patients of <80kg had significantly more dose reductions of MPA at 90 days relative to weight (RR= 1.36 [95% CI=1.1-1.68] Fisher T-Test p=0.0057) .
Patients of <60kg did not show a statistical difference vs 60kg+ population but RR = 1.86 [95% CI=0.97-3.56]

# Immunosuppression 3

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## rAnti-Thymocyte globulin. A potential beneficial effect in renal ischaemia-reperfusion in rats – preliminary report

Prabhu Nesargikar, Gilda Chavez, Brad Spiller, Rafael Chavez

*University Hospital of Wales, Cardiff, UK*

**Introduction:** The underlying mechanisms of ischaemia-reperfusion injury (IRI) are complex, with leukocytes being a key factor in the IRI process. Anti-thymocyte antibody (ATG) is a polyclonal antibody which has been shown to diminish leukocyte count, and decrease its adhesion to the endothelial cell following IR. There is limited evidence regarding the effect of ATG on IRI. The aim of this study was to define the role of rat ATG (rATG) on renal IRI.

**Methods:** Adult Lewis rats were subject to unilateral renal IR for predefined ischaemic time (30/40/45 minutes). Following establishment of 40 minute IRI protocol, titrated rATG dose was administered to the rat via a peripheral vein prior to IR. The rats were allowed to recover, and were sacrificed 48 hours later. Both kidneys were retrieved and the H&E stained kidney samples were analysed by a blinded pathologist.

**Results:** The kidney samples were analysed for IRI changes on a 10 point established scale with each parameter graded from 0 to 3, and a final score obtained by simple addition of all the points (max score=30). The mean IRI scores obtained for various groups are tabulated below:

| Groups | Baseline (n=2) | Sham (n=4) | 35 m IRI (n=3) | 40 m IRI (n=11) | 45 m IRI (n=4) | 40 IRI + ATG (n=6) |
|---|---|---|---|---|---|---|
| Mean IRI scores | 1 | 4.75 | 5.67 | 8.5 | 15.5 | 2.83 |

**Discussion:** There seems to be a protective effect of ATG on renal IRI as represented by the lower histology scores, but the exact mechanisms are not clear. Our preliminary results contradict recent studies showing limited effect of ATG on IRI, and further research towards blocking adhesion and cell trafficking molecules as possible mechanisms are underway.

**42**

## Antithymocyte globulin in acute cellular rejection: an efficacy and financial analysis

Joanna Willis, Mark Jenkins, Scott Henderson, Robert Vaughan, Lucy Galloway, David Game

*Renal Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK*

**Introduction:** Antithymocyte Globulin is used in our unit in the treatment of Banff Category 4, grade II/III acute T cell mediated rejection. Outcomes, complications and cost-effectiveness need to be audited in order to determine its future role.

**Methods:** A 3 year retrospective audit was undertaken on all patients treated with ATG for acute cellular rejection. Data was collected on mean CD3 count, response to treatment and rates of infection. A cost-analysis was also undertaken.

**Results:** Between 2008 and 2011 a total of 32 patients received ATG for acute cellular rejection, as first line treatment in 20 (63%) and after failure to respond to initial treatment in 12 (37%). The initial starting dose was 1.5mg/kg/day. Treatment was monitored with daily CD3 counts, and ATG was re-dosed only if CD3 count was >20 cellsμ/l (half-dose for 10-20 cellsμ/l). A surveillance policy was used for CMV, unless the CMV status at transplantation was D+R-, in which case Valganciclovir prophylaxis was used.

In 16 patients (50%), there was resolution of rejection following ATG treatment (94% of allografts functioning at 12 months, mean Creatinine 122umol/l), 7 patients (22%) had ongoing cellular rejection which subsequently responded to further treatment (100% of allografts functioning at 12 months, mean Creatinine 145umol/l) , 4 patients (13%) had ongoing cellular rejection which did not respond to further treatment (25% of allografts functioning at 12 months, mean Creatinine 228umol/l), 3 patients (9%) had an antibody-mediated process revealed on biopsy post- ATG which responded to further treatment (100% of allografts functioning at 12 months, mean Creatinine 131umol/l), and 2 patients had an antibody-mediated process revealed which did not respond to further treatment (both allografts non-functioning). Overall, 26 patients (81%) responded to treatment (either with ATG alone or with ATG and further treatment), and 19% did not respond to any treatment. Patients with late rejection (>1 year post-transplant) had poorer outcomes; 63% did not respond to treatment, and 50% of grafts were non-functioning at 12 months.

91% of patients achieved a mean CD3 count of <30 cellsμ/l. 17/32 patients (53%) had a CMV viraemia of at least 1000 copies/ml, 13 of whom had a high-level viraemia of >10,000 copies/ml. 6 patients (19%) had a clinically significant bacterial infection.

A course of ATG costs on average £4977 per patient (for drug costs and in-patient stay). The use of Alemtuzumab could equate to an average saving of £3960 per patient.

**Discussion:** ATG is effective at treating cellular rejection, although further treatment is often needed in order to fully reverse the process. Outcomes are significantly worse when an underlying antibody-mediated process is revealed following treatment, and in late rejection. In the vast majority of patients treated with ATG, the CD3 counts are adequately suppressed. Rates of CMV viraemia are high, highlighting the need for a review of surveillance policies. Rates of bacterial infection however are low. ATG treatment is expensive, and cheaper alternatives may have similar efficacy. Randomized controlled trials are needed to investigate this.

**43**

**Early sub-therapeutic tacrolimus levels are associated with worse clinical outcomes and reduced eGFR at one year in renal transplant recipients.**

Henry Whalen, Kathryn Stevens, Julie Glen, Colin Geddes, Alan Jardine, Marc Clancy

*Transplant Unit, Western Infirmary, Glasgow, UK*

High intrapatient tacrolimus variability is associated with worse clinical outcomes after renal transplantation. (Borra et al, NDT Vol 25 2010) Long-term high tacrolimus levels may predispose to toxicity, whilst sub-therapeutic tacrolimus levels may be associated with worse clinical outcomes by predisposing to episodes of acute rejection (AR) and therefore graft loss. We hypothesized that sub-therapeutic tacrolimus levels in the first year post renal transplant are associated with worse patient and graft outcomes.

**Methods:** Data were collected from the prospectively compiled electronic patient record for 239 adult renal transplants performed between 01/01/07 and 01/03/09. Patients received standard immunosuppression according to local protocols. Tacrolimus trough levels were considered to be therapeutic between 5-8ng/dL. All tacrolimus trough levels were recorded in the first post transplant year, and the percentage of sub-therapeutic levels were calculated. Those whose sub-therapeutic percentage fell above the observed median were considered a high risk group (HR) and those with values equal to the observed median, or who fell below the observed median were considered a low risk group (LR). HR and LR groups were then compared for episodes of acute rejection (AR), delayed graft function (DGF), graft survival, new onset of diabetes after transplantation (NODAT) and eGFR at one year.

**Results :** The median number of sub-therapeutic levels in 239 patients was 14% (range 0% -78%). There were 115 patients in the HR group, and 124 patients in the LR group. HR patients had a significantly increased AR rate of 21.7% (25/115) compared with 7.3% (9/124) for LR patients. (P= 0.0015) The eGFR levels for HR group (mean 52.5 µMol/L, SD 22.4) were significantly lower than for the LR group (mean 65.0 µMol/L, SD 17.8). (P=0.0001) DGF in the HR group was also significantly increased at 42.6% (49/115) compared with 16.1% (20/124) for the LR group. (P = 0.0001) No difference was observed between groups for the endpoints of graft survival or NODAT.

**Discussion:** Higher rates of sub-therapeutic tacrolimus levels are associated with an increased risk of AR, DGF and a lower eGFR at one year. Our follow-up period (mean 780 days, range 352 – 1591) is short and it is possible that over a longer follow-up, patients in the HR group would be at increased risk of graft loss particularly given the well known association between AR, DGF and subsequent graft loss. Some of these results may represent covariation with patient's compliance however the importance of achieving target tactolimus levels is confirmed and other causes of tacrolimus variability may represent a significant risk to the graft. The observed association between DGF and sub-therapeutic tacrolimus is likely to be a result of DGF patients being given deliberately lower doses of tacrolimus during DGF episodes. Historical outcomes suggest that higher rates of AR observed in the HR group results and lower eGFR levels at one year, predict poorer long-term graft survival rates for these patients.

**44**

## Antithymocyte globulin in acute antibody-mediated rejection: an efficacy and financial analysis

Joanna Willis, Mark Jenkins, Scott Henderson, Robert Vaughan, Lucy Galloway, David Game

*Renal Unit, Guy's and St Thomas' NHS Foundation Trust, London, UK*

**Introduction:** Antithymocyte Globulin is used in our unit during treatment for Banff Category 2 acute antibody-mediated rejection. Immunological efficacy, outcomes, complications and cost-effectiveness need to be audited to determine its future role.

**Methods:** A 3 year retrospective audit was undertaken on all patients with acute antibody-mediated rejection who received ATG. Data was collected on CD3 and CD19 counts, response to treatment, and rates of infection. A cost-analysis was also undertaken.

**Results:** Between 2008 and 2011 a total of 15 patients with acute antibody-mediated rejection received ATG. The initial starting dose was 1.5mg/kg/day. Treatment was monitored with daily CD3 counts and ATG was re-dosed only if CD3 count was >20 cellsμ/l (half-dose for 10-20 cellsμ/l). A surveillance policy was used for CMV, unless the CMV status at transplantation was D+R-, in which case Valganciclovir prophylaxis was used. 10 patients received ATG for biopsy-confirmed acute antibody-mediated rejection. In 3 patients (30%) there was resolution of rejection following ATG treatment (3/3 allografts functioning at 12 months, mean Creatinine 134μmol/l). 1 patient (10%) had ongoing antibody-mediated rejection which responded to further treatment (allograft functioning at 12 months, Creatinine 286μmol/l), but 6 patients (60%) failed to respond to either ATG or further treatment (4/6 allografts functioning at 12 months, mean Creatinine 264μmol/l). 5 patients received ATG following an initial diagnosis of acute cellular rejection and had acute antibody-mediated rejection diagnosed following treatment with ATG. 3 of these patients (60%) responded to further treatment (3/3 of grafts functioning at 12 months, mean Creatinine 131μmol/l), but 2 patients (40%) failed to respond to any treatment (both grafts non-functioning). Overall, out of the 15 patients who received ATG during their treatment for acute antibody-mediated rejection, only 7 patients (47%) responded to any treatment. The majority, 8/15 (53%) did not respond to any treatment. Outcomes were similarly poor in early (<1 year post-transplant) and late (>1year post-transplant) rejection. 83% of patients achieved a mean CD3 count of <30 cellsμ/l. None of the patients achieved a mean (or end of treatment) CD19 count that was lower than their pre-ATG CD19 count. 8/15 (53%) patients had a CMV viraemia of at least 1000 copies/ml, 4 of these 8 with a high-level viraemia of >10,000 copies/ml. 2 patients had a Norovirus-positive diarrhoeal illness and 1 patient had a clinically significant bacterial infection. A course of ATG costs on average £4977 per patient (for drug costs and in-patient stay). The use of Alemtuzumab could equate to an average saving of £3960 per patient.

**Discussion:** Acute antibody mediated rejection carries a poor prognosis for graft survival, and ATG does not appear to be a particularly effective treatment in this small cohort. ATG does not suppress CD19 counts, highlighting the need for more B-cell specific treatments. Rates of CMV viraemia in those treated with ATG are high, but rates of serious bacterial infection are low. ATG treatment is expensive, and cheaper alternatives may have similar or superior efficacy. Randomised controlled trials are needed to investigate this.

**45**

**Ethnic origin does not impact on intrapatient variability in tacrolimus exposure**

Stella Woodward[1, 2], Iain MacPhee[1,2]

*[1]Division of Clinical Sciences - Renal Medicine, St George's, University of London, London, UK, [2]St George's Renal and Transplant Unit, St George's Hospital, London, UK*

**Introduction:** Back renal transplant patients are known to have poorer outcomes than non-Black patients (Ng, *et al.* NDT 2010; 25:628). This may reflect variation in drug metabolism between ethnic groups. High intrapatient variability in tacrolimus exposure is associated with adverse outcomes for renal transplant patients (Borra, *et al*. NDT 2010; 25:2757). We have studied the influence of ethnic group on intrapatient variability of tacrolimus as a potential explanation for the influence of ethnicity on outcome.

**Methods:** Intrapatient variability in dose-normalised blood concentrations of tacrolimus was calculated for 179 patients transplanted and followed up at a single UK centre between 1 January 2000 and 1 September 2010. Tacrolimus whole-blood concentrations measured by immunoassay taken between 6 and 12 months post-transplantation were used. Median intrapatient variability in tacrolimus clearance was calculated for each ethnic group (Caucasian, Black, South Asian, Other). Subjects were also divided into high and low intrapatient variability groups using median variability as a cutoff.

**Results:** Of the 179 patients included in this study, 98 (54.7%) were Caucasian, 40 (22.3%) were Black, 37 (20.7%) were South Asian and 4 (2.2%) were 'Other'. Median intrapatient variability in tacrolimus exposure for all patients was 17.61%. Median intrapatient variability was similar across all ethnic groups; Caucasian 17.7% (inter-quartile range 13.5%-24.6%), Black 16.8% (12.9%-27.2%), Asian 18% (12.5%-23.9%); Other 22.9% (17.7%-29.7%); Kruskal-Wallace Test $p$=0.805. Patients within each ethnic group were split into high and low variability groups as defined for the whole population; of Caucasians, 49 (50%) were in the high and 49 (50%) were in the low variability group; of Blacks, 18 (45%) were in the high and 22 (55%) were in the low variability group; of South Asians, 19 (51.4%) were in the high and 18 (48.6%) were in the low variability group and of the 'Others', 1 (25%) was in the high and 3 (75%) were in the low variability group.

**Discussion:** From these data, ethnic group had no influence on intrapatient variability in tacrolimus exposure. Increased intrapatient variability is unlikely to be the factor underlying the poor long-term outcome of Black renal transplant patients.

**46**

**Differences between the branded and generic solid dosage form medicines: In-vitro dissolution testing**

Mubarak Al Ameri[1, 2], Nanda Nayuni[1], Anil Kumar[2], David Perrett[1], Arthur Tucker[1], Atholl Johnston[1]

*[1]William Harvey research Institute, London, UK, [2]UAE General Hospital, Abu Dhabi, United Arab Emirates*

**Introduction:** Dissolution is defined as the amount of substance that goes into solution per unit time under standardised conditions of liquid/solid interface, solvent composition and temperature. Dissolution is considered one of the most important tools to predict the *in-vivo* bioavailability and in some cases to determine bioequivalence. The aim of this study was t*o compare the differences in dissolution behaviour of solid dosage forms between different brands (reference products) and their generic counterparts (tested products).*

**Methods:** A PT-DT70 dissolution tester (*Pharma Test*) was used to conduct dissolution tests with time on 12 branded medicines and their generic counterparts to detect any *differences in behaviour*. The test was carried out on four replicates for each batch. Tablets and capsules contained the same amount of drug substances but different types and/or amount of excipients were obtained locally and internationally. They were tested according to the British Pharmacopeia, European Pharmacopeia and the US Pharmacopeia with the rate of dissolution determined by ultra-violet Spectrophotometery.

**Results:** The dissolution profile revealed that all the studied medicines comply with the Pharmacopeia specifications and completely dissolved within 60 minutes. However, some generics showed significant differences in dissolution rate at the 5, 15 and 30 minutes. For example, when 40% of the branded amoxicillin 500 mg capsules (antibiotic) dissolved within 5 minutes, only 10% of its generic counterpart dissolved. Dissolution test of other generics showed that they can even dissolve faster than their branded counterparts. For example, when 70% of the generic form of simvastatin 20 mg tablets (anticholesteremic agent) dissolved within 5 minutes, only 28% of its branded form dissolved. In addition, some generic medicines from different batches of the same manufacturer showed significant differences at different time intervals.

***Discussion***: All medicines studied in this experiment fulfilled the medicine agencies' requirement of bioavailability. Yet, dissolution profiles obtained from the studied formulations showed that the release characteristics vary considerably among different manufacturers and even identical formulations showed different dissolution profiles. This illustrates the importance of monitoring patients when switching their medicine.

# Infection

**47**

**Tuberculosis prophylaxis: are national guidelines being adhered to?**

Melanie Field, Andrew Clarke, Matthew Kelleher, Stephen Mellor, Ahmed Hamsho, Andrew Ready, Nicholas Inston, David van Dellen

*Queen Elizabeth Hospital, Birmingham, UK*

**Background:** Renal transplantation provides the optimal renal replacement therapy with the caveat of an associated immunocompromised state. This places recipients at increased risk of infective complications with Tuberculosis is 20 – 70 times more common in renal transplant recipients. Recent guidelines regarding routine Tuberculosis prophylaxis have recently been published in the United Kingdom (suggesting Isoniazid 300mg). We aimed to investigate prophylactic regimens in use amongst Renal Transplant units nationally, an area of particular relevance given the increasing prevalence of the disease nationally as well as its deleterious effects on patient outcome.

**Methods**: All renal transplantation centres across Great Britain and Ireland were approached for tuberculosis prophylaxis protocols post-transplantation. This was achieved via the designated renal pharmacist for each centre who was approached by e-mail and telephonically sequentially with a standardised questionnaire. This enquired as to medication used, including dosage and duration of treatment as well as patient demographics warranting inclusion for treatment.

**Results:** 23/25 (92%) transplant centres in Great Britain and Ireland responded. All centres giving prophylaxis did so in the form of Isoniazid with variable dosages given across the majority of centres although a propensity for either 200mg or 300mg was noted. (no prophylaxis: 4 centres; Isoniazid 200mg: 5 centres; Isoniazid 300mg: 8 centres; others: 6 centres) In addition, duration of prophylaxis offered also varied, with many centres offering no prophylaxis and 6 months prophylaxis having the highest incidence (no prophylaxis: 4 centres; 6 months:7 centres; 1year:4 centres; lifelong:3 centres; others: 5 centres .). There appears to be no patient demographic standard for prophylaxis in the United Kingdom with great variance amongst individual units.

**Discussion:** Tuberculosis remains an important pathogen in the immunocompromised host. Prophylaxis therefore has plays a potentially crucial role in the post-transplant population. There appears to be no national consensus or adherence to recently published guidelines to ensure standardised 'best practice'. This is occurring despite that the fact that within certain urban communities nationally, tuberculosis has reached endemic levels. It is important that a rigorous approach to TB prophylaxis is undertaken to prevent unnecessary morbidity and mortality in the transplant population. Guidelines should be adhered to ensure optimal outcomes, with great variability in prophylactic regimens being noted nationally.

**48**

**Tuberculosis prophylaxis in renal transplantation: A UK survey of current practices.**

Laura Maynard-Smith, Marc Lipman, Susan Hopkins, Mark Harber, Bimbi Fernando

*Royal Free Hospital, London, UK*

**Introduction:** Renal transplant patients with latent TB infection (LTBI) are at greatly increased risk of developing active TB disease. This is of concern as UK transplants often come from TB endemic countries. In 2010, the Joint TB Committee (JTC) of the British Thoracic Society developed management guidance for renal transplant units caring for those at risk of TB. We wished to determine whether these or other guidance were in use within UK transplant centres.

**Methods:** An electronic self-completed survey was sent to all UK renal transplant centres in October 2011. This enquired about TB risk factors within the transplant population; as well any unit protocols in place to prevent post transplant TB. Results were compared to JTC guidance.

**Results:** 74% UK transplant centres replied to the survey, with 88% providing complete responses. 4 transplant units reported >3 TB cases between 2006-10. 65% centres had a protocol (though this was no more common in high TB incidence units). Over one third reported basing their protocol on JTC guidelines, despite 25% of these not being in line with the guidance's recommendation for clinical risk assessment or prescribed chemoprophylaxis. Centres with a protocol not based on guidance gave inadequate prophylaxis 40% of the time. A further 20% used chemoprophylaxis with no evidence base. Centres with no protocol at all refer to TB services to administer prophylaxis for LTBI in a third of cases; a further third prescribe chemoprophylaxis with no evidence for its use. 60% centres screened live donors for possible TB by chest radiograph; 13% centres routinely ask about previous TB infection and reviewed any recent chest radiographs of cadaveric donors.

**Conclusion:** Transplant centres with a higher proportion of patients from a TB endemic country saw more TB post renal transplant. There is a wide variation in practice, which is unrelated to the TB incidence of various transplant centres. Centres without a protocol based on published guidance are more likely to be either providing inadequate chemoprophylaxis for patients with LTBI, or increasing the risk of drug toxicity and side effects by treating for extended periods of time. More guidance is necessary on how to deal with patients requiring a renal transplant who have had fully treated TB in the past. Increasing the screening rates of live and cadaveric donors may help to reduce the numbers of active TB infections seen post renal transplant.

**49**

## A retrospective review of urinary tract infections in our 2010 renal transplant patients: Predictors of infection, sensitivities and outcome data

Daniel Brudney, Lasantha Seneviratne, Mark Harber, Sophie Collier, Hala Kandil

*[1]Deptartment of Microbiology, Royal Free Hampstead NHS Trust, London, UK, [2]UCL centre for Nephrology, Royal Free Hampstead NHS Trust, London, UK*

**Introduction:** Urinary tract infection (UTI) is the most common bacterial infection in renal transplant recipients. The clinical presentation of post-transplantation UTI is variable and these infections can predispose to graft dysfunction.

**Aims:** The aim of this study is to determine the sub-population of patients who are at higher risk of developing UTIs and to study the isolate type and sensitivity pattern in this group. We also looked at the natural history of asymptomatic pyuria.

**Methods:** We performed a retrospective study on all adult patients (n=101) who received a renal transplant at Royal Free Hospital, London UK, from January 2010 to December 2010. The data was analysed using SPSS software.

**Results:** 59 renal transplant recipients developed UTI post transplant of which 41 had more than one episode over a mean follow-up period of 8 months. Risk factors for post-transplant UTIs were female sex (OR 5.41, 95% CI 2.06-14.25, p=0.001) and cadaveric transplant (OR 1.37, 95%CI 0.29-1.79, p=0.494). UTIs prior to transplant, age and underlying diagnosis were not significant. We looked at the effect of UTIs on graft function. We looked at how asymptomatic pyuria (WCC/$mm^3$>40-200) predicted the development of subsequent UTI in our patients. *Escherichia coli* was the commonest organism identified (60.3%). 55%, 46% and 80% of positive cultures growing enterobacteriaciae were resistant to augmentin, ciprofloxacin and co-trimoxazole respectively. Renal transplant patients are given septrin prophylaxis for 6 months post transplant. The rate of enterobacteriaciae carrying ESBL or AmpC enzymes was 33%.

**Conclusion:** Identification of the key factors which predict the development of symptomatic UTI in renal transplant patients will ultimately lead to early recognition, more detailed follow up and appropriate treatment. Looking at the sensitivity data, we no longer have a reliable empirical oral first line option. Ongoing surveillance of antibiotic sensitivities and prudent antibiotic use is needed.

**50**

**Tuberculosis infection post renal transplantation: a single centre experience**

Laura Maynard-Smith, Marc Lipman, Susan Hopkins, Mark Harber, Bimbi Fernando

*Royal Free Hospital, London, UK*

**Introduction:** Rates of TB in the UK have been gradually rising over the last 20 years. Patients who have had renal transplants are at a higher risk of developing active TB due to immunosuppression. There is also a large overlap between those patients developing chronic kidney disease requiring transplantation and patients from ethnic minority groups who are born in TB endemic countries. We report a London renal transplant unit's experience of active tuberculosis (TB) following renal transplantation. This centre performs approximately 100 transplants per year, and has between 21-40% transplant population from TB endemic countries.

**Method:** Using transplant and TB databases plus clinical records, we identified all cases of TB in the renal transplant population attending our service between 2001 – 2011. Through reviewing the clinical records, we analysed demographic data, clinical manifestations, time from transplant to a definitive diagnosis of TB, and how that diagnosis was reached.

**Results:** 9 patients developed TB between 2001 – 2011. Two patients' clinical records were unavailable for analysis. Of the remaining 7 patients, 6 patients (86%) were born in a TB endemic country, and 3 patients (43%) had a known previous exposure to TB, with one patient having previously received treatment for TB. Only one patient received tuberculosis prophylaxis following renal transplantation. The median time from transplant to TB diagnosis was 54 months (range 6 – 302). This wide range may reflect the fact that some cases will be a reactivation of latent TB, and others will be newly acquired cases post-transplant. The median time from patient-reported symptoms to definitive diagnosis was 42 days (range 20 – 78). The most common presenting symptoms were fever (86%), night sweats (71%) and weight loss (43%). Four patients had live-related transplants, and of the four donors, 75% were also born in a country where TB was endemic. Lymph nodes were the focus of infection in 4 patients (2 cervical lymph nodes, 1 mediastinal, 1 inguinal), disseminated infection (involvement of more than one organ) in 3 patients (43%) and 2 patients (29%) developed TB in the transplanted kidney. Diagnosis was made on a positive culture from biopsy (all of which were smear negative) in 3 patients (43%), histology in 2 cases (29%), a smear positive biopsy (also subsequently culture positive) in one patient (14%), and a positive TB PCR result in the final patient (14%). One patient died, but not from a TB related cause.

**Conclusion:** TB infection can occur at any time post renal transplant. The presentation is much more extra-pulmonary in nature, than in the background population where >50% develop pulmonary TB. It is important to be vigilant of TB in all possible manifestations, especially in those born in TB endemic countries. Furthermore in cases of live renal donors from these areas, it would be worthwhile to test the donor for latent TB infection. Chemoprophylaxis prior or post transplant may reduce the development of active TB.

**51**

## Acyclovir prophylaxis against cytomegalovirus in high risk paediatric kidney transplant recipients

Elizabeth Evans, Manish Gupta, David Milford

*Birmingham Children's Hospital, Birmingham, UK*

**Aims**: Cytomegalovirus (CMV) is an important infectious pathogen after kidney transplantation causing significant morbidity and mortality. Several prophylactic antiviral treatments are used and the aim of this study was to review the efficacy of acyclovir prophylaxis to prevent CMV infection in paediatric kidney transplant recipients.

**Methods**: The clinical records of kidney transplant recipients over a 20 year period were reviewed. Details of recipient and donor CMV serostatus were recorded together with information regarding prophylaxis received, evidence of CMV infection, and CMV related complications. All patients were scheduled to receive 5mg/kg loading dose acyclovir peri-operatively and then acyclovir 200mg qds for 90 days.

**Results**: 192 kidney transplants were performed in 177 children between 1991 and 2010. Only first grafts were considered in subsequent analysis. 36 recipients were identified as being at risk of CMV after transplant (i.e. recipient CMV IgG negative, donor CMV IgG positive). All of these patients received oral acyclovir prophylaxis and 58% received an intravenous loading dose. Of these 36 patients, 9 (25%) developed CMV viraemia with a positive CMV PCR. 7 patients met the criteria for CMV disease. 8 of these 9 patients developed disease whilst on acyclovir indicating active CMV replication despite treatment. There were no cases of severe infection or tissue invasive disease. There was no graft loss as a consequence of CMV infection.

**Conclusions**: The evidence supporting the choice of prophylactic treatment for CMV in paediatric kidney transplant recipients is limited. Recent data from the adult population indicate rates of disease are substantially lower in kidney transplant recipients treated with valganciclovir. These data indicate that in high risk individuals there is substantial risk of CMV disease despite prophylaxis with acyclovir and suggest that prophylaxis with valganciclovir is likely to result in significantly lower rates of CMV disease.

**52**

**BK virus nephropathy in renal transplant recipients**

Manu Prakash, Chas Newstead, Richard Baker

*St James's University Hospital, Leeds, West Yorkshire, UK*

**Aim:** To review management strategies and outcome of BK Polyoma virus nephropathy (BKVN) in renal transplant recipients.

**Methodology:** All renal transplant patients with BK nephropathy between 1994 - 2009 in the local region were reviewed.

**Results:** There were 22 cases. In twelve, the Blood viral PCR was positive within 12 months after transplantation, of which 6 were diagnosed between 3 and 6 months post transplantation. Baseline immunosuppression regimen **-** all patients except one received tacrolimus and eighteen were treated with mycophenolate mofetil. Acute Rejection occurred in 9 cases (7 cellular, 1 vascular, 1 both). Eight received leflunomide after MMF withdrawal and co-incident with reduction of tacrolimus, of which three had co-incident acute rejection. Graft failure occurred in seven cases. Six of these had acute rejection and only one of these received leflunomide. Graft failure occurred in 1 / 8 who received leflunomide, and 6 / 14 of those who did not (p=0.19, Fisher's Exact test).

**Conclusion:** The data do not provide a compelling argument for any particular management strategy for treating BK polyoma virus in renal transplant recipients. Concurrent acute rejection and BK viral nephropathy in this group had a very poor prognosis. Current local practice is to start Leflunomide once BKVN has been confirmed histologically. No adverse effects related to the drug have been reported so far.

**53**

## Graft site candidiasis and fungal ureteric obstruction of a transplanted paediatric horse-shoe kidney: a case report

Emma Aitken, David Kiggen, Colin Geddes, Enric Murio, Vladyslav Shumeyko, David Kingsmore

*Western Infirmary, Glasgow, UK*

**Background:** We present an unusual case of graft site candidiasis presenting as fungal ureteric obstruction in the adult recipient of a paediatric horseshoe kidney.

**Case report:** A 42 year-old woman with end-stage renal failure was transplanted a paediatric (DBD) horseshoe kidney with duplex collecting system. The operative procedure was uncomplicated. Proximal donor aorta and IVC were oversewn and the distal ends anastomosed end-to-side to recipient external iliac artery and vein. The donor ureters were spatulated, anastomosed and implanted onto bladder with two pigtail stents. The initial post-operative course was uneventful (discharged day 10 with a serum creatinine of 140mg/dl). 6 weeks later she represented with oliguria. Creatinine was 427mg/dl. Ultrasound revealed moderate hydronephrosis of the left moiety and a 8x4cm perinephric collection. Percutaenous nephrostomy was performed and the collection drained. 48 hours later she developed urinary peritonitis, pyrexia and elevated inflammatory markers. CT abdomen with contrast via the nephrostomy confirmed free intra-abdominal fluid, with leakage of contrast from the renal pelvis, through a breach in the peritoneum, into the abdominal cavity. Failure to improve with broad-spectrum antibiotics necessitated laparotomy. There was gross hydronephrosis and hydroureter of both collecting systems. The ureters were filled with thick "cottage cheese like" material which solidified into ureteric casts. The ureters were irrigated and re-implanted and the peritoneum washed out. *Candida albicans* was isolated from peripheral blood, urine and ureteric casts. Antimicrobial cover was provided with Tazocin and fluconazole (4mg/kg/day). The patient's condition transiently improved with anti-fungal treatment, however she again developed systemic sepsis and on day 13 (two months after transplantation), the decision was taken to undertake transplant nephrectomy. Macroscopically, the entire kidney capsule was covered in balls of white fungus. Microscopically, necrotising granulomatous inflammation was noted within the renal cortex, with fungal hyphae seen in both the renal pelvis and wall of the ureter. Post-transplant nephrectomy, the patient remained on amphotericin B for a total of 30 days and received twice daily bladder washouts. Her ongoing recovery was complicated by pulmonary thromboembolism, infected haematoma and septic shock necessitating a short admission to ICU. However she was eventually discharged after 6 weeks and has now made a complete recovery and is re-established on haemodialysis.

**Discussion:** Opportunistic infections in immunosuppressed patients are commonplace; however graft site candidiasis is rare affecting less than 1 in 1,000 renal transplants. To our knowledge, there are only two other cases of fungal ureteric obstruction following renal transplantation. In neither case was the infection donor derived. We postulate that in this case the abnormal anatomy of the donor kidney, predisposed to stagnation of the urine latent fungal infection reactivated in the immunosuppressed recipient.

# Ischaemia-reperfusion / preservation

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**Analysis of a peri-operative complement action and biochemical signals for kidney allograft regeneration during renal transplantation. a preliminary report**

Wojciech Blogowski[1], Barbara Dolegowska[1], Daria Salata[2], Marta Budkowska[2], Leszek Domanski[3]

*[1]Department of Laboratory Diagnostics and Molecular Medicine, Pomeranian Medical University, Szczecin, Poland, [2]Department of Physiology, Pomeranian Medical University, Szczecin, Poland, [3]Department of Nephrology, Transplantation and Internal Medicine, Pomeranian Medical University, Szczecin, Poland*

**Introduction**: Recently we reported that complement activation during acute organ injury may lead to stimulation of its regeneration due to mobilization of bone marrow-derived stem cells, via release of sphingosine-1-phosphate (S1P) from erythrocytes (*Leukemia 2010; 24:1667-75*). In this paper we wanted to examine peri-operative complement activation during ischemia-reperfusion injury (I/R) following kidney transplantation, and establish whether activation of the complement creates a pro-regenerative environment, as well as, if it is associated with post-transplant allograft function.

**Methods**: Renal transplant recipients (n=69) were divided into early, slow and delayed graft function group (EGF, SGF, DGF). Blood samples were collected intra-operatively directly before, and in the 1$^{st}$ and 5$^{th}$ minute of allograft reperfusion from the renal vein. Complement (C3a, C5a, C5b-9), S1P, extracellular haemoglobin, and albumin levels were measured using ELISA, RP-HPLC and spectrophotometry (respectively).

**Results**: During I/R injury significantly higher C5b-9 levels were observed in SGF and DGF patients, comparing to EGF individuals. These were correlated with peri-operative thromboxane concentrations ($R=0.69;P<0.005$). No significant differences in terms of C3a and C5a levels were observed in analyzed groups of patients. Our preliminary results indicate that peri-operative complement activation does not correlate with circulating S1P nor stromal-derived factor-1 levels, which did not significantly change within reperfusion time. Enhanced peri-operative activation of complement was associated with worst early and long-term (1 year) allograft function.

**Discussion**: During human renal transplantation selective activation of the complement cascade occurs, and is more evidently pronounced in SGF/DGF patients. Peri-operative complement levels do not seem to be involved in creation of a biochemical environment that could biochemically stimulate pro-regenerative signaling from kidney allograft to stimulate systemic bone marrow-derived stem cells mobilization.

