Welcome to Bournemouth!

As President of the British Transplantation Society I am delighted to welcome you to Bournemouth for the 14th Annual Congress of the BTS. This is the first of our three visits to Bournemouth and although I can promise you sea and sand, I can't promise you sunshine! However I can promise you a stimulating educational programme and the opportunity to meet with colleagues.

We are very grateful to the members of the Programme Committee for putting together what looks to be a stimulating, imaginative and diverse programme, with a wide range of international and national experts. We believe there will be something for everyone and we have tried to provide clinical and science strands, as well as plenary sessions that will be relevant to all. We again welcome our partner Societies and there will be joint symposia with BSHI, BASL and ITNS.

We have endeavoured to build on the success of recent meetings. In addition to the regular Congress sessions, this year there will also be two concurrent postgraduate breakfast sessions covering 'Optimising DCD donors' and 'Which donors should we use'. The moderated poster session will run in parallel with the Welcome Reception on Wednesday night and this year's Hoffenberg lecture will be given by Professor Janet Radcliffe-Richards.

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 senior corporate partners, Novartis and Astellas, who will also be hosting sponsored symposia on the Wednesday and Thursday lunchtimes.

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.

With best wishes

Keith Rigg

President

Wednesday				Thursday				Friday		
1000	**REGISTRATION & COFFEE**			0830	**HOW I DO IT: Optimising Donation after Cardiac Death** – **Tregonwell Hall (back)** *Prof David Talbot* Rutger Ploeg, Peter Friend & Gavin Pettigrew			0830	**HOW I DO IT: Which donors should we use?** – **Purbeck Lounge** *Mr John Forsythe* Nizam Mamode & Paolo Muiesan	
1100	**Looking to the Future** **Tregonwell Hall (Front)** *Keith Rigg & Lorna Marson* Stem Cells – Martin Birchall Experimental Tolerance – Kathryn Wood Clinical Tolerance – Chris Larsen			0930	**Medawar Medal** **Tregonwell Hall (Front)** *Keith Rigg & Anthony Warrens* Abstracts x 8	**BTS/ITNS session** **Purbeck Lounge** *Jane Smith & Moira Perrin* Consent in practice: discussing the options Panel discussion on consent guidelines. Panel Members: Chris Watson, John Dark, Lisa Burnapp, Christine Jansen & Paul Evans		0930	**NHSBT** **Tregonwell Hall (Front)** *Chris Dudley & Peter Veitch* The Kidney Allocation Scheme – Alex Hudson Declined liver offers from donors after brain death – Kerri Barber Influence of donor smoking on survival after lung transplant – Dave Collett Paired & domino donation – Rachel Johnson Analysis of consent rates for organ donation – Claire Counter Split liver transplant – Kerri Barber Patient management tools – Alex Hudson Patterns in ODR registration – Dave Collett	**Basic Science** **Tregonwell Hall (Back)** *Eleanor Bolton & Wilson Wong* Abstracts x 9
1200	**Challenges in Transplantation** **Tregonwell Hall (Front)** *Richard Baker & Abdul Hammad* Post Transplant diabetes mellitus – Kesh Baboolal Management of hypertension post renal transplantation – David Wheeler	**Antibody Incompatibility** **Tregonwell Hall (Back)** *Craig Taylor & Nizam Mamode* Abstracts x 6	**Pancreas / Immunosup-pression** **Purbeck Lounge** *Adam Mclean & Argiris Asderakis* Abstracts x 6	1200	**Urological Problems in Renal Transplant-ation** **Tregonwell Hall (Front)** *Hany Riad & Jonathan Olsburgh* Transplant-ation into abnormal urinary tract – Alun Williams Managing urological complications	**Ethics, Law & Public Policy** **Tregonwell Hall (Back)** *Vassilios Papalois & Antonia Cronin* Abstacts x 6	**BTS/ITNS/ NHSBT Session** *Sue Falvey* Collaboration & Co-ordination: roles and developments - Susan Richards - Moira Perrin - Liz Waite			

	Abstracts x 3				post transplant – Nilay Patel Abstracts x 2				The ATTOM Study – Rommel Ravanan	
1300	**LUNCH – Purbeck Hall**			1300	**LUNCH – Purbeck Hall**			1115	**COFFEE – Purbeck Hall**	
1330	**Novartis Sponsored Symposium** **Immunosuppression - where less means more?'** **Tregonwell Hall (Front)**			1330	**Astellas Sponsored Symposium** **Improving long-term outcomes in Transplantation – optimising immunosuppressant therapy** **Tregonwell Hall (Front)**			1130	**Award of BTS Honorary Fellowship followed by Best Abstracts** **Tregonwell Hall (Front)** *Anthony Warrens & Andrew Bradley* Minor H Antigens: tools for reprogramming rejection responses – Elizabeth Simpson	
1430	**Challenges in Transplantation : Infection** **Tregonwell Hall (Front)** *Chas Newstead & Peter Andrews* Hepatitis – Kosh Agrawal BK Virus – Rachel Hilton EBV & PTLD – Mark Harber Immunology & vaccination – Vince Emery Abstracts x 6	**Basic Science: Innate Immunity** **Tregonwell Hall (Back)** *Marlene Rose & Tony Dorling* Neutrophils - Tim Lee Monocyte Macrophage Subpopulations - Moritz Widgruber Macrophages in chronic allograft injury - Susan Moffatt - Bruce Abstracts x 3	**BASL Symposium: Selection of patients and allocation of livers for transplantation** **Purbeck Lounge** *Murat Akyol & Derek Manas* Eurotransplant - Xavier Rogiers Scandia Transplant - Michael Olaussen USA - Richard Freeman UK – Alex Gimson Abstracts x 3	1430	**Optimising Organs Ex Vivo** **Tregonwell Hall (Front)** *John Dark & Chris Watson* Lungs – Stig Steen Liver – Rutger Ploeg Kidney – Mike Nicholson	**Chronic antibody mediated rejection** **Tregonwell Hall (Back)** *Susan Martin & Phil Mason* The role of post transplant antibody monitoring – Phil Dyer The treatment of chronic antibody mediated rejection – Tony Dorling Abstracts x 3	**BTS/ITNS** *Jane Smith & Lisa Burnapp* Shaping the future Nurse led clinics - Anne Theakstone	1230	**LUNCH – Purbeck Hall** **AGM – Tregonwell Hall**	
								1300	**Transplant Links** Purbeck Lounge Jennie Jewitt Harris	
								1330	**BSHI Symposium** **Tregonwell Hall (Front)** Pre-transplant Donor Specific Antibody – What's acceptable? Clinical relevance of HLA antibody testing – Howard Gebel UK Transplant outcomes in sensitised/ non sensitised/ first grafts/ regrafts – Sue Fuggle Antibody screening & crossmatching – Paul Sinnott Antibody screening & crossmatch results (an evidence based	**Surgeons Chapter** **Purbeck Lounge** Update of TSC role and activity - Derek Manas Report from Post-CCT Fellowship holders - Anna Rizzello, Ben Lindsey & Gourab Sen "My worst nightmare" Liver implantation - Nigel Heaton Laparoscopic kidney donation - Mike Nicholson Pancreas Transplant - Anil Vaidya

									approach) – Craig Taylor	
1630	**TEA – Purbeck Hall**			1530	**TEA – Purbeck Hall**			1530	**TEA – Tregonwell Bar**	
1700	**Metabolic syndrome in transplantation** **Tregonwell Hall (Front)** *Iain MacPhee & Nick Torpey* Glucocorticoids in the metabolic syndrome -Brian Walker Transplanting the obese renal patients – Colm Magee Non alcoholic fatty liver disease - Phil Newsome Abstracts x 3			1600	**Ethics Symposium** **Tregonwell Hall (Front)** *Antonia Cronin* Organs for transplants: resources, rights & refusals Panel Participants: Janet Radcliffe Richards Marc Clancy Vassilios Papalois Lisa Burnapp Adrian McNeil	**Clinical Abstracts: Antibodies** **Tregonwell Hall (Back)** *Chris Dudley & Sue Fuggle* Abstracts x 6	1600 1700	High resolution HLA antibody analysis of renal allograft loss - Bob Vaughan	Debate: "This house believes that DCD is the blight of modern renal transplantation For: Neil Parrott Against: Chris Watson **CLOSE**
1830	**RECEPTION & POSTERS** **Purbeck Hall**			1700	**Hoffenberg Lecture: Curious & Spurious: Misdiagnosed obstructions to organ donation** **Tregonwell Hall (Front)** *Robert Sells* - Janet Radcliffe Richards					
1915	**Women in Transplantation Meeting** **'When the lights came on'** a short talk by Lorna Marson **Purbeck Lounge**			1815	**3C study Investigators Meeting** **Purbeck Lounge**					
				1930	**Society Gala Dinner – The Highcliff Marriott**					

Acknowledgements

A formal thank you to the Programme Committee, chaired by Ms Lorna Marson and the BTS Congress Organising Committee, Mr Chris Watson (chair), Mr Richard Baker, Prof Anthony Warrens, Ms Lorna Marson, Dr Chris Dudley and Mr Keith Rigg.

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

Clinical
Dr Richard Baker
Mr Hany Riad
Mr Murat Akyol
Mr Nizam Mamode
Dr Iain MacPhee

Laboratory
Prof Marlene Rose
Prof John Kirby
Prof Tony Dorling
Mr Gavin Pettigrew

Coordinator/Nursing
Ms Jane Smith
Ms Lisa Burnapp
Ms Moira Perrin

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

Ethics
Dr Antonia Cronin
Prof Steve Wigmore
Dr Peter Rowe

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

Novartis	Wednesday Lunchtime Symposia
Astellas	Thursday Lunchtime Symposia
Bristol Myers Squibb	Congress Bags

The British Transplantation Society

Company and Charity Annual General Meeting

Friday 11 March 2011 12:30 to 13:30hrs

Tregonwell Hall, Bournemouth International Centre, Bournemouth

1. Welcome
2. Apologies
3. Minutes of AGM on 19th March 2010, Kensington Town Hall, London (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. 14th Annual Congress
9. Any other business
10. Next meeting: Friday 24th February 2012, Scottish Exhibition Centre, Glasgow
11. Closure of meeting

By order of the Board of Directors

Date 19th January 2011

BRITISH TRANSPLANTATION SOCIETY
Minutes of the Annual General Meeting - *Reg. Charity 1098584 & Reg. Company 4691176*
Friday 19th March 2009 at 08.00,
Great Hall, Kensington Town Hall, London

1. KR welcomed the members present to the Annual General Meeting.

2. Apologies were received from Leslie Brent, Susan Martin, Susan Fuggle and Craig Taylor. 16 members were in attendance.

3. The minutes from the last AGM of the charity held on 24th April 2009 at the Arena & Convention Centre, Liverpool 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 for their service and particularly Chas Newstead for his long term commitment to the Society as chair of the Standards Committee.

ii. <u>What is the Society doing nationally?</u>
- ODT Programme Delivery Board.
- Transplant 2013 coalition to promote organ donation and transplantation in Parliament.
- The EU Organ Directive will be coming into place by the end of October 2010 which will bring a consistent quality agenda across Europe.

iii. <u>Who is the Society working with?</u>
- NHSBT
- DCD Working Party
- UK DEC
- Post CCT Fellows – in a joint collaboration with the Royal College of Surgeons
- Wide collaboration and representation
- ESOT reduced membership

iv. <u>What is the BTS doing for you?</u>
- The council is currently fully represented apart from the Donor Coordinator position. It was agreed in the Council meeting that KR would write to all coordinators through NHSBT and invite for a co-opted post.
- Roche has handed over the Renal Transplant Education Forum to the BTS. This is to be re launched as the BTS Education Forum on 1-3rd December 2010 in Warwick.
- There is still a struggle to engage members into using the BTS website and any ideas to increase participation would be welcome.
- KR once again thanked the work done by the sub committees and those retiring from the council this year.

- Peter Andrews becomes the new chair of the Standards Committee and has a programme of new guidelines and updates. Phil Dyer presented the "Guidelines for the detection and characterization of clinically relevant antibodies in allotransplantation" which will be posted on the BTS website for comment.
- Paul Harden becomes the new chair of the Clinical Trials Committee and plans a Renal Transplant Trials summit later in the year.
- KR would be writing to all heads of Transplant units as part of an initiative to increase membership.

5. Vice President's Report

i. The Programme for the ESOT 2011 meeting 4-7 September is coming together. John Forsythe and Alan Jardine are the chairs of the local organizing committee. The local organising executive includes the chairs of the LOC together with Peter Friend, Keith Rigg, Anthony Warrens, and Chris Watson.

ii. The next Annual Congress will be held 9-11 March 2011 at the BIC in Bournemouth. Lorna Marson is Chair of the Programme committee and work will commence soon on preparing the programme for this meeting.

iii. Dates for future Congress: Glasgow 22-24/02/2012, Bournemouth. 13-15/03/2013, Glasgow 26-28/02/2014.

iv. Marginal donors and consent. A joint BTS/NHS BT working party is being set up to examine this important issue and will consist of ethicists, lawyers, patients and transplant professionals.

6. Secretary's Report

i. Election Results: 705 online voting codes were circulated; with only 160 votes cast (22.7%). This is lower than last year.

ii. As a result of the above, the following positions have been filled:
- Councillor representing Transplant Nephrology - **Iain MacPhee**
- Councillor representing Liver Transplantation - **Murat Akyol**
- Member of the Standards Committee - **Joyce Popoola & Nadey Hakim**
- Member of the Ethics Committee - **Lisa Burnapp & Marc Clancy**
- Councillor without portfolio - **Simon Bramhall**
- Councillor representing Histocompatibility - **Craig Taylor**

iii. A total of 112 members have joined since the last AGM. This brings the total membership to 817. There was no opposition to the list presented.

iv. 221 abstracts were submitted for Congress this year. 167 Clinical, 48 Laboratory and 6 Coordinator. Out of these 193 were accepted; 61 for oral presentation and 132 poster.

v. The Roy Calne Award was presented to Dr Yunchuan Ding, University of Oxford. CD thanked Richard Smith, Paul Shiels, Kay Poulton and David Adams for judging the award.

vi. Rule 11
An amendment to rule 11 was proposed. A number of the council positions are only two year positions and it was proposed to change these to three. There was no objection to this.

7. Treasurer's Report

i. The Finances of the Society remain healthy. The total funds at hand are £472,459. AW confirmed that the Society is not in breach of the Charity Commission with having this amount in reserves.

ii. There is a significant decline in income due to the change in the structure of the Corporate Subscriptions. The senior corporate partner subscription has reduced from £65,000 to £25,000 due to the elimination of the fellowships at £40,000. The income for 2008 is also down, as is the expenditure due to the reduction in cost of the congress venues.

iii. The BTS Annual Congress has run a loss over the years however 2008 saw a surplus of £479 and 2009 £69,417. This shows the benefit of a joint congress. It is expected that 2010 Congress will break even. 2010 has seen a reduction in registration fees, 50% less than Glasgow in 2008.

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

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8. 14th Annual Congress

Bournemouth International Centre (BIC), Bournemouth 9-11 March 2011.

9. AOB

The executive were asked whether the BTS would consider joint meetings with other Societies due to the success of the 2009 Congress. The executive advised that the BTS is committed to set venues for the next 6 years but within this constraint would welcome joint meetings and would approach the Renal Association for a joint meeting in 2013. Chris Rudge advised that the BTS had a joint meeting with the Dutch Transplantation Society a number of years ago. This could be explored again.

10. Next meeting

Scheduled for Friday 11th March 2011, Bournemouth International Centre, Bournemouth

11. The AGM was closed at 08:45a.m.

ABSTRACTS

Challenges in Transplantation

Tregonwell Hall (front)

9 March 2011

12:00-13:00

Early Development Of New Onset Diabetes After Transplantation Is Associated With Impaired Long-term Survival In Renal Allograft Recipients

Pramod Nagaraja[1], Vinod Ravindran[1], Gareth Morris-Stiff[2], Keshwar Baboolal[1]

[1]University Hospital of Wales, Cardiff, United Kingdom, [2]St.James's University Hospital, Leeds, United Kingdom

Objective: (a) To understand the pathophysiology of new-onset diabetes after transplantation (NODAT) in renal transplant recipients by studying changes in insulin resistance indices and disposition index (DI) calculated from fasting glucose and insulin values (b) To analyse the long-term impact of new-onset diabetes after transplantation (NODAT) over 10 years.

Methods: Cohort observational analysis of 118 non-diabetic renal transplant recipients selected from a randomised controlled trial of tacrolimus versus ciclosporin performed from 1996-2003. Fasting glucose tolerance was determined using 1999 WHO classification. Subjects were divided into 3 groups – 1. Those who developed NODAT within 3 months of transplantation (n=25: Group 1) 2. Those who were euglycaemic at 3 months but developed NODAT later within 1 year (Group 2, n=19) 3. Those who remained euglycaemic throughout the first year (n=74, Group 3). The following insulin sensitivity and secretion indices were calculated: IR-HOMA (homeostasis model assessment of insulin resistance), McAuley's Index (McI), HOMAsecretion, DI (HOMAsec x McI). Binary logistic regression was used to identify factors predicting survival.

Results: Median follow-up time was 11 years. The incidence of NODAT at 3 months and 1 year was 19% and 37% respectively. At baseline, subjects in Group 2 were older (55 years) than those in the other 2 groups (Group 3 45 years, Group 1 49 years). There were no differences in baseline BMI, type of CNI, fasting glucose or serum triglyceride level between the 3 groups. There were no significant differences in pre-transplant insulin sensitivity, secretion or DI between the three groups. At 3 months, Group 1 had a higher IR-HOMA (6.5) than the other 2 groups (Group 2 4.5, Group 3 2.8, $p<0.01$). Group 2 had higher fasting glucose at 3 months compared to Group 3 (6.0 vs 5.5 mmol/l, $p=0.01$). In a within group analysis, there was a significant increase in IR-HOMA at 3 months compared to baseline in Group 2 (4.3 vs 2.3, $p=0.03$) and Group 1 (6.5 vs 3.6, $p=0.007$), whereas IR-HOMA fell in Group 3 patients (3.2 vs 2.8, $p=0.9$). However, in Group 2, whilst IR-HOMA continued to rise until 12 months (5.5 compared to 4.3 at 3 months, $p=0.17$), HOMAsec and DI fell from 3 months to 1 year (138 vs 100, $p= 0.31$ and 783 vs 500, $p=0.06$ respectively), rendering them at risk of becoming diabetic. Ten year patient survival rate was 79%, 66% and 50% in Group 3, 2 and 1 respectively (Kaplan-Meier log-rank test $p=0.01$). Being NODAT-free within 1 year of transplantation was a significant predictor of survival (OR=2.6, 95% CI 1.06-6.34).

Discussion: Using indices derived from single fasting glucose and insulin values, this study has demonstrated changes in insulin secretion and resistance that occur after renal transplantation. Patients who developed NODAT demonstrated early insulin resistance at 3 months and a progressive decline in insulin secretion leading to NODAT. NODAT in the 1st year post-transplantation was associated with decreased long-term patient survival.

2

Renal and cardiovascular outcomes in the UK living donor nephrectomy population

Nilay Patel, Mark Sullivan, Sally Rushton, Alex Hudson, Sanjay Sinha, Phil Mason, Peter Friend

The Churchill Hospital, Oxford, United Kingdom

Introduction

Knowledge of the long term health outcomes following living donor nephrectomy (LDN) is of great importance when counselling potential kidney donors. Using data from the NHSBT database we report on the impact of LDN on renal function, cardiovascular disease and cardiac mortality in the UK population.

Methods

Between 1 January 2001 and 31 December 2008, 4586 patients underwent a LDN in the UK. Pre and post operative data was collected prospectively by transplant units across the UK and entered into the National Health Service Blood and Transplant (NHSBT) database. This data was recovered in July 2010 with the approval of the NHSBT kidney-pancreas advisory committee.

Results

Pre-operative and 1 year follow data was available for 3424/4586 patients (75%). Complete post-operative follow up data up to year 5 was available for 784/4598 patients (17%). LDN resulted in an increase in the mean serum creatinine from 83mmol/L to 112 mmol/L at 1 year. This equated to a reduction in the mean GFR from 100 ml/min to 59ml/min. The mean GFR did not change significantly between year 1 (59ml/min) and 5 (60ml/min). In patients with 5 year follow up, new onset hypertension was noted in 79/785 patients (10%) and non fatal cardiac events reported in 3/784 patients (0.4%). Cardiac mortality was reported in 2/3424 patients (0.05%) with long term survival data.

Discussion

LDN results in a 40% decrease in the mean GFR. The GFR appears to remain stable 5 years following donation. Over a 5 year period adverse cardiovascular events and cardiac mortality are rare. Longer term follow up is required to establish the relationship between LDN, renal impairment and cardiovascular disease.

3

Isolated non-visible haematuria in living kidney donors: causes and outcomes post-donation

Mangalakumar Veerasamy, Robin Ramphul, Catherine Horsfield, John Scoble, Rachel Hilton
Guy's & St.Thomas Hospital NHS Trust, London, United Kingdom

Introduction: Isolated non-visible haematuria is common in the general population and is often considered insignificant in the absence of other features such as reduced kidney function or proteinuria. However, for the purposes of living kidney donor assessment more rigorous evaluation including kidney biopsy is recommended to exclude glomerular pathology and stratify the risk of progressive kidney dysfunction post-donation.

Methods: We retrospectively analysed all potential kidney donors who were evaluated at our centre between 1999 and 2010 and who were found to have persistent non-visible haematuria. All patients were assessed according to BTS consensus guidelines including renal tract imaging, GFR measurement, screening for proteinuria and cystoscopy. All patients underwent kidney biopsy if no other cause for haematuria could be found. Provided the sample was adequate, all biopsy tissue was submitted for H&E staining, immunoperoxidase and electron microscopic examination.

Results: 131 patients were found to have persistent non-visible haematuria during the evaluation period. 26.7% (35) were male and 73.3% (96) were female. 6.8% (9) were aged < 25 years, 61% (80) were aged 26-50 years and 32% (42) were aged > 51 years. Self reported ethnicity was Caucasion in 66.4%(87), Black in 8.4% (11), Asian in 9.1% (12), Mixed race in 2.2% (3) and ethnicity data was not available in 13.7% (18). 67.9%(89) of donors were genetically related to their recipient. 34.4% (45) were smokers, 54.2% (71) were non-smokers, 10.7% (14) were ex-smokers and smoking history was not available for 1 patient. 9.1% (12) of donors had pre-existing hypertension.

Among 131 renal biopsy specimens 4 were inadequate hence only H&E and immunoperoxidase examination was performed. The results of EM are awaited in 7 cases. Otherwise all 131 biopsies are included in this analysis. The final biopsy report was as follows: normal in 10.7%(14) of cases; Thin basement membrane lesion alone (TBML) in 17.6% (23); TBML with additional pathology in 31.3% (41) (TBM with IgA 5, IgM 6, interstitial fibrosis (TIF) and arteriosclerosis 13, mesangial hyper-cellularity 16, FSGS 1); Mesangial hypercellularity without immune deposits in 17.6% (23); IgA nephropathy in 3.8% (5); IgM nephropathy in 6.1%(8); other diagnoses in 12.9% (17) (TIF 9, FSGS 1, minor abnormalities 6, Alports 1). Among the 131 donors, 50 (38.2%) were excluded from donation on the basis of the biopsy findings, 14 (10.7%) await donation and 67 (51.1%) have completed donation. No donor has developed significant proteinuria during follow up and there was no significant decline in eGFR at 3 years compared to first year post donation value in the donors who have completed at least 3 years of follow-up (mean±SD 57.9±11.4ml/mt and 61.25±13.8ml/mt at 1 and 3 years respectively) .

Discussion: In this mainly female and Caucasian population with non-visible haematuria, TBML was the predominant finding on kidney biopsy, but other glomerular pathologies excluded kidney donation in almost 40% of patients. Donors with TBML have a favourable short-term outcome following donation.

Antibody Incompatibility

Tregonwell Hall (back)

9 March 2011

12:00-13:00

4

Effects Of Antibody To Human Leukocyte Antigen On Secretion Of VWF From Endothelial Cells

Athinoula Meli[1], Tom Carter[2], Ann McCormack[1], Matthew Hannah[2], Marlene Rose[1]

[1]National Heart and Lung Institute, Imperial College, Harefield Hospital, Harefield, London, United Kingdom, [2]National Institute for Medical Research, Mill Hill, London, United Kingdom

Antibody Mediated Rejection (AMR), caused by the presence of alloantibody on microvessels of the graft, is thought to lead to large vessel atherosclerosis or cardiac allograft vasculopathy (CAV) in heart transplant recipients. The mechanisms of endothelial damage are not well understood. Antibodies to HLA can bind to class I and class II molecules on the surface of endothelial cells (EC) and are thought to initiate signalling cascades. It has been suggested that antibody to HLA class I stimulates the release of von Willebrand Factor (vWF) from pre-formed storage organelles the Weibel Palade Bodies (WPBs) and that this may underlie thrombosis and inflammation in the graft. These studies used Enzyme–Linked Immunoassys to detect released vWF from cultured endothelial cells. Here we investigated the effect of monoclonal antibodies against HLA class I (W6/32) and class II (L2; anti-DQ) molecules on the release of vWF from primary Human Umbilical Vein EC (HUVEC), Human Aortic EC (HAEC) and Human Heart Microvascular EC (HHMEC) using a combination of biochemical and live cell imaging approaches. The kinetics and extent of WPB exocytosis, during exposure to W6/32, were analysed directly using high-speed live cell imaging in HAEC expressing the WPB specific marker Proregion-EGFP (VWF-propolypeptide-EGFP). HAEC were Fura-2 loaded allowing simultaneous visualisation of changes in $[Ca^{2+}]_i$ with WPB exocytosis.

A 1 hour incubation of HUVEC or HHMEC with 10μg/ml W6/32 did not evoke significant release of vWF above control (anti-CD3, 10μg/ml; assayed by specific ELISA). Similar results were found for 1 hour 10μg/ml L2 stimulation. In live cell imaging studies exposure of Proregion-EGFP expressing HAEC to histamine evoked increases in $[Ca^{2+}]_i$ and exocytosis of fluorescent WPBs. The time-course for WPB exocytosis evoked by 1 or 100μM histamine comprised mean delays (between the $[Ca^{2+}]_i$ rise and exocytosis) of 4.79±3.07s and 3.73±2.88s; mean maximal rates of WPB fusion of 0.98±0.70WPBs^{-1} and 1.52±1.73WPBs^{-1} and mean extent of degranulation of 19.00±12.8% and 29.90±11.18% respectively (mean±sd). No effect of pre-exposure (5 minutes) of HAEC to 10μg/ml W6/32 was found on the kinetics or extent of histamine-evoked WPB exocytosis. During exposure of Proregion-EGFP expressing HAEC to vehicle (physiological saline), 10μg/ml W6/32 or 10μg/ml anti-CD3 alone, irregular Ca^{2+} spiking was detected in 25% (6/24), 25% (4/40) and 39% (7/18) of cells studied respectively; however, there was little or no evidence of evoked WPB exocytosis.

These data show that W6/32 does not elicit significant WPB exocytosis or VWF secretion from the cultured ECs studied here and does not modify the action of the physiological secretagogue histamine. These data cast doubt on the idea that WPB exocytosis and VWF secretion evoked by exposure of ECs to HLA class I and class II antibodies alone underlie AMR. Future work will investigate whether antibodies to HLA class I and class II exert their effect on the endothelium in the presence of complement.