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## Identification of novel protein biomarkers in a Porcine model of Renal Warm Ischaemia Reperfusion injury: A preliminary report

Mohammad Ayaz Hossain[1], Helen Byers[2], Omar Jallow[2], Mei Nortley[1], Rene Chang[1], Nicos Kessaris[1], Iain Macphee[1, 3], Mohamed Morsy[1]

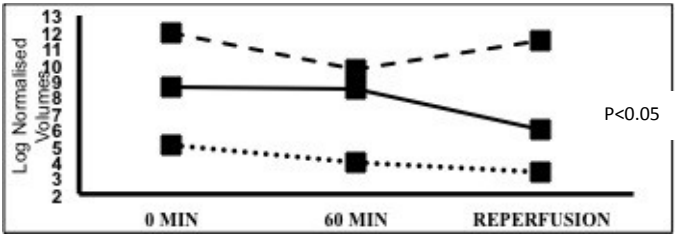
*[1]St Georges Renal and Transplant Unit, St Georges Hospital NHS Trust, London, UK, [2]SGUL Biomics Facility, Division of Clinical Sciences, St George's University of London, London, UK, [3]Division of Clinical Sciences, St George's, University of London, London, UK*

**Introduction**: Warm Ischaemia (WI) during Donation after Cardiac Death (DCD) significantly impacts on kidney transplant outcomes. The development of a biomarker of warm ischaemia would aid viability assessment prior to use and potentially open avenues for therapeutic intervention. We describe the assessment of an established porcine model of renal WI in the identification of potential novel protein biomarkers.

**Methods**: Open renal biopsies were obtained from 3 anaesthetized wild white pigs (Home Office license). Three biopsies were obtained from each pig prior to, at 60 minutes after renal artery clamping (WI) and 60 minutes following reperfusion. Protein samples were obtained after Trizol extraction and subsequent purification. 1D and 2D gel electrophoresis was performed prior to Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) for spot identification. A blinded histopathologist assessed all biopsies for tissue viability/damage.

**Results**: Nine samples were analysed (3 controls, 3 ischaemia and 3 reperfusion). Nine 2D 10% SDS PAGE gels were performed. In each gel, 967 spots were analysed of which 14 spot intensities were found to be significantly different across the 9 gels (2 way ANOVA $p < 0.05$) utilizing Progenesis Same Spot software. Selenium binding protein, Annexin A11 and Glycine amidinotransferase were significantly upregulated in WI, and downregulated after reperfusion. Immunoglobulin Lambda chain and HSP 27 ($p<0.05$ and $p=0.052$ respectively) increased in WI and reperfusion, while Beta actin and Galactose mutarotase were downregulated in WI and reperfusion. Others protective proteins are depicted in the figure.

**Conclusions**: We have demonstrated that despite the normal histological appearance of specimens, certain proteins show change in expression during 60 minutes WI and after reperfusion. Cell based models have implied that some of these proteins have a protective function. This is the first higher order animal model greater than rodent to demonstrate their expression pattern during WI alone. Further confirmatory study with RT-PCR and western blotting is underway to validate these findings. Stratification across further time points is underway. This might enable markers to be quantitatively assessed for future therapeutic and diagnostic interventions to be developed for clinical assessment of viability.



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**Feasibility study on hypothermic machine perfusion of discarded human donor livers using a pressure controlled system. Initial results on perfusion parameters (pressure, flow, resistance, temperature) and sterility**

Ali Jomaa, Pulathis Siriwardana, Kurinchi Gurusamy, Harry Parkes, Alison Winstanley, Innes Claworth, Peter De Muelder, Brian Davidson, Barry Fuller

*department of surgery-Royal Free Campus - University College London Medical School, Royal Free Hospital - 9th Floor - Pond Street - NW3 2QG, UK*

**Background:** Hypothermic machine perfusion (HMP) has shown superior results to conventional cold storage method in kidney preservation. Similar promising results have been reported for HMP of livers in large animal models; however data from human livers remain scarce. The aims of this study are to establish a reproducible method of HMP of human livers, to assess if sterility can be maintained throughout the procedure and evaluate mode of perfusions (Hepatic artery (HA) alone, portal vein (PV) alone, or both simultaneously)

**Methods:** 16 human livers rejected for transplant by all UK centres with appropriate consent for research were randomised into 4 groups. Group1: 7 hours cold storage and one hour HMP through HA alone (n=4). Group2: 7 hours cold storage (CS) and 1 hour HMP through HA and PV (n=4). Group3: 7 hours CS and 1 hour HMP through PV (n=4). Group4: 8 hours simple CS. A pressure controlled system where flow is automatically adjusted according to resistance to maintain a constant pressure (7 mmhg PV, 30 mmhg HA) was used based on the Lifeport kidney machine using Belzers KPS perfusate. Livers were perfused at 4 to 8 degree Celsius under sterile conditions. Perfusion parameters (pressure, flow, resistance and Temperature) were recorded every 15 min. Perfusate samples for microbial culture and sensitivity (MC&S) were taken before and after the perfusion.

**Results:** HA pressure of 30 mmhg and PV pressure of 7 mmhg were maintained throughout the perfusion. HA and PV flow ranged from 11 to 107 ml/min (average 59.5 ml/min) and 39 to 199 ml/min (average 96.2 ml/min). HA and PV resistance ranged from 0.17 to 1.99 (average 0.71) and 0.07 to 0.17 (average 0.08). There was no significant difference in flow and resistance between single and dual vessels groups. Temperature was maintained between 4 and 8 degree Celsius. MC&S results showed that sterility was maintained throughout the process

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## Persufflation as a means of restoring the function of hearts sourced from donors after circulatory death

Omar Mownah[1], Muhammad Khurram[1], Christopher Ray[1], Aditya Kanwar[1], Douglas Rees[1], John Brassil[1], Susan Stamp[2], Noel Carter[3], John Dark[1], David Talbot[1]

*[1]Freeman Hospital, Newcastle Upon Tyne, UK, [2]Newcastle University, Newcastle Upon Tyne, UK, [3]University of Sunderland, Sunderland, UK*

**Introduction:** Utilisation of hearts from Donors after Circulatory Death (DCD) could increase the donor pool and stem the decline in heart transplantation. Persufflation is a method of introducing oxygen into the organ during the cold preservation phase. This may offset the effects of warm ischaemia inflicted on the DCD heart, enabling a greater chance of functional recovery.

**Methods:** Seventeen cross-Yorkshire Landrace pigs (divided into three groups) were euthanased humanely by Schedule-1 (intravenous administration of phenobarbitone) or exsanguination. The non-beating hearts were procured after being subjected to 10 – 29 minutes of warm ischaemia. All hearts underwent initial antegrade flush with AQIX® RS-I solution (a novel non-phosphate pH buffered preservation solution). Group I and II hearts were subjected to static cold storage (SCS). The Group III hearts were subjected to retrograde oxygen persufflation via the coronary sinus, at a pressure of 12mmHg, whilst the heart was immersed in cold AQIX® RS-I solution. 10-12 small holes were made in the myocardium, using a 21G needle, to create an outlet for excess oxygen. Reperfusion was performed on a Langendorff modification of Model 30 Functional Circulation circuit, using a mixture of heparinised, leukocyte-depleted blood and AQIX® RS-I solution. Drugs (adrenaline, calcium gluconate, dopamine) and DC cardioversion were used to initiate left ventricular activity.

| Results: Heart number | Flush / preservation | Drugs | Activity |
|---|---|---|---|
| **GROUP I (1-6)** | 250mls RS-I / RS-I (SCS) | None +/- adrenaline | 2/6 - reanimated with ventricular contractions |
| | | | 3/6 - fibrillation only |
| | | | 1/6 - nil activity |
| **GROUP II (7-11)** | 250mls RS-I + 250mls UW / RS-I (SCS) | Adrenaline, Ca gluconate | 4/5 - reanimated with ventricular contractions |
| | | | 1/5 - nil activity |
| **GROUP III (12-17)** | 250mls RS-I / coronary sinus persufflation | Adrenaline, magnesium, Ca gluconate +/- co-amoxiclav | 5/6 - reanimated with sustained ventricular contractions |
| | | | 1/6 - nil activity |

**Discussion:** DCD hearts subjected to preservation using coronary sinus oxygen persufflation can be successfully reanimated. This study compared persufflation with a retrospective control group (SCS). However, persufflation has demonstrated promise as a potential method for introducing oxygen into the heart during the cold preservation phase, with subsequent ability to achieve sustained reanimation.

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**The oxygenated flush – a simpler way to resuscitate DCD kidneys? A porcine transplant model**

Christopher Ray[1,2], Muhammad Khurram[1,2], Omar Mownah[1,2], Aditya Kanwar[1,2], Susan Stamp[3], Douglas Rees[3], Kathryn White[3], Katrina Wood[3], Aurelie Thomas[3], Paul Flecknell[3], Noel Carter[2], David Talbot[1]

*[1]Department of Liver and Renal Transplant, Freeman Hospital, Newcastle-Upon-Tyne, UK, [2]Department of Pharmacy Health and Wellbeing, University of Sunderland, UK, [3]Newcastle University, Newcastle-Upon-Tyne, UK*

**Aims:** To test the impact of oxygenated flush preservation on the function of Maastricht category II DCD kidneys, in a porcine transplant model.

**Methods:** We used female cross-yorkshire landrace white pigs as donors (n=6) and litter matched females (n=12) as recipients. ABO incompatibility was excluded by serum-donor cell agglutination studies. Donor animals were euthanased by exsanguination. After 30minutes warm ischaemia, kidneys were retrieved en-bloc, separated, thrombolysed and flushed. Kidneys were randomised to receive either 500mls ambient room temperature oxygenated RS-I solution with 1000mg N-acetylcysteine (RS-I $0_2$ NAC) flush or 500mls hypothermic Marshall's solution flush (control). Kidneys were cold-stored statically for 24-30hrs in UW. Recipient animals underwent GA, spinal analgesia, central-venous line insertion, bilateral native nephrectomy and renal implantation – with ureteric reconstruction. A tunnelled suprapubic catheter was inserted into the bladder. Animals were administered IV steroids, antibiotics, tacrolimus syrup bd, ranitidine syrup daily and free access to food and water. Daily blood sampling was accessed by central line. Post mortem was conducted at day 6 after euthanasia.

**Results:** All animals displayed a degree of delayed graft function. 10 of 12 animals survived to 6 days. One pair of animals was euthanased on day 5 at veterinarian request (due to ataxia and poor oral intake in the control animal). Serum creatinine trends rose similarly during 6-day recovery period; to a mean 1729 *µmol/L* +/- 844 in RS-I $0_2$ NAC group versus 1540*µmol/L* +/-950 in control group (NS). Proteinuria, indicative of glomerular injury, was greater in the control group (mean 1.65g/dl control versus 0.45g/dl RS-I $0_2$ NAC) (NS). Acute cellular rejection was evident in all histology samples except one recipient from the RS-I $0_2$ NAC group. Electron microscopy examination revealed improved glomerular podocyte (FPW) preservation in the RS-I $0_2$ NAC group with less effacement (RS-I $0_2$ NAC mean FPW 366.5ηm +/- 47 versus Control 433.0ηm +/- 63) (NS).

**Discussion:** Results from this pilot transplant model suggest a preservation benefit from the addition of oxygenation and free-radical scavenge to initial organ flush. This is a simpler and rapid technique compared to ECMO or hypothermic oxygenated machine perfusion.

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## Effect of machine perfusion on the early function of kidneys from donors after cardiac death

Laszlo Szabo, William Cook, Argiris Asderakis, Elijah Ablorsu

*University Hospital of Wales, Cardiff, UK*

**Background:** Utilization of kidneys from donors after cardiac death (DCD) has been increased in recent years to overcome organ shortage. Unfortunately, these kidneys suffer from more extensive ischemic damage compared to standard criteria donors and this might have negative impact on post-transplant outcomes. Aim of this study was to assess the effect of hypothermic pulsatile machine perfusion (MP) on the early function in DCD kidneys.

**Methods:** We analysed the prospectively collected data of 12 pairs of kidney transplant recipients who received a DCD kidney from the same donor between 04 Sep 2010 and 30 Sep 2011 in our centre. The kidney transplanted first, in each pair, was stored in cold static storage (CS) and the second kidney was machine perfused (MP) using the LifePort (Organ Recovery Systems). Between these two groups, we compared the incidence of delayed graft function (according to the need for dialysis on the first post-transplant week, dDGF), the functional delayed graft function (failure to decrease serum creatinine by at least 10% daily on 3 successive days during the first post-transplant week, fDGF), as well as the levels of glomerular filtration rate in the first month.

**Results:** The average age of donors was 61.3±13.5 years (mean ± SD). There was no significant difference in recipients' age between these two groups (64.4±6.4 vs. 62.1±9.8 years, MP vs. CS, p=0.52). Cold ischemic time (CIT) was 14.3±3.4 h in the MP group compared to 8.1±2.7 h in the CS group (p<0.0001). The kidneys were perfused on the machine for 6.5±2 hours. 75% of patients in the CS group had dialysis on the first post-transplant week, but only 41.7 % of patients in the MP group (p=0.11). Functional DGF was also higher in the CS kidneys compared to MP kidneys (91.7% vs. 66.7%, p=0.16). The glomerular filtration rate after one, two, three and four weeks was 15.3±8.3, 23.5±12.6, 33.1±11.5, 37.1±10.8 in the MP group compared to 12.2±8.8, 19.7±12.4, 24.8±11.2, 32.9±11.9 mL/min in the CS group (p=0.20, 0.23, 0.04, 0.19).

**Conclusions:** Our data shows that despite a significantly longer cold ischemic time, kidneys preserved on MP had better early graft function and reduced DGF, compared to pair kidneys stored in CS. These results suggest that MP might have a positive impact on early graft function on DCD kidneys and could be effectively used in the setting of long cold ischemic times.

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## Impact of machine perfusion on outcomes of renal transplantation from deceased donors

Gabriele Di Benedetto, Bence Forgacs, David van Dellen, Titus Augustine, Afshin Tavakoli

*Manchester Royal Infirmary, Manchester, UK*

**Background:** Increasing waiting lists for renal transplantation has led to the increased use of extended criteria donor (ECD) kidneys to attempt to bridge the demand and supply gap. To ensure optimum outcomes from these marginal grafts, innovative techniques have evolved for both preservation and assessment of these kidneys, including pulsatile machine perfusion. Studies to date have not clarified the optimal use of this technique and controversies remain, including whether donor grafts should be 'pumped' at the site of procurement or rather back at the base transplant unit. We aimed to evaluate this centre's experience with machine perfusion since the introduction of this technique and also to assess whether the length of perfusion time had a significant impact on graft outcomes.

**Methods:** A retrospective analysis was made of a contemporously maintained database of kidneys machine perfused over a 2 year period (Oct 2009- Oct 2011). All kidneys were placed on Lifeport® Kidney Transporters (Organ Recovery Systems) at the donor hospital. The procured kidneys were subclassified into 3 groups based on length of time of pulsatile perfusion (A - <6hrs; B – 6-10hrs; C- > 10hrs) Outcomes were compared utilising primary non function (PNF) and delayed graft function (DGF; requirement for two or more sessions of dialysis in the first week post transplantation) as primary endpoints and biopsy proven acute rejection (BPAR), eGFR at 3 months, and graft and patient survival as secondary endpoints.

**Results:** Demographics were as follows: (equivalent cold ischaemic times; p=NS for all)

| Group | No of kidneys | DCD | DBD | Discarded | Donor age (median) | Reciepient age (median) |
|---|---|---|---|---|---|---|
| A | 13 | 11 | 2 | 4 | 43 | 50 |
| B | 14 | 12 | 2 | 1 | 48 | 53 |
| C | 13 | 13 | 0 | 1 | 61 | 56 |

Primary and secondary endpoints: (p=NS; Fisher's exact test for all)

| Group | PNF | DGF | BPAR | Death | Graft loss | eGFR |
|---|---|---|---|---|---|---|
| A | 0 | 0 | 0 | 0 | 0 | 23 |
| B | 0 | 3 (23%) | 1 (7.6%) | 1 (7.6%) | 1 (7.6%) | 24 |
| C | 1 (7.1%) | 1 (7.1%) | 3 (21.4%) | 0 | 0 | 33 |

**Conclusion:** The role of machine perfusion as an adjunct to the use of ECD remains to be conclusively defined. Our experience suggests that the length of pulsatile perfusion prior to implant has no impact on graft outcome and complications. The increased yield of ECD donor kidneys with favourable outcomes that this method provides ensures that this technique will continue to evolve. Further work is required to elucidate the importance of pulsatile resistance and what the ultimate limits to successful perfusion and subsequent transplantation may prove to be.

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## Assessing the role of an oxygenated organ flush in DCD donors - an ex-vivo renal model

Christopher Ray[1,2], Muhammad Khurram[1,2], Omar Mownah[1,2], Aditya Kanwar[1,2], Susan Stamp[3], Douglas Rees[3], Kelly Philipson[2], Robert Peaston[2], Kathryn White[3], Katrina Wood[3], Noel Carter[2], David Talbot[1]

*[1]Department of Liver and Renal Transplant, Freeman Hospital, Newcastle-Upon-Tyne, UK, [2]Department of Pharmacy Health and Wellbeing, University of Sunderland, UK, [3]Newcastle University, Newcastle-Upon-Tyne, UK*

**Aims:** While there has been extensive investigation into the benefit of ECMO and prolonged hypothermic oxygenation, the value of an oxygenated flush in renal organ perfusion and preservation in the context of donation after cardiac death (DCD) is unclear. We sought to assess this simple method adjunct in an ex-vivo model of preservation and sanguineous reperfusion.

**Methods:**
- Kidneys were procured from cross-Yorkshire landrace pigs after schedule-1 euthanasia and subjected to 30minutes of primary warm ischaemia.
- Both groups were then administered thrombolysis as per Newcastle protocol.
- Organs were flushed with 500mls of oxygenated ambient room temperature (18-23°C) Aqix® RS-I solution with N-acetylcysteine 1000mg (RSI-$O_2$-NAC) or with 500ml cold (4-8°C) Marshalls solution (control).
- Kidneys were then subjected to static cold storage for 24hours in UW solution
- Organs were reperfused on an ex-vivo sanguineous oxygenation circuit (Model 30, Functional Circulation®) to simulate transplantation and re-animation.

**Results:**
- Comparative viability testing of the organs on an extra-corporeal circuit revealed the following:
- Mean lactate at 2hours reperfusion was 1.25mmol/L +/- 0.15 in the oxygenated group (RSI-$O_2$-NAC) versus 2.10mmol/L +/- 0.46 in the control group (NS).
- Mean serum creatinine fell by 344µmol/L +/-90 in RSI-$O_2$-NAC group vs 347µmol/L +/- 70 in control group (NS).
- Renal vascular resistance was similar between groups finishing at a mean of 1.65mmHg/ml/min +/- 0.38 in the RSI-$O_2$-NAC group vs 1.63 +/- 0.68 in the control group (NS)

Electron microscopy examination of glomerular podocyte foot-process-width (FPW) revealed superior preservation with less effacement in the RSI-$O_2$-NAC group 437.0ηm +/- 102 vs 494.3ηm +/-93 in the control (NS)

**Discussion:** While biochemical performance appeared similar between groups, tissue examination suggests superior preservation in kidneys flushed with oxygenated perfusate, with the addition of a free-radical scavenger. This warrants further investigation, ideally in a transplant model.

# Kidney complications 1

**63**

## Serum concentrations of polyclonal free light chains predict post transplantation infections

Shazia Shabir[1], Anne Bevins[2], Hannah Church[1], Paul Cockwell[1], Richard Borrows[1], Colin Hutchison[1]

*[1]Renal Institute of Birmingham, University Hospital Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Birmingham, UK, [2]Binding Site Group Limited, Renal Immunobiology, Medical School, University of Birmingham. Birmingham, UK*

Polyclonal immunoglobulin (Ig) free light chains (FLC) represent the activity of the adaptive immune system. However unlike intact Ig, FLCs are principally cleared by the kidneys and have short serum half lives. Previous work has demonstrated that serum FLC concentrations are influenced by the dose of immunosuppressants used post transplantation. The purpose of this study was to determine if polyclonal FLC concentrations predict the future risk of infective episodes in renal transplant recipients.

**Methods:** Serial serum samples collected from 79 incident renal transplant recipients were assessed for FLCs, Ig and cystatin C concentrations. Combined polyclonal FLC (cFLC) concentration was calculated by summating $\kappa+\lambda$. A correction for renal function was then made with cystatin C ($[\kappa+\lambda]$/cysC). Clinical data was captured prospectively. Statistical significance was assessed using Kruskall-Wallace with Dunn's post-test and Pearson's Chi-square test.

**Results:** By day 14 post-transplant, the median eGFR was 47.50ml/min this remained stable at 12 months (median 47ml/min, range 7-90). Median serum cFLC pre-transplant was increased at 145.9mg/L (range 21.27-442.5mg/L; normal range 9.33-44.27mg/L). cFLC was significantly reduced by day 14 median 25.67mg/L, $p<0.001$, and remained reduced at 12 months (median 30.64mg/L, $p<0.001$). Baseline corrFLC was 28.7mg/L (range 12.7-77.3mg/L) these decreased to 13.7mg/L, $p<0.001$ by day 14, but then steadily increased over the follow up period ($p<0.001$). A similar pattern was observed with IgG (baseline vs. day 14 $p<0.001$, 1 month vs. 12 months $p<0.05$). Sixty of the 79 patients (76%) experienced at least one infective episode during the first 12 months post transplantation. Patients with a low corrFLC level were more likely to experience an infection in the 90 days following the sample (78%) than patients within or above the normal range (43%) ($p=0.002$). Increases in corrFLC concentrations mirrored infective episodes. There was no difference in FLC concentrations between patients who received an ABO incompatible kidney (19/79 patients).

**Conclusion:** Serum concentrations of polyclonal FLCs represent a dynamic marker of immune activity and can be used to identify patients at higher risk of infective episodes post transplantation. Future work is now required to determine if the doses of immunosuppressants can be modified 'real-time' in relationship to the cFLC levels.

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**Does a combined dietetics and physiotherapy led group approach promote weight loss in post transplant, pre and post donation patients?**

Louise Gilbert, Sally Altree

*Cardiff and Vale University Health Board, Cardiff, UK*

Increased Body Mass Index (BMI) in renal transplant recipients has been linked with shorter graft longevity. To proceed to healthy live donation, which is considered the most cost effective and successful form of renal replacement therapy, donors are advised to have a BMI<30. Levels of obesity in pre and post surgery recipients and donors are increasing in our Nephrology and Transplant Directorate.

The NICE Guidelines state that weight management intervention should be multi-component comprising of dietary advice, physical activity and behaviour change. At present weight loss advice is carried out on a one to one basis in a clinic environment. This intervention has not proved as successful as a group setting for the majority of the population.

This multidisciplinary weight loss pilot group was designed specifically for renal donors and recipients with the long term aim of achieving desired BMI, which in turn should lead to earlier live transplantation, longer graft survival, reduced surgical risk factors, and support donors post nephrectomy to maintain a healthy BMI and lifestyle.

An 8 week combined dietetics and physiotherapy programme was established with inclusion / exclusion criteria and supported by the multidisciplinary transplant team. Participants were screened and referred by the Transplant Nurse Specialists and included post transplant recipients and pre and post transplant donors.

Weekly sessions involved motivational interviewing techniques to promote healthy lifestyle change and a tailored exercise circuit class comprising cardiovascular and strengthening exercises. There were 11 participants who attended between 5 and 8 weeks of programme, 6 recipients, 4 donors and 1 waiting to donate. 1 participant did not exercise for medical reasons. Outcome measures obtained at week one and repeated at week eight showed a weight loss per person of mean 4.42kg / median 4.2kg with a range of 1.8kg to 6.65kg and percentage weight loss of mean 4.48% / median 4.45% with a range of 2.5% to 6.5%. Improved QOL, exercise tolerance, waist and hip measurements were also demonstrated.

This pilot programme demonstrated a new approach to weight management in the renal population and achieved the desired weight loss of 1-2lbs per week. The programme has supplied the participants with the skills to manage their own weight but they will receive monthly follow up for 4 months to evaluate this. The programme can now be repeated with a second group to include recipients with high BMI waiting for live transplantation from their donor. Full cost analysis studies will be carried out and Oral Glucose Tolerance Testing will be added as an outcome measure.

**65**

**Post transplant encapsulating peritoneal sclerosis has a good prognosis**

Julia Ertner, Andrew Butler, Elaine Corden, Paul Williams, Chris Watson

*Cambridge University Hospitals, Cambridge, UK*

**Introduction:** Encapsulating Peritoneal Sclerosis (EPS) is an unpleasant complication of peritoneal dialysis (PD) that usually manifests once patients have switched to haemodialysis (HD) or have a transplant (TX). Post transplant EPS has been reported to have a poor prognosis, and to be a common cause of death post transplant. Here we report the results of surgery for EPS occurring in the post transplant period, and contrast it with the results of patients developing the disease on haemodialysis.

**Methods:** From April 2009 a national surgical service for the treatment of EPS was introduced to England, based in two centres. The results of one centre were reviewed to compare outcomes of patients developing EPS post transplant with those developing it following a switch to haemodialysis. Surgery comprised decortication, whereby the inflammatory fibrous tissue was removed from the parietal and visceral peritoneum, and complete mobilisation of the small intestine. Inadvertent enterotomies were exteriorised as stomas.

**Results:** 30 patients have undergone surgery, of whom 7 developed EPS post transplant. The median (range) age of the 2 groups of patients was 55 (27–70) years for the TX patients and 52 years (23–83) for HD patients, and they had a median time on PD of 7 (4.5–9) years for the TX group, and 6 (2.25–12.75) years for the HD group. Following surgery 1 of 7 (14%) of the TX patients died, and 6/23 (26%) of the HD patients died (median follow up 8 months). The TX death was secondary to sepsis following attempted aspiration of a peritoneal fluid collection; The HD deaths were associated with further surgery at the local hospital (n=2), or from sepsis (n=4) of which two were secondary to aspiration in the first month post surgery. 2/7 of the TX patients have required readmission(s) to our centre for further intervention or surgery. This compares to 10/23 HD patients who have required readmission(s) (excluding stoma reversal surgery). 2/7 TX patients needed re-ops whereas 8/23 HD patients needed re-ops. 1/7 TX patients required stoma formation (reversed after 154 days) compared to 6/23 HD patients (2 have been reversed after 574 and 451 days). Overall the total length of stay for the TX group was 30% shorter (median of 25 days for TX patients and 36 days for HD patients); this does not include readmission bed days. The need for parenteral nutrition was also less in the TX group.

**Conclusion:** Patients who need EPS decortication surgery with functioning kidney transplants have a shorter length of stay, fewer complications and better survival following surgery for EPS than patients on haemodialysis. The shorter length of stay and absence of dialysis requirements in transplanted patients leads to lower costs.

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**Hypomagnesaemia in renal transplant recipients**

Aisling O Riordan, Robert Unwin, Jo Henry, Jane Kadourah, Gareth Jones, Mark Harber, Ben Walsh

*UCL Centre for Nephrology, Royal Free Hampstead NHS Trust, London, UK*

**Introduction:** Hypomagnesaemia has been reported with calcineurin inhibitors (CNI) and proton pump inhibitors (PPI) due to excessive urinary and gastrointestinal losses, respectively. Hypomagnesaemia can also be associated with other electrolyte abnormalities such as hypocalcaemia and hypokalaemia. Both CNIs and PPIs are routinely used in the treatment of renal transplant (RTx) recipients so the aim of this study was to evaluate the incidence of hypomagnesaemia in the first 3 months post RTx, to evaluate whether the extent of hypomagnesaemia changes with time or the cessation of the PPI and finally, to identify associated biochemical and clinical factors.

**Methods:** Biochemical analysis of serum and urine for magnesium ($Mg^{2+}$), calcium, potassium and creatinine was performed at regular intervals throughout the first 3 months post RTx in patients transplanted between December 2010 and August 2011. The fractional excretions of $Mg^{2+}$, calcium and potassium were then calculated. Parathyroid hormone, vitamin D, glucose, tacrolimus, cyclosporine and sirolimus levels were also measured and the glomerular filtration rate was estimated. Data are expressed as means +/- standard deviations and linear regression was performed using SPSS.

**Results:** 432 samples were analysed on 52 consecutive RTx recipients with full biochemical analysis of serum and urine being performed on 6.5 +/- 1.9 occasions per patient in the first 12 weeks post transplant. Tacrolimus was the principle immunosuppressant in 90% of cases, cyclosporine in 7.4% and sirolimus in the remainder. The majority (73%) of samples were taken while on a PPI. Hypomagnesaemia occurred in 86% of patients and 65% of all readings were < 0.65mmol/L (mean 0.61 +/- 0.1; minimum 0.3mmol/L). The fractional excretion of $Mg^{2+}$ was elevated at 7.2% +/- 4.42% (normal is < 2 - 4%). Only 2 patients required $Mg^{2+}$ supplementation because of palpitations. Serum $Mg^{2+}$ increased significantly over time and was lower in patients treated with tacrolimus versus cyclosporine ($P < 0.005$). The cessation of the PPI was not independently associated with an improvement in serum $Mg^{2+}$ however multivariate analysis revealed that increasing age and tacrolimus levels, lower potassium and creatinine levels were all associated with hypomagnesaemia ($P < 0.005$).

**Conclusion:** Hypomagnesaemia is very prevalent post RTx and is due to excessive urinary losses. It improves with time but is not influenced independently by the use of PPIs. It is associated with increasing tacrolimus levels and better renal function. It is rarely associated with overt clinical sequelae but further investigation will be required to examine its' impact on bone mineralization and cardiac dysrythmias.

**67**

**Kidney recipients with pre-existing diabetes or NODAT are not at increased risk of infection in the first year post transplantation – a prospective analysis.**

Shazia Shabir[1], Seema Jham[1], Baksho Kaul[2], Helen Smith[2], Richard Borrows[1], Adnan Sharif[1]

*[1]Renal Institute of Birmingham, Birmingham, UK, [2]Centre for Inflammation and Translational Research, Birmingham, UK*

**Introduction:** There is no clear evidence that either pre-existing diabetes mellitus or new onset diabetes after transplantation (NODAT) is associated with an increased risk of infection post-transplantation. In this study we prospectively monitored kidney transplant patients to ascertain any such association in the first year post-transplantation.

**Methods:** 85 kidney transplant recipients formed the patient cohort. All patients received basiliximab induction with maintenance tacrolimus, MMF and corticosteroids for immunosuppression. Oral glucose tolerance test was performed 7-days post-transplantation to ascertain early glycaemic status in patients without pre-existing diabetes. All patients received prophylaxis against oral candida and pneumocystis jiroveci (nystatin and co-trimoxazole for 3- and 12-months respectively). Patients at high risk for CMV (donor+/recipient-) and/or TB (South Asian ethnicity, previous exposure) received prophylaxis (valganciclovir and isoniazid/pyridoxine for 3- and 6-months respectively).

**Results:** 58% of the patient cohort was male. Ethnic breakdown of the recipients was; white (73%), black (8%), south Asian (16%) and other (3%). Incidence of delayed graft function was 32% and acute rejection (cellular and/or antibody-mediated) was 36%. There was no difference in any of these variables between glycaemic groups. We also did not identify any significant difference in incidence of infective episodes between glycaemic groups (Table 1):

**Table 1. Episodes per patient over 1-year post-transplantation dependent on glycaemic status 7-days post-operatively**

| | Normal | Pre-diabetes | NODAT | Pre-existing diabetes |
|---|---|---|---|---|
| Percent of cohort | 39% | 20% | 17% | 24% |
| Total infections | 4.8 | 1.2 | 6.1 | 4.2 |
| Urinary tract infections | 2.4 | 0.5 | 3.7 | 1.5 |
| Respiratory tract infections | 0.3 | 0.2 | 0.4 | 0.3 |
| Viral infections | 0.8 | 0.3 | 0.9 | 1.1 |
| Other/non-specific | 0.9 | 0.3 | 0.4 | 0.8 |

**Conclusion:** We did not demonstrate any difference in infective episodes between kidney transplant recipients with abnormal glucose metabolism in their first year post-transplantation. We speculate that the immunosuppressant milieu post transplantation is dominant and may assuage the impact of hyperglycaemia on post-transplant infections. However, we are unable to comment on the potential long-term cumulative risk of infection with the chronicity of NODAT. Further investigation of registry data is warranted to ascertain long-term risk of infection in diabetic transplant recipients.

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## A long-term prospective study of the progression of abnormal glucose tolerance in renal allograft recipients

Pramod Nagaraja[1], Adnan Sharif[2], Vinod Ravindran[1], Kesh Baboolal[1]

*[1]University Hospital Of Wales, Cardiff, UK, [2]Queen Elizabeth Hospital, Birmingham, UK*

**Introduction:** Abnormal glucose tolerance is a risk factor for the development of type 2 diabetes mellitus in the general population. In this study, we assessed the long term progression of abnormal glucose metabolism in renal transplant recipients (RTRs) using the oral glucose tolerance test (OGTT).

**Methods:** A prospective, observational study in 58 RTRs with a fasting plasma glucose of <7.0 mmol/l, who underwent an OGTT at baseline (2005, median time from transplantation 5.5 years) and after six years. Glucose tolerance was determined according to WHO classification. Body mass index (BMI), waist-hip ratio (WHR) and serum lipids were also measured at both time-points. Paired and unpaired t-tests and chi-square tests were used with significance determined as $p<0.05$.

**Results:** The table below shows glucose tolerance categories at baseline and follow-up. At baseline, 57% of patients had an abnormal OGTT – 19% impaired fasting glucose (IFG), 12% impaired glucose tolerance (IGT), 16% IFG & IGT and 10% NODAT. Patients with an abnormal OGTT had a higher WHR (0.99 vs. 0.89, p=0.03) and S. triglyceride level (2.1 vs. 1.4 mmol/l, p=0.01) compared to those with a normal OGTT. Steroid and calcineurin inhibitor use were similar in both groups. At follow-up, 40% of patients with a normal OGTT at baseline developed abnormal glucose tolerance. Of those patients with an abnormal OGTT at baseline, 36% improved, 30% worsened and 34% remained in the same glycaemic state. A further 10 patients (20%) developed NODAT - 8 with abnormal and 2 with normal OGTT at baseline (p=0.048). Although there was an increase in BMI of the whole cohort (27.7 to 28.7, p=0.003), there was no difference in the change in BMI or WHR between those who worsened and those who maintained a stable / improved OGTT.

| | **Baseline glycaemic status** | | | | |
|---|---|---|---|---|---|
| **Follow-up status ↓** | Normal n=25 | IFG n=11 | IGT n=7 | IFG & IGT n=9 | NODAT n=6 |
| Normal | 15 | 4 | 2 | 1 | 1 |
| IFG | 3 | 1 | 1 | 3 | 0 |
| IGT | 4 | 0 | 3 | 2 | 0 |
| IFG & IGT | 1 | 1 | 1 | 0 | 0 |
| NODAT | 2 | 5 | 0 | 3 | 5 |

**Conclusion:** We have shown that abnormal glucose tolerance is a risk factor for developing NODAT and is associated with high WHR and triglyceride level. Identifying these patients using the OGTT thus provides an opportunity to intervene with active lifestyle measures which have been shown to ameliorate progression to NODAT.