5

Antibody Kinetics following ABO Incompatible Renal Transplantation

Janet Lee[1], Liam O'Donohue[1], Jack Galliford[1], Gary Chusney[1], Andrew George[2], Tom Cairns[1]
[1]*Leslie Brent Laboratory, Imperial College Healthcare NHS Trust, London, United Kingdom,*
[2]*Department of Immunobiology, Imperial College, London, United Kingdom*

Introduction:

ABO incompatible (ABOi) renal transplantation at our centre is achieved by the use of pre- and post- transplant plasma exchange with Campath as our current induction treatment (previously Rituximab and Daclizumab). Graft survival occurs despite the return of ABO haemagglutinins, sometimes to levels higher than those pre-transplant. This phenomenon of rejection-free antibody/antigen co-existence is known as accommodation, but the mechanism is not fully explained, variously ascribed to acquisition of a protective endothelial phenotype or modulation of antigen. We have previously shown that some patients gain anti-ABO IgG sub-classes post-transplant that were absent pre-transplant. We have extended this study further with the aim of investigating a possible explanation for accommodation through changes in anti-ABO antibody binding kinetics post-transplant.

Methods:

Three patients have been studied to date, two with uncomplicated, rejection-free clinical courses post-transplant [both B into O], and one with early and recurrent rejection [A1 into B], treated successfully.

Serial pre- and post-transplant serum samples were used and surface plasmon resonance experiments were undertaken to determine the binding kinetics of antibody to synthetic blood group A and B antigens conjugated to HSA. Specifically, the off-rate constants (k*off*) have been established, as reflecting how transient binding is. The higher the k*off* the lower the affinity, since the affinity constant is k*on*/k*off*.

Results:

B into O transplants [n=2] The k*off* rates for anti-A and anti-B were measured for each patient: -12 days pre- to 355 days post-transplant and -12 days pre- to 136 days post-transplant. Neither of these patients experienced rejection. Anti-A k*off* rates did not alter during the pre- and post-transplant periods for either patient. The anti-B k*off* rates, however, increased in both patients, by 26% and 33% compared to pre-transplant rates, with the initial change seen by day 22 and day 136 respectively.

A1 into B transplant [n=1] This patient experienced early and recurrent rejection. The k*off* rates for anti-A decreased by 42% compared to pre-transplant, over the time course of 1 year, with an initial decrease of 8% occurring within the first 25 days.

Discussion:

We hypothesise that a heterogeneous antibody population is present in individuals against blood group A and B carbohydrate antigens and that following ABOi transplantation grafts survive because of a change in this pattern of heterogeneity reflected in antibody affinity and sub-class. Our very early data suggest that falling affinity (as reflected in k*off*) protects the graft, whereas a rising affinity is associated with rejection.

Towards Clonal Deletion Therapy – When Does the HLA Antibody Response Develop after HLA Antibody Incompatible Renal Transplantation?

Rob Higgins[1], Dave Lowe[2], Clare Collins[2], Nithya Krishnan[1], Rizwan Hamer[1,3], Daniel Zehnder[3,1], David Briggs[2]

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Introduction. It is possible to achieve excellent early graft survival in HLA antibody incompatible renal transplantation if the pre-treatment complement dependent cytotoxic (CDC) crossmatch is -ve. However, CDC +ve patients have poor results, and there is also medium term graft damage mediated by donor specific antibodies (DSA) in CDC-ve transplants. Clonal deletion therapy to stop DSA synthesis is desirable, but may consist of high intensity short acting therapy after donor specific stimulation of plasma cells. In this case, the timing of post-transplant deletion therapy would be critical to its success. Too early and the plasma cells may not be sensitive, too late and the response may be resistant. The aim of this study was to examine the timing of the antibody response early after HLAi renal transplantation.

Methods. Early changes in 176 DSA (Class 1, 89; DR, 40; DP, 9, DQ 26; DRB3-4, 12) in 78 patients who received HLAi renal transplants were examined. DSA were measured daily and we identified both the day on which DSA levels started to rise faster than 3rd party HLA antibodies, and also the day on which DSA first rose above pre-treatment levels.

Results. Of the 176 DSA, 97 (55%) showed a rise in blood levels faster than 3rd party HLA antibodies; this rate was similar for all classes of DSA except DP, though the sample was small (2/9 (22%) with increase). The increase started at a mean of 6.2 days post transplant, and is detailed in the Table. An increase in DSA above pre-treatment levels occurred in 78/176 (44.3%) DSA, at a mean of 8.2 days, detailed in the Table.

Day post transplant	1	2	3	4	5	6	7	8	9	10	11	12 +
First DSA increase	0	0	2	26	21	21	7	4	4	4	3	5
DSA > pre-treatment	0	0	0	1	9	13	19	11	7	4	4	10

Discussion. Under immunosuppression and with a graft in situ capable of absorbing antibody, post transplant DSA response was not observed in 45% of DSA, and when it did occur the rise most commonly started between days 4 and 6 post-transplant. An intensive post-transplant clonal deletion therapy may need to be delivered on an individualised basis according to the timing of the antibody response. Further understanding is required of the relationship between serum DSA levels and plasma cell activity when a transplant is in situ.

7

Clinical relevance of antibodies to denatured HLA antigens

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Introduction: Luminex technology is commonly used to detect HLA antibodies prior to transplantation. It is known that a proportion of the antigens on Luminex single antigen bead kits are in a denatured form. The aim of this study was to determine whether antibodies directed against denatured HLA antigens (dHLA) are detectable in Flow cytometric crossmatches (FXMs) and if they are associated with poor allograft survival.

Methods: Sera from 56 cardiothoracic transplant patients known to have HLA class I specific antibodies, were selected. All sera were tested by Luminex x-map single antigen bead assays (One Lambda). These were retested against single antigen beads treated with 0.3M Glycine pH2.6 to denature the HLA antigens. Antibody reactivity present in both the normal assay and the denatured assay indicates reactivity against dHLA, whilst reactivity against non-treated beads alone indicates reactivity against intact HLA (iHLA). FXMs using donor spleen cells mismatched for 1 or 2 antibody specificities were performed for 22 of the patient serum, including 11 with antibodies to dHLA.

Results: Antibodies directed against dHLA were found in 28/56 sera. In 10 of these the reactivity to dHLA accounted for the HLA specific antibody originally detected. 18 sera contained combinations of antibodies reactive with both iHLA and dHLA. The 11 FXM performed with HLA antibodies to denatured antigens were negative whilst the 11 FXM with antibodies to iHLA were positive $p<0.0001$. The graft survival at 1 year for patients with DSA against intact HLA (n=16) was 19% compared to 80% at 1 year for the 5 patients transplanted with DSA against dHLA ($p=0.0251$). There was a mean decrease in the calculated population reaction frequency (%cPRF) to intact HLA of 22% (range 0-99%) in the 28 patients with antibodies to dHLA;10 patients showed no reduction.

Conclusions: Antibodies to denatured HLA antigens do not result in a positive FXM and are not associated with poor one year survival. They should not be regarded as a contraindication to transplantation.

8

Preformed Anti-HLA -A, -B and -DR but not -DQ Complement-Activating Low-Level Donor-Specific Antibodies Predict Early Antibody-Mediated Rejection in Renal Allografts

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Donor-specific anti-HLA antibodies [DSA] are a major cause of alloimmune graft injury. Transplant recipients with negative complement-dependent cytotoxic crossmatch [CDC-XM] and flow cytometric crossmatch [Flow-XM] but who exhibit low level DSA [by Luminex] have worse outcomes compared to non-sensitized patients. The aim of this study was to establish whether the ability of pre-formed DSA to activate the classical pathway of the complement cascade is an important factor in dictating pathogenicity.

We retrospectively studied 52 patients [23m:29f, mean age 48.3 ± 11.8 years, 29 deceased donor: 23 live donor, 28 first graft: 24 subsequent graft] with pre-formed DSA detected by single antigen flow cytometric beads [SAFB]. 25 patients had class I DSA, 19 class II DSA and 8 both class I and class II DSA. Mean fluorescent intensity [MFI] of the sum of all DSAs was 3152 ± 2922. All patients were T and B cell CDC- and T cell Flow-XM negative and all patients received a steroid-sparing regimen consisting of alemtuzumab induction therapy, one week of corticosteroids and tacrolimus monotherapy.

Pre-transplant sera were retested with a modified SAFB assay using Dylight-549 labelled anti-C4d antibody to detect the presence of the complement fragment, C4d, deposited, presumably as a result of DSA-induced complement activation. 10/52 patients had C4d positive donor specific antibodies [$C4d^+$DSA], 29/52 patients had C4d positive non-donor specific anti-HLA antibodies [$C4d^-$DSA, $C4d^+$nonDSA] and 13/52 patients had no C4d positive antibodies [$C4d^-$DSA, $C4d^-$nonDSA].

Graft survival [censored for death with function] was 94.2% and 87.5% at 1 and 3 years. Two patients have died, one [with function] at 9 months, one [after graft loss] at 21 months. 14/52 [27%] patients experienced early, biopsy-proven antibody-mediated rejection [AMR]. AMR occurred in 6/10 [60%] $C4d^+$DSA, 7/29 [24%] $C4d^-$DSA, $C4d^+$nonDSA and only 1/13 [8%] $C4d^-$DSA, $C4d^-$nonDSA patients [log rank, p=0.003]. 5/6 $C4d^+$DSA patients experiencing AMR had anti-A, B or DR $C4d^+$ DSA, only 1/5 patients with anti-DQ $C4d^+$DSA experienced AMR [log rank, $p<0.0001$].

The main findings of this study are that 1] the presence of pre-formed anti-A, B or DR $C4d^+$DSA strongly predict the occurrence of AMR in patients despite a negative CDC- and Flow-XM [In this study all patients with preformed anti-A, B, DR $C4d^+$DSA experienced AMR] and 2] patients with anti-DQ $C4d^+$DSA are not at enhanced risk of AMR.

Current British Transplantation Society guidelines do not categorize patients with low-level preformed DSA with negative CDC- and Flow-XM as being at enhanced immunological risk. This study shows that some patients with low level pre-formed DSA are in fact at high immunological risk. The C4d SAFB assay may be used to identify these patients prospectively and allow intervention to address this risk, either by listing unacceptable donor antigens or by undertaking antibody removal and/or enhanced immunosuppression.

9

Can HLA Specific Antibody Tests Predict Acute Rejection?

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Introduction: Detection of HLA specific antibody (Ab) after kidney transplantation is strongly associated with subsequent immunological graft loss. The role of intensive testing as a screening strategy for early diagnosis of acute rejection is less clear.

Methods: Data from consecutive transplant recipients (1/2006-10/2009) were analysed at 12 months. Recipients with very early graft loss or incomplete follow-up were excluded (n=16). HLA specific Ab testing (Luminex) was performed prospectively at month 0,1,2,3,6,9 and 12. Patients with no new specificities (No New Ab) were distinguished from those with new Donor Specific Ab (DSA) and Non-Donor Specific Ab (NDSA). Biopsy proven acute rejection (BPAR) was the primary outcome; secondary outcomes included graft loss and eGFR.

Results: 57/196 recipients (29.1%) developed a new Ab specificity. 39% were Class I, 35% Class II and 26% Class I and II with no significant difference in HLA Class between DSA and NDSA (p=0.515). Other results are summarised below:

	DSA (n=16)	**NDSA (n=41)**	**No New Ab (n=139)**	**p**
Incidence (%)	8.2	20.9	70.9	
Female (%)	56	37	41	0.395
Regrafts (%)	19	17	15	0.903
Sensitised (%)	56.2	51.2	33.1	**0.036**
AB MM	2.56	1.46	1.73	**0.010**
DR MM	1.19	0.66	0.67	**0.037**
Graft Loss (%)	12.5	0.0	2.2	**0.021**
eGFR	41.1	45.7	48.4	0.282
BPAR (%)	37.5	19.5	6.5	**0.001**
Acute AMR (%)	25.0	2.4	0.0	**0.001**

The strong relationship between new HLA specific Ab and BPAR was confirmed in a multivariate model corrected for HLA mismatch, gender, and sensitisation (Odds Ratios: DSA 4.6[1.5-13.9], NDSA 3.1[1.2-8.1]). However, considering HLA specific Ab detection (DSA+NDSA combined) as a screening test for BPAR yields a positive predictive value (PPV) of only 25% (38% for DSA alone) and a negative predictive value (NPV) of 94% (91% for DSA alone). Ab detection occurred prior to BPAR in 5/23 cases. If only Ab detection prior to BPAR is considered as a true positive, the PPV is 10.4% and the NPV is 87.8%.

Conclusions: The utility of Ab testing in clinical practice depends on its role in the diagnosis of AMR, its NPV for rejection and its ability to predict later immunological graft loss. HLA specific Ab is often detected at the time of rejection or afterwards and many patients with new specificities do not reject. This limits the PPV of Ab detection as a screening test for BPAR despite the strong statistical relationship.

Pancreas / Immunosuppression

The Purbeck Lounge

9 March 2011

12:00-13:00

10

Percutaneous Ultrasound-Guided Biopsy of Pancreas Allograft: It Is Both Safe and Diagnostic

Jolene Witherspoon, David Martin, Michael Stephens, Audrey Yong, David Griffiths, Dawn Chapman, Kymm O'Connor, Argiris Asderakis

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Introduction

Monitoring a pancreatic allograft for rejection is difficult, particularly in patients who have not received a kidney from the same donor. Percutaneous ultrasound-guided biopsy to allow histological interrogation is an accepted technique but there are few published data on its safety and clinical role. The aim of this study was to assess the outcome from pancreatic allograft biopsy in terms of complications and diagnostic yield.

Methods

Twenty-five percutaneous US-guided biopsies of pancreatic allografts were performed on 15 patients in a single centre between April 2008 and September 2010. Ten biopsies were from recipients of Simultaneous Pancreas and Kidney (SPK) transplants, 11 from Pancreas After Kidney (PAK) transplants and 4 from Pancreas Transplant Alone (PTA) recipients. Of the 10 biopsies from SPK recipients, 7 had a concurrent renal biopsy. The indication for biopsy was hyperamylasaemia in 17 (68%) cases, hyperglycaemia in 5 (20%), renal dysfunction in 1 (4%) case, and protocol surveillance for high immunological risk recipients in 2 (8%).

Results

The biopsies were performed a median of 12 months (range 1-50) post transplant. One procedure was abandoned due to patient discomfort without obtaining a specimen. Of the remaining 24 a histologically satisfactory sample (according to the Banff schema) was achieved from 22 biopsies (92%). There was only one complication; a case of mild, self-limiting allograft pancreatitis following the procedure that had to be abandoned due to patient discomfort. Eight biopsies showed acute cell mediated rejection (ACMR, 6 Banff grade I, 4 Banff grade II), 3 showed antibody mediated rejection (AMR), 2 showed severe chronic rejection, 2 were indeterminate, and 7 (28%) showed no rejection. Of the 7 cases where a concurrent renal biopsy was taken, 3 showed histological discordance between the pancreatic and renal biopsies; in 2 cases the renal biopsy showed no rejection but the pancreatic biopsy showed ACMR, and the third case showed borderline rejection in the kidney but grade II ACMR in the pancreas. Three of the biopsies stained positively for C4d.

Discussion

In this series percutaneous US-guided biopsy of pancreatic allografts achieved a high diagnostic yield and complications were rare. Positive clinical information was identified in over 70% of cases. Concurrent biopsy of both kidney and pancreas grafts should be considered in SPK recipients as histological discordance is common.

11

Pancreas transplantation from donors after cardiac death: A single centre experience

Anand Sivaprakash Rathnasamy Muthusamy[1], Anil Vaidya[1], Sanjay Sinha[1], Jens Brockmann[3], Isabel Quiroga[1], Peter Friend[1,2]

[1]Oxford Transplant Centre, Churchill Hospital, Oxford, Oxfordshire, UK, [2]University of Oxford, Oxford, Oxfordshire, UK, [3]University Hospital Zurich, Zurich, Switzerland

Introduction: The expanding pancreas donor pool has recently included donors after cardiac death (DCD). This article summarizes a single centre experience with transplanting pancreases from controlled DCD (Maastricht III & IV).

Methods: From August '04 to November '10, 385 pancreas transplants were performed: 54 from DCD and 331 from donors after brainstem death (DBD). DCD pancreases were accepted based on donor age <60 years, BMI <32, and time to cardiac arrest from withdrawal <1 hour. All grafts had enteric exocrine and caval venous drainage. All patients received steroid-free maintenance with Tacrolimus & MMF; Campath ± Thymoglobulin was used as induction. Kaplan-Meier estimates were used to compare graft & patient survival.

Results: There were 17 SPK, 22 PTA and 15 PAK from DCD; 267 SPK, 33 PAK and 31 PTA from DBD, resulting in significantly more isolated pancreases (PAK & PTA) from DCD (p=0.0001). DCD had 12 months median follow-up (range 1-45) and DBD had 30 months' follow up (range 1-81). DCD and DBD recipients were of similar age (43±9 vs. 43±8) and body mass index (25±2.9 vs. 25±5). DCD donors were younger (33±12 vs. 37±13, P=0.03) but had similar BMI as DBD (23±3vs. 24±4). Average initial warm ischemia in DCD was 12 mins (0-21). DCD donors had less vascular cause of death (33% vs. 52%, p=0.02). DCD pancreases had longer cold ischemia (746±147 vs. 683±169 mins, p=0.008). DBD pancreas grafts had better overall survival (83% vs. 78%, p=0.03) primarily due to differences in isolated pancreas graft survival (79% DBD vs. 68% DCD, p=0.08); pancreas survival in SPK and overall patient survival was similar in both cohorts (94% DCD vs. 84% DBD, p=0.5), (95% DBD vs. 96% DCD). DCD pancreas thrombosis was more frequent than DBD grafts (11% vs. 1%, p=0.0008). DCD SPK kidneys had more frequent delayed graft function (DGF) than DBD SPK (29% vs. 11%, p=0.02). DCD pancreases had more frequent DGF (requiring insulin at discharge) than DCD pancreases (13% vs. 2%, p<0.0001). DCD grafts had similar incidence of PNF of the kidney (0% vs. 1%, P=NS) and of the pancreas (2% vs. 1%, P=NS). Re-operation (DCD 28% vs. DBD 19%, p=NS) and re-admission (13% vs. 16%, p=NS) were similar.

Discussion: DCD have a higher rate of early graft loss, primarily due to thrombosis. The differences in overall pancreas survival are explained by the higher percentage of isolated pancreases in the DCD cohort, known to have inferior survival to SPK.

Conclusion: Excellent early results from SPK in DCD suggest that the DCD cohort is a good source for pancreases, if performed simultaneously with a kidney. Further studies at understanding DCD pancreas thrombosis could increase the options for isolated pancreas recipients.

12

The Pancreas Allograft: The Impact Of The Retrieval Centre On The Utilisation Of The Organ

Anna Rizzello, Anand Muthusamy, Sanjay Sinha, Doruk Elker, Isabel Quiroga, Anil Vaidya, Peter J Friend

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Introduction: The pancreas allograft is a precious resource and is the least utilised of all abdominal organs. It is also considered to be one of the most technically challenging organs to recover. Successful retrieval and subsequent utilisation is dependent on intraoperative assessment and meticulous recovery of the organ by experienced surgeons. The aim of this study was to evaluate the impact on transplantation rate of the pancreas when procured by the same team as opposed to when retrieved by a different team

Methods: The existing NHSBT database was interrogated for the period, January 2004 to April 2010m to evaluate all pancreas grafts retrieved by one team. The dataset included type of the organ donor, whether a deceased brain dead donor (DBD) or a deceased cardiac donor (DCD). The data highlighted whether the organ was retrieved for use by the retrieving centre or for another centre, whether it was utilised and the reasons for discard.

Results: During this period the retrieving centre attended 407 pancreas donors. This comprised of 348(85.5%) DBD donors & 59(14.5%) DCD donors. Of these 323 (79.4%) pancreases were intended for use by the retrieving centre. 84(20.6%) organs were retrieved for other transplant centres. 239(73.9%) pancreas were transplanted by the same team. 51(60.7%) organs were used by other centres. The overall discard rate was 28.7%, 49% (29/59) for DCD donors while that of DBD donors was 25.2% (88/348). The common reasons for discard were a fatty organ (6.3%, 26/407), no cause specified (5.6%, 23/407), long cold ischemia (5, 1.2%), organ damage (5, 1.2%) etc. During the same period 221 pancreases were retrieved by other transplant centres for the retrieving Centre. Of these 111(50.3%) were transplanted. The main reasons for non-utilisation were fatty organ (5.8%, 13/221), damage (4.5%, 10/110) etc..

Conclusions: Pancreas utilisation is more when the retrieving and the transplant centre are the same (73.9% vs 50.3%). The exact reason for this needs analysis but is likely to be related to donor selection, confidence on the retrieving centre's assessment of the organ and procurement. This data is interesting in light of the National Organ Retrieval Service (NORS) taking over the responsibility for organ recovery in the UK in April 2010, which will increase the separation between the retrieving and transplant centre. Revisiting this data in the NORS era will help assess any likely effect and may confirm the rather subjective nature of pancreas assessment.

13

Belatacept vs Cyclosporine in Kidney Transplant Recipients: Two-Year Outcomes from the BENEFIT Study

Christian Larsen[1], Josep Grinyó[2], Bernard Charpentier[3], José Medina Pestana[4], Nassim Kamar[5], Yves Vanrenterghem[6], Chen-Sheng Lin[7], Greg Di Russo[7], Pushkal Garg[7], Flavio Vincenti[8]

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Introduction: Belatacept-based regimens were associated with superior renal function and similar patient/graft survival vs cyclosporine (CsA) at 1 year in the BENEFIT study, despite increased acute rejection (AR) in the early post-transplant period. The current analysis assesses pre-specified outcomes from BENEFIT in the intent-to-treat population after 2 years of treatment.

Methods: Patients were randomised 1:1:1 to a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids.

Results: 666 patients were randomised and transplanted; 493 completed 2 years on treatment. Patient/graft survival was similar across groups (94% MI; 95% LI; 91% CsA) at Year 2. The superior renal benefit of belatacept-based regimens was sustained through Year 2, as evidenced by a 15–17 ml/min higher measured GFR ($p<0.0001$ MI or LI vs CsA) or calculated GFR in the belatacept groups vs CsA. There were 8 additional patients with an AR episode between Years 1 and 2 (n=4 MI; n=4 CsA). The improvements in the cardiovascular/metabolic risk profile vs CsA were sustained, and an additional benefit on LDL-cholesterol emerged at Year 2 ($p\leq0.002$ MI or LI vs CsA). The overall incidence rate of malignancies and serious infections remained comparable across groups. There were 2 previously reported cases of PTLD between Year 1 and Year 2 in the MI group (total cases in BENEFIT through July 2009: n=3 MI; n=2 LI; n=1 CsA). The overall safety profile remained similar across groups.

Conclusions: At 2 years, a belatacept-based regimen demonstrated sustained superior renal function and similar patient/graft survival vs CsA. There was no additional efficacy gained by using the MI regimen vs the LI regimen. No new safety signals emerged. Belatacept is a promising therapeutic option in kidney transplant patients.

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Belatacept vs Cyclosporine in ECD Kidney Transplants: Two-Year Outcomes from the BENEFIT-EXT Study

Antoine Durrbach[1], Christian Larsen[2], José Medina Pestana[3], Yves Vanrenterghem[4], Flavio Vincenti[5], Sander Florman[6], Jun Xing[7], Alan Block[7], Pushkal Garg[7], Josep Grinyó[8]

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Introduction: Belatacept-based regimens were associated with better renal function, with comparable patient/graft survival and acute rejection (AR) vs a cyclosporine (CsA)-based regimen in ECD kidney transplant recipients at 1 year in the BENEFIT-EXT study. The current analysis assesses outcomes from BENEFIT-EXT in the intent-to-treat population after 2 years of treatment.

Methods: Patients were randomised 1:1:1 to a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids.

Results: 543 patients were randomised and transplanted; 347 completed 2 years on treatment. Patient/graft survival was similar across groups (83% MI, 84% LI, 83% CsA) at 2 years. The renal benefit of belatacept was sustained at Year 2 as assessed by mGFR (52 ml/min MI, 50 ml/min LI, and 45 ml/min CsA; p=0.028 MI vs CsA; p=0.108 LI vs CsA) and cGFR (8–10 ml/min higher in the belatacept groups vs CsA). There were 3 additional episodes of acute rejection after Year 1 (n=1 LI; n=2 CsA). The cardiovascular/metabolic risk profile benefits of belatacept vs CsA on serum lipids and blood pressure were sustained. The overall incidence rates of malignancies and serious infections remained comparable across groups. There were 2 previously reported cases of PTLD between Years 1 and 2 (n=1 each MI and LI; total cases through July 2009 in BENEFIT-EXT: n=2 MI; n=3 LI; n=0 CsA). The overall safety profile remained similar across groups.

Conclusions: A belatacept-based regimen maintained better renal function, a better cardiovascular/metabolic risk profile, and similar patient/graft survival vs CsA at 2 years. There appeared to be no additional efficacy gained by using the MI regimen vs the LI regimen. No new safety signals emerged. Belatacept is a promising option in patients receiving ECD kidneys.

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Conversion To An Everolimus/Enteric-Coated Mycophenolate Sodium Regimen In *De Novo* Renal Transplant Improves 2 Year Renal Function

Wolfgang Arns[1], Thomas Becker[2], Klemens Budde[3], Ute Eisenberger[4], W Fischer[5], S Kramer[5], Claudia Sommerer[6], P Reinke[3], Frank Pietruck[7]

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Objective In *de novo* kidney allograft patients (pts) renal function, efficacy and safety was assessed after conversion to an Everolimus/Enteric-coated mycophenolate sodium (EC-MPS) regimen after Ciclosporin (CsA) withdrawal at M24 post-transplantation (tx).

Methods In this prospective, open-label, controlled, multi-centre study renal allograft pts were randomised to a regimen consisting of either Everolimus/EC-MPS or CsA/EC-MPS at M4.5 after tx. After completion of the core study at M12, pts were included in an observational 12 Month follow-up study.

Results 300 pts were randomised to either Everolimus (n=155) or CsA (N=145), 258 (86.0%) pts completed the M24 visit. Renal function expressed as cGFR (Nankivell method) was similar in both groups at M4.5 post –Tx with an improvement by 7.84 mL/min in favour of the Everolimus regimen (p=0.0042) at M24 (61.3 ± 17.2 vs. 69.2 ± 19.0 mL/min). The observed GFR slope from M4.5 to M24 was +6.5 [3.1, 10.0] for Everolimus and -1.1 [-4.8, 2.5] mL/min for CsA pts. Similarly GFR slopes with MDRD (+9.4 [4.0, 14.9] and Cockcroft-Gault formula (+7.0 [3.4, 10.6]) were significantly better (p<0.001) in the CNI-free regimen (CsA treated pts: MDRD: -0.8 [-6.2, 4.6] mL/min: Cockcroft-Gault: -1.2 [5.0, 2.6] mL/min). Fewer pts in the Everolimus group had a decline of GFR compared to CsA pts (Nankivell: 24.7% vs 41.4%; p=0.0034).

BPAR was reported in 17 (11.0%) Everolimus vs. 7 (4.8%) CsA pts between M4.5 and M24. After M12 two additional BPAR occurred in each group. Three deaths and one graft loss was observed in the CsA group, none in the Everolimus group.

The number of pts with infections (Everolimus 35 (22.6%) vs. CsA 30 (20.7%)) and hospitalisation (Everolimus 43 (27.7%) vs. CsA 51 (35.2%)) in the follow-up period (M12-M24) was comparable.

Conclusions The conversion to Everolimus in *de novo* renal transplant pts after CNI withdrawal early after tx significantly maintains renal function over a period of 24 months without compromising efficacy and safety.

Challenges in Transplantation: Infection

Tregonwell Hall (front)

9 March 2011

14:30-16:30

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A randomised placebo-controlled trial of cytomegalovirus glycoprotein B vaccine in renal and liver transplant patients

Paul Griffiths

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We conducted a randomised controlled trial to determine if a cytomegalovirus (CMV) vaccine given to patients pretransplant could control viraemia following renal or liver transplantation.

70 seropositive and 70 seronegative patients were randomised to receive placebo or CMV glycoprotein B (gB) vaccine plus MF59 adjuvant. Three doses were given at time 0, 1 month later and six months later, but no doses were given to patients who proceeded to transplant. No patient received prophylactic antiviral drugs; instead, preemptive therapy was used to prevent CMV disease post-transplant. Patients were monitored using serial whole blood samples processed by polymerase chain reaction. Any patient with a viral load greater than 3000 genomes/ml was given ganciclovir (or valganciclovir) until two consecutive negative polymerase chain reaction results had been obtained.

The vaccine was well tolerated, with pain at the site of injection the only side-effect significantly increased in vaccine recipients. After three doses of vaccine, the titre of anti-gB antibodies was similar to that found in natural seropositives. Administration of vaccine to natural seropositives significantly boosted their titre of anti-gB antibodies. The differences in antibody titres were still significantly different at the time of transplant among seronegative and seropositive patients. 78 patients were transplanted, 27 of whom developed viraemia. The titre of anti-gB antibodies correlated inversely with duration of viraemia. In the donor seropositive, recipient seronegative subset, the duration of viraemia and duration of preemptive therapy were significantly reduced.

We conclude that CMV infection is susceptible to pretransplant immunisation.

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Pre-emptive Therapy for the Prevention of CMV infection in Patients Post Solid Organ Transplantation: The Experience of a Single Teaching Hospital in London

Sowsan Atabani, Claire Atkinson, Robert Aldridge, Mark Harber, Vincent Emery, Paul Griffiths

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Introduction: Human cytomegalovirus (HCMV) is an important opportunistic pathogen, the cause of significant morbidity and some mortality among patients undergoing solid organ transplantation (SOT). Natural history studies have shown that the magnitude of CMV DNA detected in whole blood among patients post-transplant correlates with the development of CMV end-organ disease. The regular monitoring of CMV DNA, has developed into an alternative diagnostic tool among these patients, most recently with the introduction quantitative real-time PCR (qPCR), which is a sensitive method of detection and provides the clinicians with a timely result to allow necessary therapeutic intervention in a pre-emptive approach to CMV disease prevention.

Methods: A retrospective analysis of pre-emptive CMV therapy among prospectively followed 698 patients receiving a renal or liver transplant from July 2002 till January 2010. Routine monitoring for CMV DNA in whole blood using quantitative molecular methods was deployed for the first 90 days post-transplant and treatment only begun once a defined quantity of viral load was detected (3000 copies/ml) and discontinued following two consecutive negative PCR results. This pre-emptive strategy was also used for CMV seronegative recipients of organs from seropositive donors.

Results: Post-transplant, CMV viraemia developed in 38.8% of all liver transplant recipients and in 47.2% of all renal transplant recipients. Among the patients who developed viraemia, the peak viral load was 10-fold higher in the CMV seronegative recipients of organs from seropositive donors (D+R-) compared to seropositive recipients (D+R+), with a median viral load of 18,172 vs. 2,616 copies/ml in liver transplant recipients and a median viral load of 43,722 copies/ml compared to 1908 copies/ml in the renal transplant recipients. In addition, the duration of viraemia and the number of patients requiring anti-viral medication was significantly greater in our seronegative SOT recipients, indicating that pre-existing immunity plays a role in limiting CMV replication. 1.5% of liver transplant recipients and 1.1% of renal transplant recipients developed histologically confirmed CMV tissue invasive disease. Clinical drug resistance to CMV was not reported in any of the patients who became viraemic.

Discussion: In our experience this strategy was found to be safe and effective with no significant increase in the development of CMV tissue invasive disease post-transplant. Our study highlights the role of regular viral load monitoring and pre-emptive therapy in reducing the number of transplant recipients receiving unnecessary toxic anti-viral therapy. This study provides additional evidence on the beneficial effects of the use of a pre-emptive strategy to manage CMV infection following solid organ transplantation.

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Delayed Onset Cytomegalovirus Disease In A New Era Of Prolonged Valganciclovir Prophylaxis

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Introduction: Despite advances in Cytomegalovirus (CMV) diagnosis and treatment over recent years, delayed-onset primary CMV disease remains a significant burden to the management of high-risk kidney transplant recipients post-transplantation. Following evidence from the Improved Protection Against CMV in Transplant trial (ATC, 2009), the use of prolonged valganciclovir CMV prophylaxis has been adopted in some transplant centres. The aim of the present study is to assess the impact of prolonged valganciclovir prophylaxis on the incidence and outcomes of delayed-onset primary CMV disease in high risk kidney transplant recipients (D+/R- or D+R+ where D is donor and R is recipient).

Methods: Data from all CMV D+/R- and D+/R+ kidney transplant recipients between January 2006 and October 2010 at our centre was analyzed (n=213). From May 2009, our unit protocol extended valganciclovir prophylaxis from 3 to 6 months. Group 1 included all patients before May 2009 with a functioning graft at 3 months post-transplantation (PT) who received 3 months of valganciclovir prophylaxis 900 mg once daily (n=123), and Group 2 included all patients after May 2009 with a functioning graft at 6 months PT who received 6 months of valganciclovir prophylaxis 900 mg once daily (n=90). Outcomes of CMV disease included allograft function, allograft survival and patient survival over 12 months PT. CMV was diagnosed with quantitative PCR. Statistical analysis of data included Chi-Square contingency tests, Kaplan Meir survival plots and Cox proportional hazards regression, $p<0.05$ considered statistically significant.

Results: Prophylaxis was completed in 207 patients, and stopped in six patients 1-3 months prior to completion due to leukopenia or gastrointestinal side effects. The beneficial effect of prolonged valganciclovir prophylaxis on the incidence of late-onset CMV infection was apparent in Group 2, where the CMV rate was 14% (13/90) compared with 28% (39/123) in Group 1 (p=0.004). Logistic regression analysis, after adjustment for variables that influenced CMV incidence, showed that the odds of suffering delayed onset CMV infection were lower with prolonged prophylaxis (p=0.006). Mean peak viral load was lower in Group 2 patients at 882061 (SD: 1323981) copies/ml compared with Group 1 at 1820283 (SD: 5734522) copies/ml, but this difference was non-significant. Prolonged prophylaxis neither influenced graft-function, long-term graft survival nor patient survival.

Conclusion: This study supports growing evidence that the use of prolonged 6-month valganciclovir prophylaxis significantly reduces the incidence of late-onset CMV disease in high risk kidney transplant recipients. This practice merits consideration by other transplant centres.

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Long term clinical outcome of adoptive immunotherapy for PTLD using Epstein-Barr virus (EBV)-specific cytotoxic T cells (CTL)

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Background: Epstein-Barr virus (EBV) has been associated with post-transplant lymphoproliferative disease (PTLD). PTLD lesions occur in up to 10% of the transplant recipients and can be fatal in 50% cases despite treatment. We generated a bank of EBV-specific CTL lines from healthy blood donors and used these cell lines in a phase 2 multicentre clinical trial to treat PTLD on a best HLA match basis. The trial recorded a response rate of 52% in 33 trial participants at six months. Tumour response was associated with an increase in CTL/recipient HLA matches, higher percentage of CD4+ T cells and polyclonal distribution of TCR beta chain variable gene subfamilies 2, 3, and 9 within the infused CTL lines. Here we present the long-term outcome of our trial cohort.

Methods: We obtained follow-up data from 32 of the 33 trial participants 4-9 years after their last CTL infusion and compared the long-term clinical outcome of these patients with our data at 6 months. Data were collected on tumour response, relapse, further PTLD treatment, graft functions and survival of the patients 4 to 9 years after CTL therapy.

Results: In our initial analyses at 6 months, 17 of 32 patients were responders, of which 3 had partial response (PR) and 14 had complete response (CR). Fifteen patients showed no response (NR). Follow-up data at 4-9 years showed that all those in the PR and NR groups, but none in the CR group, required further treatment for PTLD after CTL therapy. Of the 19 surviving trial participants, 13 (68%) were responders (12 CR, 1 PR) and 6 (32%) were NR at 6 months. In contrast, of the 13 patients who have died, 9 (69%) were NR and 4 (31%) were responders (2 PR, 2 CR) at 6 months. There was a significantly increased survival rate among the PR/CR group compared to the NR group ($p=0.018$).

Conclusions: Our clinical trial showed third-party CTL therapy for PTLD to be safe and effective in the short term, and this 4 to 9 year follow-up data show that CTL induce long term remission of PTLD in patients with refractory disease. We are generating a new bank of clinical-grade EBV-specific CTL under good manufacturing practice conditions to provide partially matched CTL widely.

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Evolving Experience with Donor Lung Bronchoalveolar Lavage

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Introduction

We perform on-table bronchoalveolar lavage (BAL) of donor lungs for microbiological culture before implantation. Our previous study (for the period 1997-2001) demonstrated that positive lower airway bacteriology predicted poor recipient outcome. We seek to review our practice and demonstrate a continued but evolving role for this investigation.

Methods

A retrospective review of transplant and microbiology databases for all cadaveric lung and heart/lung transplants between September 2001 and December 2009.

Results

Out of 368 transplants, 360 (98%) received a BAL. Recipient age 10-66years. Bilateral lung 61%, single lung 34% and heart/lung 5%.

Organisms were present in 43% of samples, similar to our previous study (46%). The majority (72%) grew 1 organism, maximum 4. 137 (89%) were bacterial (58 Gram positive, 52 Gram negative, 27 both). 10 (6%) fungal and 7 (5%) mixed growth. Positive culture was not related to donor age, intubation time or gas exchange.

Overall survival and length of ITU stay were no longer predicted by BAL result, or by presence of Gram –ve organisms. Suppurative lung disease accounts for 40% of our patient demographic. Comparison with non-suppurative patients shows a significant difference persists only in the latter. Positive BAL culture has a significant impact on 1 year survival for non-suppurative patients – 83% BAL negative/ 71% positive ($p=0.034$) and also significantly lengthens their ITU stay – BAL negative 3 days/ positive 5 days ($p=0.0227$). Median date to discharge is 23 days in negative patients and 26.5 days in positive patients.

Discussion

In this large updated cohort of patients we have demonstrated no change in the rate of positive culture, despite the increased use of marginal donors. In contrast to infected recipients who receive broad-spectrum antibiotics pre-operatively, non-suppurative patients continue to do less well with colonised donor lungs. This suggests the need for more aggressive use of anti-bacterial agents which can be guided by BAL results, reflecting the true state of the lung parenchyma.

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Benefit–Risk Profile of the Belatacept LI Regimen at 2 Years in EBV(+) Kidney Transplant Recipients

Flavio Vincenti[1], Josep Grinyó[2], Christian Larsen[3], José Medina Pestana[4], Yves Vanrenterghem[5], Tao Duan[6], Mamta Agarwal[6], Bernard Charpentier[7]

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Introduction: Belatacept was studied in one Phase II and two Phase III renal transplant trials (BENEFIT and BENEFIT-EXT), each of which included a more intensive (MI) and less intensive (LI) regimen. The two belatacept dosing regimens had comparable efficacy but the safety profile of the LI regimen was better than the MI regimen. There was an increased risk of PTLD, specifically CNS PTLD, in the belatacept groups; the increased risk of CNS PTLD was concentrated in EBV(–) patients and in the MI regimen. A subgroup analysis was performed to evaluate the benefit–risk profile in EBV(+) patients who received the belatacept LI regimen.

Methods: Efficacy results from the PIII studies are presented individually since they enrolled different study populations. Safety data from the Phase II and III studies were pooled to provide added sensitivity for detecting safety signals for rare events.

Results: In the 3 studies, 85% (1204/1425) of the study population was EBV(+) at baseline. The results of the EBV(+) analysis (presented in this abstract) were generally consistent with the results in the overall study population. By Month 24, fewer patients died or lost their graft in the LI group compared to CsA in each Phase III study. In BENEFIT, the mean measured GFR (mGFR) was 72 ml/min in the belatacept LI group and was 52 ml/min in the CsA group; in BENEFIT-EXT, the mean mGFR was 50 ml/min in the belatacept LI group and 46 ml/min in the CsA group. Belatacept LI was associated with fewer patients reaching CKD stage 4/5 (ie, GFR <30 ml/min) in both studies. There were more cases of acute rejection in the LI group compared to CsA in each Phase III study. There were fewer serious infections in the LI group in the pooled analysis. There were 4 cases (1%) of PTLD observed with the LI regimen in the EBV(+) population (2 renal, 2 CNS; each 0.5%) compared to none in the CsA. Although there were more cases of PTLD in the LI group, the absolute risk of PTLD was low in EBV(+) patients, and overall malignancies were similar with LI compared to CsA.

Conclusions: By 24 months, fewer deaths and graft losses occurred among EBV(+) patients in the belatacept LI group compared to CsA, despite an increased incidence of acute rejection and PTLD. In both Phase III studies, belatacept LI was associated with better renal function and with fewer patients reaching CKD stage 4/5. This analysis supports a favourable benefit/risk profile of the belatacept LI regimen in EBV(+) patients.

Innate Immunity

Tregonwell Hall (back)

9 March 2011

14:30-16:30

Porcine model of extra corporeal membrane oxygenation (ECMO) in the uncontrolled non-heart beating donor; the effect on renal viability

Christopher Ray[1,2], Aditya Kanwar[1,2], Mohammed Saleem Noormohammed[1,3], Stephen Ray[1], Susan Stamp[2], Soroush Sohrabi[1,2], Alex Navarro[1,2], Katrina Wood[3], Kath White[3], Bob Peaston[1], Anne Cunningham[2], Steve White[1,3], Noel Carter[2], Jon H Smith[1], David Talbot[1]

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Aims: We sought to compare the effect of ECMO on renal viability in a Maastricht Category II donor model, with our current standard; intravascular flush and intra-peritoneal cooling.

Methods:

•Using cross-Yorkshire-landrace pigs (n=11), we studied 2 groups. Under general anaesthetic, an initial laparotomy for probe placement and cannulation was performed.

• All animals were euthanased, and subjected to 30mins of warm ischaemia.

• Both groups were then administered thrombolysis

• In the 'Cooling' group(n=5), intravascular flush was administered, with peritoneal cooling, over a 2-hour period.

• In the 'ECMO' group(n=6), a primed extra-corporeal oxygenation circuit was commenced at this stage. The abdominal organs were perfused with oxygenated normothermic blood for 2hours.

• After this 2-hour period, the abdomen was re-opened, iced and organs retrieved.

• Throughout the period of intervention microdialysis catheters in the solid organs measured ischaemic markers.

• The kidneys underwent viability testing on cold machine perfusion (Lifeport) for 2-hours.

• After 18 hours cold machine perfusion they were each re-perfused on an ex-vivo oxygenation circuit to simulate transplantation and re-animation. The circuit was purpose built and allowed further assessment of viability.

Results

• In all parameters of viability testing the `ECMO organs' appeared superior to `Cooling organs'

• Renal arterial resistance is known to be indicative of organ damage, Glutathione-S-Transferase is a marker of cell damage and an increasing lactate-pyruvate ratio is a marker of anaerobic metabolism and cell damage

• Analysis of the trends with a repeated measure ANOVA revealed a significant difference between the groups for level of Glutathione-S-Transferase ($p<0.01$), renal resistance ($p<0.05$) but no significant difference for mean Lactate/Pyruvate Ratio.

Kidneys in the combined intravascular and intra-peritoneal `cooling' group demonstrated more severe histological ischaemic damage than the ECMO group. Mean score for the ECMO group was 3.3 (sd+/- 1.5) versus `Cooling group' mean 5.4 (+/- 1.8) $p < 0.01$.

Electron microscopic examination revealed more severe damage in the cooling group. Mean glomerular foot process width (FPW) was 538ηm (+/- 45) in the ECMO group versus 702ηm (+/- 58) in the cooling group, $p< 0.05$.

Conclusion

Initial results from this animal model suggest that extra-corporeal membrane oxygenation, applied in a Maastricht Category II donor model, is superior to combined arterial and peritoneal cooling in preservation of renal viability.

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Donation After Cardiac Death: Can Hearts Be Successfully Reanimated?

Muhammad Khurram[1], Omar Mownah[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]

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Introduction: The success of organ donation after cardiac death (DCD) has yet to extend into cardiac transplantation. Rescuing hearts from donors after cardiac death would allow significant expansion of the donor pool. This study used an *ex vivo* circuit to reperfuse porcine hearts in a simulated DCD model with the aim of restoring myocardial activity, testing various combinations of both established and novel perfusion solutions.

Materials and Methods: Eleven cross-Yorkshire Landrace pigs (mean weight 29.4kg +/- 5.7) were euthanased humanely by Schedule-1 (intravenous administration of phenobarbitone). The non-beating hearts were procured after being subjected to 10 minutes of warm ischaemia. All hearts (n=11) underwent initial antegrade flush with 250mls of AQIX® RS-I solution (a novel non-phosphate pH buffered preservation solution) at ambient room temperature. Hearts 3 to 11 were flushed with a further 250mls of either cold AQIX® RS-I (n6) or cold University of Wisconsin (UW) solution (n3). Static cold storage was in either AQIX® RS-I (n6) or UW solution (n5). 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, which was measured by ultrasonic probes on the left ventricular outflow.

Results:

n	Flush / preservation	Drugs	Cardioversion	Activity/pressure
1, 2	250mls RS-I[1] / RS-I[2]	None	None	Fibrillation only; nil ventricular contraction
3, 5, 6	250mls RS-I[1] + 250mls RS-I[2] / RS-I[2]	Adrenaline	Yes	Ventricular contractions/70mmHg *n4 nil activity*
7, 8	250mls RS-I[1] + 250mls UW[2] / RS-I[2]	Adrenaline, Ca gluconate	Yes	Ventricular contractions/90mmHg
9,11	250mls RS-I[1] + 250mls UW[2] / UW[2]	Adrenaline, Ca gluconate	Yes	Ventricular contractions/40mmHg *n10 nil activity*

1 - ambient room temperature; 2 - 4-8°C

Discussion:

Hearts sourced from DCD donors can be successfully reanimated. Factors influencing successful reanimation included adequate coronary flush, administration of adrenaline and DC cardioversion. Restoration of cardiac activity was achieved using both a conventional (UW) and novel perfusion solution (AQIX® RS-I). Further studies are needed before hearts procured from DCD donors can be incorporated into mainstream cardiac donation.

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Prevention of Thrombosis using Novel Anticoagulant Proteins in a Machine Perfused Porcine Renal Thrombosis Model

Karim Hamaoui[1], Samir Damji[1], Richard Smith[2], Anthony Dorling[2], Vassilios Papalois[3,1]

[1]Deptartment of Surgery, Imperial College London, London, United Kingdom, [2]MRC Centre for Transplantation, King's College London, London, United Kingdom, [3]West London Renal & Transplant Centre, Hammersmith Hospital, London, United Kingdom

Introduction:
Kidney transplantation is one of the most well established solid organ transplant procedures, with high success rates for patient and graft survival. Never the less, kidney allograft thrombosis is implicated in 2-7% of all cases of early graft loss in adults, and up to 35% in children. Pathogenesis of kidney allograft thrombosis is related to donor and procedural risk factors, organ procurement and preservation techniques, ischaemia/reperfusion injury, and inherent recipient hypercoagulability. Additionally grafts from 'marginal' donors are at higher risk for developing thrombosis. At present the only preventative measure in place is to provide systemic anti-coagulation, which confers a risk of bleeding. We have developed a porcine ex-vivo renal perfusion thrombosis model using autologous whole blood as the perfusate. We have used this model to test a series of novel anticoagulant hirudin based fusion proteins with endothelial binding properties. We hypothesise graft pretreatment with these proteins will ameliorate deteriorations in perfusion seen in the thrombosis model. We report our preliminary results. Methods: Eight porcine kidneys were retrieved from cadaveric pigs at a local abattoir. All were flushed with UW solution and placed on ice for transport to the laboratory (WIT=15 minutes, CIT=4-5h). Kidneys were placed on a modified Waters Medical RM3 perfusion device and perfused for 4h with UW solution at 4^{o}C. Kidneys were then perfused for 90 minutes with either HTK with a quantity of fusion proteins (Protein Test Kidneys, PT n=4) or unmodified HTK (Thrombosis Controls, TC n=4). All kidneys then underwent normothermic perfusion for 6h with autologous whole blood. Perfusion parameters were measured throughout.
Results:
Kidneys demonstrated similar stable flow rates (31.6 vs 27.1 ml/min/100g), resistances (0.76 vs 0.73 mmHg/ml) at accepted systolic perfusion pressures (47.3 vs 46.5 mmHg);TC vs PT kidneys respectively ($p>0.2$) during perfusion with UW solution. During perfusion with autologous normothermic blood PT kidneys demonstrated significantly less deterioration in flow rates and resistance indices compared to controls, with a mean decline in flow rates of 5.3% vs 29.3% ($p<0.05$), and mean increases in resistance of 17.9% vs 59.3% ($p<0.05$).
Conclusion:
Initial data from this project demonstrate that kidney graft pre-treatment with novel anticoagulant fusion proteins results in an amelioration of deterioration in perfusion dynamics seen in an ex-vivo thrombosis perfusion model. Our data suggests that there is potential for the development of an applicable strategy to provide local active anti-coagulant agents directly into the renal allograft and potentially decrease the incidence of thrombosis while avoiding the use of systematic anti-coagulation. Further work is continuing to delineate optimal dose requirements, protein pharmacokinetics, and histological outcomes.

Joint BASL/BTS Symposium

The Purbeck Lounge

9 March 2011

14:30-16:30

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ABO Mismatch an underutilized resource in pediatric liver transplantation (PLT)

Diego Davila, Ruben Ciria, Georgina Mieli-Vergani, A Dhawan, Hector Vilca-Melendez, Mohammed Rela, Nigel Heaton

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INTRODUCTION:

Organs Shortage continues to be a problem even in children despite split and living donors. ABO mismatched grafts have been proposed to increase transplantation in children in urgent situations.

PATIENTS AND METHODS:

Retrospective analysis of PLT with ABO-m from 1991-2009. Descriptive study: Proportion (chi-square Fisher test) and median-range (Mann-Whitney test) comparisons. Survival: Kaplan-Meier log-rank test. Statistically significance: $P<0.05$.

RESULTS: Fifteen PLT with ABO-m grafts were performed. Median age: 9 months (0,1–25). Diagnoses: Biliary atresia (33.3%), Acute-Liver-Failure for neonatal haemocromatosis (26.6%), and ALF of unknown causes 13.3%. Others: Familial-Iintrahepatic-Cholestasis, Alpha 1-antitrypsin deficiency and unresectable hepatoblastoma. The ABO-m was A:O= 8 (53%), B:O= 5 (33%), AB:B= 1 (6,7%) and B:A= 1 (6,7%). Immunosuppression protocol: tacrolimus with steroids (57,1%), tacrolimus with MMF and steroids (28,6%); tacrolimus and MMF (7,1%) and basiliximab and tacrolimus (7,1%). Plasmapheresis or splenectomy were not performed. Type of grafts: Donor-after-Brain-Death: 93.3% (4 whole organs, 10 Left-Lateral-Segment), one Donor-after-Cardiac-Death (reduced using the LLS). Three patients had acute cellular rejection confirmed histologically; one diffuse cholangiopathy. 1and 6-months, 1and 5-years graft survival were 93, 3%, 80%, 80% and 80%, respectively. No statistically significant differences were observed among variables studied in appearance of rejection. Age at transplant was a risk factor for graft survival. There were statistically significant differences in 1-year graft survival in patients <11 months (100%) and >11 months (40%). There were statistically significant differences in the median AST levels in the 2nd post-transplant day in the 1-year alive and dead.

CONCLUSIONS: PLT using ABO-m livers is a safe option in patients <11 months which can help to reduce waiting list mortality rates in children with decompensated liver disease

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Pediatric liver transplantation using donors with cardiac death: A feasible option with excellent results.

Ruben Ciria, Diego Davila, Wayel Jassem, Hector Vilca-Melendez, Mohamed Rela, Nigel Heaton

Institute of Liver Studies. King's College Hospital, London, United Kingdom

INTRODUCTION: Pediatric liver transplantation (PLT) is a common indication with high rates of death on waiting list due to the lack of donors. Donors with cardiac death (DCD) is becoming an increasing source of grafts.

PATIENTS AND METHODS: Retrospective analysis of King's College hospital experience in PLT (<16 years) with grafts from DCD. Descriptive comparisons: proportions (chi-square-Fisher test), medians-range (U-Mann-Whitney test). Statistical significance:$P<0.05$

RESULTS: Nineteen PLT with DCD have been performed in our Unit. Male to female ratio=10/9. Median recipient age and weight were 3.4 years (9 months-14 years) and 16.29 kg (4.9-56). Etiologies were: acute liver failure-ALF (2), extrahepatic biliary atresia (7), hemangioendothelioma (1), primary familial intrahepatic cholestasis (2), Langerhans cell histiocytosis (1), Factor VIII deficiency (2), Primary hyperoxaluria (1), neonatal sclerosing cholangitis (2) and unresectable hepatoblastoma (1). Graft distribution was: 7 whole, 9 left-lateral-segment (2 splits and 7 reduced), 2 left-lobes and 1 right-lobe (auxiliary graft). Seventeen cases (89.4%) presented as chronic liver disease; 2 (10,6%) were ALF. Median cold, donor-warm and recipient-warm ischemia times were 7.3 hours (4.4-12), 14 minutes (10-29) and 36 minutes (24-80), respectively. Median Graft-recipient-weight-ratio (GRWR) was 3.58 (1.38-7.03) with significant differences between whole (3.26 [1.76-7.03]) and partial grafts (4.83 [1.38-5.7]) ($P=0.036$). Median operation time was 4.8 hours (3.5-7.5). Donor age, weight, ITU stay and inotropes-use were 16 years (10-64), 56 kg (28-85), 4 days (0-14) and 47.4%, respectively.

One-, 3-, 12-months and 5-years patient survival is: 100%, 94.7%, 94.7% and 94.7%, respectively. There were 9 cases with rejection, 2 of which happened in ABO incompatible recipients. No cases of rejection happened in the ABO compatible group. Portal and arterial reperfusion was performed in 15 and 4 cases, respectively. Statistically significant differences were detected in AST in the second (908 [179-2100] vs 285 [263-355]; $P=0.037$) and third (301 [109-1579] vs 154 [123-185]; $P=0.037$) post-transplant days and in INR in the second post-transplant day (1.5 [1.3-2] vs (1.2 [1.1-1.3]; $P=0.006$) in the portal vs arterial reperfusion groups, suggesting better early graft function with arterial reperfusion. Two patients needed retransplant and one a new late biliary reconstruction.

CONCLUSIONS: PLT using DCD is a feasible therapeutic option in experienced Units able to perform partial transplants with excellent results after a proper donor and recipient selection criteria.

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Mitochondrial functional changes during ischaemia-reperfusion in non-heart beating donor livers.

Debabrata Roy, Karl Morten, Reza Morovat, Constantin Coussios, David Hughes, Peter Friend

John Radcliffe Hospital, Oxford, United Kingdom

INTRODUCTION: DCD (Donation after cardiac death) livers are extremely susceptible to ischaemia-reperfusion injury and the role of the mitochondria is believed to be central to his. We have investigated mitochondrial functional changes during ischaemia-reperfusion and the relationship of these to hepatocellular injury in post-ischaemic livers.