# Kidney complications 2

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## Can simple urodynamics predict patients with lower urinary tract dysfunction among anuric/oliguric patients with non urological causes of ESRD who underwent renal transplantation?

Lasantha Seneviratne, Ramesh Batra, Ben Lindsey, Mahamood Al-akraa, Gareth Jones, Bimbi Fernando, Mark Harbor, David Nicol

*Royal Free Hospital, London, UK*

**Introduction:** Although lower urinary tract dysfunction (LUTD) exist in 6-30% of patients with ESRD, its significance in post-transplant patients is under-rated. Advanced urodynamics in oligo-anurics to detect LUTD is cumbersome and is not cost effective. The physiological de-functioning of bladder in long term increases the risk post transplant UTI leading to graft dysfunction. We analysed the use of simple urodynamics in these critical subset of patients to determine its role in identifying the patients at risk.

**Method:** 48 patients were enrolled in this study after excluding patients with urological causes of ESRD, neurological lower urinary tract dysfunction and use of anticholinergics. There were 16 Anuric (urine output <50ml/24 hrs), 20 Oliguric (urine output <400ml/24hrs) & 12 Noromouric patients. Lower urinary tract was evaluated with urodynamics using flow-metry and transonic bladder scan to measure the residual bladder volume (PVR). Flow dynamics according to Abrahams criteria, occurrence of culture positive UTI and/or graft dysfunction (30% rise from its baseline creatinine) in the absence of any other causative factor was considered as surrogate end points. Statistical analysis was done using linear regression analysis (2-tailed), student t- test and chi square.

**Results:** The two groups i.e. oligo-anuric and normouric were comparable in age and sex. Amongst the two groups 61% of oligo-anurics and 58% of normouric patients had UTI with no. of episodes /year being 3.56, 2.32 respectively. Significant PVR(>100 mls or >1/3$^{rd}$ of total bladder capacity) in the oligo-anuric group with UTI was 45 % as compared to 14% without UTI in the same group ( p=0.05). Mean total bladder capacity was more in the oligo-anuric group (414 ± 201 mls) as compared to the normouric group (363 ± 119 mls) and its relationship to UTI was insignificant (p=0.42).Mean urine flow (Q mean) were 8.8 ±3.6 and 12.1 ± 6.7 in oligo-anuric and normouric groups respectively, and its relationship with UTI was also insignificant (p=0.46).

**Discussion:** These findings emphasise that oligo-anuric patients with significant PVR are at higher risk of UTI. Flow-metry (Qmean) and total bladder capacity is a poor indicator to detect risk of UTI. We therefore suggest that Post-void Bladder scan to measure PVR and the measured voided volume without flow studies is sufficient in the outpatient setting to detect high risk group of patients prone to UTI. This is not only a simple but a very cost-effective tool.

**70**

**Parathyroidectomy for tertiary hyperparathyroidism after renal transplantation**

Rong Khaw, David van Dellen, Michael Picton, Ravi Pararajasingam, Hany Riad, Neil Parrott, Titus Augustine

*Manchester Royal Infirmary, Manchester, UK*

**Background:** Tertiary hyperparathyroidism (THPT),is occasionally seen after transplantation due to autonomously functioning parathyroid glands, and considered a continuum of secondary hyperparathyroidism (SHPT) in spite of correction of renal failure with transplantation. Surgical parathyroidectomy is warranted when SHPT becomes refractory to medical treatment, especially if biochemically or clinically significant. THPT can affect graft function after successful transplantation and calcium phosphate control is important in overall post transplant care. Limited published data and experience exists regarding optimal surgical management of post transplant THPT. We aimed to evaluate post transplant parathyroidectomy and outcomes.

**Methods:** 30 Transplant patients (18M, 12F; median age 52 (range 20-73)) who underwent parathyroidectomy over a 10 year period (2000-2011) were included in this retrospective study. Patient outcomes were evaluated with regards to success of surgery and effects on graft function (Creatinine and biopsy proven acute rejection {BPAR} episodes) as primary endpoints. In addition, postoperative hypocalcemia incidence was examined as a secondary endpoint in this cohort. Time to onset and clinical manifestations of THPT after transplantation, immunosuppressive regimens in these patients, type of parathyroidectomy performed and success were also evaluated.

**Results:** Subtotal PTHx (n=13, 43%; Total PTHx,n=10; 33%) was the most performed surgical technique with 10 (33%) total PTHx. There was only one major complication (recurrent laryngeal nerve palsy) whilst all approaches were effective in therapeutic success ($p<0.001$). After kidney transplantation, there was a median duration of 20 months (range 3-124) prior to parathyroidectomy. The overall biochemical success rate was 83.3% (25/30) with a median calcium reduction of 0.38mmol/l (range -0.8 to 1.22) and decreased CaPhospate product of 0.38 (range -2.3 to 2.8)($p<0.001$, paired t-test for both). 10/30 patients had postoperative hypocalcaemia (median 1.96mmol/l (range 1.64-2.08); 3 asymptomatic. Creatinine levels differences pre- and post-surgery was found to be insignificant (median -9.5µmol.l. range -201 to 49, $p=0.36$) Alkaline phosphatase levels showed significant improvement 6 months post-surgery (median decrease 122IU/l; range -213 to333; $p=0.03$) All patients were on Calcineurin inhibitor (CNI) based immunosuppression, other than 3 cases where CNIs had been minimised and 1 on Rapamycin. There were no episodes of BPAR in any patient around parathyroidectomy. In the same period, Cinacalcet was used as an alternative to PTHx in 45 patients.

**Conclusion:** Post transplant hyperparathyroidism management is an integral component of overall post-transplant care. We demonstrate that surgical management of THPT is safe, and provides effective metabolic control with minimal morbidity and little threat to transplant function. The timing and type of parathyroidectomy requires further standardization and a comparison with calcimimetic agents following transplantation would be valuable. This could be addressed effectively by a national multicentre collaborative trial.

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## Does treatment of intra operative hyperkalaemia predict the requirement for early dialysis post renal transplantation?

Lucy V Randle[1], Tatjana Boitsova[2], Paul Gibbs[1], Nicholas Torpey[3], J Andrew Bradley[1], Chris J E Watson[1]

*[1]University of Cambridge Department of Surgery, Cambridge, UK, [2]Barts and the London School of Medicine, London, UK, [3]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

**Introduction:** Hyperkalaemia is common during renal transplant surgery, and treatment is required to prevent life-threatening arrhythmias. Hyperkalaemia may result from reperfusion of kidneys with long cold ischaemic times (CIT) or those retrieved from donors after circulatory death (DCD), as well as the use of suxamethonium, compound sodium lactate (Hartmann's Solution), and blood transfusion. We undertook a single-centre analysis to determine whether the use of short lasting measures to reduce hyperkalaemia intra-operatively (insulin and dextrose and/or salbutamol) predicted the need for urgent (<24 hours) post transplant dialysis.

**Methods:** A retrospective analysis was undertaken of 100 consecutive deceased donor renal transplants performed between 23/07/2010 – 30/07/2011. Patients receiving a kidney transplanted with another organ (e.g. liver, pancreas) were excluded. Data were collected from the electronic transplant database and from patients' medical records.

**Results:** 34 (34%) patients received intraoperative treatment for hyperkalaemia (group K). When compared to the 66 (66%) patients not requiring treatment (Group U), there was no significant difference between groups in the proportion of DCD kidneys (56% group K, 62% group U), the duration of surgery (median 287mins K, 274mins U) or cold ischaemic times (707mins K, 848mins U). The median pre operative serum potassium for all patients (n=100) was 4.5 mmol/L (range 2.9-5.7) and patients with a higher pre-operative potassium were more likely to require intra-operative treatment of hyperkalaemia: K+ <4 (n=25) 12%, K+ 4-4.5 (n=28) 32.1%, K+ 4.5-5 (n=29) 41.3%, and K+ >5 (n=18) 55.5%. 50% of patients in group K required dialysis for hyperkalaemia within 24 hours of transplant compared to 22.7% of group U (P=0.011). For patients requiring dialysis, the median serum potassium prior to dialysis was 6.8mmol/L for group K and 6.5mmol/L for group U. Using the absence of a daily fall in creatinine of 10%/d over 3 consecutive days in the first week post transplant as a definition of delayed graft function (Boom et al 2000), delayed function occurred in 83% of group K and 79% of group U patients. Median serum potassium 12 hours post transplant in patients who did not receive early (<24 hours) dialysis was 5.4mmol/L in group K and 4.9mmol/L in group U. From the non-dialysed patients, 82% of group K and 72% of group U had delayed function.

**Conclusion:** Patients with a high pre-operative serum potassium are more likely to need intra-operative treatment of hyperkalaemia, and those requiring intra-operative treatment are more likely to need urgent (<24 hours) dialysis after transplantation.

[1]Boom et al. Kidney Int 2000; 58: 859-866

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## Outcomes of methicillin-resistant staphylococcus aureus infection after kidney and or pancreas transplantation

Melissa Oliveira-Cunha, Victoria Bowman, Gabrielle di Benedetto, Maria Otilia Mitu Pretorian, Abbas Ghazanfar, Bence Forgacs, Afshin Tavakoli, Titus Augustine, Ravi Pararajasingam

*The Renal and Pancreas Transplant Unit, Central Manchester University Hospital, Manchester, UK*

**Background:** The true extent of MRSA colonization and incidence of infection after transplantation in adults and children is not well-known. Incidence varies from one transplant centre to another, reflecting the transplanted organ and the prevalence in the non transplant patient population. Little is known about the severity of infection. The aim of this study was to evaluate the incidence and the outcomes of MRSA infection following kidney and/or pancreas transplantation.

**Methods:** We reviewed the case notes of all patients who developed MRSA colonisation and infection within the first year of transplantation between September 2002 and December 2009. The natural history and clinical course of these patients were examined. The primary endpoint of this study was mortality. The secondary endpoints included morbidity, graft failure and length of hospital stay.

**Results:** 1116 transplants during the study period including 693 deceased donor kidney transplants, 245 live donor kidney transplants, 133 simultaneous kidney and pancreas transplants, 33 pancreas after kidney transplants and 12 pancreas only transplants. MRSA colonisation was detected in 14 patients (1.25%) and infection occurred in 6 cases (0.53%) post transplantation. Infection included one case of pneumonia, one case of urinary infection, two abdominal collections, one abdominal wound dehiscence and one septicaemia. Graft failure was not associated to MRSA colonization/infection in any of the cases. The median time in days between transplantation and MRSA infection was 172 days (range from 0 to 261 days).

| | **LDKT** | **CKT** | **PT** | **Overall** |
|---|---|---|---|---|
| Number of patients | 5 | 9 | 6 | 20 (1.79%) |
| MRSA colonization | 5 | 6 | 3 | 14 |
| MRSA infection | 0 | 3 | 3 | 6 |
| Overall mortality rate | 0 | 4 (33%) | 4 (66%) | 8 (40%) |
| Mortality related to MRSA | 0 | 0 | 2 | 2 (10%) |
| Median length of stay in days | 8 | 23 | 35 | 16 |
| Range of length of stay in days | 6 to 23 | 8 to 35 | 9 to 243 | 6 to 243 |

Legend: LRKT: living donor kidney transplant; CKT: cadaveric kidney transplant and PT: pancreas transplant

**Discussion:** Our study has demonstrated that the prevalence of MRSA colonization and infection in our unit is low in spite of immunosuppression. The incidence of MRSA infection is higher amongst patients that underwent pancreas transplantation. Patients that were colonized and then developed infection had higher morbidity and mortality rates. Graft failure was not associated to MRSA colonization or infection. MRSA colonization can be easily eradicated by prophylactic therapy; therefore more emphasis should be given in patients undergoing transplantation.

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## The course of post-transplantation neutropaenia varies according to the induction regimen used

Sharon Warlow, Eiddwen Glyn, Sian Griffin

*University Hospital of Wales, Cardiff, UK*

**Introduction:** Several immunosuppressant drugs and prophylactic anti-microbials used routinely post-transplantation have the potential to cause neutropaenia. The risk and timing of this potentially life-threatening complication in our transplant population was unknown.

**Methods:** Between 1/6/10 and 31/5/11, 120 patients (78 male, mean age 52 ± 15 years) received a renal transplant, of which 39 were from living donors (9 recipients underwent ABO or HLA desensitisation), 43 were from DBD donors and 38 were from DCD donors. Induction was with one of: (i) basiliximab, (ii) ATG, (iii) Campath, (iv) rituximab + PEx + basiliximab or ATG or Campath, or (v) no additional treatment. Subsequent immunosuppression was with tacrolimus (target trough level 4 – 8 □g/L), MMF (1 – 2g daily) and short term prednisolone. All patients received prophylaxis with septrin for 6 months, and valganciclovir for 3 months (unless both donor and recipient were CMV negative). The BPAR rate for the cohort was 10%.

**Results:**

| Induction Treatment | # | # (%) with NC <1.5X10$^9$/L | # (%) with NC <0.5X10$^9$/L | Median days post-transplant (range)† to NC <1.5 | Mean duration of NC < 1.5 (days) |
|---|---|---|---|---|---|
| Basiliximab | 73 | 30 (41) | 13 (18) | 88 (16 – 189) | 26 ± 24 |
| ATG | 26 | 14 (54) | 2 (8) | 75 (47 – 211) | 26 ± 14 |
| Campath alone | 8 | 3 (38) | 1 (13) | 111 (67 – 158) | 51 ± 54 |
| Rituximab + PEx + basiliximab or ATG or Campath | 9 | 8 (89)** | 6 (67)*** | 61 (54 – 81) | 31 ± 38 |
| None | 4 | 1 (25) | 0 (0) | 61 | 5 |

** p<0.01 vs basiliximab induction, *** p<0.001 vs basiliximab or ATG induction
† excluding early transient neutropaenia in first week post-transplant. NC=neutrophil count

There was no significant age difference between patients who became neutropaenic after rituximab (39±11 years) compared to those who became neutropaenic after other induction regimens (49±16 years) and those who did not develop neutropaenia (55±14 years). There was no difference in the proportion of patients in each group requiring treatment with G-CSF (rituximab 50%, others 44%). Although no patients developed severe sepsis, two developed CMV disease coincident with their neutropaenia.

**Discussion:** Patients who receive rituximab as part of their induction regimen and subsequent immunosuppression with tacrolimus, MMF and prednisolone are at particularly high risk for post-transplantation neutropaenia, which occurs predictably 11 – 15 weeks after exposure. The risk to transplant recipients who receive alternative induction regimens is less but still substantial, with the timing of their presentation being more variable.

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**Cardiovascular risk assessment for renal transplantation. are patients being managed appropriately in our hospital?**

James Rigby, Selva Velu, Mark Gunning, Kerry Tomlinson

*University Hospital of North Staffordshire, Stoke-on-Trent, UK*

**Introduction:** Cardiovascular (CV) disease remains a leading cause of post-renal transplantation morbidity and mortality. Currently, there is little consensus regarding both cardiovascular screening and management of coronary artery disease (CAD) prior to renal transplantation.

**Aims:** To determine the effectiveness of current cardiovascular risk assessment, and ascertain whether attendance at a cardio-renal clinic before renal transplantation influences the incidence of Major Adverse Cardiac Events (MACE). Furthermore we sought to evaluate the impact of coronary artery revascularisation pre-transplantation on peri-transplant MACE.

**Methods:** A specialised cardio-renal clinic was established in 2003 at our hospital. Patients that received renal transplantation between January 2003-June 2010 and had contact with the cardiology department were included in the study.

**Results/discussion:** 116 patients (41% female, 59% male) underwent renal transplantation and had contact with the cardiology department; median age 51 years (range 24-71). Time between transplantation and data collection ~3.25 years. Of the cohort, 41/116 (35%) had a cardiac problem and were seen in the cardio-renal clinic (24% low, 46% medium, 29% high CV risk). Of these, 28/41 (68%) attended the clinic pre-transplantation and 13/41 (32%) post-transplantation. Altogether, 4/41 (10%) experienced MACE; 3 had MI and 1 had cardiac arrest. Time between transplantation and MACE ~17 months. All patients reviewed in the cardio-renal clinic were free of peri-transplant MACE. A total of 20/41 (49%) underwent coronary angiography, of these 6/20 (30%) had no CAD (incidence MACE 0%) and 14/20 (70%) had CAD (incidence MACE 21%). Before transplantation, 6/41 (15%) underwent coronary artery revascularisation. None experienced MACE peri-transplantation. Incidence of MACE increased with CV risk. Low risk patients not seen in clinic (65% of cohort, 75 patients) experienced no MACE peri-transplantation or post-transplantation. Interestingly, only 9% of patients end stage renal failure (ESRF) was attributed to hypertension or diabetes mellitus, despite a high percentage of the cohort having Framingham CV risk factors.

**Conclusion:** Establishment of a specialised cardio-renal clinic at our hospital risk has contributed to effective and appropriate management of cardiac risk in renal transplant patients.

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## The management of arterio-venous malformations following transplant kidney biopsy

Rajiv Dave, Clare Ecuyer, Chas Newstead, Magdy Attia, Lutz Hostert, Krishna Menon, Niaz Ahmad

*St James University Hospital, Leeds, UK*

**Aim**: Arterio-Venous Malformations (AVM) are a rare, but recognised complication following Kidney biopsy. There is a lack of consensus regarding the natural history, pathogenesis and current management. The aim of this study is to investigate the management strategies adopted by the various transplant centres in the UK, and to examine our Unit's experience with embolisation to AVMs.

**Methods**: In the first part of the study, we investigated the incidence and management of AVMs in our department over a 5 year period. We obtained the reports of all Ultrasound Scans (USS) and all radiological interventions performed on transplant Kidneys that were available via an electronic search (June 2006 - June 2011). Patients with AVMs were identified and their electronic notes studied. In the second part of the study, an electronic survey was submitted nationally to kidney transplant surgeons and lead nephrologists. A total of 90 clinicians were successfully included in the study.

**Results**: 7 patients with AVMs were identified on the US reports. Out of these, 5 had developed AVM following biopsy. 5 went on to have further investigation in the form of MRA or Angiography. 3 patients had embolisation to the AVM. In 2 patients, the AVM was not intervened on and no longer detected in later scans. There was 1 case of graft loss. A total of 21 survey responses were received (23%). The results of the survey showed that biopsies were commonplace nationally to investigate graft dysfunction, and 57% of clinicians performed them at the time of implantation, but only 29% would perform protocol biopsies. 86% would perform biopsies on the ward under Ultrasound guidance, and in majority of cases this was performed by the Nephrologist. The impact of AVMs in the clinicians' practice was variable, with 76% of clinicians having encountered between 0-5 cases of AVM in the past five years and 24% between 5-10 cases. In clinicians' experience, 53% of cases of AVM were associated with bleeding or haematoma, 35% reported no complications, whilst only 18% of clinicians reported graft loss due to AVMs. 29% reported graft loss following selective embolisation. In non-bleeding AVM, only 22% would treat with selective embolisation, whilst 22% would treat it expectantly with no follow-up and 56% with regular imaging, with the imaging modality of choice being Doppler US (75%). In the event of spontaneously ruptured AVMs, 81% would treat with immediate selective embolisation.

**Conclusions**: Most transplant clinicians will encounter AVMs in their practice. It is a rare occurrence and remains poorly understood and there is little documentation about the pathogenesis. In both quiescent and bleeding AVMs, selective embolisation carries a risk of graft loss. Although most clinicians advocate selective embolisation in the event of spontaneously ruptured AVMs, there is still a lack of consensus regarding the management of uncomplicated AVMs. Further work is needed in order to draw out guidelines for the management of AVMs in Transplant Kidneys.

**Kidney outcome 1**

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**Low-grade proteinuria and hypertension are linked and potentially modifiable risk factors for renal transplant failure, independent of renal function**

Aravind Cherukuri, James Tattersall, Andrew Lewington, Chas Newstead, Richard Baker

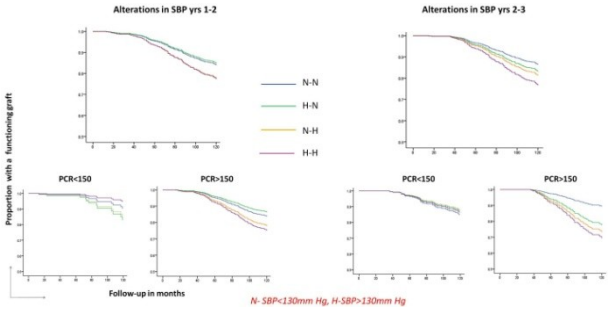
*St. James's University Hospital, Leeds, UK*

**Background:** Proteinuria (P) and systolic hypertension (SHT) are risk factors for graft failure and may vary over time. The interrelationship and the impact of modification of P and SHT over time have not been described. We have retrospectively analysed the effects of changes in P and SHT on long-term graft outcomes.

**Methods:** Clinical records of 841 adult renal transplant patients since January 1988 were analysed, including proteinuria measurements at every visit. Any patient with proteinuria >1g/day was excluded from the analysis. Mean proteinuria and systolic blood pressure (SBP) were calculated annually for years 1, 2 and 3 after transplantation. Patients were divided into groups based on the development of proteinuria (Proteinuria absent (A) <150mg/day or low-grade proteinuria (P)>150mg/day) and SBP (Normotensive (N) SBP<130mm Hg or hypertensive (H) SBP>130mm Hg). Progression of proteinuria (A-A, P-A, A-P, P-P) and SBP (N-N, H-N, N-H, H-H) between years 1 and 2 and years 2 and 3 was also analysed. Patients were followed up for a maximum of 10 years and graft survival was assessed across the groups using multivariate Cox Proportional hazards model after adjusting for potential confounders, including renal function.

**Results:** At any time point hypertensive (H) patients and those with proteinuria (P) have worse long-term graft survival. Patients who either remain hypertensive (H-H) or who develop hypertension in years 2 and 3 (N-H) have worse outcomes when compared to the other groups; however this effect was evident only in the proteinuric patients **(figure-1)**. Patients with both SHT and proteinuria have the worst graft survival at any time point. Patients who had persistent low-grade proteinuria (P-P) had the worst graft survival but there was an improvement if proteinuria regressed (P-A).

**Conclusions:** Both low-grade proteinuria and SHT were associated with poor graft survival at any time point, the combination of the two leading to the worst outcomes. The regression of SHT leads to improved graft survival in proteinuric patients only. Thus low grade proteinuria could potentially be used to risk stratify hypertensive patients. Patients with SHT and low-grade proteinuria could be a potential intervention group in any future study of modifiable risk factors for graft loss.



**77**

**Fractional excretion of protein is a sensitive and specific test to predict risk of renal transplant failure.**

Kate Stevens, Shona Methven, Rajan Patel, Patrick Mark, Colin Geddes, Marc Clancy, Alan Jardine

*The Renal Transplant Unit, Western Infirmary, Glasgow, UK*

**Background:** Proteinuria is associated with poorer outcomes in transplant recipients. Fractional excretion of total protein (FePr) may better reflect renal excretion of protein than protein: creatinine ratio (PCR). We assessed FePr and PCR as predictors of transplant failure.

**Methods:** Data were collected from the electronic patient record for recipients of a first renal transplant (Tx) between 01/01/00 and 31/12/2008. FePr and PCR were calculated (FePr = (Serum creatinine * Urine protein)/(Serum protein * Urine creatinine) %, PCR = ((Urinary Protein / Urinary Creatinine) * 1000). The primary endpoints were transplant failure and death. ROC analysis was performed for each test and patients were stratified into high/low risk groups. Kaplan Meier and Cox survival analysis were performed for each test.

**Results:** 219 recipients were followed up for a median of 4.9 years (1-11.1).11.4% (n=25) of the transplants failed at a median of 2.7 years (1.2-7.3 years). Mean eGFR at 1 year post Tx was 48.5mls/min/1.73m2 (SD 16.7). 7.7% (n=17) of patients died during the follow up period. Using ROC analysis, both FePr and PCR predict transplant failure and death. FePr had the higher sensitivity and specificity. On univariate analysis, those in the higher group of FePr had a 3.4 fold increased risk of transplant failure compared with those in the lower group (p=0.03). For PCR the higher group had a 2.1 fold increased risk of transplant failure. The higher group of FePr had a 2.3 fold increased risk of death (p=0.02) compared with a 1.6 fold increased risk of death in the higher PCR group. Those in the higher groups for FePR and PCR had a significantly lower 1 year eGFR ($p<0.001$) compared with those in the lower groups. In multivariate analysis, both tests remain independently predictive of transplant failure and death.

**Conclusion:** FePr and PCR accurately predict transplant failure and death but FePr is more sensitive and specific. It may be superior at predicting those at risk of transplant failure. Our study is limited by its retrospective nature and the small number of events. Comparison should be made between these tests and measures of albuminuria.

**78**

## Development and 3-centre validation of a prognostic risk score to predict renal transplant failure

Shazia Shabir[1], Aravind Cherukuri[2], Jean-Michel Halimi[3], Bryce Kiberd[4], David Benavente[1], Clara Addison[1], Jason Moore[5], Charles Ferro[1], Simon Ball[1], Paul Cockwell[1], Graham Lipkin[1], Richard Borrows[1]

*[1]Department of Nephrology and Renal Transplantation, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Birmingham, UK, [2]St James's University Hospital, Leeds, UK, [3]Chru Tours, Tours, France, [4]Dalhousie Medical School, Halifax, Canada, [5]Department of Nephrology, Royal Devon and Exeter Hospital, Exeter, UK*

**Background:** Although multiple risk factors for renal allograft failure in prevalent transplant recipients are recognised, there is limited data on the utility of composite risk scores to quantify that risk. The purpose of this study was to derive and validate such a prognostic tool for estimating graft failure risk at 5 years post transplantation.

**Methods:** 545 consecutive patients transplanted between 1999 and 2006, alive with graft function at 12 months, were studied. Demographic, clinical and biochemical data were analysed. Proteinuria was assessed by urine albumin: creatinine ratio (ACR) on an early morning "spot" urine. Cox Regression analysis was used to derive independent risk factors for death-censored and overall graft failure at 5 years following transplantation. Weighted risk scores based on the output of the regression analysis were then derived. The derived scores were then tested for discrimination, calibration and net risk reclassification improvement (NRI; compared with eGFR in isolation) in 3 independent cohorts from Leeds, Tours (France) and Halifax (Canada) in a population totalling approximately 2000 patients followed for five years.

**Results:** In the model-development cohort, 12-month ACR and eGFR, rejection during the first year, recipient race, age and sex, and the same variables plus serum albumin at 12 months were independently associated with death-censored and overall graft failure respectively. When tested in the 3 validation cohorts, the death-censored risk score displayed good discrimination (c-statistics 0.79-0.89) and calibration, with an NRI of 34%-69%. Results were similar for overall graft failure (c-statistics 0.76-0.81; NRI 43%-50%).

**Conclusion:** The prognostic performance of these risk scores suggest they may be of utility in predicting graft failure, and are an improvement on prognostication based solely on renal function.

**79**

## X chromosome inactivation skewing in female kidney transplant donors and recipients: an epigenetic risk factor for transplant outcome

Matthew Simmonds[1], Shazia Shabir[2], David Benavente[2], Sourabh Chand[2], Jason Moore[3], Steven Gough[1], Richard Borrows[2]

*[1]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK, [2]Renal Institute of Birmingham, University Hospital Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Mindelsohn Way, B15 2WB, Birmingham, UK, [3]Department of Nephrology, Royal Devon and Exeter Hospital, Exeter, UK*

**Introduction:** In the early stage of female embryonic development, one X chromosome from each cell is randomly inactivated, a process first recognised by Lyon in 1961, and which prevents overexpression of X-linked genes in females. Chromosome methylation is the epigenetic mechanism behind this phenomenon. Until recently, this process was believed to be random and stochastic, such that an equal proportion of paternal and maternal X chromosomes undergo inactivation. However, it is recognised in some adult females that "skewed" inactivation may occur, such that >80% of either paternal or maternal chromosomes are inactivated. Such skewing has been associated with conditions such as cancer, autoimmunity, and some X-linked disorders. Although not fully understood, there is evidence that stem cell senescence may underlie the development of progressive skewing. This is of relevance to transplantation, where recipient skewing might suggest immune senescence and reduced risk for rejection, and where donor skewing might represent a more senescent organ more prone to failure.

**Methods:** Genomic DNA was available and suitable for analysis in 212 white female transplant recipients, and 186 white female transplant donors. Recipient and donor analyses were conducted separately. X chromosome inactivation (XCI) was assessed by performing CAG nucleotide repeat microsatellite analysis and methylation sensitive *HpaII* restriction digest of the androgen receptor gene present on the X chromosome, which undergoes complete methylation during XCI. Outcomes of interest were biopsy proven acute rejection (BPAR) and death-censored graft failure. Data were collected from the prospective departmental database, and cross checked with NHSBT.

**Results:** Interestingly, a higher proportion of recipients (23/212; 11%) displayed skewing than donors (6/186;3%) [p=0.003]. In addition, Cox regression analysis revealed recipient skewing was associated with a reduced risk of BPAR (HR: 0.30; 95%CI: 0.10, 0.92). No association between recipient skewing and graft failure was observed. Although numbers were small, of the 6 donors displaying skewing, 4 kidneys failed, a rate far higher than in kidneys from non skewed donors (HR: 3.90; 95%CI: 1.10, 16.08; p=0.05).

**Discussion:** Skewing of X chromosome inactivation in female transplant donors and recipients is associated with relevant endpoints in transplantation, and may be a novel epigenetic risk factor for outcome. In addition, skewing may represent a risk factor for end stage renal disease

**80**

**The impact of social deprivation on outcome of renal transplantation**

AJ Cockbain, E Lindley, M Attia, KV Menon, N Ahmad, R Baker, L Hostert

*St James' University Hospital, Leeds, UK*

**Introduction:** There is growing evidence that social deprivation is a risk factor for both chronic kidney disease and poorer access to transplantation. Social deprivation has also been linked to poorer postoperative recovery and reduced survival in cancer patients. We aimed to assess the impact of social deprivation on outcome following renal transplantation using the indices of multiple deprivation (IMD) score, which incorporates a range of economic, social and housing issues into a single deprivation score for each area in England.

**Methods:** All adult renal transplantations between 2000-2011 were included in this single centre study. Donor, transplant and recipient data were collected from a prospectively maintained institutional database. IMD score for each patient was calculated based on their postcode at time of transplantation. Patients were stratified into 5 group based on IMD quintile. Social deprivation was analysed using Kaplan Meier curves and the log rank test of significance for effect on graft survival (GS) and overall survival (OS). The effect of social deprivation on length of hospital stay (LOS), delayed graft function (DGF) and creatinine at years 1,3 and 5 were analysed as secondary outcome measures. Categorical variables were analysed by $\chi^2$, and continuous variables by one-way ANOVA at 5% significance.

**Results:** 1441 patients were transplanted in the study period. Social deprivation had no impact on OS (p=0.645) or GS (p=0.625). There was however a significant increase in the rate of DGF in the most deprived group vs. other groups (25.6% vs 14.9-19.7% respectively, p=0.005) and a significantly higher CIT between the most deprived and least deprived groups (mean 861mins vs. 747mins, p=0.02). LOS was not significantly increased in the most deprived group (11.1 days) vs. other groups (9.1–10.5 days, p=0.513). There was no significant difference in renal function at 1,3 or 5 years.

**Conclusion:** We have demonstrated increased CIT and increased rate of DGF in the most socioeconomically deprived, with a trend towards longer LOS. As well as addressing discrepancies in access to transplantation in the socio-economically deprived, it may be important to explore reasons for increased CIT, e.g. poor transport availability, in an effort to reduce the rate of DGF in this group.

**81**

**Shedding light on "sleeping kidneys" – when does delayed graft function matter?**

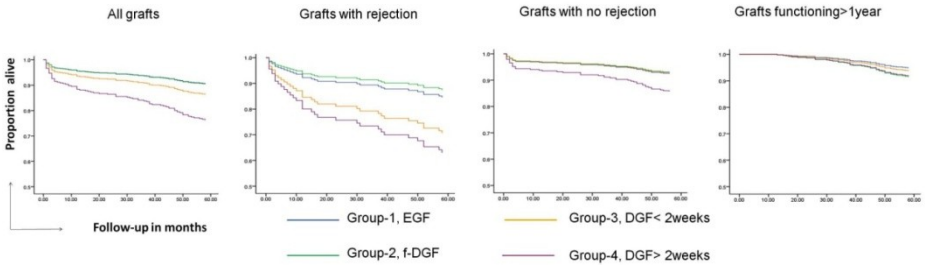
Aravind Cherukuri, Chas Newstead, Andrew Lewington, Richard Baker, Niaz Ahmad

*St.James's University Hospital, Leeds, UK*

**Background:** Delayed Graft Function (DGF) is a significant risk factor affecting long-term graft survival after renal transplantation. However DGF is a heterogeneous entity worsened by the intensity of the ischaemic insult and which may be modified by rejection episodes. In this study, we have analyzed the impact of these characteristics on graft survival.

**Methods:** Medical records of 680 renal transplants performed and followed-up between 1988 and 2006 were reviewed and data analyzed. Functional DGF (f-DGF) was defined as serum creatinine change <30% over the first three post-transplant days. DGF was defined based on the need for dialysis within the first post-transplant week. Based on the duration, DGF was defined as prolonged if >2 weeks. Patients with DGF had a biopsy done on day-7 and this was repeated every week for the duration of DGF. Based on these features various groups were defined within the study population (Group-1: No DGF, Group-2: f-DGF, Group-3: DGF<2weeks, Group-4: DGF>2weeks). Patients were also divided into groups based on DGF and rejection (Group-A: no DGF, no rejection; Group-B: DGF, No rejection; Group-C: no DGF, rejection; Group-D: DGF, rejection). Death censored graft survival (DSGS) over 5 years was analyzed with a multivariate Cox Proportional hazards model. To study the true long-term impact of DGF and the various characteristics, we have also analyzed DSGS after excluding graft losses within the first year.

**Results:** When compared to group-1, patients in groups 2-4 had progressively worse graft outcomes, even though only group-4 reached statistical significance. The impact of this classification of DGF was more pronounced in the patients who had an episode of rejection when compared to those without rejection. Interestingly when 66 grafts that were lost in the first year were excluded from the analysis, there was no significant difference between the groups (figure-1). In a similar fashion DGF in the absence of acute rejection (Groups A-B) did not have an impact on DSGS and even the effect of DGF with rejection (group-D) was dominant in the first year.




**Conclusion:** This study shows that the effect of DGF on long-term graft outcomes, irrespective of its duration and severity is minimal in the absence of acute rejection.

# Kidney outcome 2

**82**

**Help the aged? Does transplantation in older recipients result in inferior outcomes?**

David van Dellen, Melanie Field, Edwin Faulconer, Hari Krishnan, Stephen Mellor, Ahmed Hamsho, Andrew Ready, Nicholas Inston

*Queen Elizabeth Hospital Birmingham, Birmingham, UK*

**Background:** The increasing age of the population coupled with significant improvements in health care, especially in renal replacement therapy (RRT), has ensured that the demographics of potential renal transplant recipients is shifting with increasing numbers of older potential recipients being considered. Some clinicians have expressed caution in undertaking transplantation for this cohort of patients, due to concerns regarding long term patient and graft outcome as well as the potential effects of often serious co-morbidities and immunosuppressive load on surgical success. There remains scarce data regarding outcomes in this group and we aimed to examine our unit's outcomes over recent times.

**Methods:** A retrospective analysis was performed of a contemporously maintained renal transplant database at a single centre focusing on recipients older than 60 over a 6 year period (Jan 2005 to Dec 2010.) Primary endpoints were graft and patient survival. Potential confounding factors including differences in immunosuppressive regimens and demographic differences were also considered. Secondary endpoints included potential infective complications (cytomegalovirus (CMV) infection, chest and wound infection.)

**Results:** 658 transplants were performed over this period (551 <60y.o, 107 >60y.o.) Immunosuppression reflected unit protocol over this period with triple immunosuppression predominating (Calcineurin inhibitor, anti-proliferative and steroid with induction therapy) across both groups. There were more live donors in the younger group than the older in which cadaveric donors predominated (Live: 261 and 39 respectively, p=0.04; DBD: 226 and 57, p=0.02; DCD 64 and 11, p=0.86; Fisher's exact test) Total 1 year patient survival was 97.7% (<60: 98,5%, >60 93.4%; p=0.02, Log rank test) whilst 1 year graft survival was 93.4% (<60: 94.1%; >60 89.7%, p=0.26, Log rank test) There were no differences in the older group based on immunosuppression used. Patients in the older group who had a live or DCD kidney had 100% 1 year survival whilst it was 88% in the DBD group (p=0.06, Log rank test). Both groups failed to show difference in any infective complications (p=NS).

**Conclusions:** Historical concerns have pervaded regarding transplanting older patients, but we have demonstrated that renal transplantation offers a safe, reliable method of RRT. The risks of overwhelming infection in an over-immunosuppressed patient are also unfounded with good 1 year patient and graft survivals excluding non-transplant related mortality. The confounding factor of less living donor and more cadaveric transplants proportionately being performed in the older group of patients in this study should also disadvantage outcomes, but appears to have had no role in this study, although it suggests DBD kidneys should be used cautiously, potentially due to effects of cumulative risk factors. With evolving demographics of the population, renal transplantation will evolve into offering transplants to older recipients which appears to offer good outcomes.

**83**

**GAMBIT update: translating to the clinic biomarkers of tolerance in renal allograft recipients.**

Paula Mobillo[1,2], Sonia Noris[1], Estefania Nova-Lamperti[1], Irene Rebollo-Mesa[1], Yogesh Kamra[1,2], Manohursingh Runglall[1,2], GAMBIT Consortium All[4], Graham M. Lord[1,2], Robert Lechler[3,1], Maria Hernandez-Fuentes[1,2]

*[1]King's College London, London, UK, [2]NIHR Comprehensive Biomedical Research Centre at Guy's and St Thomas's Hospital; NHS Foundation Trust in partnership with King's College London and King's College Hospital, London, UK, [3]King's Health Partners, London, UK, [4]www.gambitstudy.co.uk, Europe, UK*

**Background:** Long-term graft survival in renal transplantation relies on continuous immunosuppression with drugs associated to high morbidity. A set of biomarkers of tolerance has been defined (JClin Invest, June 2010), and will form the basis for a test for safe immunosuppression minimization or withdrawal.

**Aims:** to validate the proposed biomarkers of tolerance on kidney transplant recipients to ultimately translate them into routine clinical diagnostic test. To better understand the mechanisms underlying the detection of the biomarkers identified.

**Methods:** Extensive multiparametric flow cytometry assessment of T, B and NK lymphocytes subsets, RT-PCR of genes related to tolerance, IFNγ ELISpot for analysis of CD4+ anti-donor responses and anti-HLA antibody detection. Anti-HLA Ab are detected in serum using Luminex kits. The recruited groups include (HC) healthy controls; (TOL) recipients with stable kidney function that have stopped taking all of their drugs; (STA) recipients with stable kidney function on standard immunosuppression and (CR) recipients with immunologically driven chronic allograft nephropathy despite standard immunosuppression.

**Results:** In agreement with the previous RT-PCR published data, differential gene expression is detected amongst patient groups, and it helps in identifying TOL recipients. A higher percentage of CR patients have detectable donor-specific HLA-Ab. The NK flow analysis reveals that effector, NKG2D+ and CD25+ NK cells are fewer in TOL recipients. CR patients present with the highest percentage of CD56+CD3- NK cells.

**Conclusions:** TOL recipients exhibit a regulatory NK profile compared to CR, that in turn present an effector and activated one. Additional experiments will be completed in order to validate the proposed biomarkers of tolerance and to further contribute elucidating the mechanisms involved in kidney transplant tolerance.

**84**

**Challenging the old traditions in renal transplantation: the first uk enhanced recovery programme after renal transplantation**

Ahmed Halawa, Simon Boyes, Chidambram Nathan, Abbas Ghulam, Julia Hanvere, Paresh Jogia, Fleur Roberts

*Sheffield Kidney Institute, Sheffield, UK*

**Introduction:** Recent evidence shows the benefit of multimodal care programmes bringing about enhanced recovery of patients in many surgical subspecialties. Practice in the renal transplant unit at Sheffield teaching hospitals was based on traditional pre-operative and post-operative care. These resulted in delayed discharge planning and patient education. Traditional anaesthetic techniques and management of urinary catheter, lines and drain led to longer stay and subsequent delayed recovery. There has been anxiety among renal transplant surgeons and physicians that enhanced recovery principles cannot be applied to these immunocompromised patients who are ASA III.

**Aim:** To apply the principle of the enhanced recovery programme in renal transplant recipients and assess the changes in the quality of patients' care.

**Methods:** The principle of enhanced recovery includes a multidisciplinary team approach involving surgeons, anaesthetists, physicians and nurses. Patient education and discharge planning are commenced on admission for transplantation and even earlier in live donor transplant recipients. Changes to intra operative management including goal-directed fluid management using the Lithium Dilution Cardiac Output monitor (LIDCO*rapid*) or Transoesophageal Doppler were also implemented. This helped to achieve adequate fluid balance during the operation and avoid central lines. Intrathecal diamorphine and transversus abdominis plane block (TAP block) were used to minimise use of intravenous morphine, to achieve improved postoperative pain control and decreased postoperative nausea and vomiting (PONV). Patients were commenced oral fluids and feeding few hours after the operation. Urinary catheter and drains were removed 3 to 4 days after the operation. This enabled early mobilisation and patient education resulting early discharge without increase in the readmission rate.

**Results:** Implementing the principle of enhanced recovery reduced the length of stay significantly ($P<0.001$) for living transplant recipients (Mean 6.3 vs. 10.3 days, Median 6 vs. 8 days) and for deceased donor transplant recipients (Mean 6.2 vs. 11.2 days, Median 6 vs. 9 days) compared to patients who had traditional recovery

**Discussion:** The principle of enhanced recovery is applicable in this category of immunocompromised high risk patients. When standardised, multi-disciplinary pathway is implemented and managed correctly, reduction in the length of stay can be achieved without compromising the patients' care. It also could reduce the cost of renal transplantation when applied on a large scale. Implementing enhanced recovery programme could also improve the quality of care of non-transplant patients by reallocating the nursing staff to look after them.

**85**

## Review of cancer incidence in renal transplant patients at a single centre between 1994-2010

Meghana Kulkarni, Iain MacPhee, Joyce Popoola, Sara Heap, Nicos Kessaris

*St George's Hospital, Tooting, London, UK*

**Introduction:** Malignancy is more common in patients receiving immunosuppression following organ transplantation than in the non-transplanted population. This study provides an analysis of the incidence and characteristics of malignant tumours of 332 patients who underwent renal transplantation between January 1994 and December 2010 at a single centre.

**Methods:** Data were collected retrospectively for the 332 transplants still followed up at our unit. The Renal Database (CV4), Electronic Patient Record (EPR) system and where necessary patient hospital records were used for data collection. Data collected included patient demographics and immunosuppressive medication administered at the time of transplant. Histopathology reports were used for cancer diagnoses.

**Results:** A total of 213 men and 119 women were included. The mean age at transplantation was 46 years (SD 13.2). 242 transplants were from deceased donors. 178 patients were White, 63 Black, 62 Asian and 29 from other ethnic backgrounds. The incidence of cancer post transplantation in this series was 11.7% (39 cases out of 332) during the study period. 19 of these (49%) involved the skin (8 basal cell carcinomas, 7 squamous cell carcinomas, and 1 malignant melanoma). The remaining predominant cancer types were urological (5 cases), post-transplant lymphoproliferative disorder (5 cases) and breast (3 cases). The mean time of cancer diagnosis following transplantation was 4.4 years (SD 3.5). Age at the time of transplant was found to be significantly different between the patients who developed cancer (mean age 53.8, SD10) and those who did not (mean age 44.9, SD13) [P=0.046]. History of cancer prior to transplantation was also significantly different between the two groups (P=0.035) but gender was not (P=0.111). There was no statistical difference between the cancer and non-cancer groups with respect to use of steroids, azathioprine, tacrolimus, mycophenolate mofetil and sirolimus at the time of transplant.

**Conclusions:** The above cancer outcomes are comparable to published data and highlight the importance of regular screening in patients after transplantation. Annual dermatological review is already occurring and all national screening programs are followed at our centre. Where possible, patients with a previous history of cancer are changed to sirolimus 3 months after transplantation. Our analysis did not show a difference with regard to the immunosuppressant used but this may be due to the small sample size These results will benefit our patient education by making them aware of the local cancer rates. Annual publication of cancer incidence post-transplant by each centre may show potential variability of cancer around the UK and will allow the monitoring of trends of different cancers.

**86**

## Factors predicting the adherence of renal transplant recipients to immunosuppressant drug therapy

Jasmin Cairns[1], Peter Noyce[1], Neil Parrott[2], Richard Emsley[1], Darren Ashcroft[1]

*[1]The University of Manchester, Manchester, Lancashire, UK, [2]Central Manchester University Hospitals NHS Foundation Trust, Manchester, Lancashire, UK*

**Introduction:** To minimise the risk of graft rejection in renal transplant recipients, and to maximise successful post-transplant care, adherence to prescribed immunosuppressant drug therapy is essential. Research suggests that average adherence levels in this patient population are less than optimal. While much research has explored factors affecting adherence, there is a lack of insight into their relative contributions. This study aimed at assessing and understanding the predictors of renal transplant recipients' self-reported adherence behaviour.

**Methods:** A 79-item questionnaire was constructed using the theory of planned behaviour (TPB), a social cognition model which hypothesises that behaviour is predicted by a person's intention to carry it out. Intention is, in turn, predicted by their attitude towards carrying out the said behaviour, their perception of others' expectations, and their perceived behavioural control over carrying out the behaviour. Variables added to the TPB in this study included anticipated affect, prospective memory and habit. The effect that each variable had on adherence was determined using binary logistic regression.

**Results:** The questionnaire was posted to 984 adult renal transplant recipients under the care of one hospital, and 549 were returned. Twenty-one of these were excluded for not meeting the inclusion criteria (i.e. having a renal graft and being prescribed immunosuppressants), therefore resulting in a response rate of 54.8% (n=528). Adherence levels were high, with 65.7% (n=347) achieving the maximum score of 25 on the Medication Adherence Reporting Scale (MARS), reflecting perfect adherence, and 21.4% (n=113) a score of 24. Between 94.3 and 98.7% of respondents indicated that they had not altered the prescribed immunosuppressant drug therapy or missed any doses during the month prior to completion of the questionnaire. In comparison, only 69.7% indicated that they had 'never' forgotten to take their immunosuppressants within that period. Adherence was significantly predicted by lower levels of perceived behavioural control ($OR=0.95$, $p<0.05$), and higher levels of anticipated affect ($OR=1.26$, $p=0.05$), prospective memory ($OR=1.78$, $p<0.005$) and habit ($OR=2.11$, $p<0.005$). Of the demographic data included in the questionnaire, being unemployed ($OR=1.88$, $p<0.005$) and being more recently transplanted ($OR=0.72$, $p<0.05$) significantly predicted adherence.

**Discussion:** Unintentional dose omission was the primary reason for nonadherence to the prescribed immunosuppressant drug therapy in this patient population. Habit and prospective memory had the greatest influence on adherence and, therefore, should be a key target of adherence interventions.

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**Renal and multiorgan transplantation: recent experiences**

David van Dellen, Melanie Field, Edwin Faulconer, Tofunmi Oni, Hari Krishnan, Stephen Mellor, Ahmed Hamsho, Andrew Ready, Nicholas Inston

*Queen Elizabeth Hospital, Birmingham, UK*

**Background:** Renal transplantation, either synchronously with another solid organ or subsequently, remains unusual nationally as the number of units with the multidisciplinary infrastructure to provide this service coupled with patients with adequate cardio-respiratory reserve and suitable indications for this procedure remain rare. The paucity of suitable donor organs for transplantation with lengthening waiting times has heightened interest in the suitability of transplanting this valuable resource into complex patients. We aimed to assess outcomes of kidney grafts as part of multiorgan transplant combinations either synchronously or at a later juncture.

**Methods:** A retrospective analysis was made of a renal transplant database maintained at a single institution offering multiorgan transplantation over 7 years (2005- 2011). This included patient undergoing kidney in combination with liver, heart or lung transplantation either at the time or as a result of end stage renal failure (ESRF) subsequent to previous solid organ transplantation. Patient and graft survival were assessed as primary endpoints with biopsy proven acute rejection (BPAR) and glomerular filtration rate (eGFR) at 3 and 6 months assessed as secondary endpoints.

**Results:** 19 renal transplants were performed during the study period (13 combined with other organ; 7 following previous transplant; median age 51 (range 25-65); 10M, 9F) This comprised: 15 liver/kidney, 3 heart/kidney, 2 lung/heart/kidney and 1 lung/kidney. The aetiology of ESRF included: Calcinuerin toxicity: 8, polycystic disease: 8, Diabetes mellitus: 1, reflux nephropathy: 1, IgA nephropathy 1. 1 year or latest graft and patient survival was 100% (compared to total figures of 93.4% and 97.7% respectively, $p<001$ and $p=0.12$ respectively.) Transplant median eGFr at 3 and 6 months was 57.2ml/min (range 25.1-133.7) and 60.7ml/min (range 26.7-77.4) respectively. BPAR rates in the combined group was 21 %( 4/19) compared to 13% (85/658; $p=0.14$, Fisher's exact test) for the total group.

**Conclusion:** Multiorgan transplantation appears to offer a valuable opportunity for normalisation of renal function with excellent patient and graft survival and renal function outcomes in our cohort of patients. This study is limited slightly by the heterogeneous nature of the kidney graft types uses (synchronous and delayed transplants) but the infrequent nature of this type of transplantation ensures that meaningful independent series are very difficult to collate. It is of interest that the BPAR appears higher in this group compared to the entire programme, although not statistically significant, in the combined transplant group which doesn't correlate with previous reports of the potential protective effects of combination transplantation. In carefully selected cases, it appears as though either synchronous or sequential multiorgan transplantation can be associated with excellent patient and graft outcomes and function.

# Kidney outcome 3

**88**

## Gender mismatch in living unrelated renal transplantation: the early advantage of receiving a male kidney is lost after two years

Ann Marsden, Rhian Cooke, Sian Griffin

*University Hospital of Wales, Cardiff, UK*

**Introduction:** The effect of donor gender on renal transplant survival is complex. Poorer graft survival of female kidneys in male recipients has been attributed to their smaller size and reduced nephron mass, conversely an immunological female anti-male H-Y response has been reported to adversely affect the outcome following transplantation of male kidneys into female recipients. With the wide-spread acceptance of spousal donation, in order to appropriately advise our patients of their expected outcomes we undertook a retrospective study of our results of living unrelated donor (LURD) transplants.

**Methods:** Between 1/1/03 and 31/12/10, 57 recipients received a kidney transplant from a LURD. The majority of these occurred between opposite genders (male to female, 19; female to male, 30).

**Results:**

| | Donor age (years) | Recipient age (years) | Donor eGFR (ml/min) | BPAR # (%) | I year survival (%) | | 5 year survival (%) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Graft | Patient | Graft | Patient |
| ♂→♀ | 49±10 | 47±14 | 86±15 | 1 (5) | 89 | 95 | 84 | 95 |
| ♀→♂ | 51±10 | 55±9 | 83±14 | 5 (17) | 87 | 93 | 83 | 90 |

| eGFR (ml/min) | | | | | | |
|---|---|---|---|---|---|---|
| | 3 months | 6 months | 12 months | 24 months | 36 months | 48 months |
| ♂→♀ | 60±21 | 61±18 | 64±18 | 60±16 | 52±10 | 52±14 |
| ♀→♂ | 49±12* | 48±11** | 51±10** | 49±12 | 51±13 | 49±7 |

*p<0.05, **p<0.01

Five male recipients of a male graft retained stable renal function for 48 months (only two patients have completed this period of follow up).

**Discussion:** Although there was no difference in overall graft and patient survival following LURD transplants between opposite genders, female recipients of a male graft had significantly better renal function for the first year following transplantation, which then declined. Male recipients of a female graft had a lower eGFR initially, but this remained stable, so by 36 months post-transplant their function was identical to that of female recipients of a male graft. This suggests that the initial benefit of a larger nephron dose may be off-set by subsequent attrition, possibly related to a sub-acute immunological response directed against the H-Y minor histocompatibility antigen. Longer term follow up is required to assess the ultimate impact of these factors.

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## The role of the renal pharmacist on reduction of prescribing errors on the kidney transplant wards

Stephen Hughes, Marc Vincent, Kathrine Parker, Mehvosh Aktar

*Central Manchester Foundation Trust, Manchester, UK*

**Introduction:** Prescribing of medication in transplant patients is complicated with multiple therapeutic interventions, complicated pharmokinetics and polypharmacy. Prescribing errors are common in this population and pose high risk complications to the patients. The specialist renal pharmacist can improve prescribing standards through target teaching interventions on a transplant ward.

**Purpose:** Various interventions made by specialist ward pharmacist on renal ward were made and an audit of prescribing errors before and after these interventions was completed to determine their effectiveness. Interventions included; attendance of specialist pharmacist on daily ward rounds to pro-actively assist prescribing and the introduction of prescribing information booklet focusing on renal patients for all new prescribers.

**Method:** The prescribing error rate was calculated n all new prescriptions over a two-week period for each audit. The pharmacist performed a clinical check of each prescription to determine its accuracy. The nature and incidence of prescription errors was recorded and the results collated.

**Results:** The incidence of prescribing errors has fallen from 7.7% in the two week audit in January 2011 to 2.5% (Fisher's T-test, $P < 0.001$) six months later. The total number of errors was reduced on re-audit including reduction in significant errors and no serious errors. Commonly seen errors identified on the initial audit, such as continuation of inappropriate medication post-transplant, over and under-dosing of medication relative to renal function, and inappropriate dose timings of immunosuppressant medication were not seen as frequently on re-audit. Errors such as incorrect medication reconciliation on admission were seen on both initial and subsequent audits highlighting the discrepancies with differing drug histories.

**Discussion:** Interventions made by the renal pharmacy team made a significant impact on improving the accuracy of prescribing. Common errors highlighted in the first audit were targeted through specific pharmacist interventions. The attendance of specialist pharmacist on ward round improved contact time with prescribers and any ambiguous medication issues could be discussed with pharmacist before prescribed. Additionally, the information booklet distributed on new clinician's induction was used to highlight common prescribing errors and to familiarise doctors with local policies and guidelines before they start in this clinical specialty. This pro-active approach reduces errors and improves patient safety on the kidney transplant wards.

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## Outcomes following both living and deceased donor renal transplantation in the elderly are comparable to younger recipients

Vijaya Ramasamy, Matthew Bottomley, Argiris Asderakis, Sian Griffin

*University Hospital of Wales, Cardiff, UK*

**Introduction**: Renal transplantation has previously been considered an appropriate treatment for younger patients. However, the median age at which patients start renal replacement therapy (RRT) in the UK is 65 years, and transplantation is now increasingly considered for older patients with greater co-morbidities. Given the disparity between available organs and number of patients on the waiting list, scrutiny of outcomes following transplantation into this patient group is essential to ensure appropriate use of this scarce resource.

**Methods:** 128 patients transplanted between January 2009 and August 2010 who have remained in our centre for long term follow up were identified. Data was collected from the renal and hospital databases, and notes reviewed for details of co-morbidities. Included in the analysis were: recipient age, gender, duration of RRT, donor age and type (deceased or living), duration of admission, incidence of delayed graft function (DGF), readmission within three months of transplantation, biopsy proven acute rejection (BPAR) episodes and eGFR at one year. The Beck Depression Index – short form (BDI-SF) was completed one year post-transplantation. Results were analysed after transplant recipient population was stratified into two groups by age, younger or older than 65 years.

**Results:**

| | Age (years) | Number of Recipients | Duration of Admission (median days) | DGF (%) | Re-admission Rate (%) | BPAR (%) | Mean eGFR at One Year (ml/min) | One Year Graft Survival (%) | One Year Patient Survival (%) | BDI Score >3 (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Live | <65 | 47 | 9 | 11 | 42 | 18 | 61 ± 17 | 91 | 96 | 22 |
| | >65 | 4 | 8 | 0 | 100 | 0 | 80 ± 11* | 100 | 100 | 0 |
| DBD | <65 | 35 | 8 | 6 | 67 | 15 | 53 ± 19 | 94 | 94 | 33 |
| | >65 | 8 | 10 | 50* | 50 | 0 | 46 ± 16 | 75 | 75 | 100 |
| DCD | <65 | 28 | 11 | 71 | 50 | 11 | 51 ± 16 | 86 | 93 | 33 |
| | >65 | 6 | 12 | 83 | 100 | 0 | 34 ± 10* | 100 | 100 | 0 |

*$p < 0.05$, older compared to younger recipients receiving the same type of transplant

**Discussion**: In this single centre cohort study, outcomes following renal transplantation in the elderly are comparable to younger recipients, both in terms of renal function and mood. There was no acute rejection in the 18 older recipients, whereas 16 episodes occurred in the 108 recipients aged < 65 years. Although there were no patient deaths and no graft loss in the older recipients of DCD kidneys, there was a high incidence of DGF and inferior renal function at one year, likely related to both donor and recipient factors. There was an unexpectedly high incidence of depressive symptoms in both age groups amongst those who completed the BDI-SF (65 out of 128 patients), which is a focus of further study.

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**Renal transplantation in recipients over 70 years has excellent outcomes**

Hemant Sharma, Assad Ullah, Chang Wong, Adham El-Bakry, Rahul Sinha, Matthew Howse, Sanjay Mehra, Ajay Sharma, Abdul Hammad

*Royal Liverpool University Hospitality, Liverpool, UK*

**Background**: Improvement in the quality of life and reduction in the mortality risk following a successful renal transplant has been established. Even though literature published in last 2 years has documented excellent outcomes of the transplant, evidence of efficacy of renal transplant in donors over 70 years is yet to mature.

**Aim:** To assess the outcomes of renal transplant in recipients over 70 years at our center.

**Methods:** We retrospectively reviewed our experience with renal transplantation in patients 70 years of age and older. 21 patients aged 70 years and older were transplanted at our institution in last 6 years. Demographics and outcomes were recorded.

**Results**: The median age of recipients was 73 (70-84) years. 90% (19/21) were deceased donors and 52% (N=11/21) donors were extended criteria donors. The median cold ischemia time (CIT) for transplants from deceased donors was 14.9 (581-1280) hours. The median hospital stay was 18 (6-88) days. 23% (N= 5/21) patients required ITU/HDU care post surgery. 71% (N=15/21) recipients were alive at last follow up. Patient survival at 06 months, 1 year and 5 years was 90%, 81% and 72% respectively. Graft survival was 81% at 1 year. When censored for death, graft survival at 1 year and 5 years were 100%. The delayed graft function rate was high (33%, N=6/21). 09% (N= 2/21) patients had biopsy proven rejection and were managed by pulsed steroid regime. There has been no graft loss till last follow up. The 4 week, 12 week and 24 week readmission rate was 14%, 19% and 09% respectively. Morbidities were largely related to hemodynamic (MI; CCF) and infectious events (UTI, CMV infection, BK Viremia). Cardiac failure and CMV disease was the major cause of death.

**Conclusions:** Transplant outcomes in recipients older than 70 years of age is satisfactory and despite the number of patients analysed in this study is limited, no exponential increase in complications resulting from age- related complications was noted. This report demonstrates excellent graft survival and function in a moderate-size, single-center experience. Transplantation of the elderly is thus justified in the appropriately chosen patients.

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## Ward based ultrasound guided renal transplant biopsies performed by the trainees: the Liverpool experience

Hemant Sharma, Assad Ullah, Chang Wong, Adham El-Bakry, Rahul Sinha, Ram Bhatt, Prasad Rajendran, Ajay Sharma, Sanjay Mehra, Abdul Hammad

*Royal Liverpool University Hospital, Liverpool, UK*

**Background:** There is paucity of published literature describing the effectiveness of training and results of biopsies performed by trainees. Trainees at our unit are formally trained to perform transplant biopsies under ultrasound guidance and are expected to perform a minimum of 10 biopsies during their placement.

**Aim:** To review the major and minor complication rate needing intervention and glomerular yield of renal transplant biopsies performed by transplantation surgery trainees

**Methods:** Renal transplant allograft biopsies performed from September 2010 to October 2011 were included in the study. The biopsies were primarily performed by Transplant trainees and patients were referred to interventional radiologists in following conditions a) BMI > 30 b) previous biopsy complication c) poor biopsy yield d) patient choice. All biopsies were performed under real-time ultrasound guidance using BioPince® Full-Core Biopsy Instrument 18G (1.2 mm) x 15 cm, 23 mm core. A Histopathology Scientist confirmed the initial adequacy of the samples. Adequacy of core tissue samples was judged according to number of glomeruli as defined by revised Banff criteria (7 glomeruli & 1 artery). One core sample was accepted for acute suspected transplant pathologies (< 6 months) and 2 core samples were accepted for chronic suspected transplant pathologies (> 6 months)

**Results:**

| Number of Biopsies | Performed by Trainees | Performed by Radiologists |
|---|---|---|
| N=79 (Total Patients 72) | N= 69 | N=10 |
| Specimens with adequate glomeruli (>7/core) | N=62 (89%) | N=8 (80%) |
| Inadequate Sample | N=06 | N=1 |

| complications | performed by trainees | performed by radiologists |
|---|---|---|
| hematuria | n=9 | n=6 |
| arterio-venous fistula formation | _ | n=2 |
| peri-renal hematoma/skin hematoma | n=1 | _ |

**Conclusions:** Renal Transplant Biopsies performed by trainees during supervised training is safe and there is no significant difference in complication rate of renal allograft biopsies, performed by the transplantation trainees or by radiologists in radiology departments. A Multicenter database can further robust the evidence.

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**From HLA incompatible living donor to directed DCD: a case report**

Nicola Hamilton, Tracey Fleming, Anusha Edwards, Justin Morgan, Rommel Ranavan

*North Bristol NHS Trust, Bristol, UK*

In 2009 two first cousins approached us regarding living kidney donation. They were found to be HLA incompatible and so were to be registered for paired exchange. Registration was delayed due to two other family members being diagnosed with terminal malignancy. During this time, we established an HLAi desensitisation programme and the cousins were to be considered and accepted for desensitisation with plan to proceed once the donor & recipient had completed the bereavement process following the death of the family members.

However, following the second of the family deaths the potential donor collapsed with a subarachnoid haemorrhage. The family were approached about organ donation and enquired, as living donation was planned, whether the intended live donor recipient could be a beneficiary.

Deceased donation must be unconditional but a change in allocation policy in 2010 allows directed deceased donation to proceed when living donation was planned if the donor dies before living donation occurs. On call discussions with the NHSBT duty office and Professor Neuberger confirmed the frame work within which donation and organ allocation could proceed in such circumstances. Directed kidney allocation was facilitated and the recipient underwent rapid desensitisation with ATG and a single session of plasma exchange pre-transplant with a further 9 plasma exchange sessions post-transplant. Five months post-transplant, the recipient is in good health with excellent graft function. The donor's liver and other kidney were also retrieved and transplanted.

This case report raises a number of ethical, legal, immunological and psychological issues that should be discussed with the wider transplant community.

# Kidney transplant - surgery 1

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## Effectiveness of continuous low dose local anaesthetic infusion in Transverses Abdominis Plane (TAP) for renal transplant recipients: A comparative study of 157 patients.

Abbas Ghazanfar, Otilia Pretorian, Omer Masood, Bence Forgacs, Anand Rajasekaran, Afshin Tavakoli

*Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

**Background:** Renal transplant is becoming a gold standard treatment for patients with end stage renal failure. Perioperative management of transplant recipient has much improved over the last two decades. Many efforts have been put in to reduce post operative pain in renal transplant recipients. Currently intravenous opioid administration provides the mainstay of analgesia following renal transplantation. Other techniques including local anaesthetic wound infiltration, transverses abdominis plane (TAP) block and continuous wound infusions have been reported in the literature. This present study describes our experience in multimodal/ opioid sparing analgesia regime with effectiveness of TAP continuous infusion of local anaesthetic in renal transplant recipients and its effects on patient's outcome.

**Methods:** We respectively analysed data of consecutive renal transplant recipients performed between 2009 and 2011. Patients were divided into three groups; Group I (TAP block with continuous TAP catheter infusion and Patient Controlled Analgesia {PCA}, n=43), Group II (Continuous TAP catheter infusion and PCA, n=53) and Group III (PCA only, n=61). Primary outcome was recorded as post-operative pain control. Secondary outcomes were total amount of fentanyl used; post operative wound infection, chest infection, deep venous thrombosis and length of stay in hospital. Medcal software was used for analysis.

**Results:**

| **Outcome** | **Group In=43** | **Group II N=53** | **Group III N=61** |
|---|---|---|---|
| Median pain score in recovery | 3 | 6 | 8 |
| Median pain score after 4 hrs of operation | 4 | 5 | 7 |
| Median pain score after 12 hrs of operation | 2 | 3 | 5 |
| Median pain score after 24 hrs of operation | 1 | 1 | 4 |
| Median opioid using fentanyl in mcg | 1100 | 1360 | 1920 |
| Wound infection | 2.3% | 1.8% | 4.9% |
| Chest infection | 2.3% | 3.7% | 6.5% |
| Deep venous thrombosis | 0% | 0% | 3.2% |
| Median hospital stay in days | 10 | 9 | 14 |

**Conclusion:** Our results show that TAP continuous infusion of local anaesthetic is an effective method of controlling post-operative pain and minimising opioid use in renal transplant recipients. Although median hospital stay is dependent on many factors but better pain control and early mobility may contribute to the reduction in length of stay.

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## Umbilical vein catheter (UVC) versus double J stent (JJ stent) for ureteric anastomosis in renal transplantation: interim results of a single centre randomised, open label trial

Stella Smith[1], Daniel Ridgway[1, 2], Sanjay Mehra[2], Hany Riad[1], Afshin Tavakoli[1]

*[1]Manchester Royal Infirmary, Manchester, UK, [2]The Royal Liverpool University Hospital, Liverpool, UK*

**Introduction:** Major urological complications following renal transplantation normally present within 3 months. The JJ stent creates a water-tight ureterovesical anastomosis and prevents ureteric kinking. It is removed by flexible cystoscopy. A Cochrane systematic review showed the routine use of a stent reduces risk of major urological complications. Nevertheless, the incidence in a review of case-control studies, which all used the Lich-Gregoir anastomosis and JJ stents, was 3 to 5%. Stents can increase number and severity of urinary tract infections (UTIs).

**Methods:** This was a prospective, single-centre, randomized (1:1), open-label trial of JJ stent versus a percutaneous size 6 French UVC in adults (>18 years) undergoing cadaveric or living-related renal transplantation alone. Patients were excluded if ureteric damage had occurred at retrieval; the patient had a contracted bladder or previous ureteric complications. After 6 patients with BMIs greater than 32 had attempted transplantation with an UVC, it became clear the catheter was not always long enough to reach the renal pelvis and this resulted in a protocol change. The percutaneous UVC was pulled out on day 7. The primary endpoint was to establish that UVCs do not increase the incidence of ureteric complications. Secondary endpoints were the incidence of UTIs and cost implications. A per-protocol analysis was used to detect differences between the 2 groups.

**Results:** 149 patients were entered in to the trial between November 2008 and May 2011. There were 23 protocol violations; all in the UVC group. 97 patients received a JJ stent, 52 received an UVC. All patients underwent a 3 month follow up. There were no significant differences between the 2 groups in terms of recipient age, sex, pre-operative glomerular filtration rate, proportion of cadaveric donors, donor age or total ischaemic time. There were 5 ureteric complications in UVC group: 1 patient had a ureteric stricture managed with a nephrostomy alone; 1 had a stricture requiring re-implantation; 3 UVCs fell out early and these patients underwent refashioning of the anastomosis. There were issues with securing the UVC and a policy of using at least 1 suture to hold the UVC was adopted. There were 2 ureteric complications in the JJ group; 1 patient had an anastomotic leak, managed with a nephrostomy and prolonged catheterisation; the other had a ureteric obstruction that required a nephrostomy but resolved without further intervention. Fisher's exact test was used to compare the rates of ureteric complications: two-sided P value=0.10. No patients with ureteric complications had BK virus. 35% of patients with a JJ stent developed a UTI during the follow-up period and 33% of patients with an UVC ($X^2$, p=0.77). Our unit performs approximately 130 kidney-alone transplants a year. An UVC is approximately £754 cheaper than a JJ stent. As a conservative estimate, if an UVC was used instead of a JJ stent in two-thirds of our patients, this would represent a saving of £65,600 a year.

**Discussion:** The use of an UVC resulted in a cost saving but with higher ureteric complications. The study continues with the protocol change to exclude patients with high BMIs and shrunken bladders. All UVCs are now sutured in.