METHODS: Porcine livers (Group W, n= 5) were subjected to 60 minutes of warm ischaemia and then connected to a normothermic extracorporeal perfusion circuit for 24 hours for assessment of function. Group C (Control, n=5) did not receive the warm ischaemic injury but were otherwise treated the same way. Both groups were subjected to transient cooling (60 minutes) during the bench work prior to reperfusion. Mitochondria were isolated from sequential liver biopsies and analysed for ATP content, mitochondrial function (respiratory control ratio (RCR), mitochondrial level of superoxide dismutase (SOD). The perfusate was analysed for serum transaminase, bile production and base deficit.

RESULTS: Cellular ATP levels reduced significantly during 60 minutes of warm ischaemia ($p<0.01$), but with minimal change in mitochondrial function. However, subsequent cold preservation produced a significant decline in mitochondrial function (RCR 3.97±0.43 vs. 2.45±0.21 $p<0.001$). Mitochondrial function did not recover during reperfusion after cooling and this was associated with greater transaminase release ($p<0.05$) in the perfusate. By comparison, Control livers (without warm ischaemia) maintained normal mitochondrial function during cold preservation and subsequent reperfusion with minimal hepatocellular damage.

CONCLUSIONS: The progressive damage that is seen in livers that experience sequential warm followed by cold ischaemia (the DCD donor) is mirrored by tests of mitochondrial function. This may have important implications in developing mitochondrial based therapeutic strategies for resuscitation of NHBD livers.

Metabolic Syndrome in Transplantation

Tregonwell Hall (front)

9 March 2011

17:00-18:30

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Waist-hip ratio is superior to body mass index as an assessment of central obesity post-transplantation

Adnan Sharif[1], Richard Moore[2], Keshwar Baboolal[2]

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Introduction. Central obesity, in isolation or as part of the metabolic syndrome, is associated with cardio-metabolic complications post-transplantation. Postprandial hyperglycaemia, diagnosed by an oral glucose tolerance test, is a strong predictor for diabetes and an independent risk factor for cardiovascular disease. Both central obesity and postprandial hyperglycaemia, common developments post-transplantation, are pathophysiologically inter-related by numerous mechanisms both transplant specific and non-specific. We hypothesised that utilising waist-hip ratio (WHR), independently or as a component of the metabolic syndrome, would be superior to body mass index (BMI) as a predictor for postprandial hyperglycaemia in the context of solid-organ transplantation.

Methods. We performed a post-hoc analysis of non-diabetic renal transplant recipients who underwent an oral glucose tolerance test (data from 2006-8). Central obesity measurements were assessed as waist-hip ratio and BMI. Metabolic syndrome was classified in strict accordance with both Adult Treatment Panel (ATP) III and International Diabetes Federation (IDF) classifications, with waist-hip ratio and BMI used to diagnose central obesity (a prerequisite for IDF classification). Logistic regression analysis was utilised to identify independent predictors for postprandial hyperglycaemia.

Results. Data was retrospectively analysed for 124 renal transplant recipients. Using the classifications, metabolic syndrome was diagnosed in 74 (ATP III-WHR), 59 (ATP III-BMI), 89 (IDF-WHR) and 31 (IDF-BMI) patients. Only patients diagnosed with metabolic syndrome using waist-hip ratio assessment demonstrated significant differences in postprandial hyperglycaemia: ATP III-WHR (8.2 mmol/L versus 6.0 mmol/L, $p < 0.001$) and IDF-WHR (8.0 mmol/L versus 5.6 mmol/L, $p < 0.001$). All classifications showed significant differences in fasting hyperglycaemia except IDF-BMI: ATP III-WHR (6.1 mmol/L versus 5.4 mmol/L, $p < 0.001$), ATP III-BMI (6.3 mmol/L versus 5.4 mmol/L, $p < 0.001$) and IDF-WHR (6.0 mmol/L versus 5.5 mmol/L, $p = 0.002$). Waist-hip ratio correlated well with postprandial glucose levels (2-tailed Pearson correlation, $r = 0.356$, $p < 0.001$), whilst BMI failed to have any significant correlation. In a multivariate model, waist-hip ratio ($p = 0.050$) and fasting triglycerides ($p = 0.033$) were the only independently predictive variables.

Discussion. Diagnosing metabolic syndrome using either ATP III or IDF classification is predictive for both fasting and postprandial hyperglycaemia, but only if waist-hip ratio is used to assess for central obesity. In addition, waist-hip ratio and fasting triglycerides are independently predictive for postprandial hyperglycaemia. This study confirms waist-hip ratio is superior to body mass index for assessment of central obesity post-transplantation. Further investigation is required to assess the long-term benefit of measuring waist-hip ratio as a cardio-metabolic risk prediction tool post-transplantation.

29

3 year results of the CamTac RCT: Campath and low dose Tacrolimus monotherapy compared with Daclizumab, Tacrolimus and Mycophenolate Mofetil in renal transplantation

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Imperial College Kidney and Transplant Centre, London, United Kingdom

In this study, we present the 3 year results of our randomised controlled trial [(RCT) Clinical Trials.gov: NCT00246129] of Campath induction and low dose Tacrolimus [Tac] monotherapy, compared with Daclizumab induction, conventional dose Tac and Mycophenolate Mofetil [MMF] in renal transplantation. Recruitment into this trial was completed in April 2008 and mean follow up is 37.5 months.

82 patients [54m, 28f; mean age 47.3±13.4 years] received Campath induction, low dose Tac [0.1mg/kg; target level 5-8 ng/mL] and 41 patients [27m, 14f; mean age 47.0±10.6 years] received Daclizumab, Tac [0.15mg/kg; target level 8-12 ng/mL] and MMF [target level: 1.5-3.0 mg/L]. Both groups received a steroid sparing regime [prednisolone 60mg daily day 1-3; 30mg daily day 4-7 and then stopped]. Rejection was diagnosed by biopsy and treated with steroids and the addition of MMF in the Campath group.

Table 1 shows that patient, graft and rejection free survival were similar in the 2 groups. There was no difference in the cumulative risk of rejection and no increased late rejection in the Campath group.

		Campath	**Daclizumab**
Patient survival	1 year	100%	97.5%
	3 years	97.4%	97.5%
Allograft survival	1 year	98.8%	97.6%
	3 years	91.2%	95.1%
Rejection free survival	1 year	91.2%	82.3%
	3 years	88.5%	79.6%
MDRD eGFR [Mean + 1SD]	1 year	54.5±17.0	49.3±15.4
	3 years	54.8±19.5	47.5±18.2

Allograft function [MDRD eGFR] was 5.6 ml/min [95%CI: 2.3,8.9; p=0.001] and 5.2 ml/min [95%CI: 3.0, 7.4, p<0.001] better at 1 and 3 years. [Bootstrap method] in the Campath group. 75.4% and 70.1% of the Campath group remained on Tac monotherapy at 1 and 3 years. Infection rates [positive bacterial and viral isolates, expressed as incidence/100 patient months] were similar in both groups.

This RCT shows that at 3 years, Campath induction and low dose Tac monotherapy provides excellent patient, allograft and infection free survival similar to a conventional Daclizumab, Tacrolimus and MMF protocol. Rejection free survival was similar in both groups and in particular, there was no increased rate of late rejection in the Campath group. Furthermore, allograft function is significantly better in the Campath, low dose Tac group.

30

Abnormal glucose tolerance in whole pancreas transplant recipients is characterised by a diminished acute insulin response (AIR) to intravenous glucose but not to intravenous arginine

Stephanie Eckoldt, Robert Andrews, Richard Smith

University of Bristol, Bristol, United Kingdom

Background: Approximately 20-40% of whole pancreas transplant recipients exhibit abnormal glucose tolerance (AbNGT) on oral glucose tolerance test (OGTT) after pancreas transplantation. An understanding of the pathology underlying abnormal glucose tolerance in pancreas graft recipients is essential to determining and investigating interventions that could optimise and prolong graft function. Oral glucose tolerance (OGT) status is determined by multiple variables including beta cell mass, insulin sensitivity and hormones of the entero-insular axis. We aimed to determine the contribution of beta cell mass and insulin sensitivity to OGT status in our cohort of pancreas transplant patients.

Methods: We performed 5 g arginine and 20g glucose intravenous glucose tolerance test (for estimation of beta cell mass) and euglycaemic clamp studies (for estimation of insulin sensitivity) on 24 whole pancreas transplant recipients (19 with NGT/ 5 with AbNGT) at 3 months after transplantation.

Results: Patients with AbNGT exhibited a diminished mean acute insulin response (AIR) to glucose as compared to patients with normal glucose tolerance (NGT) 22.2 vs 66.4 mIU/min respectively ($p=0.03$). AIR to arginine was not significantly different between glucose tolerance groups (AbNGT 34.3 and NGT 53.4 mIU/L $p=0.1$). Patents in the NGT group tended to be more insulin sensitive but this did not reach significance ($p=0.1$).

Conclusions: A reduced insulin response to intravenous stimuli in conjunction with no significant differences in insulin sensitivity suggest a reduced functional beta cell mass is the primary cause of abnormal oral glucose control in this patient population rather than significant insulin resistance. The contribution of the entero-insular axis needs further assessment but in the absence of an adequate beta cell mass even a vigorous gut hormone response will not be able to stimulate an adequate insulin response for a given glucose load.

Medawar Medal

Tregonwell Hall (front)

10 March 2011

09:30-11:30

M1

Longevity of the Direct and Indirect CD4 T Cell Alloimmune Responses

Jason Ali, Kathleen Elliott, Margaret Negus, Tom Conlon, Reza Motalleb-Zadeh, Eleanor Bolton, Andrew Bradley, Kourosh Saeb-Parsy, Gavin Pettigrew

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Introduction: Recipient CD4 T cells can recognise intact alloantigen 'directly' on donor antigen presenting cells (APCs), as well as recognising self-restricted processed alloantigen 'indirectly'. The direct response is particularly strong and thought to dominate the early transplant response, but because donor APCs are short-lived, the late alloresponse is thought to be mediated by the indirect pathway. The relative longevity of the two pathways has not, however, been formally examined.

Methods: The duration of direct and indirect allorecognition was assessed by comparing division (using FlowJo software) of monoclonal populations of alloreactive, CFSE-labelled TCR-transgenic CD4 T cells that were adoptively transferred into heart-allografted mice either the day after transplant or five weeks later. Direct allorecognition was examined by transfer of ABM CD4 T cells ($I\text{-}A^{bm12}$-reactive) into B6 recipients of bm12 heart grafts. Indirect allorecognition was examined by transfer of: (1) B6 TCR75 CD4 T cells ($I\text{-}A^{b}$-restricted, $H2\text{-}K^{d}$ peptide-specific) into B6 mice grafted with B6 hearts expressing $H2\text{-}K^{d}$ ($B6.K^{d}$; responses against MHC I allopeptide); (2) B6 TEa CD4 T cells ($I\text{-}A^{b}$-restricted, I-E peptide-specific) into B6 recipients of $I\text{-}E^{+ve}I\text{-}A^{-ve}$ B6 hearts (responses against MHC II allopeptide) and; (3) Mar CD4 T cells ($I\text{-}A^{b}$-restricted, H-Y peptide-specific) into female B6 recipients of male B6 hearts (responses against minor H-Y alloantigen). In the models chosen, heart allografts are not rejected acutely, permitting assay of longer term allorecognition responses.

Results: ABM CD4 T cells divided extensively when transferred to B6 recipients the day after challenge with a bm12 graft, but only minimally when transferred 5 weeks after transplant, in keeping with a self-limiting direct alloresponse due to short-lived existence of donor APCs. Similarly, indirect pathway responses against MHC II alloantigen (assessed by TEa division) were readily apparent early after transplant but were surprisingly undetectable by five weeks, presumably due to diminished MHC II antigen availability by this time. In contrast, indirect alloresponses against MHC I alloantigen (assessed by TCR75 division) were equally strong at one day and 5 weeks after transplant. Similar results were obtained when indirect alloresponses against minor H-Y antigen were studied (assessed by Mar division), although division at five weeks was less marked than immediately after transplant.

Conclusions: In addition to providing experimental evidence supporting the paradigm that direct pathway CD4 T cells responses are short-lived, our results highlight that the duration of indirect pathway responses varies according to target alloantigen. Both direct and indirect pathway responses against MHC class II alloantigen are transient.

M2

Alemtuzumab Induction is not Associated with Increased Replication of Opportunistic Viruses After Renal Transplantation

Aravind Cherukuri, Baljit Saundh, Matthew Welberry-Smith, Emma Giddings, Andrew Lewington, Chas Newstead, Anthony Hale, Richard Baker

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Background: Alemtuzumab induction after solid organ transplantation has been shown to be associated with a higher incidence of opportunistic infections. In a randomized control trial of two steroid avoidance regimes comparing alemtuzumab induction (Group-A) with tacrolimus maintenance monotherapy and basiliximab induction with tacrolimus and MMF maintenance therapy (Group-B) we compared the replication rates of three opportunistic viral pathogens (CMV, BK and JC viruses) during the first post-transplant year.

Methods: In this single centre RCT we compared the prevalence of CMV, BK and JC viruses by longitudinally analysing urine and serum samples at 1, 3, 6, 9 and 12 months post-transplantation. Viral replication was studied by RT-PCR. A CMV high risk group defined by serological mismatch at the time of transplantation (D+R-) received prophylaxis with valgancyclovir for 100 days in Group-B. However in Group-A all intermediate and high risk individuals received prophylaxis. We compared the overall prevalence of viraemia or viruria across the two groups at 1 year.

Results: A total of 1698 blood and urine samples were analysed and the summary of overall prevalence of the three opportunistic viral pathogens in urine and blood within the first year is shown in the table.

	Alemtuzumab N=56	**Basiliximab N=57**	**P-value**
CMV-URINE	19.6%	31.6%	0.1
CMV-BLOOD	8.9%	19.3%	0.1
BK-URINE	41.1%	26.3%	0.1
BK-BLOOD	7.1%	15.8%	0.1
JC-URINE	12.5%	14%	0.8
JC-BLOOD	1.8%	1.8%	-
ALL VIRUSES-URINE	64.3%	57.9%	0.5
ALL VIRUSES-BLOOD	17.9%	33.3%	0.06

With regards to the CMV mismatch status at the time of transplantation, 22.4% in Group-A and 19% in Group-B were in the high risk group (D+R-). A further 40% in Group-A were in intermediate risk group (D+R+, D-R+) and they received prophylaxis as well. Despite a slightly higher prevalence of CMV viraemia in the Basiliximab group only one patient developed CMV disease.

Discussion: Alemtuzumab induction with tacrolimus monotherapy was not associated with a higher prevalence rate of viral replication during the first post-transplant year in either blood or urine. Patients who received Alemtuzumab in this study had a lesser prevalence of CMV and BK viraemia. The lower rate of CMV viraemia is probably due to more widespread prophylaxis.

M3

Direct-pathway CD4 T Cells Are Unable To Provide Help For Class-switched Alloantibody Responses

Jennifer Cole, Kourosh Saeb-Parsy, Margaret Negus, Eleanor Bolton, Andrew Bradley, Thomas Conlon, Gavin Pettigrew

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Introduction:

Analogous to the provision of help for antibody responses against conventional antigen, indirect-pathway CD4 T cells provide help for alloantibody responses through cognate recognition of MHC class II / allopeptide complexes on allospecific B cells. Doubt persists as to whether direct-pathway CD4 T cells can also provide, through linked recognition of T and B cell epitopes on donor APC, 'non-cognate' help for alloantibody production. Here we use monoclonal populations of allospecific T cells to examine the ability of naïve and memory direct-pathway CD4 T cells to provide help for generating class-switched, anti MHC class I alloantibody.

Methods and Results:

T cell deficient, but B cell-replete, B6 (TCR KO) mice, when reconstituted with indirect-pathway, K^d-peptide-specific TCR transgenic CD4 T cells, mounted strong anti-K^d IgG responses to a Balb/c heart graft. In contrast, TCR KO mice that were reconstituted with ABM CD4 T cells (that recognise directly IA^{bm12}) did not develop MHC alloantibody responses against bm12 x Balb/c F1 heart grafts, despite the potential for ABM T cells and host B cells to interact via three cell clusters incorporating donor APC. Similarly, chimeric TCR KO mice, in which ABM CD4 T cells are continually replenished from seeded ABM bone-marrow, did not mount alloantibody against bm12 x Balb/c F1 heart grafting.

To examine whether direct-pathway memory direct CD4 T cells can provide help for the generating anti-MHC class I alloantibody, TCRKO.ABM bone marrow chimeric mice were primed with a bm12 skin graft. Skin graft rejected within 10 days, confirming the differentiation of the ABM CD4 T cells to effector status. Upon challenge six weeks later with a bm12 x Balb/c F1 heart graft, however, anti-K^d IgG alloantibody did not develop. Hearts continued to beat indefinitely.

Conclusions:

Our results demonstrate definitively that help for anti-MHC class I alloantibody responses can not be provided by naïve or memory direct-pathway CD4 T cells.

M4

Calcineurin-Inhibitor induced hypertension, hyperkalaemia and metabolic acidosis is caused by overactivity of the Sodium Chloride Cotransporter.

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Introduction: Calcineurin inhibitors (CNI) are known to provoke hypertension and hyperkalemia in many patients, the mechanisms for this are unclear. The precise syndrome that occurs is of hyperkalemia, hypertension, mild metabolic acidosis and hypercalciuria. This is the same phenotype as pseudohypoaldosteronism type2 (PHA2, Gordon's syndrome), caused by mutations of WNK kinase 1 or 4, which disinhibit expression of the Na-Cl cotransporter (NCC) in the distal convoluted tubule. We hypothesised that NCC activity is increased in CNI-induced hypertension and hyperkalemia, and that we could use a thiazide test to demonstrate NCC overactivity in the same way that it detects underactivity in Gitelman's syndrome.

Methods: The subjects were 11 renal transplant patients with CNI-induced hypertension, hyperkalemia and metabolic acidosis (CNI), 9 healthy controls (CTL) and 3 renal transplant patients with hypertension treated with Sirolimus (SIR). Baseline blood and urine samples were taken for Na^+, K^+, Cl^-, Mg^{2+}, Ca^{2+} and Creatinine measurements. 10mg of Bendroflumethiazide was given, water intake was encouraged and urine samples repeated at 30-minute intervals for 4 hours. The change in fractional excretion (FE) of each ion from baseline to the maximal FE (ΔFE) achieved was used as the outcome measure.

Before the test, plasma renin activity and aldosterone were measured, and multi-frequency bioimpedance measurements were performed to reveal extracellular body fluid (ECF) and water (ECW), to assess volume expansion.

Immunohistochemistry for NCC was performed on renal issue from the CNI group, and compared to control tissue via confocal microscopy.

Results: In response to the thiazide challenge, ΔFE_{Cl} was higher in the CNI group than the CTL group (6.9 ± 1 vs. 2.5 ± 0.2 **p=0.002**). The ΔFE_{Na} (5.7 ± 1 vs. 2 ± 0.1 **p=0.005**) and ΔFE_{Mg} (8.8 ± 1.7 vs.3.9 ± 0.5 **p=0.03**) were also higher in the CNI group. Bioimpedance measurements revealed an increase of extracellular fluid in the CNI compared to the CTL group. However, serum Renin and Aldosterone activity did not significantly differ between the two groups.

Confocal microscopy demonstrated a clear increase in the expression of NCC of CNI patients compared to control tissue.

Discussion: These data show that the CNI patients have a supramaximal ΔFE_{Cl} and ΔFE_{Na} in response to a thiazide challenge, compatible with increased NCC activity. Despite having no activation of their renin aldosterone axis, they were volume expanded: as would be expected with NCC activation. Furthermore, immunoflourescence confocal microscopy showed increased expression of NCC in renal tissue of CNI patients compared to control tissue. Taken together, these data show that the syndrome of hypertension, hyperkalaemia and metabolic acidosis seen in CNI treated patients is due to NCC activation. This suggests that thiazide diuretics would be suitable for treating this common and potentially dangerous side effect.

M5

Unlike Indirect Pathway CD4 T Cells, Recognition Of Determinants Expressed On The Graft Enables Direct Pathway CD4 T Cells To Mediate Cardiac Allograft Rejection Autonomously

Adarsh Babber, Thomas Conlon, Kourosh Saeb-Parsy, Jason Ali, Reza Motallebzadeh, Andrew Bradley, Chris Callaghan, Gavin Pettigrew

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Introduction:

Although graft endothelial cells can express MHC class II alloantigen, doubt persists as to whether they express co-stimulatory ligands to facilitate direct pathway CD4 T cell activation. Hence, the ability, in certain murine models, of direct-, but not indirect-, pathway CD4 T cells to autonomously effect cardiac allograft rejection has instead been ascribed to the much higher precursor frequency of direct pathway responses. This distinction between precursor frequency and graft epitope expression as the fundamental feature governing rapid graft rejection by direct pathway CD4 T cells has however not been formally addressed.

Methods:

Murine H-2^d to H-2^b heart transplant models were designed, incorporating monoclonal populations of allospecific TCR-transgenic CD4 T cells to limit recognition to the direct or indirect pathway. Monoclonal T cell populations were used either on a $RAG^{-/-}$ background (neither CD8 T cells nor B cells present) or adoptively transferred into T cell-deficient, but B cell-replete, hosts (TCR-KO). IgG anti-K^d alloantibody responses were measured using K^d-specific ELISA, and cell proliferation was assessed using flow cytometry of CFSE-labelled cells.

Results:

BALB/c heart grafts were rejected rapidly by wild-type B6 recipients (MST 7d), with strong anti-K^d alloantibody responses, but had prolonged survival in either TCR-KO hosts (MST >50d) or in $RAG^{-/-}$ TCR75 mice containing K^d-peptide specific, I-A^b-restricted, monoclonal CD4 T cells (MST 63d). Adoptive transfer of TCR75 CD4 T cells to TCR-KO mice restored alloantibody production and rapid BALB/c heart graft rejection (MST 7d). In contrast, transfer of irrelevant, H-Y-peptide specific, Marilyn CD4 T cells into TCR-KO recipients of female BALB/c heart grafts had no effect. Surprisingly, $RAG^{-/-}$ TCR75 mice rapidly rejected heart grafts from MHC class I-mismatched B6 donors that expressed additional H-$2K^d$ alloantigen as a transgene (B6.K^d, MST 11 d). This ability of $RAG^{-/-}$ TCR75 recipients to reject B6.K^d grafts, but not BALB/c grafts, was not due to augmented T cell priming from recognition of I-A^b-restricted K^d-peptide on donor B6.K^d DC, because TCR75 T cell proliferative responses to BALB/c and B6.K^d grafts were equivalently strong. Finally, wild-type B6 recipients did not reject B6.K^d hearts (MST >100d), unless TCR 75 T cells were adoptively transferred (MST 8d).

Discussion:

The difference in the ability of direct and indirect pathway CD4 T cells to autonomously effect cardiac allograft rejection is not due to differences in T cell priming, but presumably instead to expression of target epitope on graft cells, most likely endothelium. To effect graft rejection autonomously, direct pathway CD4 T cells are required at relatively high precursor frequencies.

M6

Clinical Islet Transplant Outcomes Using Islets Isolated From A Single UK Islet Isolation Centre

Jonathan Neil Walker[1], Stephen Hughes[1], Maciej Juszczak[1], Sarah Cross[1], Elisa Maillard[1], Raina Ramnath[1], Anne Brownson[4], Ali Aldibbiat[3], Derek Manas[5], Phil Boardman[4], Richard Smith[2], Jim AM Shaw[3], Derek WR Gray[1], Paul RV Johnson[1]

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Introduction: In April 2008, the National Commissioning Group (NCG) initiated NHS funding for clinical allogeneic islet transplantation in the UK. Concurrently, the National Institute of Clinical Excellence (NICE) provided guidance about the target outcomes to be achieved by this procedure, namely, improvement of glycaemic control, normalised C-peptide levels (indicating graft function), and reduction in severe hypoglycaemic episodes. Here we report the outcomes using islets from a single UK islet isolation centre and compare these with the NICE Guidelines.

Methods: Between April 2008 and Oct 2010, twelve islet preparations were transplanted into eight people with type 1 diabetes experiencing severe, life-threatening hypoglycaemic unawareness. Eleven transplants were transplanted locally and one at a single satellite centre. Five patients had a single graft, two had two grafts and one had three grafts. The median graft size was 5,389 IEQ/kg (range 3,421- 12,000 IEQ/kg).

All transplants were transplanted intraportally using percutaneous transhepatic cannulation of the portal vein under radiological guidance. All patients received Alemtuzumab induction with Tacrolimus and Mycophenolate maintenance therapy.

Results: Primary graft function was achieved in all cases. At 6 months, 7/8 patients (87.5%) continued to maintain graft function and showed a significant improvement in glycaemic control. For these patients HbA1c returned to a non-diabetic range in all cases (mean pre-transplant 7.77% ± 0.37, 6 months post-transplant 5.81% ± 0.15) with a mean reduction in insulin requirements from 0.51units/kg ± 0.04 to 0.16units/kg± 0.04. All patients showed a significant reduction in severe hypoglycaemic episodes (mean reduction in severe hypos episodes 98%). 6/8 patients (75%) continue to maintain graft function at a median follow up of 14.5 months (range: 7- 26 months).

Discussion: These data show that a UK centre can reach the clinical target outcomes instigated by NICE, and achieve islet transplant outcomes comparable to leading international centres. These outcomes also demonstrate that quality islets can be transported to a satellite centre in the UK and be transplanted successfully.

M7

Steroid avoidance in renal transplantation; a randomised controlled study comparing alemtuzumab and tacrolimus monotherapy with control therapy

Matthew Welberry Smith, Aravind Cherukuri, Andrew JP Lewington, Chas Newstead, Niaz Ahmad, Krish Menon, Steve Tibble, Emma Giddings, Richard Baker

St. James' University Hospital, Leeds, United Kingdom

Introduction: Since 2004 steroid avoiding immunosuppression has been used at this institution for recipients of renal transplants with low immunological risk. This consists of induction with basiliximab and maintenance with tacrolimus (TAC) and mycophenolate mofetil (MMF). Induction with alemtuzumab poses the possibility of long-term TAC monotherapy thereby avoiding MMF. We conducted a prospective randomised controlled trial comparing these two regimes between December 2006 and November 2010.

Methods: At the time of renal transplantation, 116 adult patients were recruited and randomised to either the control group (basiliximab followed by TAC and MMF) or induction with Alemtuzumab group (ALEM) - induction with alemtuzumab and TAC monotherapy) The primary endpoint was DTPA isotopic GFR at one year; secondary endpoints included patient and graft survival, incidence of delayed graft function, incidence/severity of steroid-treated presumptive and biopsy-confirmed acute rejection.

Results: The two groups were well matched for all baseline demographics including age, gender, percentage of diabetics / group, types of transplant, mean HLA mismatches, and warm and cold ischaemia times

	ALEM	**CONTROLS**
n	58	58
DGF (%)	21 (36.2)	18 (31.0)
Graft survival (%)	53 (94.6)	52 (96.3)
Patient survival (%)	56 (96.6)	56 (96.6)
Clinically treated rejection*	7 (12.1)	14 (24.1)
BPAR (%)**	6 (10.3)	14 (24.1)
Banff 2/3 or humeral rejection (%)	2 (3.4)	5 (8.6)
Steroid free at 12 months (%)	47 (81.0)	43 (74.1)
Mean isotopic GFR (ml/min)	56.1 ± 26.3	54.3 ± 19.9

*p=0.082; **p=0.049, both by Chi-squared testing

Similar rates of cardiovascular and neoplastic events were seen in the two groups, though more hospitalisation for episodes of infection occurred in the ALEM group (38 vs 30 in controls). None of these differences were significant and the two regimes were equivalent in terms of outcome. 47 (81.0%) patients in the ALEM group remained on TAC monotherapy at 12 months.