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**Renal transplantation in 51 patients with spina bifida: A single centre experience**

Abbas Ghazanfar, Salmaan Hafez, Otalio Pretorian, David van Dellen, Bence Forgacs, Ravi Pararajasingam, Tunde Campbell, Afshin Tavakoli, Neil Parrott, Hany Riad, Malcolm Lewis, Titus Augustine

*Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

**Background:** Spina bifida is a complex central nervous system abnormality that comprises varying degrees of spinal cord malformation and neurologic deficits. Urological complications associated with deranged neurologic function in the urinary outflow tract in spina bifida are a major source of morbidity and mortality associated with a high incidence of end stage renal failure (ESRF). This study describes our experience with the outcome of patients with spina bifida who received a kidney transplant.

**Methods:** A retrospective analysis of 51 patients with spina bifida as primary diagnosis who received a renal transplant between 1985 to 2010 was performed. We recorded basic demographics of donor and recipients and their pre-transplant co-morbidity. Outcomes were measured in terms of complications, patient and graft survival. Numeric variables were compared using the independent samples t-test. Survival analysis was carried out using Kaplan–Meier estimates.

**Results:** Out of 51 transplants 8, 6 and 37 were Living donor (LD), Non-heart beating donor (NHBD) and Heart beating donor (HBD) respectively. Median age at transplant was 31 years (range 12-56 years). 21.5% of recipients were wheelchair bound and 13.7% required assistance during walking due to neurologic defects. Other co-morbidity included hypertension (60.7%), respiratory morbidity (25.5%) and diabetes mellitus (7.84%). 39.21% had pre-transplant bilateral nephrectomy whereas 9.8% had unilateral nephrectomy. 66.66% kidneys were transplanted into an ileal conduit fashioned at a minimum of 3mths to a median of 18 months before transplantation. 23.5% kidneys were positioned up side down. Primary graft function, delayed graft function and primary non-function was noted in 76.47%, 21.56% and 1.96% respectively. Complications after transplantation included haemorrhage requiring re-exploration 7.8%, urinary leaks 33.33% (17.64% required operative intervention), hydronephrosis requiring intervention 23.5%, urinary tract infection 72.54%, pyelonephritis 11.76%, ureteric stricture 13.72% (7.84% anastamotic) and collections requiring drainage 17.64%. Other complications with less than 5% incidence were urostomy blockage, prolapsed ileal conduit and transplant renal artery stenosis.

Table: Survival outcome of spina bifida cohort.

| Out come | Spina bifida | Overall DCD/DBD | Overall LD |
|---|---|---|---|
| 1 yr graft survival | 95% | 95% | 97% |
| 1 yr patient survival | 97% | 97% | 99% |
| 5 yr graft survival | 67% (100% in last 10yrs) | 83% | 87% |
| 5 yr patient survival | 89% (100% in last 10yrs) | 90% | 97% |

**Conclusion:** This large series show that excellent outcomes can be achieved by transplantation as renal replacement in patients with spina bifida in spite of severe co-morbidities and a fair degree of perioperative complications. We suggest that renal transplant should be considered early in patients with spina bifida approaching ESRF.

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## Split horse-shoe kidney transplantation for two recipients: first reported case series from the UK

Abdul Hakeem, Soulat Raza, Raman Girn, Clare Ecuyer, Andrew Lewington, Lutz Hostert, Magdy Attia, Niaz Ahmad, Krishna Menon

*Department of Renal Transplantation, St James's University Hospital NHS Trust, Leeds, West Yorkshire, UK*

**Aim:** Horse-shoe kidney is an anomaly of the urinary system with a reported incidence of one in 400 to 800 births. There are a range of anatomic variations in the way the two sides of the horse-shoe kidney are connected via an isthmus. This ranges from a fibrous tract to a full thickness parenchyma. In this study, we report three horse-shoe kidneys that were split for transplantation into six recipients. This is the first reported series of split horse-shoe kidney transplant from the United Kingdom.

**Methods:** Retrospective data collection for the horse-shoe kidney transplants done over the last 5 years. All continuous variable are expressed as mean+/-SD. Two of the kidneys were split using scalpel and the cut edges were sutured with running 3-0 PDS suture, whereas one kidney was split using CUSA (Cavitron Ultrasonic Surgical Aspirator).

**Results:** Three horse-shoe kidneys were accepted for transplantation in our department over a period of 5 years (July 2006, December 2008 and August 2011). Two were from DBD donors and one from DCD donor. The mean donor age was 44.3 +/- 14.7 years and all of them were male. The mean donor creatinine at retrieval was 89.6 +/- 24.4 umols/L and the mean eGFR was 91.3 +/- 25.7 mls/min/1.73 $m^2$. The mean recipient age was 45.5 +/- 25.7 years and there were equal number of males and females. The mean HLA mismatch was 2 and mean total ischaemia time was 20 hours and 59 minutes. The mean number of arteries in each kidneys were 3 (range 2-4). 5 out of 6 patients had primary function (83.3%). Overall, the mean creatinine at the end of follow-up (median 33 months) was 95.7 +/- 40.7 umols/L and the mean eGFR was 75.7 +/- 30.9 mls/min/1.73 $m^2$. There was one graft loss in this series due to arterial thrombosis, where there had been previous damage to lower polar artery. The only other morbidity in this series was post-operative polyuria in one patient, which lasted for 14 days. The patient and graft survival at the end of follow-up was 100% and 83.3% respectively.

**Conclusion:** Split transplantation of horse-shoe kidney is safe and should be encouraged in the current climate of donor organ shortage. 5 out of 6 patients in our series had good graft function with no major morbidity. Variations in arterial anatomy with multiplicity of vessels are common in these kidneys and therefore, we believe careful enbloc retrieval and back bench reconstruction are essential for successful outcome.

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## The UK approach to preoperative peripheral vascular risk assessment for kidney transplantation surgery

Christine Gan, Debasish Banerjee, Mohamed Morsy, Nicos Kessaris, Sarah Heap

*St. George's Hospital, London, UK*

**Introduction:** Renal transplantation surgery is only technically feasible if the recipient blood vessels are of sufficient quality for the vascular anastomosis to be successful without compromising the outcome of the patient or the graft. The evidence behind preoperatively assessing peripheral vasculature is deficient, and there is a lack of guidelines as to which investigation is favored.

**Method:** An anonymous web based questionnaire was sent to all UK renal transplant units. The respondents were asked to declare whether their units had guidelines, and which factors would influence the need for further investigations of the iliac vessels. Multiple answers were allowed for some questions.

**Results:** Of the 23 questionnaires that were circulated, 10 responses (43.5%) have been obtained so far. Only one unit who replied had guidelines and these were based on clinical experience rather than evidence-based guidelines. Factors that would initiate further investigation included the patients' age being over 50 years, patients' length of time on dialysis, smoking history, history of diabetes, IHD, PVD or vascular surgery, and weak or absent pulses. These patients would undergo pelvic x-ray every 5 years. Of the remaining 9 units, a history of vascular surgery, claudication, and weak or absent pulses would prompt the clinician to request further imaging. 7 of the 9 respondents (77.8%) would be concerned if the femoral pulses were calcified. 5 of the 9 units (55.6%) would require further investigations if the patient was diabetic. Other factors that caused some, but lesser concern included patient age greater than 60, patients' length of time on dialysis, history of PVD or IHD, smoking history or a previous transplant.The investigation that was most commonly requested was Doppler of the femoral vessels (77.8%), followed by either pelvic x-ray, CTA or MRA. The majority of units (88.9%) would repeat investigations if clinical condition changes. There were 9 different responses to the management plan if a problem was identified from the imaging. This ranged from only listing for a deceased donor transplant, listing only for a live donor transplant, to using the aorta, to referring for an aorto-iliac graft or not listing at all. If calcification was found at time of transplant, most (77.8%) would try to use the internal iliac vessel, 4 (44.4%) would perform an endarterectomy, 4 (44.4%) would explore the other side and 3 (33.3%) would consult a vascular surgeon.

**Conclusion:** There is a lack of clear evidence and a great deal of variability as to how patients with vascular calcifications are managed. When establishing unit guidelines the experience of the team and availability of resources are determining factors in identifying high risk patients with calcification.

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**"Local donor to local recipient" after therapeutic nephrectomy**

Muhammad A Khurram[1], Colin H Wilson[1], Lisa Silas[2], Peter Robinson-Smith[1], David A Rix[1], Neil Sheerin[1], David Talbot[1], Derek M Manas[1], Lisa Burnapp[2], Jonathon Olsburgh[2]

*[1]Freeman hospital Newcastle upon Tyne Hospitals NHS trust, Newcastle upon Tyne, UK, [2]Guy's and St Thomas' NHS Foundation Trust, London, UK*

Nephrectomy is occasionally still required for benign renal conditions such as chronic loin pain, pelvic kidney and irreparable ureteric injuries. In such cases autotransplantation (AT) may be considered as a treatment option, but if the remaining kidney has good function, nephrectomy may be considered. We present 2 cases from two institutions where a resected kidney was transplanted.

**Case 1:** A 61 year old male presented for elective closure of a defunctioning colostomy**.** Post operatively he developed a urine leak from his left kidney and imaging confirmed an irreparable high ureteric injury. Radioisotope studies demonstrated adequate function in the right kidney and the patient rejected the idea of AT in view of his multiple previous surgeries and potential for further complications. He was then approached for consent to use his left kidney as an allograft and readily approved. After approval from the Human Tissue Authority and NHSBT we selected a local 69 year old man from our local cadaveric waiting list as a potential recipient. Following informed consent a sequential live donation procedure was planned. Although the ureter (4 cm), vein and artery were short, transplantation was possible. At 6 months follow-up donor and recipient are doing well.

**Case 2:** A 22 yr old female patient with chronic pelvic pain secondary to an ectopic kidney was assessed at her request for nephrectomy. After appropriate evaluation the urological team agreed to the procedure and she suggested the kidney be re-used for transplantation. After the precedent in Case 1, a local 42 yr old male was selected as an appropriate recipient. A sequential live donation procedure was successfully performed. At 3 months follow-up both patients are doing well.

**Conclusion:** Patients who require nephrectomy may value the opportunity to become a live organ donor and, in particular situations, this option may be possible. The kidney removed may pose specific technical problems and a local recipient from the cadaveric pool can be selected to minimise the potential risks of complications. With the success of these two cases it is recommended that a local recipient is chosen for the best outcome and this has been endorsed by KAG and NHSBT.

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**Live donor kidney transplantation after large angiomyolipoma excision**

Hamid Abboudi[1], Pankaj Chandak[1], Nicos Kessaris[1], Jiri Fronek[1, 2]

*[1]St George's Hospital, London, UK, [2]Institute for Clinical and Experimental Medicine, 2nd Medical Faculty, Charles University, Prague, Czech Republic*

A 47 year old female underwent assessment for living (unrelated) kidney donation for her husband who had ESRF due to adult polycystic kidney disease. Routine pre-operative CT angiography demonstrated a large 6x4cm angiomyolipoma (AML) arising from the upper pole of the right kidney. Right sided hand assisted retro-peritoneoscopic live donor nephrectomy with bench tumour excision was subsequently performed. Recipient implantation was unremarkable with no haemorrhage. Histology confirmed a 7cm AML. At 11 months follow up the recipient's serum creatinine was 190 µmol per litre and eGFR 30 ml/min without the need for dialysis at any stage. Angiomyolipoma is not a contraindication for live donor transplant despite a size of 7cm; both donor and recipient had successful outcomes. To our knowledge this represents the largest AML tumour excised from a donor kidney resulting in a successful outcome for the recipient.

# Kidney transplant - surgery 2

**101**

**How to train a renal transplant surgeon? A survey of consultants and trainees**

Miriam Manook[1], Bimbi Fernando[2], Jonathan Olsburgh[1]

*[1]Guy's Hospital, London, UK, [2]Royal Free Hospital, London, UK*

**Introduction:** Surgical training in renal transplantation is not standardised, and has traditionally drawn surgeons from diverse backgrounds with a wide variety of experience and skill. As surgical training becomes increasingly specialised, a new training program in transplantation has been developed and is being offered to General Surgical trainees by the London Deanery. We surveyed trainees and consultants for their experience in transplantation and views on what sub-specialties this program should offer, as well as the number of index operations required to demonstrate sufficient competency to be awarded the certificate of completion of specialist training (CCST).

**Methods**: An on-line survey of all Pan-Thames group renal surgical consultants and trainees. Consultant response rate was 50 % (11 respondents) trainee response rate 54% (12 respondents). 54.5% of trainee respondents (TR) were in a designated training post. 75% of trainees intended to train in transplantation. Half of the consultant respondents (CR) had been in post for 0-6 years.

**Results:** All trainees and the majority of consultants (87.5%) felt that it was important to experience more than 1 transplant unit during training. 62.5% of CR;s had experience of 4 transplant units, 41.7% of TR's had experience of 3 units. Regarding surgical training experience, both groups were broadly agreed about the breadth and duration of surgical placements, which included at least 6months of vascular surgery, urology, emergency surgery, endocrine, colorectal, upper GI, paediatric, HPB and liver transplantation TR's felt more vascular experience was appropriate compared to CR's (6-12months, compared to 0-6 months). In terms of the number of index operations to be completed to acquire a CCST, there was a difference between CR and TR: All CR's thought that a transplant trainee should have completed 15-60 renal transplants as lead surgeon but the majority of TR's (58.3%) thought that they should complete >60 renal transplants as lead surgeon before acquiring CCST. 50% of TR's wanted experience of > 60 laparoscopic donor nephrectomies as lead surgeon, while 37.5% of CR's thought it was acceptable to complete 0-15; 25% 15-30 and 37.5% 30-60. 71.5% of CR's thought that immunology and 87.5% that histocompatibility/tissue typing should be offered formally as non-surgical options of a transplant training program, compared to 36.4% and 36.4%, respectively of trainees. TR's felt it more important than CR's to have accreditation in a 2$^{nd}$ subspecialty alongside transplantation. Of those who supported a second accreditation, urology or vascular surgery were the most popular choices in both groups.

**Conclusion:** Training in transplant surgery requires a wider surgical exposure than is currently available within general surgical training, in addition to specific non-surgical skills such as knowledge of immunology and histocompatibility. New programs need to address not just the difficulties of a competency based training following the introduction of the EWTD, but also the breadth of experience required to manage vascular access work and complex urology for adults and children in an increasingly sub-specialised training system.

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**Minimal access kidney transplantation: an alternative technique**

Abbas Ghazanfar, Omer Masood, Dan Ridgway, Tunde Campbell

*Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

**Introduction:** Kidney transplantation is the treatment of choice for patients with end stage kidney failure. The surgical technique used to implant the kidney is well established and has been practiced by surgeons the world over for more than 40years. The access to the iliac vessels and bladder to which the kidney is surgically attached, is achieved through a muscle cutting extraperitoneal, incision in the iliac fossa. It is widely recognised that techniques that minimise surgical trauma of access often result in quicker patient recovery and have potential health gains. Lately, there is increasing interest in the development of minimally invasive surgical techniques which is slowly replacing well established more invasive techniques for many surgical procedures. We report on an open, less invasive technique compared to the standard.

**Method:** We propose a less invasive open technique to achieve access to the operative site without the need to cut muscles, blood vessels (inferior epigastric ) and nerves. The iliac vessels and bladder is accessed through a midline, subumblical, extraperitoneal incision to enable successful implantation. The surgical equipment used is similar to that used for the standard operation. The implantation procedure itself is also similar to what is known as standard.

**Results:** This technique was used so far for 4 kidney transplant recipients. Patient 1 was a patient who had simultaneous kidney pancreas transplant. Patient 2 was a fitness instructor & trainer who was keen to return to work as quickly as possible following a successful live donor kidney transplant. Patient 3 is a Jehovah's Witness who does not want blood transfusion. Patient 4 is a 12 year old paediatric recipient. All 3 patients except patient 1 did well with no technical post op complications. Patient 1 lost both Pancreas and kidney to sepsis.

**Conclusion:** We believe that our technique is safe and can potentially reduce post op complications related to surgical access such as blood loss, post-operative pain, and use of narcotic analgesics, neuralgia and challenging incisional hernia. We believe that this is an alternative technique with potential benefits for patients and can be quickly mastered by practicing surgeons. There is a need to subject this technique to a multicentre clinical trial comparing it with the standard technique.

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**The use of pre-printed operation notes leads to better data collection**

Najma Hannah Maple, Jonathon Olsburgh

*Guy's Hospital, London, UK*

**Aim:** An audit was conducted to ascertain whether pre-printed operation notes lead to improved data collection for Renal Transplant cases.

**Method:** The audit commenced on 29th June 2011. Pre-printed operation notes were used for 10 Renal Transplants occurring on and after this date. The categories for completion were based on the Royal College of Surgeon's 'Good Surgical Practice' guidelines and the UK Transplant 'Hot A' form. 10 free-text operation notes preceding this date were collected for comparison. Data collection categories were as follows: Recipient dialysis details, Donor details (including demographics, cause of death, CMV status and mismatch), Organ details, Timings, Operation details and Post-operative instructions.

**Results:** 20 operation notes were collected for Renal Transplants performed between 12th May 2011 and 2nd July 2011. 12 (60%) were from living donors and 8 were from deceased donors. All of the operation notes contained patient demographic details, the name and date of the procedure and details of the surgeon and assistant. The pre-printed operation notes resulted in better data collection across each of the categories: Recipient dialysis details, Donor details (age and mismatch), Organ details (number of arteries and ureters, side of kidney, retrieval damage), Time of organ retrieval and Operation details (operation time, blood loss and documentation of correct swab count). Some information was collected equally well on both types of operation note: gender of donor, cause of death, time out of ice, time of perfusion, cold ischaemic time and documentation of drain, stent and catheter placement. Donor and recipient weights, donor creatinine and post-operative instructions were poorly completed on both types of operation note with only 10 (50%) containing a post-operative plan. Donor CMV status and request for post-operative ultrasound were recorded better on the free-text operation notes. Only 17 operation notes (85%) were completed with a signature. All surgeons used the free-text space for further procedural details and 18 (90%) contained a diagram.

**Discussion:** This audit has demonstrated that pre-printed operation notes lead to an increase in data collection. Pre-printed operation notes should be encouraged for use for all Renal Transplant cases to ensure essential information is documented accurately at the time of surgery. This will benefit the surgeon, their team and other clinicians involved in the post-operative care of the transplant patient. It will also lead to more accurate completion of UK transplant forms and provide more precise information for future audit and research purposes. Our operation notes will soon be uploaded into an electronic format after each case to complement our paper-light clinical environment.

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**Assessment of blood utilisation and blood loss in a single centre and review of the UK practice in amount of blood crossmatched for renal transplant surgery**

Steven Hamm, Sarah Heap, Kelly Feane, Nicoletta Fossati, Mohamed Morsy, Nicos Kessaris

*St Georges University of London, London, UK*

**Introduction:** In our unit we crossmatch 4 units of blood for each renal transplant operation. The aim of this study was to assess blood loss and blood utilisation during renal transplantation locally and to review how much blood is requested in other units in the UK.

**Methods:** All renal transplants performed locally between April 2011 and July 2011 were included in this study. Data regarding blood requested/utilised, estimated blood loss, patient's age, sex, haemoglobin (Hb) before and after the transplant and transplant type were collected. In addition, an electronic questionnaire was sent to all renal transplant units asking how much blood is crossmatched for each transplant to assess UK practice.

**Results:** Twenty-one patients had received a transplant during the study period (4F, 17M). The mean age was 50 years (SD 13.7, min 27, max 72). Nine of the twenty-one procedures (43%) were live donor transplants, with the remaining being from deceased donors. Blood loss was recorded either by the surgeon or by a nurse in all but one case. In six cases the estimated blood loss was recorded as 'minimal'. The maximum blood loss was 630ml. If the 'minimal' blood loss is taken to be 50ml, then the mean blood loss was 229ml (SD 205ml). On average, 3.8 units of blood were requested per patient. Out of a total of 80 units requested, one was transfused intra-operatively, three were wasted and the rest returned after the operation. The mean starting Hb was 12.1g/dl (SD1.7) and the mean Hb following transplant was 10.7g/dl (SD 1.4). The mean drop in haemoglobin was 1.45g/dl with the maximal drop of 3.7g/dl. Ten of the twenty-one (47.6%) patients required transfusions in the days following the transplant prior to discharge. One was a 'code red' and required 21 units in total. So far nine other transplant units responded to our questionnaire. One centre performs a group and save, seven centres crossmatch 2 units and 1 crossmatch 3 units of blood prior to transplantation. There was no significant change in the responses had the recipient had severe iliac calcification.

**Discussion:** Despite the fact that transplantation is a major operation on high risk patients, the mean blood loss is not excessive and blood utilisation is low during surgery. Almost half the patients require blood transfusion later on as we aim to have a haemoglobin level 10g/dl prior to discharge. Other centres crossmatch fewer units peri-operatively.

We are currently reviewing our policy of requesting 4 units of blood for renal transplant procedures, while considering the dangers of operating on uremic patients that may be on antiplatelets/anticoagulation medications and have surgery on their iliac vessels. Reducing the requested blood units from four to two might be a more reasonable option that should be safe and cost effective.

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**Small paediatric donors – a valuable source of organs**

Khalid Akbari, Mei Nortley, Robina Aslam, Sanjay Sinha, Peter Friend

*Churchill Hospital, Oxford, UK*

**Introduction:** In the UK, the 'organ-gap' is increasing due to the rise in demand for transplant organs when compared with organ donation. Paediatric donors can be a valuable source of organs. In the current UK kidney allocation scheme, kidneys from donors aged 4 years and under are offered as en bloc pairs. It is at the discretion of the transplant centre whether to transplant singly or en bloc. In this report, we present a case of an adult who underwent a simultaneous pancreas and kidney (SPK) transplant, using organs from a paediatric donor - without en bloc kidney implantation.

**Case study:** A 30-year-old lady with chronic kidney disease secondary to type 1 diabetes mellitus (DM) presented for SPK transplant. She had been on renal replacement therapy via peritoneal dialysis for 2 years. Despite best medical management, her blood sugar control was erratic and she suffered frequent hypoglycaemic attacks with hypoglycaemic unawareness. Other diabetic complications included retinopathy, neuropathy, and severe gastropathy. This lady had an SPK transplant using organs from a 23-month-old heart beating donor with a body weight of 12 kg. The pancreas was small in size. Donor portal vein was anastomosed to recipient inferior vena cava; an arterial Y-graft (donor common iliac bifurcation) was anastomosed to recipient right common iliac artery and donor duodenum was drained enterically. En bloc donor kidneys were split and a single 7cm kidney was implanted into the right iliac fossa retro-peritoneally with standard anastomoses. Ureteric anastomosis to bladder was made over a JJ stent. Post operatively, there was primary function of both organs. Normal creatinine levels were achieved by day 5 post op. Oral glucose tolerance test at 2 weeks was within normal limits. Her insulin levels and c-peptide levels increased to non-diabetic levels at day 17. Follow up at 8 weeks has shown normal biochemical parameters of kidney and pancreatic function and she has returned to her usual daily activities.

**Conclusion:** This case report demonstrates that en bloc kidneys from paediatric donors, even under the age of 2, can be split and singly implanted to attain normal graft function in adult recipients. Paediatric donors are a valuable source to meet the increasing transplant demand in adults.

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## Conventional versus piggyback techniques: do they have different outcomes? a comparative study

Mohamed Ghazaly, Brian Davidson

*University Department of Surgery and Liver Transplant Unit, Royal Free Hospital Trust and Royal Free and University College School of Medicine, Hampstead Campus,, London, UK*

**Introduction:** Conventional orthotopic liver transplantation (CON-LT) includes resection of the native liver of the recipient, together with the retro hepatic inferior vena cava (IVC), while in Piggyback the recipient's vena cava is preserved and the donor's vena cava is anastomosed with the recipient's hepatic veins. So the caval flow is maintained during explantation, but on the other hand, there is need to dissect the cava completely from the liver, with prolongation of the hepatic excision phase.

**Objective:** Comparison of both techniques (Conventional and Piggyback) in terms of outcomes. We implied the primary outcome for serious adverse events or complications, and secondary outcome for graft survival for three and twelve months, quality of life, ITU stay, and the total hospital stay, days spent on ventilator.

**Materials and methods:** Within a 2-year period, from 3 January 2007 to 31 December 2008, there were 120 Liver Transplant patients divided into two groups; Group A: Conventional LT (Number 93 pt.) and Group B: Piggyback LT (Number 27 pt.).

**Results:** There was no significant difference between both groups when comparing the intra-operative and post-operative complications, graft survival for three and twelve months, quality of life and the hospital stay. However, the ITU stay median of 2. (Range 1-101days) vs 3 (1-60days) and the number of days on Ventilatory Support median 1 of (0-41 Days) A vs 2 (1-60 Days) were notably lower in Group A.

**Conclusion:** When comparing the conventional technique with Piggyback in terms of the ITU stay, and the number of days spent on ventilator we can find that the conventional LT technique had significantly much better Results:

# Live donor – medical

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## Hypertensive live kidney donors have an exaggerated increase in serum creatinine in the post donation period compared with age and sex matched "normotensive" controls

Diana Chiu, Olumide Ogundare, Muir Morton, Sue Kost, Janet Gill, Bence Forgas, Afshin Tavakoli, Ravi Pararajasingam, Hany Raid, Titus Augustine, Neil Parrott, Michael Picton, Tunde Campbell

*Manchester Royal Infirmary, Manchester, UK*

**Background:** The number of live donor kidney transplantation in the United Kingdom is increasing[1]. There is evidence for better graft and recipient outcomes compared to cadaveric kidney transplantation[2]. Hypertensive individuals are being accepted in live related programs as part of an effort to increase the number of transplantation. However, little is known of the trajectory of serum creatinine after donation in hypertensive live kidney donors.

**Method:** Medical records and laboratory results of 121 living kidney donors from our database of live donations from 2002 to 2010 were reviewed. Donors with hypertension at first clinic visit [defined as blood pressure > 130/80mmHg] or who was taking anti-hypertensive for known hypertension were identified. Serial creatinine following nephrectomy was analysed. Peak creatinine was identified and proportional change in creatinine was calculated as: (peak creatinine – pre-operative creatinine) ÷ pre-operative creatinine. The proportional change in creatinine was compared with sex and age matched "normotensive" live donors.

**Results:** 24 live donors [age range 27 - 66 years, 13 males and 11 females] were identified. 11 patients were on anti-hypertensive medication(s). The proportional change in creatinine was significantly greater in the hypertensive group compared with age and sex matched controls {0.7 [95% CI 0.63-0.79] vs 0.6 [95% CI 0.53-0.67]; P value 0.0337} Figure 1. There was no difference in pre-donation creatinine between the groups {mean creatinine 75 µmol/l vs 77 µmol/l; P value 0.50}.

**Conclusion:** To our knowledge, no study has looked at the effect of kidney donation on future creatinine in hypertensive donors. Our results indicate that there is an exaggerated change in creatinine in the immediate post donation period in hypertensive donors compared with "normotensive" age and sex matched donors. This may be due to a difference in the adaptive capability of the single kidney in hypertensive donors. It may be a marker of future renal function, but further studies are necessary with larger numbers of donors and longer period of follow-up to confirm these findings. This also raises the question of how to counsel hypertensive prospective donors prior to nephrectomy.

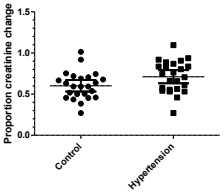


Figure 1. Scatter Plot showing proportion change in creatinine post donor nephrectomy between control and hypertensive groups (Mean and 95% confidence intervals are indicated within plot)

**References:** 1. NHSBT- Organ Donation Statistics.
2. High survival rates of kidney transplants from spousal and living unrelated donors. Pl Terasaki, et al. Engl J Med 1995; 333:333-6

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**Is donor age a barrier for living renal transplantation? An outcome analysis of renal transplants from above 60 years old donors.**

Abbas Ghazanfar, Gabriele Benedetto, Bence Forgacs, Ravi Pararajasingam, Afshin Tavakoli, Neil Parrott, Titus Augustine, Hany Riad, Tunde Campbell

*Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

**Background:** There is a general anxiety and reluctance to consider living kidney transplants from above 60yrs old donors. This is primarily out of concern with morbidity in the donor and the functional status of the older kidney in the recipient. This study describes donor and recipient outcomes for LD renal transplant above 60 years of age in our centre.

**Methods:** We retrospectively analysed our LD transplant data from 1992 to 2010. 56 transplants from donors above 60 yrs were included. Donor and recipient outcomes, graft and patient survival were recorded and were compared with that of donors < 59yrs in our centre.

**Results:** Out of 56 donor recipient pairs. Male:Female was 2:1. The median age of donor was 64 (SD $\pm$3.62) while the median age of recipient was 42.52 (SD $\pm$11.61). There were 19 open and 37 laparoscopic hand assisted donor nephrectomies.

**Table 1: Donor outcome**

| | | Donor > 60 years | Donors >18 to 59 yrs |
|---|---|---|---|
| Haemorrhage | | 3.5% | 4.5% |
| Infections | Chest | 16.0% | 8.0% |
| | Wound | 5..0% | 3.5% |
| | UTI | 3.5% | 2.5% |
| Re-exploration | | 2.0% | <1% |
| Mean hospital stay in days | | 6 | 7 |
| Median eGRF | 1 day | 44 | 47 |
| | 1 year | 56 | 54 |
| | 5 years | 53 | 59 |

**Table 2: recipient outcome**

| | | Donor > 60 yrs | Donors >18 to 59 yrs |
|---|---|---|---|
| Haemorrhage | | 4.5% | 4.0% |
| Rejection | | 11.0% | 10.0% |
| Urological complications | Leaks | 3.5% | 3.0% |
| | Stricture | 3.5% | 3.0% |
| | Infections | 7.0% | 7.0% |
| Graft functions | PGF | 96.5% | 98.5% |
| | DGF | 3.5% | 1.5% |
| Graft survival | 1 year | 96.5% | 97.0% |
| | 5 years | 85.5% | 87.0% |
| Patient survival | 1 year | 100% | 99.0% |
| | 5 years | 95.8% | 97.0% |

**Conclusion:** Our data indicates that LD kidneys above 60 years of age are a valuable resource for living donor transplantation. With the current drive nationally to increase living donors there is perhaps a need to review this on a national basis.

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**The cost of assessing non-proceeding living donors**

Anusha Edwards, Nicola Hamilton, Tracey Fleming, Najib Kadi

*North Bristol NHS Trust, Bristol, UK*

**Introduction:** The establishment of successful living kidney donation programmes has led to more potential donors coming forward to be assessed. However, not all proceed to donation. We performed a study of our potential donors who do not proceed to donation in order to establish the financial cost of their assessment.

**Methods:** Our prospectively kept database of all patients wanting to be considered as donors but who ceased to be between 1st January 2006- 31$^{st}$December 2009 was analysed. Details regarding which investigations they underwent and the cost of these were determined.

**Results:** Over the 4 years 180 potential donors were assessed to varying degrees and did not proceed to donation. The total cost of their assessment was £173813, giving an average of £966/per potential donor assessed. Over this same time period 159 living transplants in our unit did proceed. In 2006, there were 36 non-proceeding donors who were worked up at a cost of £20689. In 2007, this increased to 32 non-proceeders at a cost of £31070. In 2008, we assessed 62 non-proceeding donors at a cost of £55799 and in 2009, 56 were assessed for £66851. This gives an average cost per non-proceeding donor of £575 in 2006, £970 in 2007, £900 in 2008 and £1194 in 2009. Only twenty five potential donors made it all the way through the assessment process at a total cost of £43 432. The most common reason for then not proceeding, in 10 of these cases, was the offer of and subsequent transplantation with a DCD or DBD organ.

**Conclusions:** This study demonstrates that there is a significant cost associated to the assessment of potential living kidney donors, who don't proceed to donation. In our unit for every living transplant performed approximately two potential donors undergo some degree of assessment. It also shows that increasing numbers of potential donors are coming forward each year at a rising cost, but this is having minimal impact on the number of living donor transplants that we are performing.

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**The impact of donor nephrectomy on donor renal function in a single centre series**

Sarah Richards, Kay Hamilton, Chris Dudley, Najib Kadi

*Southmead Hospital, Bristol, UK*

**Aim:** United Kingdom Guidelines for Living Donor Transplantation place an appropriately heavy emphasis on donor GFR to ensure long-term donor safety. We examine a cohort of donors accepted for donation at our institution over a three-year period. We seek to analyse their pre-donation eGFR, isotope GFR and the impact of donation on their renal function in an attempt to determine the efficacy of these guidelines.

**Methods:** All patients undergoing live donor nephrectomy at our institution between January 2007 and January 2010 were reviewed retrospectively. Preoperative eGFR and isotope GFR were recorded and the accuracy of the estimated test calculated. Postoperative eGFR on day 1, 6 weeks, 6 months and 1 year were compared where available with pre-operative renal function. Cockroft and Gault Creatinine Clearance preoperatively and at one year were also compared.

**Results:** 123 live donors proceeded over the three year period. The mean age at donation was 48 +/- 13 years and 54% were female. Preoperative eGFR for the whole patient group was 86 +/- 17 mls/min/1.73m$^2$ and isotope GFR was 96 +/- 16 mls/min/1.73m$^2$. The mean error in the estimated test was 11 +/- 19%. The mean residual eGFR drop on day 1, 6 weeks, 6 months and 1 year postoperatively was 60%, 67%, 65% and 68%. Residual Creatinine Clearance at one year post operatively was 70%. Preoperative isotope GFR correlated well with post-operative eGFR (Pearson's coefficient 0.4, $p< 0.05$). As renal function appeared to plateau by six weeks an attempt was made to categorise age of donor to chronic kidney disease (CKD) at this time point.

| Donor Age (yrs) | CKD 1 (%) | CKD 2 (%) | CKD 3A (%) | CKD 3B (%) |
|---|---|---|---|---|
| <46 | 0 | 45 | 52 | 2 |
| 46-50 | 9 | 36 | 55 | 0 |
| 50-59 | 0 | 43 | 38 | 19 |
| 60-69 | 5 | 60 | 35 | 0 |
| 70-79 | 0 | 0 | 67 | 33 |

**Conclusions:** eGFR appears to be an unreliable test when compared to the isotope gold standard, thus post operative values using this measure should be interpreted with caution. This study shows that post operative renal function is on average 68% of pre-donation values. Further categorising donors by age and classification of CKD reveals the true impact of nephrectomy on donor status.

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**Trends in live donor nephrectomy in the United Kingdom: an audit showing a decade of change.**

Dan Ridgway, Tunde Campbell, Rachel Johnson, Titus Augustine

[1]*Central Manchester University Hospitals NHS Foundation Trust, North West Region, UK,*
[2]*NHS Blood & Transplant Service, Bristol, UK*

**Background:** Live donor nephrectomy is a safe procedure, well established and widely practised in the UK but variation exists in the methods used to procure the donor kidney. Live donors now comprise more than a third of UK kidney grafts. These techniques have changed with the introduction of Laparoscopic techniques in 2001. This study sought to clarify the changes in the decade 2000 to 2010.