Conclusions: Renal transplantation with alemtuzumab induction followed by tacrolimus monotherapy leads to good short term graft and patient outcomes and is equivalent to a control regime containing MMF.

M8

Induction of long-term human skin allograft survival by human regulatory T cell monotherapy

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Introduction: Tolerance is an ideal solution to the problems of drug toxicity and chronic rejection in transplantation. In composite tissue allotransplantation, rejection rates are particularly high due to the presence of skin in the transplanted tissue. Tolerance to skin is notoriously difficult to achieve experimentally, and while regulatory T cells (Treg) have shown promise in animal models of transplantation, their efficacy in humans is not clear. In this study we investigated the potential of *ex vivo*-expanded human Treg therapy to prolong human skin allograft survival in a humanised mouse model. **Methods**: Human naturally-occurring Treg were expanded *in vitro* by culturing flow-sorted $CD4^+CD25^+CD127^{lo}$ cells from healthy human donor buffy coats with recombinant human IL-2 and αCD3/αCD28 beads over two 7-day rounds. *Ex vivo*-expanded Treg were tested for *in vitro* suppressive capabilities in a ^{3}H-thymidine incorporation assay. Immunodeficient Balb/c $Rag2^{-/-}IL2R\gamma^{-/-}$ mice were transplanted with a $1cm^2$ human skin graft and 5 weeks later received an adoptive transfer of $5x10^6$ human peripheral blood mononuclear cells (PBMCs) with or without $5x10^6$ human Treg monotherapy. **Results**: Expanded human Treg displayed potent suppressive activity *in vitro* towards both polyclonally-stimulated and alloantigen-stimulated autologous PBMCs. Pre- and post-expansion suppression levels were comparable. Over 90% of Balb/c $Rag2^{-/-}IL2R\gamma^{-/-}$ mice receiving $5x10^6$ PBMCs successfully reconstituted their immune systems with levels of human leucocyte chimerism of >1% in the spleen. Reconstituted mice rejected human skin allografts with a median survival time (MST) of 40 days (n=5), whereas mice not receiving cells engrafted human skin transplants long-term (n=5, MST >100 days). At day 21 post-adoptive transfer, human leucocytes and human IgM and IgG were detectable in the peripheral blood of mice, and skin allografts were heavily infiltrated with $CD45^+$, $CD4^+$ and $CD8^+$ human cells. Human $CD31^+$ vascular endothelium was maintained in animals not receiving cells, but destroyed in those receiving an adoptive transfer of PBMCs. With the addition of a single dose of $5x10^6$ *ex vivo*-expanded human Treg (autologous to the PBMCs), long-term survival of skin grafts was attained (n=4, MST >100 days). All Treg-treated mice included in the survival analysis attained adequate reconstitution levels of >1% splenic human leucocyte chimerism. At day 21 post-adoptive cellular transfer, a reduction in the intragraft infiltration levels of human $CD8^+$ cells was observed in Treg-treated animals, along with a significant reduction in peripheral blood human IgM and IgG levels. In long-term surviving (>100 days) skin grafts from Treg-treated animals, skin microarchitecture was grossly maintained, and an intragraft $FoxP3^+$ population of human cells was detectable. **Conclusion**: In summary, we demonstrate the potent suppressive capabilities of *ex vivo* expanded $CD4^+CD25^+CD127^{lo}$ human Treg both *in vitro* and *in vivo*. The ability of Tregs to prevent the rejection of human skin in a clinically-relevant humanised model is highly encouraging for future clinical trials of Treg therapy in transplantation.

Urological Problems in Renal Transplantation

Tregonwell Hall (front)

10 March 2011

12:00-13:00

31

Laparoscopic donor nephrectomy: the Level 1 evidence.

Colin Wilson, David Talbot, David Rix, Naeem Soomro

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Introduction Laparoscopic donor nephrectomy (LDN) techniques have been adopted by many centres to reduce morbidity and encourage donation. The vast majority of published series comparing open donor nephrectomy (ODN) with LDN are single centre, retrospective case series. We aimed to review the randomised controlled trials (RCT's), as part of a Cochrane systematic review, and present the Level 1 evidence on advantages and disadvantages of LDN.

Methods All RCT's examining the use of LDN techniques (hand assisted and "pure" LDN) were identified by a combination of computer literature searches (MEDLINE, EMBASE, CENTRAL etc.), hand searching and personal communication. Quantitative data on the benefits and harms of LDN was then pooled using a random effects model and expressed as relative risk for discontinuous variables and standardised mean difference (SMD) for continuous variables. Data analysis was performed using RevMan Version 5.0 according to the principles of the Cochrane Collaboration.

Results 5 RCT's (over 500 donors) fulfilled the inclusion criteria and were suitable for analysis. There were no reported donor deaths. The conversion rate for LDN techniques was between 1 and 1.8%. LDN was associated with a highly significant reduced morphine usage (SMD 0.45, $p=0.01$) and a quicker return home (SMD 0.68, $p=0.02$). However, the primary warm ischaemia time was longer (SMD -1.91, $p<0.0001$), there were similar numbers and severity of complications and the procedures were longer (SMD -1.44, $p=0.0005$). All other indices of donor and recipient morbidity and mortality were comparable (blood loss, graft loss, reoperations, etc.).

Discussion LDN is associated with less pain and hospital stay, when compared with ODN, but equivalent numbers of complications and a significant number of peri-operative events requiring further intervention. The kidney extracted is exposed to longer periods of warm ischaemia, although this does not appear to be associated with obvious consequences.

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Safety Profile of Belatacept in Kidney Transplant Recipients from a Pooled Analysis of Phase II and Phase III Studies

Josep Grinyó[1], Bernard Charpentier[2], José Medina Pestana[3], Yves Vanrenterghem[4], Flavio Vincenti[5], Rebecca Shi[6], Mamta Agarwal[6], Dolca Thomas[6], Christian Larsen[7]

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Introduction: The current analysis focuses on pooled safety data for belatacept vs CsA used in combination with basiliximab, MMF, and steroids through July 2009.

Methods: Patients in 3 core studies were randomised to a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA. The pooled analysis included 1425 intent-to-treat patients. Median follow-up was ~2.4 yrs; some patients were followed for ~7 yrs.

Results: The incidence of deaths (MI: 7%; LI: 5%; CsA: 7%) and serious adverse events (MI: 71%; LI: 68%; CsA: 69%) were lowest in the belatacept LI group. The overall incidence of malignancies remained low, but was slightly higher in the MI group (MI: 10%; LI: 6%; CsA: 7%). 16 cases of PTLD occurred (n=8 MI; n=6 LI; n=2 CsA) across the 3 studies (including 1 case after July 2009), and 9 cases involved the CNS (n=6 MI; n=3 LI). The excess PTLD risk was concentrated in EBV(–) recipients and in the MI regimen. The frequency of serious infections was 37%, 32%, and 36% in the MI, LI, and CsA groups, respectively. Rates of polyoma (MI: 7%; LI: 3%; CsA: 6%) and fungal infections (MI: 22%; LI: 17%; CsA: 21%) were lower in the LI group vs the MI or CsA groups. 1 case of progressive multifocal leukoencephalopathy was reported in the MI group. Tuberculosis occurred in 10 patients (n=5 MI; n=4 LI; n=1 CsA); mostly in endemic areas. There were no reports of hypersensitivity to belatacept.

Conclusions: Longer-term treatment with belatacept-based regimens was generally safe. CNS PTLD was more frequent in belatacept vs CsA, especially in EBV(–) patients and with the MI dose. The overall balance of safety favoured the LI regimen over the MI regimen.

Ethics, Law & Public Policy

Tregonwell Hall (back)

10 March 2011

12:00-13:00

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Patients' Views on Kidney Allocation in the UK

Talya Kobrin[2], Iain MacPhee[1,2], Helen Gregson[1], Jiri Fronek[1], Nicos Kessaris[1]

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Introduction:

The main aim of this study was to assess patient understanding of the priorities used to allocate kidneys on the waiting list. 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 on our hospital waiting list (REC Reference 10/H083/61). Part 1 assessed patients' knowledge of the current priorities and their own priorities. Part 2 was completed after the responder read the UK Transplant kidney allocation guidelines. The patients understanding and agreement with these guidelines was assessed.

Results:

The response rate was 52 out of 124 questionnaires sent out (42%). Two did not want to participate. The remaining group included 15F and 35M with an overall mean age 55 (min 27, max 74).

The key issues that patients think should be taken into consideration are the degree of tissue matching between recipient and kidney (82%), the time spent on the waiting list (76%), the likelihood the patient will die soon (72%) and whether the patient will take their medication after transplantation (80%).

Ability to pay (76%), contribution to society (48%), ethnic origin (66%) and whether the recipient smokes (42%) were the issues that most people did not think should be part of the guidelines. 10% thought the ability to pay for a kidney is part of the allocation system and 16% were not sure if it was part of it.

Responders were the most unsure about the importance of the number of kidneys imported and exported by their regions (68%). 40% were unsure about whether the recipient having rare tissue type is an important factor.

After reading the enclosed guidelines, there was an increase in understanding of the system from 32% to 78% saying that they mostly or completely understand the guidelines now. Finally, 80% said they mostly or completely agree with the current guidelines.

Discussion:

Patients seemed incompletely informed regarding the current guidelines. Provision of more information and greater patient involvement in the prioritization may increase understanding of the system and help with management of expectations for patients on the transplant waiting list.

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Biographical disruption and narrative reconstruction after a kidney transplant

Jim Ottaway

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This paper reports on findings from the Medication Use Amongst Adult Kidney Transplant Study (MUSE): a qualitative study of adult transplant patients investigating the problems that patients face with medication-taking after their transplants. The study was conducted at the MRC Centre for Transplantation, King's College, London (Guy's Hospital), as part of the NIHR-funded Biomarkers of Clinical Tolerance study.

The study involved in-depth interviews with a purposive sample of 23 adult kidney transplants who were recipients of organs from deceased donors, from 3 months to 25 years post-transplant. The interviews were one-hour long semi-structured interviews taking place at the participants' homes.

The paper draws upon sociological theories of biographical disruption and narrative reconstruction to examine how kidney transplant patients attempt to recreate a sense of a normal life after their transplant.

While the receipt of a kidney transplant is ostensibly the recovery from a chronic illness, for most patients it replaces of one set of difficulties related to end-stage renal disease and renal replacement therapies, with another, principally related to medication-taking, side-effects, and dealing with episodes of rejection.

The theory of biographical disruption is used as a framework for understanding how patients make narrative sense of their new experiences. Transplantation produces a particularly compelling moral problem for patients since, over and above those moral problems posed by chronic illness, they must also do justice to the gift implied by the donation itself.

This paper makes use of Bury's distinction between contingent and moral narratives to understand how patients produce a context of justification for their handling of the contingencies they face after their transplant. In particular, it describes how attempts to minimize the impact of the transplant on everyday life and to provide an account of "doing justice" to the donor in terms of minimization may be confounded by contingencies such as side-effects and rejection, and uncertainties about the prospects of the transplanted organ.

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Access to kidney transplant for ethnic minorities in UK. Is live donor transplantation the answer?

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In UK 25% of patients waiting for a kidney transplantation (ktx) are from minority ethnic groups (MEG). In our waiting list (W/l) for ktx the proportion of Caucasian Vs MEG is 45% Vs 55% of whom 32% are Pakistani, Indian and Bangladeshi (PIB). Previous data from our group showed an average waiting time for a Cad ktx of 1442 days for PIB population versus 976 for Caucasian with evident repercussions on graft and patients survival. In this retrospective study we analyse access to live and cadaveric ktx of Caucasian Vs PIB in two different periods : period A from 01/05 to 03/08 were 211 ktx were performed and period B from 04/08 to 03/10 were 239 ktx were performed, during period B two main factors contributed to the increase number of KTX, the new allocation scheme in UK for cad ktx with advantage for the long waiters and expansion of live donor program from 7 pmi to 17 pmi. Results: Caucasian cad period A n84 (64%) period B n71 (44%) p ns, PIB cad period A n24 (18%) period B n52 (32%) $p<0.022$, Caucasian LD period A n53 (67%) period B n43 (56%) p ns, PIB period A n15 (19%) period B n 26 (34%) $p<0.028$. These results showed that in period B there is a good balance W/l numbers of kts to the access both to cad an LD for PIB population but in this population cad kts represent a resource achievable after very long waiting time with evident repercussion on the outcome while the expansion of LD program gave the opportunity to have as well as a balanced access to ktx with a source of kidney that will give better chance of outstanding outcome.

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ELPAT's new classification for living donor transplantation

Nizam Mamode[1], Emma Massey[2], Mihaela Frunza[3], Rachel Johnson[4], Annette Lennerling[5], Charlotte Loven[5], A Pascalev[6], Sigrid Sterckx[7], Kristoff Van Asche[7], W Zuidema[2], Wilhelm Weimar[2], Frank Dor[2]

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Introduction: With the recent expansion of living donation to include a variety of donor-recipient scenarios, confusion currently exists regarding appropriate terminology for different types of donation. For example, some donations are termed 'altruistic' yet all donation could be considered so. Alternatives, which include 'good Samaritan' donation (religious and cultural specificity make this unsuitable), and 'non-directed' donation (in some countries this may be directed at specific individuals or groups) are similarly problematic. 'Related' donations imply a genetic relationship but there may be no pre-existing emotional relationship, whilst in 'unrelated' donation there may be a profound emotional but no genetic relationship. Further confusion arises when considering paired exchange programmes, in which the donation is directed to an unknown individual. This is an anonymous yet directed donation, but is performed in order to help a third individual with whom the donor has some relationship.

Methods: In order to provide clarity regarding definitions in living donation, a working group of ELPAT (Ethical , Legal and Psychosocial Aspects of Transplantation), a sub-group of ESOT, recently convened in Sofia (October 2010) and proposed a new system of classification. The aim was to propose a workable classification system for living organ donation that avoids morally or religiously loaded concepts and enables coherent discussion and comparisons.

Results: The proposed system is as follows:

Specified donation:

- **Direct donation**: when a person donates directly to his or her intended recipient.

  -donation to genetically and emotionally related recipient
  -donation to genetically unrelated but emotionally related recipient
  -donation to genetically related but emotionally unrelated recipient
  -donation to genetically and emotionally unrelated recipient, but the recipient (or the group to which he/she should belong) is specified

- **Indirect donation**: when a person donates indirectly to his or her intended recipient

  -donation to a specified recipient through an exchange programme

Unspecified donation:

-donation to an anonymous and unspecified recipient

Conclusions: The proposed new system of classification for living donor transplantation will ensure clarity and consistency as new approaches to such transplants are more widely adopted.

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Effect of age or obesity on the short-term and long-term outcomes in living kidney donors: A single centre experience (2001-2009)

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Introduction: The demographic of the kidney donor population is changing. The proportion of older and more obese donors is increasing. Though the risk of donating a kidney seems to be minimal in carefully selected individuals, there is limited data on the short-term and long-term complications in elderly or obese living donors

Aims: To evaluate short-term and long-term complications in elderly or obese living kidney donors.

Methods: This study involved a retrospective review of the medical records of living kidney donors who underwent donor nephrectomy from 2001 to 2009. The donor kidney transplant database, hospital records, operative notes, follow-up clinic visits and correspondence from general practice were reviewed.

Results: A total of 237 living donor nephrectomies (laproscopic nephrectomy 200 and open nephrectomy 37) were performed from January 2001 to December 2009. The mean age at the time of donation was 46.9±10.9 yrs and mean BMI 27.6±3.6 . 25.7% of donors were aged 55 yrs or more and 23.6% of donors were obese at the time of donation with BMI ≥ 30. 4.1% of donors aged < 55 compared to 3.8% donors aged ≥ 55 and 4.9% of donors with BMI< 30 compared to 2.4% of donors with BMI ≥ 30 developed Grade 3 complications (The Clavien Dindo Classifcation) following laproscopic nephrectomy. There were no life-threatening complications (Grade 4), post-operative deaths (Grade 5), or conversion to open nephrectomy. The mean duration of follow-up was 46.5 months. A total of 172(73%) patients were evaluated for renal function and blood pressure and we included only those patients who had been followed up for at least 12 months. GFR measured by Cr-EDTA clearance was significantly higher in donors aged <55 vs ≥55 (100 ml/min vs 88 ml/min, p=0.001). In the absence of repeat measures of GFR, we used estimated GFR (4 point MDRD) to assess function. The difference in mean eGFR was 6, 6 and 13 mls/min at 1, 3 and 5 years (p= 0.08, 0.17 & 0.009, <55 vs ≥55). 85.2 % of donors aged ≥ 55 yrs fit criteria for CKD 3 compared to 56.3% of donors aged < 55 one year post donation. Predonation GFR was similar in donors with BMI < 30 and ≥ 30 and the difference in means was 3 , 4 and 1 ml/min at 1, 3 and 5 years (p=0.3,0.4 & 0.9). 62.7% of donors with BMI< 30 developed CKD 3 compared to 69.6% of donors with BMI ≥ 30 at one year. The difference in mean systolic BP between donors aged < 55 and ≥ 55 at year 5 was 5 mm and this difference was 9 mm between donors with BMI <30 & ≥ 30 . Hypertension one year postdonation (>140/90 or antihypertensive medication) was present in 17.4 % of donors aged< 55 compared to 25% of donors aged ≥ 55 (p=0.3) and 15.9% of donors with BMI< 30 compared to 15.2% of donors with BMI ≥ 30.(p=0.9).

Conclusion: Short-term complications were not significantly higher for older (≥ 55) or obese donors. The high prevalence of hypertension and CKD 3 in older or obese donors highlights the need for long-term follow-up and interventions to minimize cardiovascular risk

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A Review Of Trends And Changes In Cold Ischaemia Times Of Deceased Donor Kidneys Transplanted In UK Centres Between 2000 And 2009

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Introduction. It is well established that a prolonged cold ischaemia time (CIT) is associated with poorer outcomes following kidney transplantation, with higher incidences of delayed graft function, acute rejection and reduced long term graft survival. A recent UK-wide study of transplants using kidneys donated after cardiac death (DCD) showed that CIT beyond 12h was associated with a doubling in the risk of graft failure. It is therefore imperative to reduce CIT to improve short and long term outcomes in kidney transplants.

Methods. UK Transplant Registry data on over 12000 adult, deceased donor, kidney only transplants performed from 2000 to 2009 throughout the UK were reviewed. Activity for each of the 23 transplant centres including the number of donation after cardiac death (DCD) and donation after brain death (DBD) kidney transplants and CITs were reviewed for each year.

Results. A total of 12067 deceased donor kidney only transplants were performed; 82.6% were from DBD donors and 17.4% were from DCD donors. The number of transplants per year increased from 1164 in 2000 to 1324 in 2009. The proportion of transplants from DCD donors increased from 3.9% in 2000 to 36.2% in 2009.

After remaining relatively stable between 2000 and 2004, median CIT for national DBD donor transplants declined from 18.5h in 2004 to 16.4h in 2009, $p<0.001$. During the whole time period, the inter-quartile range also decreased consistently from 7.5h to 6.0h, suggesting less variability in CIT in more recent years. Median CIT (2000-2009) fell significantly in 11 of the 23 transplant centres for DBD donor transplants. There was a reduction of over 9h in one centre (from 24h to 15h), and an average fall of 3.9h in the remaining 10. Comparison of multi-organ and kidney only transplant centres showed no difference in median CIT.

For DCD donor transplants, the median CIT fell significantly from 18.0h in 2005 to 15.9h in 2009, ($p<0.01$), with a reduction in variability over time.

Discussion. These data demonstrate an overall reduction in cold ischaemia in deceased donor kidney transplantation in UK transplant centres in the last decade, although the median CIT still exceeded 15h in half the centres in 2009. Studies show no clear cut-off for CIT beyond which transplantation should not proceed. Instead, the effect appears to be linear, with progressively worsening transplant outcomes with increasing duration of CIT. A recent UK-wide study shows a 4% increase in graft failure with each additional hour of CIT beyond 21h. Further efforts should be made to minimise CIT by identifying and influencing potentially modifiable factors contributing to CIT to maximise the outcome for kidney transplants, which is the aim of our recently initiated multicentre prospective collaborative study.

Chronic Antibody Mediated Rejection

Tregonwell Hall (back)

10 March 2011

13:30-14:30

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Alloreactive IFNγ-Producing CD4+ T-cells From Renal Transplant Recipients With Chronic Antibody-Mediated Rejection (CAMR) Are B-cell Dependent *In Vitro*

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Introduction: HLA-specific antibodies (HLA Ab) are strongly associated with premature graft loss. In many of these cases, the graft develops CAMR. Whilst T cell donor reactivity has also been shown to be associated with chronic rejection, the role of B cells acting as antigen-presenting cells (APC) *in vitro* to alloreactive T cells has not been tested before.

Methods: The ELISPOT assay was modified to compare the number of IFNγ-producing CD4+ T cells in CD8-depleted peripheral blood mononuclear cells (PBMC) before and after depletion of CD19+ B cells. Assays were similarly performed after depletion of both CD19+ B cells and CD25+ T cells. PBMC were incubated for 24h in the presence of membrane protein preparations derived from donor or surrogate donor cells, as a source of mismatched donor antigens. To control for antigen processing and presentation, a series of controls utilising recombinant whole varicella zoster virus and cytomegalovirus proteins were designed and optimised in healthy volunteers and renal transplant recipients. Donor-specific IFN reactivity (DSR) was tested in a group of transplant recipients (n=15) with stable graft function who had a protocol renal biopsy (performed at a median of 8 (6.8 to 10.7 IQR) months post-transplant) showing histological evidence of CAMR. Of these, 13/15 had HLA or MICA Ab on luminex testing (5 with donor-specific HLA Ab); and 11/15 had linear C4d positivity (2 in peritubular capillaries, 2 in glomerular endothelial cells and 7 in both). All patients had at least two blood samples taken for HLA Ab and ELISPOT testing: the first within 45 days of the protocol biopsy, the second 10 (5.6-16.2) months later (n=32 samples).

Results: Evidence of DSR by CD8-depleted PBMC (≥25 IFNγ-producing cells/million CD4+ cells (spot-forming cells, SFCs) over background) was found in 13/32 (40.6%) of samples analysed. In a further 6/32 (18.8%) samples, DSR was revealed by depletion of CD25+ T cells, suggesting regulation of the donor-specific response by regulatory T cells. Depletion of CD19+ B cells significantly reduced the number of IFN SFCs in 10/13 samples (77%) with DSR, and in 4/6 (66%) samples with evidence of CD25 regulated DSR. B-cell dependence appeared alloantigen-specific: CD19 depletion did not reduce SFCs to viral proteins in patients or in 8 volunteers. The association between IFN production and B-cell dependence was strongest in samples from the second timepoint (first timepoint X^2=4.95, p=0.05997; second timepoint X^2=11.25, p=0.003, analysis by Pearson's Chi-squared test with simulated p-values).

Discussion: This is the first demonstration that indirect pathway alloreactivity evidenced by IFNγ production by CD4+ T-cells from transplant recipients with CAMR is dependent on B-cells *in vitro*. Considering that IFN- production in this ELISPOT assay requires antigen processing and presentation, the most logical explanation for this data is that B-cells are acting as APC for alloantigen-specific CD4+ T-cells. Further work is in progress to correlate the results of ELISPOT assay with graft outcome.

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Detection of donor specific antibodies predicts antibody mediated rejection and transplant glomerulopathy

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Acute antibody mediated rejection [AMR] and transplant glomerulopathy [TG] respectively, are the leading immunological causes of renal allograft loss.

In this paper, we show that the early detection of donor specific antibodies [DSAbs] by single antigen beads at the time of transplantation [preformed] or subsequently [de novo] predicts rejection, both AMR and acute cellular rejection [ACR], TG and graft loss.

We retrospectively analysed 469 patients [M:F 308:161, DD:LD 241:228, 1stgrafts:regrafts 412:57, mean HLA mismatch 3.23 ± 1.61] who received an ABO compatible renal transplant.

All patients had a negative CDC and FCXM crossmatch at the time of transplantation and received monoclonal antibody induction with a steroid sparing immunosuppressive regime. All patients' sera were tested pre and post transplant at 3 months and then at 6 monthly intervals or when clinically indicated by Luminex methods.

51/469 [10.9%] of patients were found to have preformed DSAbs and 74/418 [17.7%] patients developed de novo DSAbs. Table 1 shows the 54 month event free survival in patients with preformed DSAbs compared with DSAb- patients.

	Allograft loss	Rejection	ACR	AMR	TG
DSAb+	85.8%	65.5%	89.9%	73.6%	87.7%
DSAb-	93.7%	79.6%	84.8%	91.4%	95.8%
p value	0.04	0.0069	0.38	<0.0001	0.0095

Table 2 shows the 54 month event free survival in de novo DSAb+ and DSAb- patients.

	Allograft loss	Rejection	ACR	AMR	TG
DSAb+	85.0%	46.6%	72.1%	60.3%	80.8%
DSAb-	95.6%	86.9%	87.4%	98.2%	99.1%
p value	0.0006	<0.0001	0.0014	<0.0001	<0.0001

We calculated that detecting pre-transplant DSAb or de novo DSAb in the absence of allograft dysfunction increases the risk of graft loss [OR: 3.49 (1.35-9.03), p=0.001], all rejection [OR:3.51 (2.09-5.88), p<0.0001], AMR [OR:19.02 (7.57-47.81), p<0.0001] and TG [OR:27.39 (7.95-94.36), p<0.0001].

The identification of DSAbs at the time of transplant and their subsequent development is a powerful predictor of rejection and graft loss. Not all patients with DSAbs develop rejection and further work to determine which antibodies are pathogenic is in progress.

Risk stratification strategies should be developed to either avoid transplanting these patients, augment their immunosuppression and facilitate informed consent.

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De novo HLA-DQ donor specific antibodies are associated with a higher risk of rejection and transplant glomerulopathy.

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It has long been established that a mismatch at the HLA-DR loci in renal transplantation is associated with inferior allograft survival and this has been incorporated within the NHS Blood and Transplant organ allocation scheme. More recently studies have shown that HLA Class II donor specific antibodies [DSAbs] and particularly antibodies against HLA-DQ specificities are associated with transplant glomerulopathy. The aim of our study is to determine the incidence and outcomes of patients who develop HLA-DQ DSAbs post transplant.

We retrospectively studied 434 patients who were transplanted at our centre between 2005-2009. [M:F 294:140, mean age at transplant 47.43 ±13.15 yrs, DD:LD 238:196, 1st graft:regrafts 398:36, mean HLA MM 3.26±1.65]. All patients received Campath induction and tacrolimus monotherapy. Patients received a steroid sparing regime which consists of 1 week of corticosteroids only. We excluded ABO and HLA [positive flow crossmatch and preformed DSAbs with a negative crossmatch] incompatible patients. All donors and recipients were typed for HLA -A,-B,-Cw,-DR (both DRB1 gene products and those of the other functional DRB genes) and -DQ antigens. Post transplant patients were screened for DSAbs at regular intervals or when clinically indicated using luminex beads. Mean follow up was 23.71±13.96 months.