**Materials & methods:** A retrospective observational study using data supplied to NHSBT was conducted. Data fields captured included year of procurement, laterality of kidney, method of nephrectomy and whether the surgeon used hand assistance. The identity of the centre performing each surgery was obtained but anonymised by numerical coding rather than by name.

**Results:** In the period 2000-2010, 6678 live donor nephrectomies were performed in the UK. Twenty-five centres had experience of LDN by the end of the decade studied. An increase in the number of centres performing LDN was observed throughout the study period. The number of units performing each type of donor nephrectomy differed markedly between the 2000-2004 and 2005-2010 eras. The era 2000-2004 saw the majority of LDN performed using an open technique either with or without rib resection. However, a consistently low number of open transperitoneal and anterior extra peritoneal donor nephrectomies continue to be performed. This might reflect the activity of a small number of individual surgeons or centres but is more likely to be the persisting use of these open methods to procure technically challenging grafts in many centres. However, the number of centres performing laparoscopic donor nephrectomy grew linearly throughout the decade. 2006 was the first year that more centres used laparoscopic LDN to procure kidneys than any open method. In the final year studied, 89% of live donor grafts were procured using a laparoscopic technique. Concomitantly, the proportion of hand assisted laparoscopic donor nephrectomies (HALDN) increased whilst that of pure laparoscopic donor nephrectomy (PLDN) declined. The laterality of procured kidneys remained static in distribution throughout the decade and with the advent of the Laparoscopic techniques. The proportion of right kidneys varied between 16 and 31 percent.

**Summary:** The suspected change in UK practice was confirmed by this study. It's interesting to find that HALDN and intraperitoneal techniques now predominates as the most frequent methods used to procure live donor kidneys. This finding may have implications for training of future transplant surgeons and service delivery.

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## Magnetic resonance (MR) venography, arteriography and urography in live donor assessment for kidney transplantation: a correlation with operative findings

Emma Aitken, Reddi Yadaval, Ram Kasthuri, David Kingsmore, Marc Clancy

*Western Infirmary, Glasgow, UK*

**Background:** Computerised Tomography (CT) is the established method of assessment for live donor kidney transplantation. Whilst CT is robust in the evaluation of arterial anatomy, venous assessment is considered suboptimal. The need to image patients in multiple post-contrast phases also results in exposure to high radiation doses. The decision to choose left or right kidney for donation is based largely on MR findings.

**Aim:** The purpose of this study was to evaluate the accuracy of MR imaging in predicting arterial, venous and pelvi-ureteric anatomy and determine whether inaccuracies altered the surgical decision-making process.

**Materials and methods:** Over a 30 month period, 140 MR assessments were performed for potential renal donors. 61 patients proceeded to donation. The renal arterial, venous and pelvic-ureteric anatomies were correlated with surgical findings. In cases of discrepancy between imaging and intra-operative findings, the radiological report was subsequently revised to reflect the intra-operative findings and a blinded transplant surgeon asked to retrospectively choose which kidney would have been chosen for transplantation based on the new information in conjunction with differential function and eGFR.

**Results:** MR venous anatomy correlated accurately with surgical findings in 57/61 patients (93.4%). 3.3% had incomplete imaging and there were two cases of missed renal veins. Arterial anatomy correlated accurately in 56/61 (91.8%) patients. 6.6% had a missed upper polar artery. The pelvi-ureteric anatomy correlated with surgical findings on imaging in 53/61 (87%). There was one discrepant case (1.6%) where a bifid collecting system was suggested on imaging. Adequate assessment of the pelvi-ureteric system was not possible in 7/61 (11.4%). On review of the imaging corrected for surgical findings, the opposite kidney would have been chosen for donation in 4 of 8 non-concordant cases (6.5% of the total).

**Conclusion:** Appropriate MR imaging including venography and delayed images can predict arterial, venous and renal pelvi-ureteric anatomy with a high degree of accuracy in potential renal donors. MR assessment gives high quality and accurate information without the need for ionising radiation in this young patient group. Nevertheless, in cases of non-concordance, surgical decision-making may be adversely affected by discrepancies in the imaging.

# Live donor surgery

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## Perioperative complication rates after hand-assisted laparoscopic donor nephrectomy: what to tell patients

Yazin Marie, Francis Calder, Jonathan Olsburgh, Martin Drage, Nizam Mamode

*Guy's and St Thomas' NHS Foundation Trust, London, UK*

**Background:** Kidney transplantation from living donors is known to have the best outcome for patients with end stage renal disease. Hand-assisted Laparoscopic Donor Nephrectomy (HALDN) is the procedure of choice in many renal transplantation centres for procurement of living donor kidneys. There are now extensive data about mortality rates after this surgery, but little data is available about peri-operative complications. We report complication rates in a large consecutive series of patients undergoing HALDN.

**Methods:** Data were collected retrospectively for 585 consecutive living kidney donors who donated between 01/01/2003 and 31/12/2010 in a single centre in the UK using HALDN through a transperitoneal approach. We collected data from patients' notes, including electronic patient record (EPR), anaesthetic charts and drug charts. A questionnaire was also sent to the general practitioners.

**Results:** There were no perioperative deaths. The mean age of donors was 45 years (range 20-84). 53.2% were female donors. The mean operative time was 198 min (86-365 min). 84% of the kidneys were left sided. Five donors (0.85%) were converted to open and five (0.85%) had major complications in the early postoperative period and were re-operated on, three of which had negative laparoscopy. 15.4% had minor complications of which 6.3% had wound infection, 2.7% had pneumonia and 3.7% had a UTI. 14 donors (2.4%) had incisional hernia. The average stay in hospital (including preoperative night stay) was 3.9 days.

**Conclusions:** This study confirms that HALDN has a good safety profile. It has few perioperative major complications and donors have a short duration of in-hospital stay. Minor complications are more frequent but this study provides data with which to inform patients.

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## A laparoscopic donor nephrectomy learning curve. Increasing surgeon experience correlates with a reduced patient stress response

Sarah Richards, Matthew Jaring, Kay Hamilton, Najib Kadi

*Southmead Hospital, Bristol, UK*

**Aims:** We seek to analyse one surgeon's learning curve undertaking laparoscopic donor nephrectomy. Many studies have looked at complication rates and operating times during a laparoscopic learning curve, but we aim to analyse changes seen in patients operated on in such a series. We look at several parameters including the neutrophil to lymphocyte ratio (NLR). The NLR can be used to measure stress induced by major surgery and correlates well with organ dysfunction scores.

**Methods:** 150 laparoscopic donor nephrectomies were undertaken at our institution between October 2006 and September 2011 by a single surgeon. Data were collected on patient demographic, length of stay and complication rate. Changes between pre-operative and day one albumin, haemoglobin and haematocrit level and NLR change were calculated for every patient. As a means to assess the impact of the surgeon's learning curve the first 50, middle 50 and last 50 patients were compared. Data are presented as mean +/- SEM and an ANOVA used for statistical analysis.

**Results:**

| Parameter compared | Cases 1-50 | Cases 51- 100 | Cases 101-150 | p value |
|---|---|---|---|---|
| **Age (years)** | 45.7 +/- 11.8 | 47.6 +/- 13.5 | 47.8 +/- 10.4 | NS |
| **Length of Stay( days)** | 5.5 +/- 1.3 | 4.9 +/- 1.2 | 4.7 +/- 1.0 | 0.003 |
| **Albumin change (g/l)** | -11.5 +/- 4.3 | -10.0 +/- 3.8 | -10.7 +/- 2.7 | NS |
| **Hb change (g/l)** | -1.9 +/- 1.1 | -1.8 +/- 0.9 | -2.0 +/- 0.8 | 0.05 |
| **Haematocrit change** | -5.8 +/- 3.3 | -4.5 +/- 2.9 | -5.8 +/- 3.0 | NS |
| **NLR change** | 8.7 +/- 6.9 | 5.3 +/- 4.4 | 3.4 +/- 3.7 | <0.001 |
| **Complication rate** | 26% | 12% | 10% | |

**Conclusions:** As previously shown by others this study shows a reduction in post-operative stay and complication rate as the series progresses. However, it also shows a marked reduction in the inflammatory stress response induced by surgery in a series of patients as one surgeon seeks to improve his technique. To our knowledge no previous study has investigated and reported improvements in patients' physiological stress during the learning curve of a laparoscopic procedure.

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**External or internal iliac arterial anastomosis- does it affect the outcomes in a live donor kidney transplant programme?**

Atul Bagul, Jodie Frost, Thair Doughman, Michael Nicholson

*University of Leicester & Leicester General Hospital, Leicester, UK*

**Introduction:** In live donor transplantation the best surgical technique [internal (IIA) or external iliac anastomosis (EIA)] still creates a dilemma to the surgeon, due to the absences of a Carrel patch and lack of evidence based literature. We compared the outcomes of live donor renal transplant recipients with renal artery (RA) to EIA, with the outcome of patients undergoing a RA to IIA anastomosis.

**Methods:** A total of 130 live donor kidney transplants were included in this 3 year retrospective analysis from 09/2007-09/2010. Demographic data included donor and recipient variables. In addition length of hospital stay, serum creatinine, eGFR, surgical and clinical complications were assessed for both groups.

**Results:** The analysis of 130 recipients included 74 receiving an EIA anastomosis while 56 an IIA anastomosis. The recipient demographics showed no statistical difference with an exception to donor age (EIA: 50±12 vs IIA: 45±12, P=0.011) and M: F sex ratio (EIA 50:24 vs IIA 22:34, P=0.0023). The donors were matched for age, CMV status, M: F sex ratio and HLA match. There was no difference in the anastomosis times (EIA: 26±5 vs IIA:25±7, P=0.069), though the Ist warm ischaemic times (EIA:4±1.6 vs IIA:5±2, P=0.002), cold ischaemic times (EIA:191±43 vs IIA: 215±45, P=0.02) and total ischaemic times (EIA:219±47 vs IIA: 245±46, P=0.002) were significantly less for the EIA group. The serum creatinine (SrCr) and eGFR showed no difference in both groups at 6 and 12 months [SrCr 12M (EIA: 131±38 vs IIA 126±40, P=0.286) and eGFR 12M (EIA:53±13 vs IIA: 52±14, P=0.829).

One year graft survival was 98.46% (EIA:2 failures due to recurrent diseases). Surgical complications included; arterial stenosis 2 (1.54%) [EIA: 2 (2.7%) vs IIA: 0 (0%)], no thrombosis recorded, haematomas 5 (3.84%) [EIA: 4 (5.4%) vs IIA:1 (1.8%)], lymphocoele 6 (4.6%)[EIA:3 (4%) vs IIA (5.3%)] and major urological complications 4(3%). These included urine leaks 1(0.07%) [EIA: 1 (1.35%) vs IIA:0) and ureteric stenosis 3 (2.3%)[EIA: 2 (2.7%) vs IIA:1 (1.8%)].

**Discussion:** The results with both techniques showed similar outcomes at one year, though the IIA dissection leads to increased cold and total ischaemic times. The ischaemic times seem to bear no effect on one year graft survival. However IIA anastomosis techniques are particularly beneficial to deal with multiple renal arteries using the explanation of IIA technique and the presence of a severely atherosclerotic EIA.

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## Total laparoscopic donor nephrectomy of obese living kidney donors: evolving trends and the impact on early complications

Lasantha Seneviratne, Amanda Shepherd, Ramesh Batra, Ben Lindsey, Bimbi Fernando, Peter Veitch, David Nicol

*Royal Free Hospital, London, UK*

**Introduction:** Currently there is no consensus regarding the use of obese live donors who are regarded at potential increased risk of peri-operative complications. Within the UK there is considerable variation in policy regarding the use of obese live donors. In this study we reviewed outcomes related to Body Mass Index (BMI) in live donors undergoing pure laparoscopic donor nephrectomy.

**Methods:** Prospective data was collected on all patients undergoing laparoscopic donor nephrectomy since January 2005. Demographic details, BMI (in $kgm^2$ ) and information regarding early complications were recorded. Patients were divided into 2 groups (BMI≥ 30 = obese (OB) group and BMI<30 = non-obese (NOB) group) for analysis using Pearson Chi-square or T-Test as appropriate.

**Results:** Data from 219 patients was available from January 2005 to October 2011. There were 52 in OB and 167 in NOB group with data missing in 3 overseas donors at one year follow up. Mean BMI in OB versus the NOB group was 32.97±2.67 (30 – 40.55) and 24.98±3.02 (17.19-29.82) respectively. Means BMI from 2005 to 2011 were 23.40±3.56, 25.13±4.39, 27.32±4.84, 28.69±5.16, 26.96±3.63, 27.18±4.26 and 27.51±4.26 respectively. More importantly OB donors increased as a proportion of the donor population from 5% of donors in 2005 to 25% (P=0.002 ANOVA). Groups were comparable with regard to age (P=0.52) sex (P=0.544), smoking status (P=0.496), duration of operation (P=0.07), length of hospital stay (P=0.96), side and complexity of the anatomy (P=0.339). Conversion to open and iatrogenic injuries were comparable between the 2 groups (OB=1.9% vs NOB=2.4%) P= 0.91. Although complications appeared to occur more frequently in OB group (40.4% versus NOB=29.9%), this was not significant (P=0.39). No differences were observed complication rates of any type including wound infections (P=0.199) respiratory infections (P=0.760) venous thromboembolism (P=0.769) or bleeding complications (P=0.662).

**Discussion:** Obese donors have increased significantly over the past 6 years and now account for approximately 25% of all live donors. Whilst total laparoscopic living donor nephrectomy is more challenging in the markedly obese donors; they do not appear to suffer significantly more complications based on our experience. This however may reflect careful selection of cases based on other parameters with respect to peri-operative morbidity. Consequently BMI as a single parameter may not be an accurate discriminator of surgical risk for laparoscopic donor nephrectomy. Longer term follow-up is required to determine other implications of nephrectomy in this group compared to non-obese donors.

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## Wound infection following hand-assisted laparoscopic donor nephrectomy in a single centre in the UK

Yazin Marie, Irene Rebollo-Mesa, Francis Calder, Jonathan Olsburgh, Martin Drage, Nizam Mamode

*Guy's and St Thomas' NHS Foundation Trust, London, UK*

**Background:** Although much data is available on mortality after laparoscopic donor nephrectomy, no detailed studies have been performed on wound infections and their causes, despite this being a significant problem. In hand-assisted laparoscopic donor nephrectomy (HALDN), this may be a particular issue due to repeated re-insertions of the hand into the surgical wound. We present the first detailed study of wound infections in a large consecutive series of patients undergoing HALDN.

**Methods:** The study included 585 consecutive living kidney donors undergoing HALDN through a transperitoneal approach. We reported wound infections diagnosed clinically by surgeons in addition to data collected from general practitioners (GPs) through a postal questionnaire conducted. The association of wound infection with potential causative factors was tested using Wilcoxon, chi-squared or Fisher's exact tests as appropriate.

**Results:** There was a total of 37 cases of wound infection (6.3%). 4 were laparoscopic port site infections. Wound infection was associated with younger age (Wilcoxon p=0.001), longer operative time (Wilcoxon p=0.001) and higher BMI (Wilcoxon p=0.001). Administration of prophylactic antibiotics in general had no statistical significance in preventing wound infection regardless of the type of the antibiotic given. (Chi-square p=0.26), although this may be because most donors received antibiotics. There was no relationship between the incidence of wound infection and gender (Chi-square p=0.53), ethnicity (Fishers' exact p=0.61), laterality of kidney (Chi-square p=0.78), the use of drains (Chi-square p=0.53) or length of hospital stay (Chi-square p=0.90). It was not possible to correlate wound infection to donors' co-morbidities as the number of donors with co-morbidities is low in our study. Presentation ranged between 3 to 42 days postoperatively (mean 12.3 days) with more than half of the cases presenting to general practitioners. Antibiotics were effective in treating wound infection while only one case required exploration and drainage of an abscess.

**Conclusion:** The incidence of wound infection after HALDN is significant. High BMI, longer operative time and young age were associated with higher rates of wound infection. It is unclear whether prophylactic antibiotics are useful. Patients often present to their GP rather than to the hospital team. Attempts should be made to reduce the incidence and improve the management of wound infections in these patients.

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**Retroperitoneal total laparoscopic live donor nephrectomy (RTLLDN): first three case in the UK/Europe**

Hemant Sharma, Pranjal Modi, Adham El-Bakry, Chang Wong, Ajay Sharma, Matthew Howse, Graham Bell, Abdul Hammad, Sanjay Mehra

*Royal Liverpool University Hospital, Liverpool, UK*

**Background**: Laparoscopic Living donor Nephrectomy is a standard method of donor nephrectomy across in most of the transplant centres. Though trans-peritoneal approach is used widely, retroperitoneal access implies direct approach to the retroperitoneal organs. This offers an intrinsic advantage of minimizing the early and late potential intra-peritoneal complications. Retroperitoneal donor nephrectomy is infrequently performed and there has been no documented European experience in this technique. However, given the potential advantages, few centres in the US have started the transition from trans-peritoneal to retroperitoneal technique. We report the first three cases in the UK performed at our centre.

**Aim:** To report the safety, feasibility and outcomes of the retroperitoneal total laparoscopic live donor nephrectomy.

**Methods:** The donor nephrectomies with retroperitoneal technique were performed in June 2011 and were analysed retrospectively. The donors were evaluated according to BTS guidelines for living donors. The side of the nephrectomy was chosen as per renal vascular anatomy and split GFR

**Results:** Donor Outcomes

| | Donor 1 | Donor 2 | Donor 3 |
|---|---|---|---|
| Age | 39 | 31 | 53 |
| Gender | F | F | F |
| BMI | 24 | 23 | 26 |
| Side | Left | Left | Left |
| Vascular Anatomy | Single renal artery; single renal vein | Single renal artery; two renal veins | Single renal artery and vein, upper polar accessory artery |
| Operative Time | 130 mins | 150 mins | 125 mins |
| Warm Ischemia time | 02 :35 mins | 05:10 mins ( Stapler Failure) | 02:40 mins |
| Blood Loss | <50 ml | <50 ml | <50 ml |
| Analgesic Requirement | 24 Hours(PCA down time) | 32 Hours(PCA down time) | 24 Hours(PCA down time) |
| Hospital Stay | 48 hours | 72 hours | 72 hours |

Recipient Outcomes

| | Recipient 1 | Recipient 2 | Recipient 3 |
|---|---|---|---|
| Age | 31 | 58 | 25 |
| Gender | M | M | F |
| Cold Ischemia Time | 92 min | 61 min | 77 min |
| Rejection | No | No | No |
| Mean Creatinine -3 Months (µmol/L) | 94 ±12 | 111 ± 16 | 122 ± 9 |

**Conclusion:** Our primary experience shows RTLLDN is as safe as other conventional techniques and excellent primary graft functions were obtained.

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## Hand-assisted laparoscopic nephrectomy in adult polycystic kidney disease patients: a uk centre experience

David Mak, Lyndon Gommersall, Christopher Luscombe, Anurag Golash

*University Hospital of North Staffordshire, Stoke-on-Trent, Staffordshire, UK*

**Introduction:** Adult polycystic kidney disease (APCKD) is an autosomal dominant genetic disorder that is characterised by the development of renal cysts and other extra-renal manifestations. APCKD is responsible for causing 10% of all end-stage renal failure (ESRF). In such patients, renal cysts can enlarge significantly and impinge on anatomical space required for future renal transplantation. Unilateral or bilateral nephrectomy is a treatment option. Laparoscopic nephrectomy in APCKD patients is an uncommon procedure and presents unique surgical challenges. We report our experience with hand-assisted laparoscopic (HAL) bilateral and unilateral nephrectomy in patients with APCKD.

**Materials & methods:** Between November 2009 and November 2011, 3 APCKD patients underwent synchronous bilateral HAL nephrectomy and 2 APCKD patients underwent unilateral HAL nephrectomy at our institution. Indications for nephrectomy included recurrent cyst haemorrhage, impaired gastrointestinal function and early satiety due to direct intestinal compression by large polycystic kidneys, and anatomical lack of space for future renal transplantation. We retrospectively reviewed the records of these patients and report our experience.

**Results:** Three patients successfully underwent synchronous bilateral HAL nephrectomy with a mean operating time of 208 minutes (range 195 to 220). Unilateral HAL nephrectomy was performed in 2 patients with a mean operative time of 102 minutes. There were no conversions to open procedure. Blood loss was less than 100 ml in all cases. Mean renal unit size was 2037 g (range 1798 to 2214). Hospital stay ranged from 10 to 12 days. One patient developed a chest infection postoperatively and suffered from a prolonged ileus. Another patient developed a retroperitoneal haematoma, which was treated conservatively.

**Discussion:** HAL nephrectomy is a feasible and safe procedure in APCKD patients, which has potential benefits of shorter hospital stay and reduced morbidity and mortality in comparison to open procedure.

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## The surgeon's preference for side in live donor kidney procurement: a single centre experience

Gabriele Di Benedetto, Daniel Ridgway, Vishnu Venkatanara, Abbas Ghazanfar, Afshin Tavakoli, Tunde Campbell

*Manchester Royal Infirmary, Manchester, UK*

**Introduction:** The decision to select a kidney in a live donor for transplantation can be challenging for the surgeon. In the interests of the donor, the better kidney is left behind. This is determined usually by the value of the split function & the size of the kidney. Other considerations include, vascular anatomy, ureteric anomalies, presence of pathology, i.e cystic & solid lesions and the preference of the surgeon.

**Aim:** In this study we evaluated the impact of the split function (Tc DTPA) in the surgeon's decision making.

**Method:** A retrospective analysis of 199 live donor nephrectomies performed at our centre (2005-2010) was done. These kidneys were removed using both open and laparoscopic techniques. They were divided into three groups according to the surgeon's choice and the split function. In Group A the functionally worse kidney was removed. In group B the functionally better kidney was removed. In group C both kidneys had equal function. The data were collected from operation notes, Clinical Work Station and CT angiogram report.

**Results:** The median donor and recipient's age and donor BMI were comparable between the three groups. In the study group 136 (68%) left kidneys and 63 (32%) right kidneys were removed. In Group A, the left kidney with the worse function was chosen in 66% of patients. All patients in group B had functionally better Kidney removed and out of these, 75 % were left kidneys. For the left kidneys,28% had simpler vascular anatomy and 6% a cyst, in the remaining 66% of cases, there were no other justifications other than the preference of the surgeon. In group C with equal split function, the left kidney was chosen in 60% of the donors. Out of 82 right kidneys which were indicated to be worse functionally as split function, only 31 (37%) were removed. However, donor post operative renal function (median eGFR in ml/min) was comparable between the three groups.

| N = 199 | R Kidney | L Kidney | Median Cr at discharge | (6/12) | 1 year |
|---|---|---|---|---|---|
| Group A 93 | 31 (33%) | 62 (66%) | 62 | 60 | 61 |
| Group B 68 | 17 (25%) | 51 (75%) | 60 | 58 | 67 |
| Group C 38 | 15 (40%) | 23 (60%) | 66 | 62 | 66 |

**Conclusion:** It appears that donor surgeons tend to prefer to retrieve the left kidney even when split function values direct otherwise. We can hypothesize that this is because the left kidney has a longer renal vein and therefore the ease of recipient implantation procedure especially in obese recipients. There appears to be an universal anxiety about retrieving the right kidney among individual surgeons and centres. Further studies are required to obtain evidence for donor surgical preference for the left kidney

# Marginal organs 1

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## The outcome of renal transplants using grafts from donors in evolving, established, or recovering renal impairment

AJ Cockbain, A Tomkinson, HRS Girn, L Hostert, M Attia, KV Menon, A Lewington, N Ahmad

*St James' University Hospital, Leeds, UK*

**Introduction:** There is increasing evidence for the transplantation of grafts from marginal donors, with centres achieving acceptable short and long term Results: The majority of centres decline grafts from patients with renal impairment, despite many such potential grafts coming from young donors in a period of recoverable acute tubular necrosis. There is little evidence informing this debate, therefore we evaluated our experience transplanting such grafts.

**Methods:** Data for all adult renal transplantations between 2000-2011 were collected from a prospectively maintained institutional database. Donor renal imparient was defined as either 1) urine output <20ml/hr in 1hr prior to retrieval or <480ml in 24hr prior to retrieval, or 2) creatinine >150 or need for haemofiltration. Donors fulfilling these criteria were categorised as evolving (normal creatinine and low urine output), established (high creatinine and low urine output), or recovering renal impairment (high creatinine, low urine output). All other donors were used as a control group. Donor renal impairment was analysed using Kaplan Meier curves and the log rank test of significance for effect on graft survival (GS) and overall survival (OS).

**Results:** Grafts were transplanted from 8 donors with evolving, 9 with established, and 54 with recovering renal impairment. Mean donor age was 44.0yrs, 36.9yrs and 43.4yrs respectively. DGF rate was 28.6%, 57% and 33.3% in the evolving, estabilised and recovering renal impairment groups respectively. Only 1 patient experienced primary non-function in the established and evolving renal impairment groups. There was a non significant increase in LOS in the established renal failure group (19.8 days vs. 8.4-11.0 days). 1, 3 and 5yr GS was 85%, 63% and 63% respectively in the established renal failure group, 87%, 80% and 80% in the recovering renal impairment group, and 95%, 90% and 85% in the control group. There was no significant difference in 1,3 or 5yr eGFR between groups.

**Conclusion:** Contrary to expectation, 43% of grafts from established renal impairment donors do not show delayed function, and demonstrated acceptable short and mid-term graft survival. Despite limited numbers, the data so far is encouraging for centres selectively accepting these marginal grafts from young donors.

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## Outcomes of kidney transplants from DCD donors declined by the primary regional centre

Elizabeth Wlodek, Chris Callaghan, J Andrew Bradley, Gavin Pettigrew

*Cambridge Transplant Centre, Addenbrooke's Hospital, Cambridge, UK*

**Introduction:** The recent expansion in donation after cardiac death (DCD) kidney transplantation within the UK has generated uncertainty regarding donor suitability, particularly the use of elderly donors. Here we report our experience using DCD kidneys declined from other centres.

**Methods:** A retrospective review of all DCD kidney offers to our centre from April 2008 to July 2011 was performed with outcomes of the kidneys implanted then analysed. This follows the NHSBT policy change towards national offering of DCD kidneys once refused by the regional centre. Donor characteristics, reasons for non-acceptance by regional centre and graft outcomes (primary non-function (PNF), delayed graft function (DGF), 3 month estimated GFR and one year patient and graft survival [censored for death with functioning graft]) were recorded and analysed.

**Results:** During the study period, 154 DCD kidneys from 110 donors were offered from outside our region; representing a three-fold increase since 2008. Of the total offers, we accepted 66 (43%) kidneys. These had been declined by the primary centre for a variety of reasons, which were often not recorded, but included: donor age, past medical history and logistical problems. Of the 66 kidneys accepted, we subsequently declined 31 (47%) for reasons including: failure of the donor to reach asystole; damage and either macroscopic disease or histological confirmation of significant chronic baseline disease. The median (range) donor age was 58 (1-77) years, but notably, only 8 (40%) were less than 60 years old and 7 (35%) were greater than 70. Only one death was trauma-related. Median (range) terminal creatinine of the donors was 67 (44-124). Despite transit of these kidneys (median [range] distance: 93.2 miles [58.9-166.8]), acceptable cold ischaemic times were achieved (median; range: 13h 53m; 6h 46m – 24h 21m). Both kidneys from three donors were implanted into single recipients. There was 1 case of PNF in this series. DGF occurred in 23 (66%) and lasted for an average (range, SD) 17.17 days (1-113, 26.9). Estimated median (range) GFR at three months was 34 (7->60). Three deaths occurred during follow up; at six, eight and twelve months due to sepsis. Of those patients with follow up greater than one year (n=12), graft and patient survival at twelve months was 93% and 86% respectively.

**Conclusions:** Although follow up is short, these early results indicate that outcomes for kidneys transplanted from other centres are acceptable and highlight the potential for obligatory national offering of DCD kidneys to expand the donor pool. Given current considerations as to a national sharing scheme for DCD kidneys, our results also highlight that transit between centres is possible without prejudicing outcomes.

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## Increased the risk of delayed graft function from male donors: immediate outcomes of renal transplantation from donors after circulatory death

KS Benaragama[1], BJ John[1], B Lindsey[1], J Olsburgh[2], Y Marie[2], M Morsy[3], S Hosny[3], R Uwechue[3], G Maytham[3], R Cacciola[4], C Puliatti[4], Z Buckhoree[4], V Papalois[5], A Syed[5], T Tymkewcycz[6], BS Fernando[1]

*[1]Royal Free Hospital, London, UK, [2]Guys and St. Thomas Hospital, London, UK, [3]St. George's Hospital, London, UK, [4]Royal London Hospital, London, UK, [5]West London Transplant Centre, London, UK, [6]NHSBT, London, UK*

**Introduction:** Delayed Graft Function (DGF) is higher following cadaveric renal transplants from Donors after Circulatory Death (DCD) grafts. DGF increases in-hospital stay, hospital costs and perhaps decreases long term graft function. The increasing use of DCD donors for organ supply makes this a significant problem. We investigated donor and recipient factors associated with DGF in a large population undergoing cadaveric renal transplantation from DCD donors alone.

**Methods:** Retrospective analysis of renal transplants from DCD donors within the Pan Thames, London region from 2002 to 2010. Information retrieved from the UKT Hot A form, medical databases and patient notes. Data included donor/recipient demographics and co-morbidities, graft and implantation variables and DGF as the outcome variable. All patients with incomplete data, primary non-function and those undergoing multiple transplantations were excluded.

**Results:** 278/327 DCD transplants were included. Factors influencing DGF on univariate analysis included recipient age and pre-transplant dialysis; donor age, male sex, hypertension and creatinine and, cold ischemia time (CIT) and concomitant pancreas retrieval. Recipient age and pre-transplant haemodialysis, donor male sex [p=0.01, OR 2.1(95% CI 1.18-3.63)] and, CIT maintained significance on multivariate analysis. Recipients under the age of 40 years had a significantly lower chance of developing DGF following DCD [p=0.001, OR 2.8(95% CI1.5-5.20]. The incidence of DGF in grafts with a CIT<12 hours was significantly lower than otherwise [p=0.005, OR 2.9(95% CI 1.38-6.08)].

**Conclusion:** Although some data is consistent with published literature in CIT and recipient age being risk factors for DGF, our study show that male donors increase the risk of DGF. Further investigation is indicated.

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## Single centre experience of renal transplant form cardiac death donors at extremes of age

Syed Soulat Raza[1], Abdul Hakeem[1], Matthew Stanford[1], Shahid Farid[1], Clare Ecuyer[1], Krish Menon[1], Lutz Hostert[1], Magdy Attia[1], Chas Newstead[2], Niaz Ahmad[1]

*[1]Division of Surgery, Department of Transplantation, St James University Hospital, Leeds, UK, [2]Department of Nephrology, St James University Hospital, Leeds, UK*

**Aim:** We report our experience of DCD renal transplant performed in Leeds between April 2002 and April 2011.

**Methods:** Data were collected for all DCD renal transplants performed over last 9 years. Data were obtained from prospectively collected database at the NHSBT and the transplant and nephrology department at Leeds. All continuous variables are expressed as mean+/- SD. Patient and graft survivals were analysed by a Cox Proportional hazards model and are expressed as percentage.

**Results:** In the period between April 2002 and March 2011 we performed 271 DCD kidney transplants in to 264 recipients. Of the 264 recipients, 51 received grafts from donors at extremes of age: 3 from donors under 5 years and 48 from donors over 60 years of age. The remaining 216 recipients received kidneys from donors between the ages of 5 and 60 years. Kidneys from donors under 5 were transplanted en bloc in single recipient. Six pairs of DCD donor kidneys were transplanted as dual grafts in to single recipient and all but one donor was under 60. The mean donor and recipient ages in the three groups were [a] 38.34 ±14.49, 46.37± 13.85 years [b] 65.38 ± 5.03, 65.26 ± 7.19 years and [c] 13 months ± 1.00 respectively. The incidence of DGF were 50%, 81 % and 0% respectively whereas the duration of DGF was 10.17 ± 6.37, 13.55 ± 9.99 and 0 days respectively. Primary non-function rates were higher in younger DCD group (5.5%) compared to older DCD donors (2.38%) and paediatric donors (0%). One-year graft survival was comparable at 93% (in both under 60 and over 60 groups) and 100% (under 5 years). The patient survival at 1,3 and 5 years was 98%, 96% and 91% in under 60 group compared to 93%, 89% and 79 % in the over 60 group. The graft survival at 3 and 5 years were 90%, 84% in the under 60 group and 79 %, in the over 60 group. Long-term data from paediatric DCD donors (under 5) are awaited

**Conclusion:** Renal transplantation from DCD donor produce comparable short and medium term graft and patient outcome. Kidneys from donors at extremes of ages, particularly, older donors also produce acceptable Results: All kidneys from small paediatric donors and some older DCD donor kidneys are transplanted in pair in order to offset the disadvantage posed by reduced nephron mass. Expanding donor pool by utilizing kidneys from DCD donors at both extremes of age donors is justifiable.

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## Economic analysis of DBD versus DCD kidney transplantation – Is higher DCD costs justified?

Abdul Hakeem, Soulat Raza, Sharib Khan, Clare Ecuyer, Richard Baker, Lutz Hostert, Magdy Attia, Krishna Menon, Niaz Ahmad

*Department of Renal Transplantation, St James's University Hospital NHS Trust, Leeds, West Yorkshire, UK*

**Aim:** The shortage of donor organs has challenged the transplant community to maximise the use of organs from all available donors. In the current economic climate within NHS, it is important to maximise the available resources, so as to cater the ever-growing transplant waiting list. Although much has been written concerning the clinical outcome of DCD transplants, little has been published concerning the cost-effectiveness of their use. The purpose of this study is to compare the one-year post-transplant costs of DBD and DCD kidney transplantation.

**Methods:** We estimated direct medical costs of transplantation, inpatient and outpatient costs for DBD and DCD transplantation done during 2009. Paediatric and multiorgan recipients were excluded from analysis. All continuous variables are expressed as mean +/- SD.