155/434 [35.71%] of patients were DQ matched, 39/279 [13.99%] of mismatched DQ patients developed de novo HLA-DQ DSAbs [DQ+] post transplantation. 4 year patient survival was similar in the DQ+ and DQ- groups [97.2% in the DQ- group, 100% in the DQ+ group, p=0.29]. Allograft survival at the end of follow up was 87.2% in the DQ+ group and 94.9% in the DQ- group [p=0.053]. DQ+ patients had an increased risk of experiencing an acute rejection episode. The 4 year rejection free survival was 51.3% and 86.3% in the DQ+ and DQ- groups respectively [p<0.001]. DQ+ was associated with ACR and AMR. ACR free survival was 71.8% in DQ+ patients and 89.6% in DQ- patients [p<0.001]. AMR free survival was 64.1% and 95.7% in the DQ+ and DQ- groups respectively [p<0.0001]. DQ+ patients were also at higher risk of developing transplant glomerulopathy, with a TG free survival of 79.5% in the DQ+ group compared with 98.7% in the DQ- group [p<0.0001].

This study shows that the de novo DQ DSAbs are associated with acute rejection and transplant glomerulopathy with a trend to inferior short term allograft survival.

Antibodies

Tregonwell Hall (back)

10 March 2011

16:00-17:00

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UK Registry of Antibody Incompatible Transplantation 2001-2010

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Introduction. Antibody incompatible renal transplantation (AIT) is widely practiced, but the majority of outcome reports are from single centres, especially for HLA antibody incompatible transplants. The UK Registry is the first comprehensive national registry for HLA and ABO AIT.

Methods. Data for all UK transplants are already collected. An additional AIT dataset was introduced in 2008, collecting data on transplants since 2001 with ABO incompatibility (ABOi), or donor specific HLA antibodies (HLAi) detectable in the immediate pre-transplant period. Those with historic positive, current negative DSA were not included.

Results. The Registry is aware of 381 AIT transplants; 213 HLAi, 150 ABOi (37 full reports to registry awaited), and 18 were both HLAi and ABOi. In 2009, of the 972 living donor transplants performed in the UK, 49 (5%) were HLAi, and 64 (7%) were ABOi.

Fourteen centres reported HLAi transplants, number per unit ranging from 1-76. The pre-treatment complement dependent cytotoxic (CDC) crossmatch (XM) was +ve in 29% of cases. Flow cytometric (FC) XM was +ve but CDC XM –ve in 49%, and 22% had donor specific antibodies (DSA) detectable only by microbead or other solid phase assay. 179 (77%) grafts used kidneys from a living donor while 52 (23%) used kidneys from a deceased donor. Centres used different combinations of IVIg and CD20 as well as plasmapheresis prior to transplantation.

For ABOi cases, excluding the HLAi and ABOi cases, 146 were planned ABOi in living transplants, 3 were deceased donor transplants in a planned programme of A2 donor into selected B recipients at a single centre. ABO antibodies were removed with plasmapheresis in 76% of cases, antigen-specific absorption in 18%, and 6% had no antibody removal.

Three year graft survival (death and graft loss) was 84 (95% CI 69-92)% in ABOi transplant, and 84 (69-92)% in HLAi transplants, compared with 92 (91-93)% for all other living donor transplants, and 84 (83-85)% for all other deceased donor transplants.

Discussion. 12% of living donor renal transplants in 2009 were antibody incompatible, and over three quarters of the transplant units in the UK have reported AIT transplants to the Registry. Overall three year graft survival rates were comparable with the results of ‘antibody compatible’ deceased donor transplantation.

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HLA Antibody Incompatible Renal Transplantation; Outcomes According to CDC Crossmatch Status and Medium Term Follow Up

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Introduction. HLA antibody incompatible renal transplantation has been increasingly performed since 2000, but with few data on the medium term outcomes. The purpose of this study was to review patients transplanted across a pre-treatment donor specific antibodies in our institution.

Methods. Between 2003 and 2010, 80 patients received renal transplants across a pre-treatment donor specific antibody (DSA) level of at least median fluorescence intensity (MFI) 500 measured by microbeads. Seventeen had positive non-AHG enhanced complement dependent cytotoxic (CDC) crossmatch (XM) with mean microbead total reactivity MFI 18423 (SD 8397); 42 had CDC-ve and flow cytometric (FC) +ve XM with mean MFI 5428 (3706); 21 had DSA detectable by microbead only with mean MFI 1561 (1183). There was overlap between the CDC+ve and FC+ve groups, 11/42 (26%) FC+ve patients having MFI >10000, and 4/17 (24%) CDC+ve patients having MFI <10000. 28 patients sensitised for HLA antibodies but who received a DSA negative transplant over the same time period were also followed.

Results. Patient survival was 97.3% at 1, 3 and 5 years. Death censored graft survival at 1,3 ,and 5 years was, 98.1%, 92% and 88.7% in all CDC-ve XM patients, and 88.2%, 76% and 57% in the CDC+ve XM patients ($p<0.05$). Of the losses in CDC-ve patients, all occurred after 6 months, 1 was in FC+ve group and 3 were in microbead+ve group.

Acute antibody mediated rejection (AAMR) occurred in 38/80 (48%) in the first three months. Treatment was most often with muromonomab CD3 or ATG, and careful monitoring was used to intervene as early as possible in the rejection process. One graft was lost from AAMR in this period, giving 97% treatment response rate. Proteinuria developed in 39% of CDC+ve patients at risk at 3 years, and 17% of CDC-ve patients, though this did not proceed to progressive graft dysfunction in all cases.

In the 28 sensitised but DSA-ve transplants, the death censored graft survival was 100% at five years, the early rejection rate was lower than for the DSA+ve group, but the proteinuria onset rate at 3 years was similar to the DSA-+ve CDC-ve transplants.

Discussion. HLA antibody incompatible renal transplantation may have a high success rate if the non-AHG enhanced CDC crossmatch is negative. The CDC crossmatch was a better predictor of outcome than the DSA level as measured by microbead. Further work is required to improve outcome in CDC+ve grafts, and also to target AAMR and transplant glomerulopathy.

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A new approach to the paediatric deceased donor renal transplantation waiting list: low titre ABO-incompatible transplantation.

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Introduction: The published outcomes for ABO-incompatible (ABOi) living donor renal transplantation are comparable to ABO-compatible transplantation. However, its use in deceased donor renal transplantation is limited by the unplanned nature of the donation, restricting the use of desensitisation strategies for patients with high antibody titres: only 1 pre-operative cycle of plasma exchange (PEX) would be feasible given time constraints. ABOi living donor renal transplantation can be performed safely with minimal or no desensitisation in recipients with low antibody titres. Group O paediatric renal transplant recipients, at present, are restricted to only group O deceased donors, as they possess both anti-A and anti-B antibodies.

Hypothesis: Some blood group O paediatric patients on the deceased donor renal transplant waiting list will have sufficiently low anti-A or anti-B antibodies that they will be suitable to receive a blood group A or B kidney without major desensitisation, thereby shortening their waiting time.

Study population: All blood group O patients from two paediatric nephrology centres, who were on the national deceased donor waiting list for >200 days. Mean waiting times in days (95% CI) for paediatric patients on the deceased donor waiting list are as follows – O: 340 (251-429), A: 174 (99-249), B: 320 (179-461), AB: 125 (0-332) [courtesy of NHS Blood and Transplant].

Method: All patients had anti-A and anti-B antibody titres (total immunoglobulin load) measured using DiaMed gel cards.

Results: Of 18 children screened, 5 (28%) had titres of either anti-A or anti-B antibodies of 8 or lower (4 anti-B and 1 anti-A), meaning they could receive the relevant blood group kidney without the need for desensitisation procedures. A further 2 (11%) had an anti-B antibody titre of 16, meaning they could receive a blood group B kidney after 1 session of PEX.

Discussion: This is the first time that ABO blood group system antibody distribution has been reported in a paediatric population. These results indicate that a significant proportion (39% in this population) of group O paediatric patients have low anti-A or anti-B antibody titres. The presence of a low anti-A titre in a patient effectively means that a blood group O recipient can be treated as a blood group A recipient (for the purposes of matching and waiting times) reducing the mean waiting time by 166 days; the presence of a low anti-B titre effectively means a recipient can be treated as a blood group B recipient, reducing the mean waiting time by 20 days.

Conclusion: The strategy of routinely measuring anti-blood group antibody titres is applicable to all paediatric patients who are entered onto the deceased donor waiting list. This could reduce waiting times significantly, thereby decreasing renal replacement therapy related morbidity and mortality.

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High Resolution Analysis of Renal Allograft Rejection – HLA Class I specific antibodies

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Aim: To analyse the HLA Class I mismatch and alloantibody specificity at high resolution in 100 renal transplant recipients who lost their graft to rejection.

Methods: Nucleotide sequencing was used to define the allele level HLA Class I specificities in donor and recipient. The HLA Class I specific antibody that was associated with the allograft loss was analysed using single-antigen beads and Luminex technology. Mismatching was evaluated using the HLA Matchmaker programme (an algorithm that considers *eplets* as critical elements of the epitopes recognized by alloantibodies) by subtracting the HLA Class I alleles of the recipient from the donor.

The antibody specificity was correlated with the *eplet* mismatch to determine the likely epitopes the alloantibody was binding.

Results:

Class I Ab+ recipients (n=73)				**Antibody response**		
HR HLA-A MM 86	**HR HLA-B MM 94**	**HR HLA- C MM 90**		HLA-A	HLA-B	HLA-C
Total theoretical eplets: 622	Total theoretical eplets: 526	Total theoretical eplets: 426		Ab bound to # eplets: 453	Ab bound to # eplets: 291	Ab bound to # eplets: 200
Eplets/MM 7.32	Eplets/MM 6.01	Eplets/MM 5.05		Eplets elciting a response: 70%	Eplets elciting a response: 56%	Eplets elciting a response: 44%

Ab= antibody, HR= High Resolution, MM= mismatches, #= number

The results indicate that the number of epitopes to which HLA specific antibodies were generated was generally very high after allograft loss, potentially involving multiple B cell clones. Furthermore HLA-A has more eplets per mismatch (χ^2=26.95,df=2,p<0.001) and this apparently results in more antibody clones directed at HLA-A than HLA-B or -C despite a similar degree of allele specific mismatches at each of these loci (χ^2=4.22,df=2,p<0.001).

Conclusions: This in depth analysis suggests that the HLA Class I specific antibody generated during graft rejection is complex. This complexity can only be effectively assessed by the high resolution analysis outlined and implementation of these methods would greatly extend the number of patients for which "virtual" cross-matching would be appropriate.

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Is there an effective treatment for Transplant Glomerulopathy?

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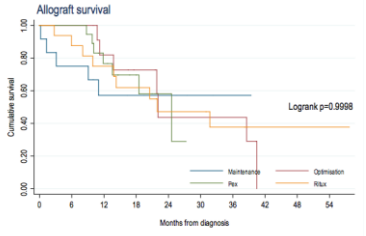
Transplant Glomerulopathy [TG] was first described over 4 decades ago and is commonly associated with proteinuria, donor specific anti-HLA antibodies [DSAbs], C4d deposition on biopsy and late allograft failure. Although several small studies have shown that Rituximab [Rtx], intravenous immunoglobulin [ivIg] and oral immunosuppression with Tacrolimus [Tac] may be effective in the short term, there is no established treatment or reports describing long term outcome.

In this study, the largest reported to date with the longest follow up, we describe our medium term experience of 4 treatment strategies for TG after indication biopsy; defined by double contours in GBM (Banff score cg1-3) on light microscopy in the absence of an immune complex GN or any other clear cause of TMA.

56 patients were diagnosed with TG [32M, 24F, mean age 47.1±12.0 years]. 23/56 patients had class II DSAbs, 66% of which were directed at the DQ epitope. The mean urinary PCR at diagnosis was 164±184 mg/mmol [32/56 had a urinary PCR ≥ 100; 8/56 ≥ 300]. 12 patients [7M, 5F] had cyclosporine based oral immunosuppression switched to Tac [5-8 ng/ml (LCMS)] with the addition of MMF [1.2-2.4 mg/l (LCMS)]. 11 [9M, 2F] patients, already on Tac, continued on Tac and MMF. Fifteen patients [5M, 10F] received Tac, MMF and Rtx [1g day 0 and 14]. A further 18 patients [11M, 7F] received Tac, MMF and 4 monthly courses of plasma exchange [Pex] with ivIg [4g/kg per course].

The table below shows that none of the treatment strategies improved allograft survival which is 70% at one year but as a group overall only 17% at 4 years.



Using a mixed effect model to adjust for repeat measurements on the same patient, MDRD eGFR falls by -4 ml/min/1.73m2 per year [95% CI -8.9,0.2; p=0.069]. Risk of allograft failure with time increases with accelerated rate of pre diagnosis eGFR fall, but this did not reach statistical significance [HR 3; 95%CI 0.8-11.4; p=0.102]. There was no statistically significant histological feature that conferred a survival advantage and neither the amount of proteinuria [logrank p=0.65] or the presence of Class II DSAbs at the time of diagnosis alter outcome [p=0.67]. 3/15 [20%] in the Rtx group had a serious infection with 1 death from sepsis and 3/18 [17%] in the Pex group.

We have not been able to demonstrate that there is an effective treatment for TG and that some may be dangerous.

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Preserved Efficacy and Renal Function From 12 To 24 Months With Everolimus Facilitated CsA Reduction

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Everolimus is an mTOR inhibitor that has immunosuppressive and anti-proliferative properties. Study A2309 is a registration trial in 833 *de novo* renal transplant recipients to assess the efficacy and safety of everolimus with ciclosporin (CsA) minimisation.

A2309 is a 24-month, randomised, multicentre, open-label study comparing 2 targets of everolimus (EVR) (C0 3-8 ng/mL or C0 6-12 ng/mL) with reduced CsA exposure versus a control group receiving enteric-coated mycophenolate sodium (MPA) 1.44g/day with standard exposure CsA. All patients received basiliximab induction and steroids per centre practice. The endpoints at 24M were composite efficacy (incidence of graft loss, death, BPAR, loss to followup-LTF), plus renal function and safety comparisons between the EVR groups and the MPA control.

Donor and recipient characteristics were comparable between the groups. Around a 60% reduction in CsA exposure for both EVR groups continued to be maintained from 12M to 24M versus MPA control group (mean C0 at 24M: 52, 50 & 135ng/mL for EVR 3-8ng/ml, 6-12ng/ml & MPA groups, respectively). Mean 24M calculated GFR (MDRD) values were 52.2, 49.4 and 50.5 mL/min/1.73m2 for EVR 3-8, EVR 6-12 and MPA respectively, and comparable renal function was maintained from 12M to 24M.

Results for the ITT population at 24M by treatment group*. All values are n (%)

	EVR 3-8ng/mL	EVR 6-12ng/mL	MPA 1.44g
Primary Composite Efficacy*	91 (32.9)	75 (26.9)	76 (27.4)
Death	9 (3.2)	10 (3.6)	8 (2.9)
Graft Loss	16 (5.8)	17 (6.1)	11 (4.0)
Death, or Graft Loss	23 (8.3)	26 (9.3)	18 (6.5)
Loss to follow up	21 (7.6)	14 (5.0)	12 (4.3)
Treated BPAR**	55 (19.9)	42 (15.1)	53 (19.1)

*ITT analysis. **Only the first treated BPAR event included in composite score.

The incidence of notable AEs was higher in the EVR 6-12ng/mL group at 24M (75%), but the incidences for EVR 3-8ng/mL vs MPA were comparable, (68 vs 66%)

This analysis confirms that efficacy parameters and renal function achieved at 12M with a combination of EVR and 60% lower exposure to CsA as compared to MPA control were maintained at 24M.

Basic Science

Tregonwell Hall (back)

11 March 2011

09:30-11:00

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A Novel Mechanism for Alloantibody Production

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Introduction: We have recently shown that *donor* CD4 T cells provide help to recipient B cells through graft-versus-host (GVH) allorecognition of surface MHC II (Win TS et al 2009). Only autoantibody was produced, yet theoretically all B cells, irrespective of BCR specificity receive equivalent help, and we hypothesise that simultaneous BCR ligation by constitutively-expressed autoantigen provides an essential additional signal for plasma cell differentiation. If so, antibody responses should also develop against non-self antigens (including alloantigens) that are encountered concurrently.

Methods: The role of donor CD4 T cells in providing help for alloantibody production was examined by adoptive transfer into T cell deficient B6.TCR-KO animals. NK cells were depleted using anti-NK1.1 antibody (0.5mg i.p on D-2,0,2). IgG autoantibody responses were assayed by indirect immunofluorescent staining of nuclear-antigen-expressing Hep2 cell and alloantibody by H-2K^d-specific ELISA.

Results: Upon injection of bm12 CD4 T cells into TCRKO mice, GVH allorecognition of the disparate I-A^b MHC II on recipient B cells provoked strong autoantibody responses. Similarly, injection with bm12 CD4 T cells that expressed transgenic H-2K^d (bm12K^d) prompted strong auto- and anti-K^d IgG alloantibody responses. Autoantibody and anti-K^d IgG alloantibody responses were also detected following bm12K^d heart transplantation into TCRKO recipients. This ability of bm12K^d CD4 T cells to provide help for anti-K^d humoral immunity is not due to recognition of K^d-peptide, but instead to GVH recognition of recipient B cell MHC II, because these cells are tolerant to self; bm12K^d mice challenged with H-2^d heart allografts do not produce anti-K^d antibody. Self-tolerance does not, nevertheless, prevent alloantibody-mediated destruction, because whereas bm12 CD4 T cells survived indefinitely in TCRKO hosts, the development of anti-K^d alloantibody coincided with disappearance of bm12K^d CD4 T cells. Injection of BALB/c x bm12 F1 CD4 T cells into TCRKO mice generated neither auto- nor alloantibody. This likely reflects NK cell-mediated killing of the more disparate F1 cells, because whereas bm12 and bm12K^d cells survived indefinitely upon transfer into B6 $RAG^{-/-}$ mice, the F1 cells were detectable only if NK cells were simultaneously depleted. Depletion of NK cells in TCRKO mice resulted in strong, rapid anti-K^d alloantibody responses upon injection F1 CD4T cells, confirming that disparate donor CD4 T cells can also provide help for alloantibody generation if NK cell recognition is circumvented. Finally, injection F1 CD4 T cells into NK-depleted B6 mice also provoked autoantibody indicating that CD8 T cell recognition and killing of donor CD4 T cell does not occur quickly enough to prevent GVH-mediated humoral immunity.

Conclusions: Our results demonstrate a novel, donor CD4 T cell dependent mechanism for production of class-switched effector alloantibody. Although normally prevented by NK cell recognition of donor lymphocytes, this mechanism may be particularly relevant to clinical transplant tolerance achieved through formation of bone marrow chimerism and may explain allo- and auto-antibody responses described recently in such patients.

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Up-regulation of extracellular signal-regulated kinase 1 and 2 signalling in rat kidney allograft rejection.

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Introduction: Given the efficacy of modern regimens of immunosuppression in the prevention of acute rejection, a primary goal in the development of novel therapeutic strategies is improvement in long term renal allograft outcome. Extracellular signal-related kinases 1 and 2 (ERK 1/2) mediate T cell proliferation and Th1 differentiation playing a role in the immunological response to the allograft. Additionally they transduce key fibrogenic signals from cell surface receptors (e.g. platelet derived growth factor receptor) to the nucleus. Thus ERK 1/2 signalling may be of vital importance in the pathogenesis of chronic immunological graft injury. To investigate this further, activated (phosphorylated) ERK 1/2 expression was examined in kidney allografts performed between Dark Agouti (DA) and Wistar Furth (WF) rat strains. DA-WF transplantation provides an immunologically accelerated model of chronic allograft injury.

Methods: Male DA ($RT1^{av1}$) and WF ($RT1^{u}$) rats weighing 200-250 g were used. Kidney transplantation was performed under isoflurane anaesthesia using end-to-side anastomosis of aortic and vena caval conduits to recipient aorta and inferior vena cava. The systemic blood pressure of donor and recipient was maintained during surgery by intravenous fluid administration. Recipient native right kidney was removed 2 to 3 weeks post-transplant. Recipient rats were followed for upto 12 weeks, receiving daily ciclosporin 1.5 mg/kg subcutaneously, starting on the day of transplantation.

Results: DA-DA isografts, receiving ciclosporin 1.5mg/kg, survived for 12 weeks post transplant with normal tissue histology at termination. DA-DA isografts were normotensive for both systolic blood pressure (135±5 v 135±2 mmHg) and diastolic blood pressure (82±8 v 89±2 mmHg). Serum creatinine remained unchanged (47±2 v 54±3 µmol/L) and values for protein excretion at termination were within the normal range (46±3 mg/24h). In marked contrast, 9 DA-WF allografts receiving ciclosporin 1.5mg/kg, were lost to acute rejection following removal of the right native kidney. The DA-WF allografts which survived to 12 weeks developed inflammatory cell infiltration, vascular intimal thickening and tubulointerstitial fibrosis. Functional measurements showed the DA-WF allografts to develop hypertension for both systolic (122±3 v 148±8 mmHg, $p<0.01$) and diastolic (78±2 v 104±6 mmHg, $p<0.01$) blood pressure. Serum creatinine was elevated at an early stage and the increase sustained (184±48 v 160±46 µmol/L) together with an increase in urinary protein excretion at termination (77±10 mg/24h, $p<0.05$). Phosphorylated ERK 1/2 levels as measured by western blotting were significantly higher in surviving allografts than isografts and almost non-existent in the naive DA kidney.

Conclusion: The DA-WF allografts which survived to 12 weeks showed features of both acute and chronic rejection. This was associated with increased phosphorylated ERK 1/2 expression as compared to DA-DA isografts (controls) which showed stable renal function over a period of 12 weeks with no change in kidney histology. Inhibition of ERK 1/2 signalling may attenuate the immunological component chronic allograft injury.

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Human induced pluripotent stem cells for autologous cell based transplantation

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Introduction: Human induced pluripotent stem cells (hiPSC) offer the promise of generating unlimited quantities of autologous cells as a novel resource for transplantation. Here we set out to investigate the possibility of deriving genetically corrected functional hepatocytes from patients with the commonest inherited metabolic liver disorder - α_1-antitrypsin deficiency.

Methods: Skin biopsies taken from patients attending clinic, were reprogrammed to hiPSC using the four classical 'Yamanaka factors'. The genetic defect responsible for α_1-antitrypsin deficiency was then targeted using a Zinc finger nuclease based strategy. Corrected cells were differentiated into hepatocytes and assayed for their hepatic functionality and loss of disease phenotype.

Results: Patient derived hiPSC displayed all the hallmarks of pluripotent stem cells such as in vitro expansion and ability to form cells of the body's three germ layers. Following gene targeting, genomic sequencing demonstrated highly efficient simultaneous bi-allelic correction of the mutation in the *SERPINA1* gene responsible for α_1-antitrypsin deficiency had been achieved. Subsequently differentiated cells bore key features of hepatic functionality such as Albumin secretion, Glycogen storage and CytP450 metabolism. Crucially, genetically corrected cells retained hepatic function but in addition restored normal functionality to the previously deficient α_1-antitrypsin protein.

Conclusion: We believe this is the first demonstration that a homozygous point mutation can be genetically corrected in hiPSC. Our results therefore provide the first proof of principle for the use of hiPSC as a source of autologous hepatic cells for personalized cell based transplantation in treating patients with inherited metabolic liver disorders like α_1-antitrypsin deficiency.

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Epigenetic silencing of MHC class II genes in tissues differentiated from mouse epiblast stem cells

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Introduction: Mouse epiblast stem cell (EpiSC) are pluripotent stem cells derived from late epiblast layers dissected from post-implantation embryos, and strongly resemble human embryonic stem cells (ESC). ESC and EpiSC are relatively non-immunogenic since they express little MHC class I and no MHC class II antigens, but they have the capacity to differentiate into immunogenic tissues that may also incorporate dendritic cells. Their utility for developing material for transplantation to replace diseased or damaged tissue may thus be dependent upon their potential immunogenicity. We have found that EpiSCs, and their derivatives differentiated in vitro into the three developmentally distinct germ layers (mesoderm [that produces leukocytes, antigen presenting cells and endothelial cells], endoderm and ectoderm) do not express MHC class II upon stimulation with IFN-gamma, although they express genes that regulate MHC II, namely RFX5 and CIITA. We therefore investigated whether MHC II expression in these cells is silenced by epigenetic mechanisms, particularly by histone modification including histone deacetylation and DNA methylation.

Methods: EpiSCs were grown and differentiated in chemically defined medium with specific growth factors. Cells were treated with Trichostatin A (TSA, an HDAC inhibitor) or 5-azacytidine (inhibitor of DNA methylation) for 0-24hr and MHC expression was determined by flow cytometry and Q-PCR. In addition, we performed chromatin immunoprecipitation (ChIP) assays to examine the role of histone methylation in MHC class II transcription.

Results: TSA treatment induced the expression of MHC class II molecules in undifferentiated EpiSC and in differentiated cells. Cells also expressed high levels of RFX5 and moderate levels of CIITA after treatment with TSA, but inhibition of DNA methylation did not restore MHC II expression in these cells. Finally, we found an increase of H3 lysine 4 methylation (which is involved in gene transcription) and absence of H3 lysine 27 methylation (which is involved in gene repression) in the MHC class II promoter.

Conclusion: Our data suggest that EpiSCs and differentiated derivatives have the potential to express MHC class II genes but this expression is silenced by epigenetic mechanisms, possibly as an embryonic survival mechanism.

Overexpression of A20 in late outgrowth endothelial progenitor cells enhances their therapeutic potential for application in transplant vasculopathy

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Introduction: Chronic allograft vasculopathy (CAV) is a major, untreatable, cause of organ transplant failure. Endothelial damage and apoptosis contribute to CAV, while strategies for protecting endothelium and maximizing endothelial repair may diminish it. Late outgrowth endothelial progenitor cells (LO-EPC) are known to differentiate into vascular endothelial cells, implying a role in vascular repair. However little is known about their susceptibility and response to persistent transplant-related inflammation. In this study, we evaluated the effect of tumour necrosis factor (TNF)-α on LO-EPC and their response to inflammation. Overexpression of A20 delivered by a lentiviral vector was able to protect LO-EPC from TNFα-mediated dysfunction.

Methods: Lentiviral vectors containing A20 were generated from an HIV-1 construct, in which the viral promoter had been inactivated and virtually all the viral accessory proteins had been deleted for maximum safety. LO-EPC from human umbilical cord were used in this study. A20 gene expression in transduced LO-EC was confirmed by Western blot. LO- EPC activation was assessed by adhesion molecule expression and cytokine array assay. Apoptosis was assessed using Annexin V/PI staining analysed by FACS. Cells were assessed for their ability to form vascular networks in Matrigel.

Results: TNFα activates LO-EPC and induces an inflammatory phenotype, triggering release of an array of cytokines/chemokines and upregulating expression of the adhesion molecule, ICAM-1. When protein synthesis was inhibited, TNFα induced LO-EPC apoptosis and impaired their ability to form vascular networks. Overexpression of A20 in LO-EPC maintained their angiogenic phenotype, provided resistance against TNFα mediated apoptotic death, and markedly reduced expression of ICAM-1 and inflammatory cytokines including GM-CSF, MCP-1, IL-6 and soluble ICAM-1.

Conclusion: Overexpression of A20 in LO-EPC protected LO-EPC from TNFα induced activation and apoptosis, and maintained their capacity for network formation in an inflammatory environment. This approach enhances the therapeutic potential of LO-EPC to effect vascular repair and reduces their proinflammatory potential.

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Regulatory T cells and Th17 T cell responses in the control of autoantibody-mediated allograft vasculopathy.