**Results:** 82 cadaveric transplants were performed in the calendar year 2009, of which there were 39 DBD's and 43 DCD transplants. 2 paediatric recipients and 1 liver-kidney transplants were excluded from the study. Donor and recipient demographics were comparable for DBD and DCD transplants. Delayed graft function (22.2% versus 41.8%, p=0.092), Acute Rejection (19.4% versus 20.9%, p=1.000), Graft survival (97.3% versus 90.6%, p=0.369), one-year mean creatinine (151.8+/-64.8 umols versus 160.4+/-117.1 umols, p=0.591) and patient survival (94.4% versus 97.6%, p=0.588) were not statistically different between patients who received DBD versus DCD kidneys respectively. Number of post-operative dialysis sessions (8.8+/-5.2 versus 3.3+/-1.6 sessions, p=0.000), length of post-operative stay (14.3+/-8.6 versus 10.8+/-5.2 days, p=0.034) and number of days of re-admissions during the first year (8.8+/-7.8 versus 5.4+/-6.8 days, p=0.044) were significantly higher in the DCD group in comparison to the DBD group, respectively. One-year post-transplantation costs were higher for DCD transplants by approximately 1247.3 GBP per transplant (p=0.000).

**Conclusions:** Higher rates of post-operative complications and delayed post-operative graft function translate into markedly increased direct medical costs for DCD transplants. Despite the increased costs of DCD transplantation, it does carry similar patient and graft survival at the end of one-year follow-up in comparison to DBD transplantation. There are also other potential benefits in terms of reduced waiting list deaths, reduced waiting list time and overall better quality of life.

# Marginal organs 2

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## Acceptable short term outcome in recipients of dual kidney transplants: a single centre experience

Hemant Sharma, Chang Wong, Adham El-Bakry, Rahul Sinha, Sanjay Mehra, Abdul Hammad, Ajay Sharma

*Royal Liverpool University Hospital, Liverpool, UK*

**Background:** Acceptance of Expanded Criteria Kidneys (ECD) for donation is a strategy to expand the donor pool for renal transplantation. Dual-kidney transplantation rather than single-kidney transplantation for ECDs is a new approach.

**Aim:** To assess the short-term outcomes of DKT (Dual Kidney Transplant) at our center. To compare the results with age, gender and time matched cohort of SKT (Single Kidney Transplant) and to identify any need for change in practice.

**Methods:** Case Notes review of all DKTs (performed at Royal Liverpool University Hospital in last 5 years. It was compared to age, gender and time match cohort of SKTs selected by 2 independent assessors.

**Results:**

| | Dual Kidney Transplant (DKT) (N=10) | Single Kidney Transplant (SKT) (N=10) |
|---|---|---|
| Median Recipient Age (Years) | 56 (36-71) | 57 (36-63) |
| Median Donor Age (Years) | 75 (43-80) | 64 ( 53-68) |
| Simulect Induction | 6/10 | 7/10 |
| Campath Induction | 4/10 | 3/10 |
| Cold Ischemia Time (hours) | 13.4 | 14.2 |
| Peak Panel Reactive Antibodies > 20% | 1/10 | 05/10 |
| Donor History of Diabetes | 2/10 | 1/10 |
| Donor History of Hypertension | 6/10 | 5/10 |
| Donor History of Intracranial Accident | 9/10 | 9/10 |
| Donor Creatinine >132µmol/l | 2/10 | 3/10 |
| Mean FK506 Levels at 4 weeks post Transplant | 7.9 | 8.1 |
| Delayed Graft Function | 4/10 | 3/10 |
| Fall in Serum Creatinine at 12 weeks (compared to pre transplant creatinine) | 83% | 77% (p= 0.6) |
| CMV Infection | 2/10 | 3/10 |
| Polyoma Virus Infection | - | 1/10 |
| Hospital Stay | 22 days | 16 days |

All patients had FK506 and myco-phenolate mofetil as maintenance immunosuppression

**Conclusions:** DKTs with ECD criterion has good short- term outcome results and are comparable to SKTs. A change in practice cannot be commended because of small sample size. A multi-centric data study is needed for more evidence.

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**Dual kidney transplant from extended criteria donors – a single-centre experience**

Abdul Hakeem, Soulat Raza, Kelda Sheridan, Clare Ecuyer, Richard Baker, Lutz Hostert, Magdy Attia, Krishna Menon, Niaz Ahmad

*St James's University Hospital NHS Trust, Leeds, West Yorkshire, UK*

**Aim:** Dual Kidney Transplant (DKT) from adult extended criteria donors is preferred when a single kidney transplant is unlikely to provide enough nephron mass to impart the advantage of renal transplantation. This potentially increases utilisation and decreases discard rate in deceased donor renal transplant. We discuss short, medium to long-term outcome of DKT's performed in our centre.

**Methods:** Patients who underwent DKT transplantation over the last 5 years were retrospectively studied. Continuous variables were expressed as mean+/-SD.

**Results:** In the last 5 years, 13 DKT's were carried out in our centre (DCD=9, DBD=4). The mean donor age was 71.7 +/- 8.4 years (range 51-82 years) and majority were females (n=8, 61.5%). The cause of death was Cerebrovascular Accident (n=9) and Sepsis (n=4). The mean donor creatinine at retrieval was 90.1 +/- 48.1 umols/L and mean eGFR was 68.0+/-19.5 mls/min/1.73 $m^{2.}$ The mean recipient age was 64.5 +/- 7.1 years (range 57-79 years) and majority were males (n=10, 76.9%). The mean HLA mismatch was 2.9. 12 out of 13 DKT's were implanted unilaterally (92.3%). The mean total ischemic time was 14 hrs 48 mins and 16 hrs 23 mins for first and second implanted kidney respectively. Delayed graft function was noted in 5 recipients (38.4%) and mean DGF duration was 7.4 +/- 5.8 days. There were two deaths in our group (15.4%). One due to immediate post-operative MI and another at 3 months from overwhelming sepsis. The overall morbidity was 7 out of 11 (63.6%) - Ureteric stricture requiring reconstruction (n=1), transplant kidney stones (n=1), main renal artery stenosis requiring stenting (n=1), Post Transplant Lymphoproliferative Disorder (n=1), CMV disease/acute rejection (n=1), fast AF/urinary retention (n=1) and incisional hernia (n=1). The mean follow-up was 20.4 +/- 18.8 months. The mean creatinine at the end of follow-up was 153.2+/-90.8 umols/L and mean eGFR was 39.3+/-13.1 mls/min/1.73 m2. The overall graft and patient survival at the end of follow-up was 84.6%.

**Conclusions:** The present retrospective study noted encouraging outcomes for graft survival and graft function following DKT from extended criteria donors. With the continuing organ shortage and increasing waiting times for cadaveric kidney transplantation, dual-kidney transplantation using organs that would otherwise be discarded offers a good option for older individuals who may not withstand a long waiting period. The implementation of a DKT program in our unit safely increased the pool of organs from the marginal donors.

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**Dual transplantation of DCD kidneys: An audit of potential change in practice**

Anusha Edwards, Motaz ElMahdy, Diane Evans, Najib Kadi, Justin Morgan

*North Bristol NHS Trust, Bristol, UK*

**Introduction:** The ever widening gap between organ demand and supply for transplantation has led to the introduction of a number of changes in practice.

The use of marginal kidneys from DCD donors as a dual transplant may increase the number of organs available for transplant by minimising the discarding of potential donor organs. We decided to audit our practice to see what how the transplantation of dual DCD kidneys may impact our practice.

**Method:** Prospectively collected data regarding creatinine clearance of potential donors over an 18 month period from 2010-2011 was analysed retrospectively. The data was analysed according to whether donation proceeded or not. eGFR in DCD organ recipients over the same time period at one month, six months and one year post transplantation were also studied.

**Results:** Over the study period 31 DCD donors proceeded in our unit, with a mean age of 47+/- 13. The mean creatinine clearance at the time of offer was 123 +/- 46.There were 24 non proceeding donors over the same time period. They had a mean age of 61 +/- 9 with a mean creatinine clearance at the time of offer of 79 +/- 30. Of these non-proceeders, three did not have a documented reason for not proceeding. Of the remaining 21 only six donors were declined on age and poor renal function. The remainder would not be considered appropriate donors, even for dual transplantation. The mean creatinine of these six was 72+/-18 and the mean age 61+/-9. In the 31 single kidney recipients of organs from DCD donors over the 18 month period the mean eGFR was 39 +/- 19 at one month, 47+/- 18 at six months and 47 +/- 16 at 12 months.

**Conclusion:** This retrospective analysis shows that over an 18 month period there were six potential DCD donors who may have been suitable for dual kidney donation. Obviously, careful consideration would have to be given to the recipients of these organs. This study has demonstrated that in principle dual kidney transplantation may provide a further resource for our unit.

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## Kidney transplantation from donors after circulatory death – single centre experience

KS Benaragama[1], BJ John[1], T Tymkewycz[2], PS Veitch[1], B Lindsey[1], DL Nicol[1], BS Fernando[1]

*[1]Royal Free Hospital, London, UK, [2]NHSBT, London, UK*

**Introduction:** The acute shortage of organs for transplantation has led to the increasing use of organs from donors after circulatory death (DCDs). It is well known that short term outcomes are better following transplantation of organs harvested from donors after brain death (DBDs) although, the long term impact is unclear. We present our 8 year experience of DCD kidney transplants.

**Methods:** Retrospective analysis of DCD kidney transplants at the Royal Free Hospital, London from 2002-2010. Information retrieved from the UKT Hot A form, medical databases and patient notes. Data included donor/recipient demographics and co-morbidities, graft and implantation variables, delayed graft function (DGF) and graft survival/death.

**Results:** A total of 78 DCD transplants were performed during this period. 2 patients were lost to follow up. The overall patient survival was 72/76(95%). Overall incidence of graft loss was 11/78(14%). The 1-, 3- and 5- year graft survival was 93%, 90% and 77% respectively.

**Conclusion:** Kidneys from DCDs provide excellent short term outcome in terms of graft survival, equivalent to those from Donors after Brain Death (DBD). Increased utilization of DCD organs will shorten waiting times. Our data supports findings from literature

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## Factors influencing short-term renal function following Renal transplantation from Donors after Circulatory Death (DCD)

KS Benaragama[1], BJ John[1], B Lindsey[1], J Olsbeurgh[2], Y Marie[2], M Morsy[3], G Maytham[3], S Hosny[3], R Uwechue[3], R Cacciola[4], C Puliatti[4], Z Buckhoree[4], V Papalois[5], A Syed[5], T Tymkewycz[6], BS Fernando[1]

*[1]Royal Free Hospital, London, UK, [2]Guys and St. Thomas Hospital, London, UK, [3]St. George's Hospital, London, UK, [4]Royal London Hospital, London, UK, [5]West London Transplant Centre, London, UK, [6]NHSBT, London, UK*

**Introduction:** The 12 month serum Creatinine predicts long term graft function. Delayed graft function (DGF), donor age and male recipients are commonly associated with worse 12 month creatinine. We looked at the factors influencing short term graft outcome as measured by 3 and 12 month serum creatinine in a cohort of DCD renal transplants alone.

**Methods:** Retrospective analysis of renal transplants from DCD donors within the Pan Thames, London region from 2002 to 2010. Information was retrieved from the UKT Hot A form, medical databases and patient notes. Data included donor/recipient demographics and co-morbidities, graft and implantation variables, DGF and 3 and 12 month creatinine as the outcome variable. All patients with incomplete data, graft loss within 12 months and those undergoing multiple transplantations were excluded.

**Results:** Complete data was available in 258/327 patients at 3 months and 239/327 at 12 months. 5 patients had graft loss during this period and were excluded. Risk factors for a higher creatinine at both 3 and 12 months included increasing donor age (p=0.001 & 0.008), DGF (p=0.001 & 0.005) and male recipients (p=0.003 &0.017) respectively.

**Conclusion:** DGF, increasing donor age and recipient male sex have higher creatinine at both 3 and 12 months. Although, the impact of serum creatinine on long term graft survival is unclear, strategies to reduce DGF and careful recipient selection may be of benefit.

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## The marginal liver allograft: comparison of outcomes for adult split and donation after cardiac death liver transplants

Mekhola Mallik, Chris J Callaghan, Paul Gibbs, Michael Hope, Sue Davies, William Griffiths, Gavin J Pettigrew

*Cambridge Transplant Centre, Cambridge, UK*

**Background:** Adult extended right lobe donation after brain death (ERL-DBD) and whole organ-donation after cardiac death (DCD) liver transplants are considered marginal, but direct comparison of outcomes has rarely been performed. Such a comparison may rationalise use of DCD livers, which varies widely between UK centres.

**Methods:** Outcomes for 18 adult ERL-DBD livers and 32 'controlled' DCD liver transplants performed at our centre between 1st January 2004 and 31st December 2010 were compared retrospectively.

**Results:** No patients in the DCD cohort suffered early graft failure, whereas five occurred in the ERL-DBD cohort (hepatic artery thrombosis (3); progressive cholestasis (1); small-for-size syndrome (1)). Early allograft dysfunction occurred in a further six (33.3%) of the ERL-DBD and five (15.6%) of the DCD groups (p=0.172). In the DCD group, ischaemic cholangiopathy developed in six patients (18.8%), resulting in graft failure within the first year in two; the others remain stable. The incidence of biliary anastomotic complications was similar in both groups. Kaplan-Meier survival analysis confirmed superior graft survival in the DCD liver group (92.6% at 3 years vs 66.7% in the ERL-DBD cohort, p = 0.023), that was comparable to survival of contemporaneous whole DBD liver transplants (93.0% at 3 years, p=0.689). Patient survival was similar in all groups (3 year survival DCD cohort, 88.5% vs 94.4% for ERL-DBD cohort, p=0.343; DBD cohort 91.1%).

**Conclusions:** For our centre, expanding DCD liver criteria while refining donor-recipient selection for ERL-DBD transplants is likely to increase numbers without prejudicing Results: An analysis of national outcomes is warranted to define acceptable failure rates for marginal grafts.

# Paediatrics

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**Paediatric blood group incompatible transplantation: the initial UK experience**

Nizam Mamode[1], Judy Taylor[2], Yincent Tse[3], Stephen Marks[4]

*[1]Guys and St Thomas Hospital, London, UK, [2]Evelina Children's Hospital, London, UK, [3]Great North Children's Hospital, Newcastle, UK, [4]Great Ormond Street Hospital, London, UK*

**Introduction:** Although blood group incompatible transplantation (ABOi) has become common in many adult centres, there are very few reports worldwide of ABOi in children. The prioritisation of children in the UK allocation system and the stronger immune response in children are two reasons for this reluctance. We report the initial experience in the UK with ABOi in children from 3 centres.

**Methods:** Recipients were selected on the basis of low isoagglutinin titres and/or a long wait on the deceased donor list. One recipient had been unsuccessful despite repeated runs in the paired exchange scheme. Isoagglutinin levels were measured using Diamed gel cards, and a titre level of 1 in 8 was used as a threshold for proceeding with surgery. Antibody modulation was tailored according to titre level, with a combination of anti-CD20 antibody and plasmapheresis. One patient received pre-operative IvIG.

**Results:** 5 patients underwent ABOi. Graft and patient survival was 100%. The results are shown in the table below:

| Age (yrs) | Baseline isoagglutinin titres | Pre-op treatment | Rejection? | Lastest creatinine | Follow-up (months) |
|---|---|---|---|---|---|
| 15 | 32 | Ritux, pex, IviG | No | 85 | 60 |
| 8 | Neat | Nil | Yes | 278 | 50 |
| 14 | 8 | Ritux | No: Biopsy C4d neg | 133 | 26 |
| 8 | 64 | Ritux, DFPP | No: Biopsy C4d neg | 63 | 8 |
| 11 | 16 | Rituximab, DFPP | No: Biopsy C4d neg | 98 | 4 |

**Conclusions:** Initial results suggest outcome after ABOi in children is good, and may provide an additional route for transplantation. C4d may be negative in contrast to adult ABOi. Careful monitoring of outcomes, particularly as indications are extended to those with higher titres, is necessary to ensure long term outcomes remain good.

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**Think transition: An essential link to improve paediatric transplant outcome**

Abbas Ghazanfar, Denise Roberts, Anne Palmer, Mohen Shenoy, Afshin Tavakoli, Hany Riad

*Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

**Purpose:** Arranging an efficient and caring transition service has been highlighted as one of the great challenges facing health service provision for the next century. For young people with functioning transplants, transition to adult services is a significant life event which needs careful planning and consideration. Adolescents following transfer are particularly vulnerable and are at high risk of adopting non-concordant behaviour and are at risk of losing their "precious transplant". according to Watson 8 out of 20 kidney transplants failed within 36 months of the transfer of the recipients to adult services, with seven (35%) of these failures being unexpected.

**Methods:** this study comprises of two mile stone retrospective audits performed in our unit over the last two decades. The first audit period namely "pre-transitional audit" was from 1980 to 1997 and the second period namely "post-transitional audit" was from 2001 to 2010. The three important end points were rate of "Did Not Attend" at outpatient clinics, and mean patient and graft survival at 1 and 5 years.

**Results:** these results have shown that after introduction of the transition pathway for paediatric transplant patients there have been a statistically significant improvement in patient and graft survivals.

**Conclusion:** adopting to transition pathway with clear objectives, easy access and flexibility according to young people needs not only improves patient and graft survival but also have a significantly positive psychological and socioeconomic impact on their life.

Table: Comparison of Pre and Post transitional pathways

| | Pre transition | Post transition |
|---|---|---|
| Period | 1980-1997 | 2001-2009 |
| No of patients | 58 | 78 |
| DNA at 1 year | 10% | 6% |
| DNA at 2 years | 24% | 25% |
| DNA at 5 years | 15% | 9% |
| Unexpected graft loss at 1 year | 1.72% (n=1) | 0 |
| Unexpected graft loss at 3 year | 5.17% (n=4) | 1.28% (n=1)* |
| Unexpected graft loss at 5 year | 10.34% (n=6) | 3.84% (n=3)* |
| Graft survival at 1 year | 93.11% (n=54) | 98.72% (n=77) |
| Graft survival at 3 year | 89.66% (n=52) | 94.88% (n=74)* |
| Graft survival at 5 year | 86.20% (n=50) | 94.88% (n=74)* |
| Patient survival at 1 year | 94.83% (n=55) | 100% (n=78) |
| Patient survival at 3 years | 91.4% (n=53) | 100% (n=78)* |
| Patient survival at 5 years | 88% (n=51) | 96.15% (n=75)* |

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## Can pre-implantation biopsies predict renal allograft function in paediatric renal transplant recipients?

Alison Ma[1], Ismail Mohamed[2], Stephen D Marks[1]

*[1]Department of Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Trust, London WC1N 3JH, UK, [2]Department of Transplant Surgery, Guy's Hospital, London SE1 9RT, UK*

**Introduction:** Pre-implantation renal transplant biopsies are a valuable tool in delineating objective information about the donor organ, which can be important in understanding the aetiology of chronic changes subsequently in renal transplant biopsies. We aim to determine the utility of pre-implantation biopsies to predict long term renal allograft outcome in paediatric renal transplant recipients (RTR).

**Method:** Single centre retrospective review performed on all patients who underwent pre-implantation renal transplant biopsies from 2003 to 2011 with evaluation of the clinical characteristics of recipients, the presence of delayed graft function (DGF) and renal allograft function in the immediate and subsequent post-transplantation period.

**Results:** 32 (57% male) patients aged 1.5 - 16 (median 10.2) years of whom 56% received deceased donor renal transplants (DD) and had pre-implantation biopsies performed during the study period with follow-up of 6 to 78 (median 33) months. The characteristics between DD and living donors (LD) were similar with donor age of 30 - 50 (median 41.3) and 34 - 51 (median 45.3) years. There was no significant difference between the histological findings of LD and DD. 47% (15) of biopsies were reported as showing minor chronic vascular changes while three were reported with moderate to severe vascular changes. 9% of patients displayed DGF and 21% had acute rejection episodes. The presence of pre-existing vascular changes did not appear to be related to DGF. No correlation was observed between renal allograft function and the presence of minor vascular changes at 3, 6 and 12 months post transplant.

**Discussion:** 46% of pre-implantation renal transplant biopsies displayed minor vascular changes. These minor histological changes did not show major impact on subsequent renal allograft function in paediatric RTR but helped delineate changes which could be of donor or recipient origin. We would recommend the routine practice of pre-implantation biopsies in children, which provides important baseline information of the graft with implications on the subsequent medical treatment for paediatric RTR.

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**The prevalence of de novo food allergy in paediatric renal transplant recipients**

Charlotte Davies, Stephen D. Marks

*[1]UCL Medical School, London, UK, [2]Department of Paediatric Nephrology, Great Ormond Street Hospital for Children NHS Trust and UCL Institute of Child Health, London, UK*

**Introduction:** Food allergy affects 6% of children and causes 85% of childhood anaphylaxis. It is a public health concern as anaphylaxis hospitalisation rates multiplied sevenfold between 1990 and 2000 in England. New-onset food allergy after liver transplantation as well as cardiac and intestinal transplantation has been reported but it is unknown if it is increased in paediatric renal transplant recipients (RTR).

**Methods:** We investigated whether de novo allergy development occurred in RTR, using three questionnaires regarding general health, food allergy and atopy, by patient and/or parent interview. We obtained blood samples from children under 18 years who had undergone renal transplantation, from our single centre and analysed for eosinophilia, total-IgE, and cow's milk, egg and peanut-specific IgE. Questionnaire and IgE results were presented to a blinded allergist to determine allergic status.

**Results:** Seventy (60% male) children aged 30 – 207 (median 161) months and 0 – 161 (median 37) months post-renal transplantation were included of whom the primary renal disease was non-immunologically based (62% congenital abnormalities of the kidneys and urinary tract). Our cohort were compared to healthy controls in the normal population. Eleven (16%) RTR were sensitised to at least one food (cow's milk [6], egg [9], peanut [7]) and eight (11%) were deemed clinically 'allergic'. Total IgE results ranged from 1.0 to 2872.0 (median 16.5 kUIgE/L) for this cohort. Eosinophil counts ranged from 0.0 to 1.07 (median 0.14 $x10^9$/L). Nine (13%) participants reported experiencing food allergy symptoms by questionnaire. Six (9%) reported parental history of food allergy. There was a significantly low breastfeeding rate (61%) and duration, range 0 - 26 (median 0) weeks, in RTR. There was a significant difference in gestation, range 24 - 43 (median 40) weeks ($p=0.05$), and birthweight, range 0.7 - 5.7 (median 3.2) kilograms ($p=0.03$), between sensitised and non-sensitised children.

**Discussion:** The prevalence of food allergy in paediatric RTR was not increased to the general population (rates of 6 - 22%) with no clear evidence of allergy being passively transferred from donor to recipient. There was no association with recipient-specific factors, such as immunological cause of renal disease, post-transplantation immunosuppression (as tacrolimus has been implicated) or degree of renal function.

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## Successful outcome of first paediatric renal transplant for HIV associated nephropathy

SD Marks, M McCulloch

*Great Ormand Street Hospital, London, UK*

**Introduction:** Classical HIV-associated nephropathy (HIVAN) was first described before the advent of highly active anti-retroviral therapy (HAART) in late stages of HIV disease with high viral load and low CD4+ cell count. Renal transplantation guidelines for adults with HIVAN have been developed[1] with comparable patient and renal allograft survival[2, 3]. We report the successful outcome of living related renal transplantation in an 8 year old girl on haemodialysis due to HIVAN.

**Methods:** The patient is a vertically HIV-infected girl who was initially lost to follow-up but represented aged 5.5 years with lymphocytic interstitial pneumonitis (LIP) and CDC stage 1. She was not initially commenced on HAART but subsequently developed acute kidney injury and renal biopsy confirmed HIVAN. Haemodialysis and HAART (lopinavir / ritonavir, lamivudine and abacavir) were started at 6.5 years.

**Results:** Pre-transplantation screening showed an undetectable HIV-1 viral load and CD4 counts of 43% (1990/$mm^3$). She underwent a living related renal transplant from her 56-year old maternal grandmother (mismatch 1, 1,1; donor and recipient both CMV negative and EBV positive). There was a historical B-cell positive cross-match, and she was therefore treated as a 'high-risk' transplant using induction therapy with basiliximab, tacrolimus, mycophenolate mofetil and corticosteroids. Tacrolimus was started six weeks prior to transplantation in order to stabilise levels. HAART (lopinavir / ritonavir, abacavir and lamivudine) was continued together with isoniazid, azithromycin, co-trimoxazole and fluconazole prophylaxis. Currently, she is two months post-transplant with excellent renal allograft function (plasma creatinine of 41 - 48µmol/l with estimated glomerular filtration rate of 80 - 94mls/min/1.73$m^2$. She has mild hypertension requiring two anti-hypertensive agents and low-grade albuminuria (25mg/mmol). Therapeutic tacrolimus levels are achieved with once-daily tacrolimus given 5-days per week only. She has an undetectable HIV-1 viral load and CD4+ counts of 240/$mm^3$. Protocol biopsy at six weeks post-transplant shows mild chronic changes and she has no donor specific antibodies with normal transplant renal ultrasound. There have been no HIV-related complications.

**Discussion:** This is the first reported case of successful renal transplantation in a child with HIVAN in the United Kingdom. Adult experience suggests a higher risk of acute rejection and careful monitoring for long-term HIV-associated complications.[3]

Ref: 1 = Bhagani S et al (2006); 2 = Landlin L et al (2010); 3 = Stock PG et al (2010)

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## Paediatric renal transplantation in a patient with bardet-biedl syndrome (bbs) and situs inversus

Jodie H Frost[1], Ismail H Mohamed[2], Geoff Koffman[2]

*[1]University Hospitals Leicester, Leicester, UK, [2]Guys and St Thomas Hospital, London, UK*

**Introduction**: Bardet-Biedl syndrome (BBS) is a rare autosomal recessive condition characterised by a genetic dysfunction that causes cystic malformation of the kidneys alongside features such as postaxial polydactyly, central obesity and mental retardation. Very uncommonly, it presents with situs inversus. It is a rare cause of renal failure in children that ultimately requires transplantation. We report the first case of successful renal transplantation in a 3 and half year old child with both BBS and situs inversus.

**Methods:** The patient had commenced peritoneal dialysis 14 months prior to transplant due to end-stage renal failure. Transplant work up commenced and after her father was deemed a suitable donor; a right sided hand assisted laparoscopic donor nephrectomy was performed. The recipient then underwent the transplant with a midline incision to allow access to the aorta and inferior vena cava to which the anastomoses were made. The kidney then was placed in the left iliac fossa. The native kidneys were deemed not necessary to be removed and the abdomen was closed with PD catheter removed at time of transplant.

**Results:** Post-operative transplant ultrasound scan demonstrated good global perfusion of the kidney with no hydronephrosis or perinephric collection. The patient had immediate graft function, with maintenance immunosuppression of Tacrolimus and Mycophenolate Mofetil.

| Date | Creatinine | Urea | Tacrolimus |
|---|---|---|---|
| Pre-transplant | 859 | 23 | N/A |
| Day 1 | 652 | 19 | N/A |
| Day 2 | 35 | 4.2 | 7 |
| Day 3 | 15 | 1.9 | Not performed |
| Day 4 | 13 | 1.2 | 6 |
| Day 5 | 13 | 1 | 7 |
| Day 6 | 14 | 0.7 | 8 |
| Day 7 | 15 | 3.0 | 7 |
| 1 week | 15 | 3.0 | 9 |
| 1 month | 20 | 2.0 | 7 |

**Discussion:** Less than ten cases of renal transplantation in BBS have been reported in the literature; this is the first case report of a successful renal transplantation in a child with both BBS and situs inversus. We therefore conclude that such anatomical malformations such not be considered a contra-indication for renal transplantation in children.

# Pancreas / Islet transplantation 1

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**Post-operative computed tomography in pancreas transplantation**

Faye E. Powell[1], Chris J. Callaghan[1], Simon J.F. Harper[1], Ashley Shaw[2], Edmund Godfrey[2], Andrew Bradley[1], Christopher J.E. Watson[1], Gavin J. Pettigrew[1]

*[1]University Department of Surgery, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, [2]Department of Radiology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK*

**Introduction:** The aims of this study were to examine the use and utility of CT scanning in pancreas transplant recipients.

**Methods:** Ninety-eight patients underwent simultaneous pancreas-kidney (SPK) transplantation between January 1st 2005 and August 1st 2010. Indications: CT findings and whether imaging altered management were determined by retrospective analysis.

**Results:** Following transplantation, 257 CT scans were performed on 91 patients (median (range) number of scans per patient 2 (0-15)). Common indications for scanning included suspected intra-abdominal collection (31.1%) or investigation of elevated serum amylase/lipase (24.1%). CT findings were variable, but most commonly showed non-specific mild intra-abdominal inflammation (27.6%), a normal scan (17.1%), and intra-abdominal fluid collections (16.3%). We investigated if certain indications for scanning were associated with a higher incidence of a specific CT finding. Of the four indication/finding pairs examined (suspected collection/collection identified, high capillary blood glucose (CBG)/vascular abnormality, suspected obstruction or abdominal pain/bowel abnormality, elevated serum amylase or lipase/pancreatitis), only high CBG was significantly associated with its specific finding ($P<0.001$). Most scans did not alter patient management (58.4%). Notably, the first scan performed influenced management in 21.5% of patients, whereas repeat scanning within the first four weeks after transplantation led to a major change in only 10.3%.

**Discussion:** Pancreas graft recipients often undergo multiple CT scans in the post-operative period, and, despite identifying a variety of abnormalities, relatively few alter management significantly. A more selective approach to CT use, perhaps by limiting scans to particular indications and avoiding repeated imaging, is warranted.

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## Vascular catastrophes following Pancreatic Transplantation: is systemic anti-coagulation necessary?

Iestyn Shapey, David van Dellen, Otilia Mitu-Pretorian, Abbas Ghazanfar, Ravi Pararajasingam, Babatunde Campbell, Bence Forgacs, Hany Riad, Neil Parrott, Titus Augustine, Afshin Tavakoli

*Manchester Royal Infirmary, Manchester, UK*

**Introduction:** Vascular complications present a major challenge in Pancreas Transplantation (PT) and are a significant contributor to both morbidity and mortality. Because of relatively low portal pressures, systemic anti-coagulation has evolved to become a vital and routine part of early post-operative management of PT and is essential in minimizing graft thrombosis. This conversely however increases the risk of bleeding and haematoma negatively impacting on patient outcome. We aimed to describe our 10 year experience with PT and identify the impact of vascular complications on outcome in an attempt to establish the relative risks of thrombosis and haemorrhage on outcome.

**Methods:** A retrospective analysis was made of a contemporaneously maintained database of all PT's (simultaneous pancreas kidney (SPK); pancreas after kidney (PAK) and pancreas transplant alone (PTA) performed in a single institution between the inception of the programme and the present (June 2001 to May 2011). Rates of graft thrombosis, bleeding and haematoma were assessed and their impact on outcome identified. All patients were given adequate heparin thromboprophylaxis intravenously post-operatively as per defined unit protocols (initially S/C heparin leading to increased thrombosis rates, then systemic heparinisation with concomitant risks of haemorrhage, with the current policy judicious use of body weight adjusted systemic heparin.) Primary endpoints used were patient and graft survival with post-operative complications (including biopsy proven rejection, intra-abdominal sepsis and re-operation) as secondary endpoints.

**Results:** 230 PTs were performed over the study period (180 SPK's, 13 PTA's and 37 PAK's; 143 M, 87 F; median age 41 (range 15-67). Bleeding and haematoma occurred in SPKs (16, 9%), PTAs (3, 23%; p=0.09) and PAKs (2, 5%; p=0.30, Fisher's exact test), whilst graft thrombosis occurred in SPKs (17, 9%), PTAs (3, 23%; p=0.14) and PAKs (7, 19%; p=0.06). Graft loss was significantly higher due to thrombosis than post-operative bleeding (34% vs 8%, p<0.002, Z-ratio) such that 25/27 thrombosed PT grafts underwent transplant pancreatectomy. Patient survival was 92% at 1 year and 76% (censored; mean follow up 4.3 years) However, re-operation rates due to thrombosis and bleeding were similar (23% vs 24%, p=NS). Rates of intra-abdominal sepsis, wound infection and BPAR did not differ according to graft thrombosis or bleeding (p=NS).

**Conclusion:** The development and improving success of whole organ pancreas programmes internationally is at least partially due to increased recognition of and attention to the importance of adequate thromboprophylaxis. Previous experiences coupled with justified reticence on the part of clinicians to expose patients to the risks of peri-operative bleeding have historically led to bias towards minimal anti-coagulation. However, this study has demonstrated that the risk of graft loss is significantly higher due to thrombosis than haemorrhage and that peri-operative thromboprophylaxis should be tailored to this end. Our practice has evolved towards systemic anti-coagulation with current thrombosis rates less than 5%

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## Ipsilateral simultaneous pancreas and kidney transplantation: a single centre experience

Bence Forgacs, Gabriele Di Benedetto, Abbas Ghazanfar, Maria Mitu-Pretorian, David Van Dellen, Tunde Campbell, Hany Riad, Ravi Pararajasingam, Titus Augustine, Neil Parrott, Afshin Tavakoli

*The Renal and Pancreas Transplant Unit, Manchester Royal Infirmary, Manchester, UK*

**Background:** The most commonly used technique for simultaneous pancreas and kidney transplantation is placement of pancreas into the right iliac and the kidney to the left iliac fossa. However implantation of both allografts to the same side remains controversial. It may be argued that ipsilateral placement of both grafts may jeopardise the 'down-stream' graft (usually the kidney), but conversely the technique is far quicker, and preserves the other side for any future transplants. The aim of this study was to review the safety of this procedure and to review its outcome if different.

**Material and methods:** From October 2008 to October 2011 67 simultaneous pancreas and kidney transplantations were performed in our unit. In 18 cases both pancreas and kidney were placed to the right iliac fossa (ipsilateral graft placement) and in 49 cases as conventional procedure the pancreas in the right and the kidney in the left iliac fossa (contralateral graft placement). Patient and graft survival, surgical and non surgical complications, length of ITU/HDU and hospital stay were compared between the two groups.

**Results:**

| | Ipsilateral graft placement | Contralateral graft placement |
|---|---|---|
| Case number | 18 | 49 |
| Male patient | 28% | 90% |
| 1 year patient survival | 100% | 96% |
| 1 year pancreas survival | 89% | 78% |
| 1 year kidney survival | 94% | 94% |
| Patient required reoperation | 22% | 35% |

There was no difference in donor and recipients demographics. The frequency of non surgical complications (Cardio respiratory complications, sepsis, CMV infection, DVT, pulmonary emboli, acute rejection) were similar. The ITU/HDU and overall hospital stay were also comparable.

**Summary:** Ipsilateral placement of pancreas and kidney transplants is safe and results similar patient and graft survival as contralateral placement of the grafts. The incidence of surgical and non surgical complications are also comparable. Ipsilateral graft placement may preserve the contralateral side for future transplants.