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Introduction

We have recently reported a role for autoantibody in the development of mouse heart graft vasculopathy that was surprisingly dependent upon donor CD4 T cells within the heart graft for its development. Regulatory T cells (Tregs) are important in protection against autoimmunity but in the presence of IL-6, their differentiation is instead skewed to a Th17 response, which may exacerbate disease. Here we examine the inverse reciprocal arrangement between the development of Th17 and Tregs in the development of autoantibody and allograft vasculopathy (AV).

Methods

The contribution of Tregs and Th17 T cells to AV and autoantibody development was studied in an MHC II-mismatched mouse model of heart transplantation, by treating recipients with either anti-CD25 (PC61 antibody i.p. on day -1, 1, 3, 5, 7) or anti-IL-17 antibody (50µg i.v. on day 1,3,5 and weekly thereafter) and by adoptive transfer the day after transplant of naturally occurring $CD25^{+ve}$ Tregs (nTregs) (purified from either donor or recipient strains). Graft survival was assessed by daily palpation and autoantibody production assayed by indirect immunofluorescence of nuclear-antigen-expressing HEp-2 cells.

Results

Anti IL-17 treatment of B6 recipients of bm12 hearts influenced neither development of autoantibody nor progression of AV. In contrast, depleting recipient Tregs markedly exacerbated autoantibody production and accelerated graft rejection (MST 20d vs. WT 95d). Heart grafts from CD4-T cell-depleted donors provoked significantly less autoantibody and survived longer (MST 32d, $p<0.01$) than unmanipulated hearts in the Treg-depleted recipients, indicating that accelerated rejection following Treg depletion is partly due to exacerbation of humoral autoimmunity. Finally heart grafts from Treg depleted donors transplanted into WT B6 recipients were rejected rapidly (MST 18d). Surprisingly, whereas adoptive transfer of recipient (B6) nTregs influenced neither autoantibody production nor allograft survival, transfer of donor (bm12) nTregs abrogated autoantibody development. Severity of AV in those recipients that received B6 nTregs was comparable to WT controls (mean intimal stenosis 70.29% vs 71.38%), whereas it was significantly reduced in recipients that received bm12 nTregs.

Conclusions

Our results demonstrate a previously unrealized mechanism whereby Tregs contribute to graft survival by preventing effector autoantibody responses. We hypothesise that donor nTregs are more effective than recipient Tregs at preventing graft-versus-host 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 that are passengers within the heart graft.

Alemtuzumab Induction Leads to a Peripheral Regulatory B Cell Phenotype That Correlates With Graft Function

Aravind Cherukuri[1], Clive Carter[1], Natuley Smalle[1], Maria Hernandez-Fuentes[2], Alan Salama[3], Brendan Clark[1], Richard Baker[1]

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Background: Recent studies in kidney transplant recipients have linked the presence of B regulatory phenotypes with functional tolerance. The profile of such cells in routine patients on immunosuppression remains unknown. In the context of a randomized controlled trial (RCT) of two steroid avoidance regimes in renal transplantation we have studied the peripheral blood phenotype in patients after induction with either alemtuzumab (Group A) or basiliximab (Group B) and correlated the phenotype with graft function

Methods: In this single centre RCT we compared various lymphocyte and monocyte subsets in the peripheral blood using flow cytometry at a mean of 25 months post-transplantation. Patients were categorized into subsets defined by phenotype and the effect on graft function was analysed. Serum samples were also analyzed for the development of HLA-specific antibodies using single antigen luminex beads.

Results: Blood samples from 96 of the 116 patients who were randomized were collected. The table below summarizes significant differences.

	Group-A (n=51)	**Group-B (n=45)**	**P-value**
B cells (CD19+)/µL	297	182	<0.001
B cell-Naïve/ Memory ratio	6.1	2.5	<0.001
Transitional B cells/ µL	29.4	10.7	<0.001
Regulatory B cells/ µL	36.3	16.2	<0.001
NK cells (CD56+cd16+)/ µL	286	187	0.001
T cells (CD3+)/ µL	782	1167	<0.001
Helper-T cells (CD4+)/ µL	300	574	<0.001
Helper T-naïve/memory ratio	0.9	1.7	<0.001

For patients in Group A, the frequency of Regulatory (β=0.37, p=0.01), Transitional (β =0.5, p<0.001) and the naïve B cells (β =0.5, p<0.001) correlated with e-GFR change from 6months to time of sampling (2 years). Patients with the highest tertile population of these regulatory type B cell subsets had the best graft function (highest tertile e-GFR 59.9mls/min, lowest tertile 45.5mls/min, p=0.05) with no DSA (highest tertile 0%, lowest tertile 22.2%, p=0.05). e-GFR improved in 89% of the patients in the highest tertile in comparison to only 48.5% showing improvement in the rest (p=0.004). A similar relationship could not be established within group B or with other cell types.

Discussion: Patients who received alemtuzumab had a significantly higher population of regulatory B cell subsets. Patients with the highest numbers of these cells had superior and more stable graft function. This phenomenon requires prospective study to see whether this phenotype could be used to aid therapeutic decision making.

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Does Remote Inter-Organ Ischaemic Preconditioning Alter Microdialysis Biochemical Markers Of Ischaemia In A Renal Porcine Model?

Mei Nortley, Raphael Uwechue, Mohammad Hossain, Nicos Kessaris, Rene Chang, Mohamed Morsy

St. George's Hospital & University of London, London, United Kingdom

Introduction: Remote inter-organ Ischemic Pre-Conditioning (RIPC) induces ischaemic tolerance and has been demonstrated to work in a biphasic manner – early phase (up to 3 hours) and a late phase (12-72 hours) - post IPC stimulus[1]. We had previously demonstrated in our porcine model could tolerate nearly 3 times more than the reported limit of warm ischaemia[2]. We wanted to test the hypothesis that the late phase effect of RIPC might also be lengthened; as a prolonged effect may increase the scope for its utilisation. Microdialysis has been used extensively to measure tissue markers of ischaemia in real-time[3-4]. This study aims to assess the response of porcine kidneys to ischaemia 7 days after RIPC stimulus using microdialysis markers.

Methods: Data for this study was obtained under project license number PPL70/6580-UK. A RIPC stimulus was achieved by clamping the left renal artery of wild white female pigs (50-70kg) for 60 minutes. 7 days later the right kidney was exposed to another 60 minute ischaemic injury by direct clamping of the renal artery. Biochemical tissue responses were sampled by way of microdialysis with concentrations for lactate, pyruvate, glucose and glycerol analysed. Microdialysis markers were compared for left kidneys without a RIPC stimulus (Group A) and right kidneys after RIPC stimulus during ischaemia (Group B). Microdialysis sampling was performed at 15 minute intervals.

Results: Six pigs underwent a RIPC stimulus resulting in 6 kidneys in Group A and 6 kidneys in Group B. All microdialysis markers responded appropriately in both groups (glucose decreased, lactate increased, glycerol increased, pyruvate decreased). At 60 minutes Group A vs. Group B microdialysis parameters (median values) were 0.06 vs. 0.02mmol/l for glucose ($p=0.25$), 1.82 vs 1.17 mmol/L for lactate ($p = 0.7$), 1.3 vs. 1.7 µmol/l ($p = 0.7$) and 100.6 vs 121.2 µmol/l for glycerol ($p=0.7$). There was also no statistically significant differences in the responses between Groups A & B at 15, 30 and 45 minutes of ischaemia.

Discussion: We concluded that it was not possible to demonstrate with microdialysis markers any protective effect of RIPC after a delay of 7 days. More studies with other markers are required.

References:

1. Yellon DM. Baxter GF. J Mol Cell Cardiol 1995; Apr 27 (4): 1023-34
2. Reference omitted to prevent identification as per submission guidelines.
3. Keller A, Jorgensen T, Olsen H, Stolle L. J Urology 2008 Vol 179, 371-375
4. Kannerup et al. Hepatol Int 2009 3:310-315

56

Donor Telomere Length in Pre-implantation Biopsies Is Predictive for Renal Allograft Function at Six Months Post-transplant

Marc Gingell-Littlejohn[1,2], Dagmara McGuinness[1], Liane M McGlynn[1], Colin Geddes[2], David Kingsmore[2], Marc Clancy[1,2], Christian Koppelstaetter[3], Paul G Shiels[1]

[1]Institute of Cancer Sciences - University of Glasgow, Glasgow, United Kingdom, [2]Department of Transplantation - Western Infirmary, Glasgow, United Kingdom, [3]Division of Nephrology, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria

Introduction

Bio-age, as defined by CDKN2A expression, has recently been demonstrated to be a superior pre-transplant predictive marker for post-transplant function. Traditionally however, bio-ageing has been assessed through a measurement of telomere length. Telomeres are nucleo-protein complexes with a DNA component that provide stability and protection of chromosome ends. With age and increased environmental stress, telomere length is shortened which in turn may be adversely related to donor organ function. We measured renal pre-implantation telomere length and determined associations with organ function at six months post-transplant with a view to using it as a further biomarker of organ function in kidney transplantation, which may be used in combination with CDKN2A and donor chronological age.

Methods

DNA was extracted from time zero biopsies (n=32) using a Maxwell®16 DNA purification robot and quantified using a Nanodrop® apparatus. Telomere length determination was by Q-PCR using a specified assay protocol. Telomere length was then analysed with respect to donor age and sex, cold ischaemic time and renal function 6 months post-transplant as determined by serum creatinine (SC) levels.

Results

Donor telomere length was observed to shorten as a function of increasing chronological age ($p=0.018$). We observed no significant difference with respect to sex of the allograft, but did observe significantly inferior renal function, in those who received organs with shorter telomere lengths ($p=0.025$) as measured by recipient creatinine at six months. Linear regression analyses indicated that at 6 months post-transplant, donor age explains 12.0% of the variability in SC levels, while telomere length accounted for 7.9%.

Conclusions

This study confirms that measurement of donor bio-age pre-transplant can predict post-transplant function. It indicates that telomere length is inferior to donor chronological age when it is used as a bio-marker. This is in keeping with previous observations indicating that CDKN2A is a superior bio-marker. Telomere length in addition to donor age and other promising biomarkers of ageing may provide 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.

Best Abstracts

Tregonwell Hall (front)

11 March 2011

11:30-12:30

B1

CD8 T cells receive help from indirect pathway CD4 T cells by processing alloantigen acquired from MHC I and other alloantigens on graft cells.

Kourosh Saeb-Parsy, Thomas Conlon, Marg Negus, Eleanor Bolton, J Andrew Bradley, Gavin Pettigrew

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Indirect CD4 T cell help is fundamental to allograft rejection and is likely to be particularly important late after transplantation. However, it is unclear how indirect allorecognition by CD4 T cells primes development of effector mechanisms for graft destruction. We thus investigated how indirect-pathway CD4 T cells that recognise processed alloantigen presented by recipient antigen presenting cells (APCs) provide 'unlinked' help for direct pathway cytotoxic CD8 T cells recognising intact allo-MHC I on donor cells.

TCR75 mice (B6 RAG1$^{-/-}$, with a monoclonal population of TCR transgenic I-A^{b}-restricted CD4 T cells recognising H2-K^{d} indirectly) acutely rejected BALB/c grafts (MST 15 d) when reconstituted with CD8 T cells from WT but not MHC II$^{-/-}$ (MST 39 d) or H-2DMa mice (which are unable to process antigen; MST 55 d). Conversely, rejection of B6xBALB/c grafts, in which additional 'linked' help via direct allorecognition of *both* TCR75 CD4 and CD8 T cell target epitopes on *donor* APCs is possible, was similar in recipients reconstituted with CD8 T cells from WT, MHC II$^{-/-}$ and H-2DMa mice. Furthermore, flow cytometric analysis revealed acquisition of MHC II by activated CD8 T cells *in vivo* and *in vitro* upon culture with WT (but not MHC II$^{-/-}$) APCs. We thus hypothesized that indirect pathway CD4 T cells provide help to allospecific CD8 T cells through recognition of alloantigen that is internalised by CD8 T cells via the TCR and presented as processed allopeptide on acquired MHC II, analogous to the provision of cognate T cell help to B cells.

Surprisingly, female Mar (B6 RAG2$^{-/-}$) recipients, whose monoclonal CD4 T cells recognise self-restricted male H-Y peptide indirectly, also rejected male BALB/c heart grafts more rapidly if reconstituted with CD8 T cells from WT (MST 12d) rather than MHC II$^{-/-}$ (MST 21d) or H-2DMa (MST>50d) mice. As expected, B6xBALB/c grafts, which permit provision of direct linked help, were rejected with a similar tempo in all three groups. In contrast, WT CD8 T cell-reconstituted Mar recipients challenged with male B6 APCs mounted minimal cytotoxic CD8 T cell responses and did not reject female BALB/c grafts, despite effective activation of the Mar CD4 T cells. Effective help was thus only generated when H-Y and MHC I alloantigens were co-expressed on graft cells. This suggests that CD8 T cells are able to receive help from indirect pathway CD4 T cells by acquiring additional alloantigens to their MHC I target alloantigen (H-Y in this model) during TCR engagement.

Our data suggest that indirect pathway CD4 T cells provide help to allospecific CD8 T cells through recognition of MHC I-derived or other alloantigen that is internalised by CD8 T cells via the TCR and presented as processed allopeptide on acquired MHC II.

B2

Over–Expression Of Hsp-27 In Donor Hearts Allows Enhanced Cardiac Allograft Survival

Borggia Seemampillai, Ann McCormack, Renee Germack, Marlene Rose

National Heart and Lung Institute, Imperial College London, Harefield Hospital, Harefield, United Kingdom

Hsp-27 is a constitutively expressed heat shock protein. In humans hsp-27 is constitutively expressed in endothelial cells and smooth muscle cells; expression is increased during stress. A number of 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. Murine hearts over-expressing human hsp-27 have been shown to be resistant to ex-vivo induced ischemic damage. The purpose of this study was to determine whether over expression of hsp-27 protects the heart from acute rejection and if so, to define the mechanisms of its protective effect. 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, but not endothelial cells or smooth muscle cells of hearts from hsp-27 tg mice. Hsp-27 tg hearts and wild-type hearts were exposed to 10 minutes of cold and 40 minutes of warm ischemia ex-vivo and the extent of apoptosis was determined using TUNEL assay and caspase-3 activity. Ischemia induced an increase in numbers of apoptotic cells in wild-type mice (from 13.8 cells/field up to 34.4 cells/field) but hsp-27 tg hearts showed less apoptotic cells in response to ischemia (12.7 cells/field up to 19.5 cells/field, p=0.0013). Similarly, the increase in caspase 3 activity was significantly reduced in transgenic hearts (1.84 fold increase) compared to wild-type (2.60 fold increase) following ischemia. B10.A hearts from hsp-27 tg or wild-type litter mate controls were transplanted into the abdomen of C57BL/6 wild-type recipients, representing a class I mismatch. Daily palpation of the transplanted hearts revealed significantly prolonged cardiac allograft survival of hsp-27 tg hearts (time to heart beat cessation, 35 days +/- 10.37, n=10) compared to survival of hearts from litter mate controls (13.6 days +/- 3.06, n=10, p=0.0004). The data so far suggest that hsp-27 may delay acute allograft rejection by limiting ischemia-induced apoptosis. Current studies are analysing presence of effector cells, cytokines and myeloperoxidase by RT-PCR to investigate whether hsp-27 inhibits the cellular infiltrate at early times after transplantation.

Posters

The Purbeck Hall

9 March 2011

18:30 – 19:15

Antibody Incompatible

Moderator: Craig Taylor & Simon Ball

High pre-transplant serum ATPase activity may be protective against rejection within the first six months in recipients of ABO blood group incompatible (ABOi) living kidney transplants

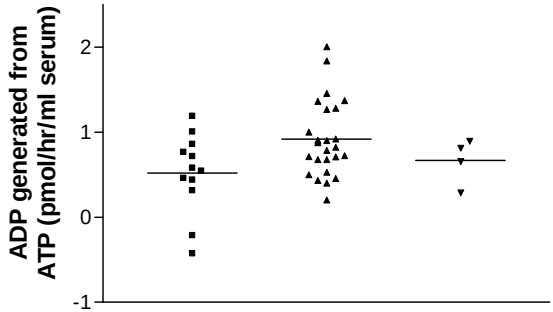
Gowrie Balasubramaniam, Anthony Dorling, Nizam Mamode, Rachel Hilton, Lynette Fairbanks, Anthony Marinaki, Bob Vaughan

Guy's and St Thomas' NHS Trust, King's Colege London, London, United Kingdom

Background. Extracellular adenosinergic signalling plays an important role in thromboregulation, endothelial cell activation and cellular immune responses. Extracellular ATP and ADP are broken down by a series of membrane bound and circulating enzymes. Mouse models of cardiac transplantation have shown that the donor endothelium loses an important surface ATPase, CD39, putting it at risk of ischaemia-reperfusion injury, thrombosis, immune cell infiltration and rejection. We hypothesised that circulating ATPase activity (i.e. from the recipient) plays a role in protecting the donor endothelium in ABOi transplants.

Methods. Stored serum from 37 consecutive ABOi transplanted patients between 07/05 and 12/09 were analysed. Serum taken immediately before desensitization from patients who rejected at 6 months was compared with serum from patients who had not rejected at 6 months. High performance liquid chromatography was used for analysis of ATP breakdown.

Results. Characteristics of recipients who had a rejection episode by 6 months (n=12) vs. no rejection (n=25) were: mean age (years± SD) 49.6 ± 14.7 vs. 51.8 ± 13.8; Male:Female 6:6 vs.15:10; mode of renal replacement therapy (HD:PD:Pre) 8:2:2 vs. 10:6:9; and number receiving second transplant 2 vs. 3. There were no significant differences in donor characteristics: mean donor age (years± SD) was 45.4 ± 9.7 vs. 48.6 ± 7.4; donor eGFR (mls/min/1.73m^2 ±SD) was 89.3 ± 12.0 vs. 84.2 ±11.6 and Male:Female 6:6 vs 6:19. Further details to be shown on poster. Serum ATPase activity is shown in graph 1.



Graph 1. Baseline serum ATP activity (ADP generation) in ABOi kidney allograft recipients who had rejection by 6 months (n=12) vs. those who didn't (n=25) $p < 0.05$. Normal values shown for comparison.

Conclusion. Patients who had a rejection episode within 6 months of transplantation had lower baseline serum ATPase activity than those who had no rejection. This suggests a possible role for recipient adenosinergic regulators in preventing rejection and provides a foundation for further research into this important system in transplantation.

2

The memory response predicts outcome in HLA antibody incompatible renal transplantation

Nicholas Barnett[1], Olivia Shaw[2], Martin Drage[1], Vassilis Hadjianastassiou[1,3], Jonathon Olsburgh[1], Robert Vaughan[2,3], Nizam Mamode[1,3]

[1]Guy's Hospital, London, United Kingdom, [2]GSTS Pathology, London, United Kingdom, [3]King's College, London, United Kingdom

Introduction: HLA antibody incompatible renal transplantation (transplantation across a pre-desensitisation positive crossmatch) is becoming more widespread as a strategy to combat the rising waiting list for transplantation. Post-operative outcomes vary significantly – the underlying reasons for this are poorly understood and few attempts at risk stratification have been made. HLA specific antibody may be generated as a result of exposure to non-self HLA antigen: including from previous transplantation or pregnancy. When this non-self HLA antigen is also present in the donor kidney we term this a repeat mismatch.

Method: Since 2005, 19 renal transplants have been performed across a pre-desensitisation positive crossmatch alone, and 4 across a positive crossmatch with co-existing ABO-incompatibility. These 23 patients were analysed for any previous sensitising events, and repeat HLA mismatches relating to the current transplant. Patient outcome data was analysed for graft survival, patient survival, length of time to graft loss, and numbers of biopsy proven acute rejection (BPAR) episodes.

Results: Patients were followed up for a mean of 798 days post-transplant.

Type of repeat Mismatch	Number of transplants	Number of grafts lost	Mean time to graft loss (days)
None	**11**	**3**	**483.67**
Repeat Mismatch	**12**	**5**	**173.40**
- Class I Transplant	2	1	622.00
- Class II Transplant	4	0	-
- Class I Pregnancy	1	0	-
- Class I+II Pregnancy	5	4	61.25

In total, 3 patients died – 1 died with a functioning graft (Class II Transplant mismatch), 2 died after graft loss (1 with no repeat mismatch, 1 with Class I+II Pregnancy repeat mismatches).

Mean BPAR episodes per patient in the 'No repeat mismatch' group was 0.64 and in the 'Repeat mismatch' group was 1.92 ($p=0.11$).

Conclusion: Although the numbers are relatively small, this data suggests a trend (not statistically significant) for a worse outcome in HLA-incompatible transplants performed with repeat mismatches than those without previous specific sensitisation. This represents a paradigm shift in risk stratification: it may not necessarily be the antibody present prior to transplantation that is responsible for poor outcomes; rather it is the immunological memory's potential to recognise and respond to a previously encountered antigen that is the key.

ABO Incompatible Transplantation Without Augmented Immunosuppression – Pre-Transplant Antibody Level Is The Determinant.

Vaughan Carter[1], W. Martin Howell[1], David Bruce[1], Roderick Babb[1], Alison Brown[2], David Talbot[2], Kim Russell[2], Nicholas Torpey[3]

[1]Dept of H&I NHSBT, Newcastle upon Tyne, United Kingdom, [2]Dept of renal transplantation, Newcastle upon Tyne, United Kingdom, [3]Dept of renal medicine, Cambridge, United Kingdom

Introduction- ABO blood group antibodies have historically been regarded as a barrier to transplantation. Crossing this barrier has led to hyperacute rejection in all forms of solid organ transplantation. However, the development of living donor transplantation has allowed development of protocols for transplantation of organs across immunological barriers. Early efforts to cross the ABO blood group barrier included splenectomy or the use of potentially toxic drugs such as cyclophosphamide alongside antibody removal using plasma exchange. In 2003 Tyden *et al*[1] reported a less invasive technique allowing kidney transplantation across the ABO barrier using the humanised anti-CD20 monoclonal antibody rituximab and specific treatment to reduce antibody levels to titres of < 8 in patients immediately pre-transplant.

Methods – Here we report a series of five ABO mismatched transplants performed at our centre where pre-transplant patient IgM and IgG anti-A or B antibody titres were below 8 on at least two occasions in the pre-transplant testing phase. Antibody titre testing was performed using DiaMed gel-cards with DTT treatment for IgG levels. All patients received basiliximab induction followed by maintenance immunosuppression with tacrolimus, MMF and prednisolone, The important feature of this series is that in four cases transplants were performed with no augmented immunosuppression, with one further case receiving pre-emptive MMF only. None required pre or post-transplant antibody removal.

Results – All transplanted grafts had immediate graft function and there were no unexpected complications or any rejection. Graft function remains good in all cases with an average serum creatinine of 126µmol/l (range 98-150) currently, with the follow up period being between 4 months and 3 years post transplantation.

Discussion- We have shown that ABO mismatched live donor renal transplantation can be performed safely without the need for enhanced immunosuppression or a requirement for antibody removal in patients with antibody titre of 8 or lower. This finding may allow more live donor transplants to be performed where historically donors would have been considered unsuitable. It also raises the question whether ABO titres should be determined for all patients on the waiting list for deceased donor transplantation, partially addressing the inequity caused by ABO blood group.

Reference – Tydén G, Kumlien G, Fehrman I. Successful ABO-incompatible kidney transplantations without splenectomy using antigen-specific immunoadsorption and rituximab.

Transplantation. 2003 Aug 27;76(4):730-1.

4

Rising blood group antibody titres following ABO incompatible (ABOi) renal transplantation are not predictive of acute rejection or renal dysfunction

Sian Griffin[1], Rhian Cooke[1], Ann Marsden[1], Frances Boyns[2], Emma Burrows[2], Amy De'ath[2], Laura McBride[2], Kim Powell[2], Tracey Rees[2], Argiris Asderakis[1]

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

Introduction: ABOi renal transplantation is increasingly performed, with the recognition that outcomes are comparable with those carried out between ABO compatible pairs.

Methods: Since May 2008, 15 patients (6 female, mean age 42 +/- 12 years) have received an ABOi renal transplant from a live donor (LD) in a single centre (14.5% of all LD transplants). Four patients were also HLA incompatible with defined donor specific antibodies (all cytotoxic cross match negative). Eight patients had received one previous renal transplant, one patient had received two. ABO antibody titres were determined by serial dilution of recipient plasma and measured using a DiaMed-ID card, with anti-human globulin (AHG) enhancement. Titres prior to desensitisation ranged from none detectable (one patient) to 1:512 (median 1:64). The desensitisation regimen comprises rituximab 375mg/m^2 4 weeks prior to transplantation, double filtration plasmapheresis (1.5 plasma volumes per treatment), induction with basiliximab or alemtuzumab (if also HLA incompatible), and subsequently triple oral immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil. ABO antibody titres are monitored frequently for 3 months post-transplant.

Results: Patients required 0 – 14 treatments with DFPP prior to transplantation, at the time of which all their titres were <1:8. All patients commencing desensitisation were transplanted, and all transplants functioned immediately. The median eGFR at one week was 63 +/- 13 ml/minute; at one month, 67 +/- 17 ml/minute and at one year or latest follow up 70 +/- 17 ml/minute (median follow up 9 months, range 1 – 30 months). The median creatinine at 1 month, 3 months and 6 months post-transplant in the ABO incompatible group (104, 100, 107 micmol/l) was the same as in the blood group compatible patients (120, 122, 126 micmol/l). One graft was lost following an arterial thrombosis on post-operative day 4, and one patient died of encapsulating peritoneal sclerosis 7 months following transplantation.

Eight patients had a rapid rise in their ABO antibody titres post-operatively, to a titre of 1:32 or greater, and in most patients this level was maintained over the subsequent three months. Seven of these patients had ABO antibody titres prior to desensitisation of 1:64 or greater. The rise in titres was not associated with graft dysfunction or rejection. There was one episode of acute rejection, Banff 1a, at week 6, in the patient who had received a third transplant. This responded to intravenous methylprednisolone. Two further patients had biopsy changes of borderline rejection, two weeks and 7 months post-transplantation. This incidence of rejection compares favourably with the overall rejection rate of this programme.

Conclusion: This study confirms that LD ABOi renal transplantation is associated with an excellent outcome, and low rejection rate despite rapid reconstitution of ABO antibody titres post-operatively. Renal function in the medium term remains excellent, and at least as good as following LD ABO compatible transplantation.

Cryofiltration as a Novel Method to Remove Antibodies before HLA Antibody Incompatible Renal Transplantation

Rob Higgins[1], Devlan Sinha[1], Rizwan Hamer[1,3], Mark Lambie[1], Kath McSorley[1], Nithya Krishnan[1], Dave Lowe[2], David Briggs[2], Simon Fletcher[1], Daniel Zehnder[3,1]

[1]University Hospital Coventry, Coventry, United Kingdom, [2]NHS BT, Birmingham, United Kingdom, [3]University of Warwick, Coventry, United Kingdom

Introduction. Cryofiltration is a technique in which plasma is separated from blood and chilled, leading to formation of 'cryogel', a composite of heparin, fibronectin, fibrinogen, immunoglobulins and other proteins. Cryogel is retained by filtration and remaining plasma is returned to the patient. There may be a role for cryofiltration in the treatment of cryoglobulinaemia or where the application of other forms of plamsapheresis or immunoadsoorption is limited.

Methods. Five patients received six courses of cryofiltration. The treatment was associated with few adverse effects, and it was possible to treat up to 120 ml/kg plasma per session. Three patients were treated before HLA antibody incompatible renal transplantation and two patients had cryoglobulinaemia.

Results. There was a good clinical response in four patients. One patient was switched back to DFPP because cryofiltration seemed to remove HLA antibodies less effectively, but the other two transplants have excellent function and the cryoglobulinaemia patients went into remission.