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**Vascular choices in pancreas transplantation: does it matter?**

Iestyn Shapey, David van Dellen, Otilia Mitu-Pretorian, Abbas Ghazanfar, Ravi Pararajasingam, Babatunde Campbell, Hany Riad, Neil Parrott, Bence Forgacs, Titus Augustine, Afshin Tavakoli

*Manchester Royal Infirmary, Manchester, UK*

**Introduction**: Surgical techniques, particularly vascular anastomoses, for Pancreas Transplantation (PT) vary widely according to local expertise, surgeon preference and may also reflect implant experience. Enteric drainage has become the preferred route for exocrine drainage, due to improvements in organ assessment and quality allowing greater reliability in predicting outcomes, improving outcomes for recipients post-operatively. However, there is no clear consensus as to optimal positions for vascular anastomoses, with individual surgeon and unit preferences directing approach. We aimed to describe our 10 year experience with PT and identify impact of surgical choices on graft outcomes.

**Methods:** A retrospective analysis was made of a contemporaneously maintained database of all PT's (simultaneous pancreas kidney (SPK); pancreas after kidney (PAK) and pancreas transplant alone (PTA) performed in a single institution between the initiation of the programme and the present (June 2001 to May 2011). Patients were divided according to surgical implantation position in an attempt to establish optimal anastomotic configurations. Primary endpoints used were patient and graft survival with post-operative complications (including haemorrhage, biopsy proven rejection and re-operation) secondary endpoints.

**Results:** 230 PTs were performed over the study period (180 SPK's, 13 PTA's and 37 PAK's; 143 Males, 87 Females; median age 41 (range 15-67).Data was available for 177 of these cases. Portal vein (PV) was anastomosed to Inferior Vena Cava (IVC, 58, 33%), Common Iliac Vein (CIV, 78, 44%), and External iliac vein (EIV, 41, 23%) with arterial anastomoses to the Common Iliac Artery (CIA, 150, 85%), External Iliac Artery (EIA, 25, 14%), internal iliac artery (IIA, 1, 0.5%) and Aorta (1, 0.5%). Arterial anastomosis choice had no impact on outcome but post-operative bleeding was significantly higher in IVC than CIV group (26% vs. 9%, p=0.01, Fisher's exact test) Rates of intra-abdominal sepsis (6.9% vs 21.9% p=0.05) and wound infections (10.3% vs 24.4% p=0.03) were lower in PT's with IVC than CIV anastamoses, but did not differ with EIV. Incidence of thrombosis (11.2%), rejection (23.5%) and transplant pancreatectomy (15.1%) did not vary according to choice of anastamosis (p=NS). 68% of PT's with EIV underwent re-operation compared with IVC and CIV configuration (45% & 49%; p=0.025 and p=0.05 respectively)

**Conclusion:** The evolution of pancreatic implantation techniques has undoubtedly contributed positively towards improvement in graft outcomes. Together with more rigorous donor and recipient case selection, surgical technique has proven to have a significant positive impact on outcome following PT. There is no optimum combination which improves graft survival, but it appears that anastomosis of PV to the IVC may have inferior outcomes in terms of haemorrhage risk. It appears that judicious anatomical decisions and important and coupled with meticulous technique may ensure improved outcomes.

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## Incidence and outcomes of acute rejection after pancreas transplantation: A single centre ten year review

Omar Masood, Abbas Ghazanfar, Victoria Bowman, Titus Augustine, Hany Riad, Afshin Tavakoli

*Manchester Royal Infirmary, Manchester, UK*

**Background:** Pancreas transplantation historically shares a similar time course to renal transplantation but the relatively higher complication and rejection rates have had an impact on prognosis. Advances in immunosuppression, stricter criteria for donor selection and technical advances have improved outcomes in recent years. This ten year review of the pancreas transplant programme in one centre focuses on rejection at 1 and 5 years with outcomes in this group. Those with clinical or biopsy proven rejection were treated with either methylprednisolone alone or additionally with anti-thymocyte globulin (ATG). The centre uses a universally accepted immunosuppression regime of an induction agent (Basiliximab and most recently Alentuzumab) + Calcineurin inhibitor (Tacrolimus) + an anti-proliferative agent ( MMF or more recently Myfortic) with or without steroids, with avoidance in those recipients who have had alentuzumab

**Methods:** The study group included all pancreas transplants (SPK, PAK, PTA) performed between June 2001 and June 2011. Data were obtained from a contemporaneously maintained pancreas transplant database and was analysed to determine if clinical factors had an effect on pancreatic rejection and subsequent graft survival. Statistical analysis was done using Wilcoxon, Student's t-test and chi-square tests.

**Results:** 229 pancreas transplants were performed during the study period. Median recipient age was 41 (inter-quartile range 36-49.) Male: Female ratio of patients was 142:87. One year and five year graft survival rates for SPK (n=178) versus pancreas only (PAK + PAT, n=51) group were found to be significantly better at 78.9% for 1 year and 72.7% for five years versus 64% and 48% for pancreas only p=0.02 and p=0.0007 respectively. Diagnoses of 65 graft rejection episodes were made in 50 patients. 40 out of 50 patients treated for rejection, were treated with methylprednisolone (MP) alone. 27 patients, 67.5%, had a functioning graft in 5 years. Three were treated with anti-thymocyte globulin (ATG) alone. All 3 had a functioning graft at 5 years. 7 patients were treated with MP and ATG, with 5 patients, 71%, still having a functioning graft at 5 years, p=0.0651. There were no significant relation between the number of rejections and patient and graft survival.

**Summary:** Acute rejection in pancreas transplantation when diagnosed early and adequately treated did not have an adverse effect on the outcome. Our data shows a 70% (5 year graft survival) success rate in patients treated for rejection and in our series we did not observe any relation between the rejection episodes and patient or graft survivals.

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**Impaired glucose tolerance predicts early failure in pancreas transplantation**

Shruti Mittal[1,2], Rachel Franklin[2], Myura Nagendran[2], Edward Sharples[1], Stephen Gough[1,2], Peter Friend[1,3]

*[1]Churchill Hospital, Oxford, UK, [2]University of Oxford, Oxford, UK, [3]Nuffield Department of Surgical Sciences, Oxford, UK*

**Introduction:** Pancreas transplantation aims to restore normoglycaemia in type 1 diabetics thus increasing life expectancy and controlling diabetic complications. However, graft survival rates remain modest with 1 year survival of 85% after SPK and 75% after PTA. Data is currently lacking to indicate an easily measurable predictive marker of graft dysfunction to inform clinicians and guide management to optimise outcomes.

**Aim:** Post-operative oral glucose tolerance tests (OGTT) are performed routinely on all pancreas transplant patients prior to discharge. This study aims to assess the role of postoperative oral glucose tolerance testing as an early predictor of pancreatic graft failure.

**Method:** Patients with graft failure were identified from a prospectively maintained clinical database, with graft failure defined by pancreatectomy or return to insulin-dependence. OGTT results were retrospectively collected for 36 patients with graft failure and 72 patients with functioning pancreas grafts matched for age, gender and type of transplant (SPK/ PTA/ PAK). OGTT results were interpreted as normal, showing impaired glucose tolerance (IGT) or diabetes using 1999 WHO Diabetes criteria. The results were analysed to determine associations between OGTT result and the incidence of early graft failure (<3 months post-operatively) and late graft failure (>3 months). Donor data was also collected and analysed.

**Results:** 108 patients underwent early OGTT testing, of which 74 were interpreted as normal while 34 showed IGT. The presence of IGT showed an association with pancreatic graft failure with a relative risk of 2.18 (1.30-3.63), p=0.0029. Further analysis of early and late failures showed presence of IGT to have a higher predictive value for early graft failure with a relative risk of 2.45 (1.03-5.79), p=0.04. Donor factors including donor age, donor type (DCD/DBD) and donor BMI had no significant predictive value for the diagnosis of IGT. There was no association between cold ischaemia time and the presence of IGT.

**Conclusion:** IGT diagnosed using OGTT performed within the first month postoperatively is a sensitive predictive factor for graft failure. IGT increases the relative risk of graft failure, and in particular the relative risk of early failure (RR 2.45). Although we may hypothesise this to be associated with response to ischaemia-reperfusion injury and graft pancreatitis, an association with donor factors was not observed in this cohort. Therefore abnormal postoperative OGTT can provide an inexpensive and easily measurable early risk factor of pancreatic graft dysfunction.

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**The impact of the modality of dialysis on pancreas transplant outcomes**

Abbas Ghazanfar, Otalia Pretorian, Gabriele Benedetto, Omer Masood, Tunde Campbell, Bence Forgacs, Hany Riad, Neil Parrott, Ravi Pararajasingam, Titus Augustine, Afshin Tavakoli

*Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*

**Background:** The effect of pre-transplant dialysis modality (PTxDM) on allograft and recipient survival after transplantation has not only been of long standing interest but also controversial. Some authors suggest that peritoneal dialysis (PD) is associated with lower incidence of delayed graft function but with greater risk of graft thrombosis. However, other studies reported equivalent or inferior results for PD patients as compared with hemodialysis (HD) patients. Previous analyses have showen a direct relation between dialysis duration and patient and graft survival in renal transplant recipients. The impact of PTxDM on pancreas transplant outcome is not well studied. In the present study, we evaluated the influence of the PTxDM on early and late pancreas graft function. We also compared various complications in the early and late post-transplant period and causes of graft loss in PD and HD groups.

**Methods:** we retrospectively analysed data of 243 pancreas transplants from 2001 to 2011. This included, 192 Simultaneous Pancreas and Kidney (SPK), 37 Pancreas After Kidney (PAK) and 14 Pancreas Transplant Alone (PTA). Patients with PTA (n=14) and pre-emptive transplant (n=45; SPK 32, PAK 13) were excluded from the study. Out of 184 patients we compared outcomes of recipients between HD (n=88) and PD (n=96) groups. Survival analysis was carried out using Kaplan–Meier estimates. For differences in survival, a log-rank test was used. Cox proportional hazards analyses were used to assess the relative risk of pre-transplant dialysis on patient and graft survival.

**Results:**

| Outcome | PD group (96) | HD group (88) | Statistical significance |
|---|---|---|---|
| Thrombosis (n=21) | 17 (17.7%) | 4 (4.5%) | <0.05 |
| Post opt haemorrhage (n=25) | 19 (19.79%) | 6 (6.2%) | <0.05 |
| Wound infection (n=30) | 21 (21.87%) | 9 (9.3%) | <0.05 |
| Collections (n=36) | 27 (28.12%) | 9 (9.3%) | <0.05 |
| Major fistula (n=19) | 15 (15.6%) | 4 (4.5%) | <0.05 |
| Peritonitis (n=26) | 19 (19.79%) | 7 (7.2%) | <0.05 |
| Rejections (n=31) | 24 (25%) | 7 (7.2%) | <0.05 |
| Pancreatectomy (n=30) | 23 (23.9%) | 7 (7.2%) | <0.05 |
| 1 year graft survival | 71.6% | 93.5% | <0.05 |
| 1 year patient survival | 89.59% | 95.46% | NS |
| 5 year graft survival | 67.2% | 74.3% | NS |
| 5 year patient survival | 86.46% | 92.05% | NS |

**Conclusion:** Dialysis mode appears to have a direct effect on the outcome of pancreas transplantation. Recipients on HD have statistically superior post operative outcomes when compared to PD. In the PD group there is direct impact of the length of dialysis on outcome.

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## A single centre experience of pancreas allograft core biopsies between 2001 and 2011

Fiona Allan, Colin Forman, Catherine Horsfield, John Taylor, Nizam Mamode, Anthony Dorling, Martin Drage

*Guy's and St Thomas's, London, UK*

Since the advent of enteric-drained pancreas transplantation, monitoring of the pancreas allograft has traditionally been performed using the surrogate marker of renal allograft rejection. Serum markers of pancreas inflammation (amylase, lipase) are non specific and raised serum glucose is a late indicator of islet destruction. Pancreas biopsies have traditionally been avoided due to possible complications.

**Method:** We performed 28 core biopsies on 21 patients. 1 patient had a pancreas transplant alone, 18 had simultaneous pancreas kidney transplants, while 2 had repeat pancreas transplants after SPK. 17 were performed under ultrasound guidance, 2 under CT guidance, 4 were open and in a further 6 it was unclear.

**Results:** 7 biopsies were inadequate for diagnosis (25%, 6 under US, 1 under CT). There was one case of a major complication with a bleed resulting in laparotomy and explantation of the graft (biopsied under US guidance). No other patient had a recorded complication (after extensive interrogation of the notes).

**Diagnoses:** 13 rejection episodes (10 patients), 4 pancreatitis episodes (4 patients), 1 infarction, and 2 normal. Outcome of rejection by indication for biopsy:

1) On protocol biopsy: 1 patient remained insulin independent for 28 months after treatment of rejection, before graft failure. 1 patient was not treated and had a functioning graft 36 months later.

2) For raised blood glucose: 4 patients who were all commenced on insulin immediately and did not regain independence, and 1 who was treated and remained insulin independent for 3 months before graft failure

3) For raised amylase: 2 patients had incidental rejection with histological pancreatitis, they were not treated and still have functioning grafts. 1 had rejection treated and remained insulin independent at 18 months.

Including histology from 12 explanted pancreas grafts, we identified 13 pairs of simultaneous pancreas and renal biopsies. 4 of these (31 %) showed discordant rejection (2 with pancreatic rejection in the absence of renal rejection). Many of the pancreatic rejections without a paired renal biopsy occurred without a rise in creatinine, and so may also reflect discordance.

**Conclusion:** Pancreas biopsies can be done with a relatively low complication rate. Indication biopsies appear unable to alter the graft outcome, suggesting high glucose demonstrates irreversible islet loss. High discordant rejection rates suggest we cannot rely on renal biopsy to exclude the diagnosis of pancreas rejection.

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**Mycotic aneurysms following pancreas transplantation: A single centre experience.**

Bence Forgacs, Gabriele Di Benedetto, Abbas Ghazanfar, Maria Mitu-Pretorian, David Van Dellen, Tunde Campbell, Hany Riad, Ravi Pararajasingam, Titus Augustine, Neil Parrott, Afshin Tavakoli

*The Renal and Pancreas Transplant Unit, Manchester Royal Infirmary, Manchester, UK*

**Background:** Mycotic aneurysms following pancreas transplantation are rare but its clinical manifestations can be dramatic and cause significant mortality.

**Aim and Materials:** Retrospective review of 243 consecutive pancreas transplants performed in a large centre (July 2001 to October 2011). Simultaneous Pancreas and Kidney SPK=192, Pancreas after Kidney PAK=37 and Pancreas Alone PTA=14. We aimed to analyse the incidence, risk, contributing factors, treatment modality and outcome in recipients who developed a major arterial mycotic haemorrhage following pancreas transplantation.

**Results:** 9(4%) patients developed intra abdominal arterial perianastomotic mycotic infections following pancreas transplantation (SPK=7, PAK=1, PTA=1). All patients had organs transplanted from donors after brain death and all were primary transplants. 3 had bladder drained pancreas transplants and 6 were enterically drained. 7 out of 9 recipients who developed this complication died as a consequence of the mycotic infection with superadded diabetic complications. The median time from transplant to death was 127 days (ranging from 40-1052). 2 patients died due to haemorrhagic shock caused by mycotic arterial rupture (40 and 95 days post transplant). The other 7 patients underwent pancreatectomy with further complications. The median time from transplant to pancreatectomy was 56 days (ranging from 14 to 274). 2 of these patients died within 90 days post transplant pancreatectomy. Donor and recipients demographics were not specifically characteristic.

**Summary:** Perianastamotic arterial mycotic infection is a devastating complication of pancreas transplantation with a high mortality and morbidity. An early and aggressive surgical approach is required for damage limitation. It may require unconventional and innovative techniques and a multidisciplinary approach. The number of patients in our study is small. A collaborative national or international approach with collection of cases and root cause analysis of all intra abdominal mycotic infections may provide valuable data on management. This study highlights the stringent efforts and attention to detail that must be paid right from donor management to implantation to prevent intra-abdominal infection in pancreatic transplant recipients.

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## Early re-laparotomy after combined kidney and pancreas transplantation: incidence, indications and outcomes

Pamela Sun, Asif Jah, Andrew Butler, Gavin Pettigrew, Andrew Bradley, Christopher Watson

*Addenbrooke's Hospital, Cambridge, UK*

**Introduction:** The reported incidence of re-laparotomy for combined kidney and pancreas transplantation (SPK) is high; at over 30% at 3 months. Few publications have analysed how re-laparotomy influences transplant outcome. Here we report our experience, focusing on whether different indications for re-laparotomy impact differently upon graft survival.

**Methods:** The re-laparotomies of 131 consecutive patients who received SPK transplants from brain death (n=107) and circulatory death (n=23) donors between January 2001 and July 2011 at our centre were reviewed retrospectively, with follow up ceasing in November 2011. Implantation was performed using porto-systemic venous drainage and roux-en-Y enteric drainage. Patients received enoxaparin (40mg daily) post-operatively. Data were collected on: donor and recipient demographics; operative details at SPK transplant and re-laparotomy; and graft and patient survival. Patients requiring re-laparotomy following SPK were compared to the 'control' group (n=76) of patients who did not require re-laparotomy.

**Results**: During follow-up, 55 (42%) patients underwent 104 re-laparotomies, with a median of 2 (range 1-8) per patient. The majority of the first re-laparotomy (n=43 patients, 78%) occurred within 30 days. The most common indication for these early re-laparotomies was suspected vascular complications (n=30, 70%), of which 22(51%) were performed for intra-abdominal haemorrhage and 8(19%) for suspected graft thrombosis. Thirteen further re-laparotomies were performed for various reasons including intra-abdominal collections, abdominal compartment syndrome and bowel obstruction. A third of haemorrhages necessitating a re-laparotomy occurred within 24 hours and the majority (92%) within 7 days. Of those with suspected graft thromboses, 5 were subsequently confirmed as true graft thromboses and resulted in graft loss. The overall 1 year graft survival was 91%. Graft survival for the early re-laparotomy group was reduced compared to the control group (76% vs 100%). This reduction was largely a consequence of the necessity to perform re-laparotomy for thrombosis; and 1 year graft survival in the patients requiring early re-laparotomy for intra-abdominal haemorrhage was comparable to the control group (90% vs 96%). Graft survival in the 13 patients reoperated upon for miscellaneous reasons was 83%. One patient in the re-laparotomy group died in the first year, giving a 1 year survival of 98%; compare to no deaths in the control group.

**Conclusions:** Combined kidney and pancreas transplantation (SPK) is associated with a high rate of re-laparotomy, most frequently for suspected haemorrhage, perhaps reflecting aggressive post-operative anticoagulation. However, the low rate of graft thrombosis and acceptable one year graft survival vindicate such a policy.

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**Transplant pancreatitis: histological definition of graft failure**

David van Dellen, Stephanie Trevelyan, Otilia Maria Mitu-Pretorian, Abbas Ghazanfar, Bence Forgacs, Babatunde Campbell, Neil Parrott, Hany Riad, Afshin Tavakoli, Titus Augustine, Ravi Pararajasingam

*Manchester Royal Infirmary, Manchester, UK*

**Background:** Pancreas transplantation has evolved to become an effective long term treatment modality for complicated Insulin Dependent Diabetes Mellitus (IDDM). However, allograft failure or severe concomitant rejection remains an obstacle to successful transplant outcome, occurring in 21% of recipients within one year and often resulting in graft failure. The potential role of transplant pancreatitis in the process of failure and rejection has never been clearly delineated. This study aimed to define both quantitative and qualitative evidence of transplant pancreatitis in explanted pancreata.

**Methods**: Retrospective analysis was performed of a prospectively maintained database of 203 consecutive patients undergoing pancreas transplantation since the initiation of our programme (2001-2010; SPK=155, PAK=36, PTA=12). The histological reports (performed by consultant histopathologists) for explanted pancreata (44) were correlated against terms most commonly associated with acute and chronic native pancreatitis as previously defined.

**Results:** 61% of patients with explanted allografts had histological evidence of pancreatitis. The most commonly described feature was fat necrosis (21/27, 83%), followed by inflammatory or neutrophil infiltrate (13/27, 48%). Specimens with evidence of pancreatitis had a similar rate of co-existing histologically confirmed vascular and cellular rejection and vascular thrombosis than those without (p=NS). However, specimens demonstrating histological evidence of pancreatitis were significantly more likely to be explanted late (>7 days post-transplantation) than those without evidence of pancreatitis (65% (17/26) and 25% (4/16) respectively; p=0.02; Fisher's exact test).

**Discussion:** Pancreas transplantation has evolved as an effective treatment for glycaemic control but allograft failure remains a considerable challenge. Pancreatitis appears to play an important contributing and additive factor to this adverse sequence. It appears that transplant pancreatitis, a distinct entity from allograft rejection, may be crucial in contributing to later failure of these grafts. Recognition of this complication may aid in successful transplant salvage thereby ultimately improving outcomes in this cohort of patients.

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## Peri-pancreatic fluid collections after simultaneous kidney-pancreas transplantation: impact on outcomes, and risk factor analysis

Rajinder Singh, Georgios Vrakas, Samiha Hayek, Neal Banga, James Pattison, Francis Calder, Nizam Mamode, Johnny Olsburgh, Geoff Koffman, John Taylor, Martin Drage

*Guys & St Thomas' Hospital, London, UK*

**Introduction:** To evaluate the impact and associations of peri-pancreatic fluid collections (PPFCs) after simultaneous kidney-pancreas transplantation (SPKTx).

**Methods:** Retrospective single centre study for all consecutive SKPTx performed from 08/1996 thru 06/2011. PPFCs included only those collections that required drainage, and were not related to bleeding.

**Results:** Of 216 SPKTx performed during study period, PPFCs were seen in 30 (14%), all in immediate post-operative period. Of these, persistent and increased serum amylase (>200 within day-14, 'graft pancreatitis') was seen in 17 (57%), pancreatic enzyme leak in 15 (50%, 8 with obvious duodenal stump (DS) leak, and 7 without), and urine leak in 2(7%). All except 2 cases of enzyme leak also had associated 'graft pancreatitis'. The 30 PPFCs were compared with the remaining group (non-PPFC, n=186). Actuarial survival analysis showed that PPFCs had significantly lower 1yr (70% PPFC vs. 94% non-PPFC) and 5 yr (66% PPFC vs. 86% non-PPFC) total pancreas graft survival (all $p<0.02$, log rank test), but statistically similar 1yr (89% PPFC vs. 95% non-PPFC) and 5 yr (85% PPFC vs. 87% non-PPFC) total kidney graft survival, 1 yr (97% PPFC vs. 98% non-PPFC) and 5yr (88% PPFC vs. 95% non-PPFC) patient survival, compared to the non-PPFCs. PPFCs cohort had significantly higher biopsy proven acute rejection (BPAR) rates (53% PPFC vs. 35% non-PPFC), mean donor age (38 yrs vs. 31 yrs), mean donor BMI (25.7 vs. 23.4) and 6 antigen mismatch transplants (7% vs. 0.5%) (all $p<0.05$), and higher trend with donors dying from stroke (68% vs.51%, $p=0.1$) compared to non-PPFCs. Pancreas cold ischaemia time (mean 12 hrs in both) and donation after cardiac death donors (10% PPFC vs. 5% non-PPFC) were statistically not different. As a direct consequence of PPFCs, there were 2 (7%) patient deaths (from sepsis), 10 (33%) pancreatic graft loss (PGL), and 3(10%) kidney graft loss within the 1st year, and persistent sinus in 1 (3%). Of the 2 recipients with urine leak, one had ureteric necrosis, PPFC in addition, had kidney graft loss and died of sepsis; the 2$^{nd}$ recipient developed new DS leak after laparotomies for repair of urine leak, and lost both grafts. Collections were infected in 15 (50%), all with bacteria, and 2 (7%) in addition with candida, and 4 (13%) with multi-drug resistant bacteria. BPARs in kidney grafts within 3 months of transplant were seen in 8 (27%) of PPFCs (mean duration of 42 days after transplant, range 6-85, SD 30). Radiological drainage resolved 1 (3%) case, and the remaining 29 (97%) required surgical drainage. Mean number of laparotomies for draining PPFCs was 3.9 (SD 6.6). PPFCs fully recovered in 20 (67%) without impacting either graft function. Sub-group analysis comparing PPFCs without complication (n=20) with those with complications (graft/patient loss, n=10) showed presence of pancreatic enzyme leak (80% vs. 35%) and mean donor age (44 yrs vs. 36 yrs, all $p<0.05$) as significant associations.

**Discussion:** Peri-pancreatic fluid collections have significant associations with donor age and BMI, pancreatic enzyme leak, 'graft pancreatitis', acute rejection, cause recipient morbidity and impact resource utilization.

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## Single centre experience of solitary pancreas transplants: graft and patient outcome

Ismail Mohamed, Georgios Vrakas, Martin Drage, Nizam Mamode, Francis Calder, Jonathon Olsburgh, John Taylor, Geoff Koffman

*Guy's Hospital, London, UK*

**Introduction:** Solitary pancreas transplantation (PTA/PAK) is a small but growing part of pancreatic transplantation. The aim for PTA is to treat severe hypoglycaemic unawareness and in PAK to restore insulin independence and reduce diabetic complications in patients with a functioning renal allograft. We aim to evaluate our practice in order to provide objective information regarding graft and patient outcome.

**Methods:** A single centre retrospective review of all solitary pancreas transplants was performed between 2006-2011. Clinical characteristics of patients, graft and patient outcomes were analysed.

**Results:** 12 solitary pancreas transplants were performed, of which 10 were PAK transplants (all enterically drained). The latter consisted of 4 patients who had undergone live renal transplants, 1 deceased donor renal transplant, 4 simultaneous pancreas kidney transplants (SPK) with a failed pancreas allograft and 1 patient who had had a failed PAK followed by a live renal transplant. Mean (SD) ages for recipients and donors were 38 (8) and 34 (13); gender (M:F) of recipients and donors were 4:8 and 5:7. Graft and patient survival are shown in Table 1. Of the 3 grafts lost in the first 3 months, 2 were due to venous thrombosis (one subsequently diagnosed with hyperhomocystenaemia), and 1 due to anastomosis leak; these patients had prior failed pancreas transplant and deceased donor renal transplant. 4 patients suffered acute rejection. Post transplant laparotomies were performed in 2 patients. In contrast, 1 and 2 year SPK graft survival in the same period in our centre were 93% and 89% respectively; 1 and 2 year patient survival were 98%.

| | Graft survival | Patient survival |
|---|---|---|
| 6 months | 75% (9/12) | 100% |
| 1 year | 70% (7/10) | 100% |
| 2 years | 50% (4/8) | 100% |

Table 1: Solitary pancreas transplant graft and patient survival

**Conclusion:** Long term graft survival in solitary pancreas transplantation remains challenging despite advances in surgical techniques and immunosuppression. The outcome of these patients, which represent a subset group which have had previously failed pancreas transplants are inferior to those of SPK's in our centre. Meticulous assessment of suitable patients and intensive monitoring with the use of protocol biopsies alongside early intervention are crucial. Finally, the distinct characteristics of these patients, many of whom have received prior transplants merit recognition and further evaluation.

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**Establishing a GMP pancreatic islet isolation laboratory in Scotland**

Neil McGowan[1], Donna Mitchell[1], Lindsay Fraser[1], Alan Timpson[1], Lora McCracken[1], Peter Henry[1], Tom McQuillan[1], John Drain[1], George Galea[1], John Casey[2]

*[1]SNBTS Tissues & Cells, Edinburgh, UK, [2]Royal Infirmary of Edinburgh, Edinburgh, UK*

An islet cell transplant service was commissioned by the Scottish Government in 2009. Following collaboration between the existing Transplant Unit at Royal Infirmary of Edinburgh and SNBTS Tissues and Cells a pancreatic islet cell transplantation service for Type I diabetic patients presenting with poor glycaemic control and/or awareness, often associated with numerous hypoglycaemic events was developed.

Over the last 18 months SNBTS Tissues and Cells have installed and commissioned a new Grade B/C processing facility and established the islet isolation service (mirroring that of the Edmonton Protocol), to the appropriate Good Manufacturing Practice (GMP) and legislative standards, creating in excess of 150 controlled documents and completing over 20 individual equipment and process validations. Staff with little or no experience in the islet isolation process had to be trained and confirmed competent in the process.

Following commissioning of the facility, the actual process had to be qualified. During this qualification period, organs which were not suitable for whole transplant were used for education and training to develop the process. This was done in conjunction with Edmonton and other world wide laboratories whose knowledge and expertise was invaluable. 29 organs were used during the qualification process and islets isolated after only 6 organs, with the remaining used to further refine the isolation process. Once the process was established and staff competent, 3 procedures had to be performed to confirm the consistency of the process using the selected equipment, reagents and consumables while producing successful product outcomes. A clinical service was launched in December 2010 following successful process qualification and an audit of both the facility and process by internal and external experts.

Since a clinical service was established in December 2010, 14 isolations have been performed with 72% success rate i.e. met all product specific release criteria. Of these 10 isolations, 6 have been transplanted into 4 patients in Scotland and 2 transported and transplanted into patients in England. all of these transplants have been deemed successful as evidenced by a reduction in insulin requirements, reduced hypoglycaemic events, restoration of glycaemic awareness and production of c-peptide, a marker of endogenous insulin production.

It has been demonstrated that in a short period of time a clinical islet isolation laboratory can be set up with good clinical outcomes. This is mainly due to developing an existing facility and building on the appropriate skills and expertise in GMP, and successful collaboration between NHS Lothian, SNBTS Tissues and Cells and the world wide experts in islet isolations.

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**Reduction in body weight and energy intake following islet transplantation in subjects with type 1 diabetes in Scotland**

Debbie Anderson[1], Kirsty Duncan[2], Janet Barclay[1], Christine Jansen[2], Tammie McGilvary[2], Janice Davidson[2], John Casey[2,3], Shareen Forbes[1,3]

*[1]Diabetes and Endocrinology Unit, Royal Infirmary of Edinburgh, Edinburgh, UK, [2]Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK, [3]University of Edinburgh, Edinburgh, UK*

**Introduction:** Subjects with Type 1 diabetes who have recurrent hypoglycaemia are at risk of impaired awareness of hypoglycaemia (IAH). Hypoglycemia may be corrected by taking carbohydrate. Those with IAH may be eligible for islet transplantation. This may improve awareness of hypoglycaemia, reduce the frequency of hypoglycemia and stabilise blood glucose levels. A Scotland-wide Islet Transplant Programme has been established at the Royal Infirmary, Edinburgh. We hypothesised that post transplantation a reduction in weight would be evident secondary to a reduction in caloric intake due to a reduction in spontaneous hypoglycaemia.

**Methods:** Subjects were assessed by our multidisciplinary team pre-and post-transplant. A dietary questionnaire was used to assess the calorific treatment of hypoglycemia pre and post transplant. Body weight and composition on admission for islet transplantation was compared with weight and composition post transplant. Body composition was analysed with a bio-electrical impedance meter (Tanita bc 420 p ma). Assessments recorded post-transplant were the most recent clinic assessments (range 1-6 months).

**Results:** 4 c-peptide negative patients received 6 islet transplants (3 recipients single, 2 recipient two grafts). Engraftment was successful in all patients (all c peptide positive) with an improvement in glycaemic control. Frequency of hypoglycaemia decreased significantly in all cases (pre-transplant 7±3 vs. post-transplant 1±1 episodes/week; $p<0.01$). Excess caloric intake attributable to hypoglycaemia pre transplant was (mean±SEM) 237±120 and post transplant 34±17 kcals ($p<0.01$). Pre-transplant weight of the recipients was 75.8±6.2 kg, BMI 28.5±1.0 kg/m$^2$ and post transplant 71.4±5.9 kg BMI 26.5±1.0 ($p<0.01$). Percentage fat mass pre transplant was 33.8±1.4% and post transplant 33.1±1.9% ($p=0.43$).

**Conclusions:** Weight loss following islet transplantation is common and may be due to the reduced caloric intake secondary to reduced hypoglycaemia. During this short term follow up there have been no body compositional changes. Longer term monitoring of our patients is underway.

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## Insulin independence after islet transplantation from a DCD donor- the first case in the UK

John Casey[1], Neil McGowan[2], Donna Mitchell[2], Kirsty Duncan[1], Christine Jansen[1], Debbie Anderson[1], Janet Barclay[1], James Gordon-Smith[1], Shareen Forbes[1]

*[1]Royal Infirmary, Edinburgh, Edinburgh, UK, [2]SNBTS, Edinburgh, UK*

Islet transplantation is now recognised as an effective therapy for some patients with type I diabetes and hypoglycaemic unawareness. In the UK, over 20 islet transplants have been carried out since the new pancreas allocation scheme began in December 2010, 6 of these in Scotland. Islet transplantation from DCD donors is rarely described outside of Japan and here we describe the first UK case which has resulted in persisting insulin independence.

A 52 year old patient with type I diabetes and longstanding severe hypoglycaemic unawareness underwent first islet infusion in February 2011. The patient received 292,000 islets prepared at the Scottish Islet lab at SNBTS in Edinburgh (4101 IEQ/Kg, 73% purity, 96% viability) from a 35 year old DBD donor. The islets were infused percutaneously into the main portal vein in the standard fashion under local anaesthetic and sedation. This resulted in restoration of hypoglycaemic awareness and a reduction in insulin requirement of 50%. The patient was priority re-listed for a second islet graft 1 month later. In April 2011 she received 348,000 islets again prepared at the Scottish islet lab (5039 IEQ/Kg, 73% purity, 95% viability) from a 30 year old DCD donor with a withdrawal to asystole time of 20 minutes and warm ischaemic time of 22 minutes. The islet preparation was placed in culture for 48 hours post isolation and reassessed for cell number, purity and viability. Careful assessmant of islet architecture was also carried out prior to transplantation. Insulin therapy was withdrawn 2 weeks after this infusion and the patient has remained insulin independent since then (>7 months) with a HbA1c of 5.7% (8.2% pre transplant) and no hypoglycaemic episodes. Immunosuppression consisted of Alemtuzumab induction 30mg 1 hour prior to the first graft and maintenance with tacrolimus and mycophenylate mofetil.

Since this first DCD islet transplant, a further patient in the Scottish programme has received a first islet graft from a DCD donor resulting in a 40% reduction in insulin requirement and excellent metabolic control (HbA1c 5.3%). The expansion in DCD organ donation in the UK presents many challenges to the transplant community. Unlike vascularised organ transplantation from DCD donors, islets can be placed in culture post isolation to allow for assessment of graft viability and function prior to transplant. We have shown that islets transplanted from DCD donor pancreata can produce clinical and metabolic outcomes comparable to DBD islet preps in the UK setting and pancreata from DCD donors should be considered for islet isolation and transplantation.

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