In the cryoglobulinaemia patients there was excellent clearance of cryoglobulins during each treatment (mean fall 78.2 (2SEM 14.1)% per treatment), but compared with double filtration plasmapheresis (DFPP) there was less removal of immunoglobulins, mean percentage reductions in IgG per treatment were 36.0 (4.0)% for cryogolubilinameia and 59.2 (2.5)% for DFPP ($p<0.01$), with respective mean plasma volumes treated 64.2 (10.3) and 71.1 (6.8) ml/kg. Similar results were obtained for IgG and IgM clearances.

The treatment volumes were limited by the speed with which plasma could be chilled in the cooling bath used; a larger bath will enable the volume to be increased to 3000ml/hr, comparable to DFPP. The use of a more selective fractionator should allow more immunoglobulins to be filtered with the cryogel, and increase efficiency of treatment without removing large amounts of albumin.

Discussion. Cryofiltration offers a treatment choice in patients who may not be able to tolerate high volume DFPP. Although less effective than DFPP in this experience, modifications of the procedure will allow larger volumes of plasma to be treated with more effective immunoglobulin removal.

6

The effect of pre-existing HLA antibodies on graft outcome and biopsy proven acute rejection after HLA incompatible transplantation

Shivakumar Kenchayikoppad[1], Olivia Shaw[2], Nicholas Barnett[1], Nizam Mamode[1,3], Robert Vaughan[2,3]

[1]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom, [2]GSTS Pathology, London, United Kingdom, [3]Kings College London, London, United Kingdom

Introduction: The significance of pre-existing HLA antibodies in the presence of a negative flow crossmatch is not very well understood though recent observational studies have suggested that Donor Specific Antibodies (DSA) may be predictive of acute rejection episodes and subsequent graft outcome after transplantation.

Aim: To evaluate the effect of pre-transplant HLA antibodies on episodes of rejection and graft outcomes in our transplant population.

Methods: HLA antibody testing using single antigen Luminex beads has been in use in our transplant centre since 2005. Retrospective data was collected by two independent reviewers for all renal transplant recipients (between Jan 2005 and Nov 2009) who had pre-transplant HLA antibodies.

82 patients were identified, of which 43 patients were flow cross-match negative but had 3rd party antibodies, 19 had DSA but were crossmatch negative and 20 had DSA and a positive flow cross-match (HLAi). Outcomes were graft and patient survival at 1, 2 and 3 years and episodes of biopsy proven acute rejection (BPAR) over the follow up period.

Results: The results are tabulated below:

Group	n=	Uncensored Graft Survival			Patient Survival			MBPAR
		1 yr	2 yrs	3 yrs	1 yr	2 yrs	3 yrs	
3rd Party	43	38/43	24/27	18/20	41/43	26/27	20/20	0.53
DSA	19	18/19	11/12	8/9	19/19	12/12	9/9	0.89
HLAi	20	14/20	7/11	5/8	18/20	10/11	6/8	1.35

Mean BPAR (MBPAR) is increased in the HLAi group and was significantly higher than the 3rd party group (p=0.013) but not the DSA group (p=0.18).

The 1-year graft survival is worse in the HLAi group compared to the other two groups.

Out of the 8 grafts lost in the HLAi group 6 were lost in the first year post transplantation.

Conclusion: When transplanting in the presence of HLA specific antibody (DSA or 3rd party) our evidence suggests that HLA antibody incompatible transplantation carries a higher risk of BPAR and graft failure in the first year post transplantation.

The episodes of MBPAR are statistically different between the 3rd party antibody group and the HLAi group suggesting there may be an intermediate immunological risk in those patients with DSA and a negative crossmatch.

7

Haematological Problems and Solutions in ABO-Incompatible (ABO-I) Transplantation

Nicos Kessaris[1,2], Steven Wiltshire[3], Peter Andrews[2], Mohamed Morsy[1], Jiri Fronek[1], Iain MacPhee[1,3]

[1]St George's Hospital, London, United Kingdom, [2]St Helier Hospital, Carshalton, Surrey, United Kingdom, [3]St. George's, University of London, London, United Kingdom

Introduction:

As more centres undertake ABO-I living donor kidney transplantation, it is becoming apparent that there is under-reporting of the haematological problems that may arise during the recipient preparation. We report some problems and our adopted solutions.

Methods:

Between September 2009 and November 2010 we performed four ABO-I transplants using the Swedish protocol (Tydén G et al 2007). Our transfusion policy includes:

For emergency:

-Red cells: high titre (HT)-negative red cell units, ABO/D compatible with recipient
-Platelets: (HT)-negative platelet units, ABO compatible with donor
-Plasma: Fresh Frozen Plasma (FFP), type AB
In all other cases:

-Red cells: washed red cells, ABO/D compatible with recipient
-Platelets: platelets in platelet suspension medium (PSM), ABO compatible with recipient
-Plasma: FFP, type AB

Results:

Two patients dropped their haemobglobin from a maximum of 10.3 g/dl and 10.2 g/dl at the time of immunoadsorption (IA) to 8.7 g/dl and 8.3 g/dl the morning before transplantation. Two units of washed red cells were therefore given at the time of surgery. Furthermore, one patient dropped his platelets from 118 x 10^9/l before IA to 74 x 10^9/l the morning before transplantation. He only had two IAs and his PF4-heparin antibody for HITS came back as weak positive. He received two pools of platelets in PSM at the time of surgery. A further observation was made regarding the white cell count. There was a significant rise after most IA sessions. The highest rise was from 15 to 39 x 10^9/l after a single IA session, and were mainly neutrophils. All three transplants proceeded uneventfully. Our fourth did not require blood products but experienced an episode of rejection requiring ATG. All grafts are doing very well with a maximum follow up of 14 months (mean creatinine 103 μmol/l). There were no clinically relevant rises in the white cell count after transplantation, and no episodes of significant infection.

Discussion:

Patients with haemoglobin <10 g/dl undergoing ABOI-transplantation will benefit from optimisation using iron and erythropoietin stimulating agents prior to starting IA. If transfusion is necessary, giving washed red cells or platelets in PSM seems to be one successful way of avoiding problems at the time of surgery. However, more time is required to prepare such blood products, and they are more expensive. Non-significant rises in white cell counts can be expected following IA.

Eculizumab reverses resistant acute Antibody Mediated Rejection and prevents allograft loss

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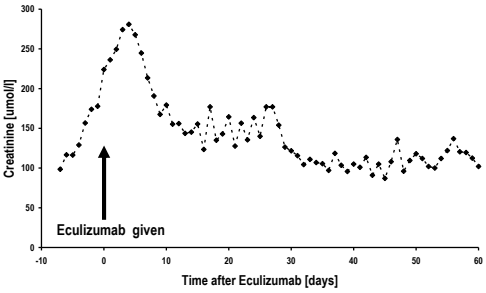
Severe acute antibody mediated rejection [aAMR] is a common cause of renal allograft failure. Allograft loss occurs despite conventional treatment with either poly or monoclonal antibodies, ivIg, plasma exchange and splenectomy. During AMR DSAbs activate the complement cascade resulting in the formation of the membrane attack complex [MAC] and cell death. Consequently Eculizumab, an antibody to C5a, which blocks the formation of the MAC, may be a useful agent when other therapies are ineffective and allograft loss seems inevitable.

In this study, We describe our preliminary experience of Eculizumab therapy. 4 patients [1M, 3F; mean age 49.2 ± 13.9 years] underwent transplantation using Campath induction and Tacrolimus monotherapy. 2 received antibody incompatible transplants and underwent pre-transplant plasma exchange [1 ABOi and 1 FXM+ transplant]. All had negative CDC and FXM crossmatches at the time of transplantation although one 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 AMR 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 Eculizumab was administered to each patient at weekly intervals for a total of 6 doses. At this time plasma exchange was stopped, and has only been repeated in one patient who had glomerulitis on a biopsy after Eculizumab therapy. Mean follow up is 6.4 ± 5.7 months. No patients have developed proteinuria although DSAbs have persisted in all but one patient, who has been biopsied and shows no rejection or alloimmune process [C4d+ve but ABOi].



Patient and allograft survival is 100%. There have been no infective complications.

In the short term Eculizumab is highly effective at preventing allograft loss from aAMR. However, since the antibodies persist in the majority of patients, longer term outcomes such as the development of transplant glomerulopathy are unclear.

Antibody Mediated Rejection & DSA

Moderator: TBA

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Acute cellular rejection with a humoral component is associated with increased risk of subsequent antibody mediated rejection, transplant glomerulopathy and allograft loss

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Mixed rejection can be described as acute cellular rejection [ACR] with a humoral component [either C4d or donor specific antibody (DSAb) positive] and can be classified by Banff as either ACR or antibody mediated rejection [AMR]. Evidence on how to best manage these patients is scarce. The aim of our study was to analyse the outcomes of pure ACR compared with mixed ACR .

We retrospectively analysed 683 patients transplanted at our unit between 2005-2010. All patients had received monoclonal antibody induction and a steroid sparing immunosuppressive regime. Rejection was diagnosed by allograft biopsy and categorised by Banff 2007 criteria, C4d+ was defined as both focal (11-50%) and diffuse (>50%) PTC staining by immunoperoxidase. DSAbs were screened using single antigen beads. All cases of ACR were treated with 3 x 0.5g methylprednisolone with the introduction of oral steroids, along with mycophenolate mofetil in those patients receiving tacrolimus monotherapy. Mean follow up from time of index biopsy was 18.4 ± 12.6 months.

100/683 [14.6%] of patients developed ACR. 54/683 [7.9%] patients were identified as having pure ACR and 46/683 [6.7%] patients were classified as having mixed ACR. 22/46 [47.8%] were DSAb+ but C4d-, 12/46 [26.1%] were DSAb- but C4d+ and 12/46 [26.1%] of cases were C4d and DSAb+. Clinical outcomes following the index biopsy are shown in the table below.

	Pure ACR	**Mixed ACR**			**p value**
	DSAb-C4d- n=54	DSAb-C4d+ n=12	DSAb+C4d- n=22	DSAB+C4d+ n=12	
Patient survival	96.3%	90.0%	100%	100%	0.48
Allograft survial	90.7%	76.2%	66.7%	58.3%	0.025
AMR free survival	90.4%	91.7%	81.1%	50.0%	0.0053
TG free survival	92.1%	75.6%	91.7%	49.4%	0.0093

This study shows that mixed ACR treated is associated with subsequent AMR, TG and allograft loss. Such patients might benefit from treatment directed at antibody removal.

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Efficacy Of Intravenous Immunoglobulin (IVIg) In The Management Of Acute Antibody Mediated Rejection (AMR)

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Introduction

IVIg has been used in the management of acute AMR in a number of centres with varying success but lacks robust evidence. In the UK this resource has become the subject of restriction due to its high cost and potential shortage. Acute AMR is diagnosed by evidence of acute tissue injury on biopsy consistent with acute AMR, the presence of circulating donor specific antibody (DSA) and positive C4d staining (C4d+).

Method

We retrospectively looked at the outcomes of patients treated with IVIg for suspected acute AMR over a 1 year period from May 2009 to May 2010.

Successful outcome was defined as a functioning graft with stable serum creatinine at 6 months post treatment.

IVIg was given at a total dose of 2g/kg over 2-5 days in all courses of treatment except one in which 3g/kg was given. 5 days of plasma exchange (PEX) was given unless considered inappropriate by the treating clinician (n=10).

Results

14 patients received 24 courses of IVIg for the treatment of suspected acute AMR.

11 patients had biopsy confirmed acute AMR. Of these, 8 also had DSA and C4d+, 2 had only DSA and 1 had only C4d+.

The remaining 3 patients were found on biopsy to have thrombotic microangiopathy (TMA) without DSA or C4d+ (n=1), background chronic antibody mediated rejection (CAMR) with DSA but no C4d+ (n=1) or refused biopsy but had DSA (n=1).

Treatment was successful in 8 out of 14 (57%) patients, of which 3 patients required 2 courses of treatment.

1 patient had a graft nephrectomy secondary to surgical complications on day 6 post-transplant.

2 of the patients in whom treatment was unsuccessful received 3 and 4 courses of treatment respectively and despite this suffered complete graft failure within 7 months of the initial diagnosis of acute AMR. Both were highly sensitised HLA antibody incompatible transplant recipients and began treatment for acute AMR within 2 weeks post transplant.

2 other patients in whom treatment was unsuccessful had CAMR or refused a biopsy and treatment was initiated on the basis of a DSA.

Conclusion

IVIg (plus plasma exchange unless considered inappropriate) is an effective treatment for biopsy confirmed acute AMR supported by the presence of DSA and/or C4d+. Two courses of treatment may be required to resolve the rejection episode.

Repeated courses (>2) may not be effective in highly sensitised HLA antibody incompatible transplant recipients who fail to respond. This group of patients may be appropriate for consideration of novel rejection therapies.

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Factors influencing renal allograft survival after antibody mediated rejection

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Acute antibody mediated rejection [AMR] is associated with inferior allograft survival. The current Banff criteria for diagnosis include morphological evidence of tissue injury, C4d positivity and circulating donor specific antibodies [DSAbs]. Despite this, there are few published correlations between these findings and clinical outcome.

In this study we compare the nature of tissue injury, C4d positivity and DSAb characteristics with clinical outcome.

We retrospectively studied 473 patients who received renal transplants between 2005-2010. We excluded all ABO and HLA [positive flow crossmatch] incompatible patients. All patients received Campath induction and tacrolimus monotherapy. Rejection was diagnosed by allograft biopsy, C4d staining was by immunoperoxidase and classified as focal [PTC C4d+ 11-50%] or diffuse [PTC C4d+ >50%]. DSAbs were detected by luminex single antigen beads. AMR was treated with plasma exchange, iv Ig, steroids and mycophenolate mofetil.

48/473 [10.1%] patients were treated for AMR. 30/48 [62.5%] of the cases fulfilled the Banff criteria for definite AMR, whilst 18/48 [37.5%] were categorised as suspicious for AMR [tissue injury with either C4d staining or DSAbs]. 369/469 [78.7%] patients without rejection [AR-] served as controls.

Pre-transplant sensitisation, high HLA mismatch and level of –DR loci mismatch were baseline risk factors associated with the development of AMR [p=0.0016, 0.001, 0.012 respectively]. The median time to rejection in the AMR group was 1.55 months [0.2 - 31.7 months]. There was no difference in 4 year patient survival between the AR- and AMR+ groups, which was 95.9% and 94.1% respectively [p=0.54]. 4 year allograft survival in the AR- group was significantly better at 97.0% compared with 70.2% in the AMR+ group [p=0.0001]

42/48 [87.5%] of patients with acute AMR+ were DSAb+ whilst only 68/369 [18.4%] of AR- patients were DSAb+ [p<0.001]. Patients with both CI and CII DSAbs had inferior allograft survival [p=0.036] when compared with DSAb- patients at the time of AMR. Both the mean cumulative and immunodominant mean fluorescence intensity were higher in those patients who subsequently lost their grafts [p<0.001].

Patients with diffuse C4d staining had inferior 4 year allograft survival than those with either focal C4d or no staining; 56.0%, 76.2% and 92.9% respectively [p=0.02]. There was no significant difference in survival by histological grade but patients with evidence of tissue injury, C4d staining and DSAbs had the worst [60%] 4 year survival.

This study identifies patients at particular risk of graft failure from AMR. These patients may benefit from newer therapeutic strategies including the use of eculizumab or bortezomib.

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High dose IvIg in renal live donor recipients with pre-existing DSA.

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The clinical relevance of HLA donor specific antibodies (DSA) is not well understood, but from several reports its clear that graft survival is affected with an inferior outcome when pre-existing DSA are present. This is due to the higher incidence of both acute cellular and humoral rejection. Different protocols are in use to improve the graft outcome in this group of patients, most are with plasma exchange, mono and polyclonal antibodies at induction.

We report our initial experience of eight kidney recipient from a live donor where there was evidence of pre-existing DSA.

From February 2009 to November 2010 all eight recipients received 2g/Kg IvIg over 48 hours before the kidney transplant. Induction was with Basiliximab 20 mg day 0 and day 4. Maintenance immunosuppression was with CNI, MMF and steroids.

All patients were transplanted with pretreatment negative CDC crossmatch, and 5 out of 8 with a flow positive crossmatch.

Result with a follow-up of 1-21 months was: no evidence of acute humoral rejection, 1 patient experienced early acute cellular rejection on day 4 with concomitant sub-therapeutic Tacrolimus level, proteinuria with PCR of 138 is evident in 1 patient, no histological features of chronic humoral rejection. Post transplant DSA remained positive in 3/8 recipients. All grafts are functioning with a SCr ranging 50-163mmol/l, no evidence of opportunistic infection, no mortality.

Limitations of this study include small numbers and short term follow-up, but the results are encouraging in terms of incidence of acute rejection, graft and patient survival, and absence of opportunistic infections.

We conclude that high dose of IvIg in pre transplant positive DSA in live donor recipients, is effective in prevention of rejection, furthermore there was no evidence of over-immunosuppression.

Longer follow-up together with histological and immunological monitoring is necessary to prove the efficacy of IvIg at medium and long term.

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Association between transplant renal artery stenosis and donor specific antibodies.

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Donor specific antibodies [DSAbs] are associated with allograft coronary artery disease post cardiac transplantation. Although immunological causes of endothelial damage have been demonstrated in transplant renal artery stenosis [TRAS], there are no studies which have analysed an association between the presence of DSAbs post renal transplantation with the development of TRAS.

We retrospectively studied 524 renal transplant recipients who were transplanted between 2005-2010. We identified all patients who had been screened for TRAS by MRA. Those found to have a stenosis proceeded to formal angiography (angioplasty ± stent insertion), those with no evidence of TRAS on MRA served as controls. All patients were screened pre-transplant for the presence of DSAbs by luminex and then screened at 3 months then 6 monthly intervals or when clinically indicated post transplant. All patients received monoclonal antibody induction with a steroid free immunosuppressive regime.

67/524 [12.78%] patients were found to have TRAS [M:F 47:20, LD:DD 22:45, 1^{st}:$\geq 2^{nd}$ graft= 59:8, mean HLA mismatch 3.38 ± 1.66, age 51.38 ± 13.62 years]. 311/524 [59.35%] had a negative screening MRA. TRAS was more common in deceased donor recipients [p=0.0028] and older patients [p=0.04]. The mean time to detection was 3.34 ± 2.13 months. 14/67 [20.89%] of TRAS+ patients had ≥2 arteries compared with 39/311 [12.54%] of TRAS- patients, p=0.077.

There was no difference in patient and allograft survival. Patient survival was 97.1% and 95.5% in the TRAS+ and TRAS- groups respectively, p=0.56. Allograft survival was 88.2% and 93.1% in TRAS+ and TRAS- patients, p=0.15. Rejection free survival was also comparable between the 2 groups; TRAS+ 73.0% and TRAS- 76.7% at 5 years, p=0.43.

TRAS+ patients were more likely to have DSAbs 25/67 [37.3%] than TRAS- patients 76/311 [24.4%], p=0.032. There was no difference in the HLA Class of DSAb [TRAS+: CI(9), CII (11), CI+CII (4); TRAS-: CI (29), CII (32), CI+CII (16)] p=0.29. Also there was no difference between preformed and de novo DSAbs [TRAS+:9,16 and TRAS-:35,41 respectively], p=0.52.

This is the first study demonstrating an association between DSAbs detected by sensitive luminex methods and the development of TRAS. Accelerated arteriosclerosis in renal transplants may be immunologically driven. Patients with DSAbs may benefit from being screened for TRAS.

14

Eculizumab for salvage in post-transplant Thrombotic Microangiopathy

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Introduction: Eculizumab, a humanised monoclonal antibody targets complement protein C5, inhibiting cleavage into C5a and C5b, and therefore preventing formation of the Membrane Attack Complex (MAC). It has been used rarely in renal transplantation, for atypical Haemolytic Uraemic Syndrome (aHUS) post-transplant. There are two published case reports of its use in confirmed Antibody Mediated Rejection (AMR), but none in post-transplant Thrombotic Microangiopathy (TMA)

Method: A 42 year old woman, with underlying secondary Focal Segmental Glomerulosclerosis (FSGS) and a lupus anticoagulant, received a live donor renal transplant from her brother. 17 years earlier she had received a deceased donor renal transplant from a 39 year old donor with a 1-2-0 mismatch. The present transplant was across ABO blood groups (donor A2 to recipient B) and with Donor Specific Antibody (DSA) to A2 and B37. The Flow Cytometry cross-match was negative.

The immunosuppression regimen used consisted of alemtuzumab (Campath) induction, with tacrolimus, mycophenolate mofetil and steroid maintenance. HLA antibodies were measured pre- and post-operatively using Luminex based antibody screening with single antigen beads.

Anti-A antibody titres (total immunoglobulin load) were measured using DiaMed gel cards.

Results: After initially good renal transplant function (with a trough creatinine on day 5 of 75) on day 7 her creatinine increased suddenly. A renal ultrasound showed no abnormalities. The anti-A antibody titre had increased from 4 to 8, so it was decided to commence plasma exchange (PEX) with IVIG.

A biopsy performed on day 8 post-operatively showed acute TMA. At this point, the underlying cause was unclear, with possibilities including AMR, a calcineurin inhibitor reaction and antiphospholipid syndrome. PEX and IVIG were continued, tacrolimus was withdrawn and heparin was continued. However, there was no improvement: haemodialysis was required, and eculizumab was commenced to protect the allograft. Following this, DSA to A2 and B37 was found to have increased and the diagnosis of AMR was suggested on renal biopsy. The antibody levels began to fall slowly after PEX and IVIG treatment, although it was only on day 20, after the second dose of eculizumab, that renal function began to improve. The patient has since had 3 further doses of eculizumab, and the creatinine has returned to a baseline of 138.

Discussion: This is the first report of the use of eculizumab in a patient with post-transplant TMA of unknown cause. The diagnosis of TMA was made from a biopsy before any significant rise in DSA could be detected. Eculizumab was used to protect the renal allograft while the underlying cause of TMA was determined, and it allowed time for accommodation to occur. We conclude that eculizumab can be used as salvage therapy in cases of TMA of unknown cause, preventing allograft damage while diagnostic measures and appropriate treatments are performed.

Cancer & Infection 1

Moderators: Paul Harden

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Cancer Screening in Kidney Transplant Recipients

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Introduction Immunosuppressive therapy places kidney transplant recipients at increased risk of malignancy. The incidence of lymphoma and skin cancers is significantly elevated, and there is also an excess of solid organ tumours including lung, prostate, colorectal, breast and uterine. In all malignancy, early detection and treatment contribute to reducing morbidity and mortality. Screening programmes and patient awareness of 'red-flag' cancer symptoms are important components of this.

National screening programmes exist for breast, cervical and colon cancer amongst certain age/gender groups but it is unclear whether these serve the transplant population appropriately. Most transplant patients consult their transplant physician every 3 months and there is concern that interaction with their GPs and primary care services may be limited.

The aims of this study were two-fold: 1) to assess the extent to which kidney transplant recipients were concordant with national cancer screening programmes; 2) to gauge the willingness of kidney transplant patients to consult a physician for 'red-flag' cancer symptoms.

Methods Transplant patients attending a District General Hospital transplant out-patient clinic from November 2009 to March 2010 were given the opportunity to complete a paper-based questionnaire. Questionnaires were completed by the patient alone, or with the attending clinician. No attempt was made to validate the answers provided. During 4 months from November 2009, 116 replies were received from a transplant population of approximately 260. No record was kept of patients declining to complete the questionnaire.

Results Of 23 eligible participants, 78% had undergone breast screening in the previous 3 years. This compares to a national average of 76.5%. Of 42 eligible participants, 72% had undergone cervical cancer screening within the previous 5 years, compared to a national average of 78.9%. Only 43% of 37 eligible participants had participated in the bowel cancer screening, but the programme had only recently been rolled-out to this region. Of 13 patients reporting red-flag cancer symptoms within the previous 3 months, 100% had sought further medical advice. 24 patients reported new rashes/moles – 88% had sought further medical advice.

Discussion These data indicate that this cohort of transplant patients are as compliant with national rates of inclusion into cancer screening programmes as the general population. Given the high risk for malignancy in this group, however, a greater level of compliance would be desirable. These patients do, in general, seek appropriate medical intervention for red-flag symptoms. However, it is important to note that the transplant physician does, in many instances, replace the GP as the first-call physician.

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PSA Monitoring In Male Renal Transplant Recipients

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Introduction: Solid organ transplant recipients are more likely to die from malignancy than the general population and European Best Practice Guidelines suggest screening for certain malignancies in these patients. In particular, they recommend PSA screening annually in men aged 50+ as data suggests early diagnosis is associated with improved survival.

Aims: To review all eligible male renal transplant recipients (aged 50+) ensuring they have had a PSA performed in the last 12 months. To analyse how many of those patients tested had elevated levels and whether they were associated with confirmed malignancy.

Methods: Using data derived from the renal and hospital databases and electronically held clinic letters, all male patients with a functioning renal transplant aged 50-74 were retrospectively analysed. The length of time they had had a functioning renal transplant, their treatment and survival were analysed.

Results: 132 patients transplanted between 1977-2009 fulfilled the age criteria (73% deceased donor recipients & 27% living donor recipients). The mean age was 59.2 years, and they had had a transplant for an average of 9 years 4 months (range 11-390 months). 11% had not had a PSA checked and 36% of these patients were less than 12 months post transplant. Of those with a PSA check (n=118), 83% had had one in the last 12 months, and in just 9% was it elevated. Those patients with elevated PSA levels were not older but had been transplanted for longer than the cohort mean. Most patients had been seen by urology and were under a 'watch and wait' policy. The mean elevated PSA reading was 6.7, 2 patients had a biopsy, 1 was benign, 1 malignant. All had survived to date.

Conclusion: This methodology potentially failed to pick up those men who may have prostate cancer and a normal PSA, but only a minority of men had elevated levels on screening. Our unit had much lower then expected levels of prostate cancer and results raise the question of the economic benefit of screening these men annually.

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Risk factors for malignancy in renal transplant patients receiving Tacrolimus based immunosuppression.

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Malignancy is a significant cause of morbidity and mortality in patients with long term renal transplants.

The purpose of this study was to determine the incidence, nature and risk factors for malignancy in our transplant population over the last 15 years following the introduction of a Tacrolimus based immunosuppressive regime.

1288 patients [492f, 796m; 136 Afro Caribbean, 338 South Asian, 746 Caucasian, 68 others; mean age 46.3+12.7 yrs; mean follow up 48.1 + 42.2 mths; 1096 kidney only, 74 antibody incompatible kidney transplants; 118 kidney and pancreas transplants] transplanted between 1st Jan 1995 and 1st August 2010 in our centre were included in this study. Patients transplanted after 2002 routinely received induction with monoclonal antibodies [Campath or Daclizumab] with a steroid sparing regime. All patients received Tacrolimus.

1216 [94.4%] patients were followed up in our unit until graft failure or death. 52 [4.0%] cases of malignancy were identified from patient and pathology records. 22 [42.3%] cases were skin malignancies, 7 [13.5%] were urological, 6 [11.5%] were gastroenterological, 4 [7.7%] were haematological, 3 [5.7%] were respiratory and 3 [5.7%] were angiosarcomas in thrombosed arteriovenous fistulae [AVFs].

Overall patient and allograft survival at 15 years were 84.6 and 66.8% respectively. 13/70 deaths were malignancy related. Cumulative malignancy free survival was 85.2% at 15 years after transplantation. Patients aged 60-70 had a 5.2 fold increase in risk of malignancy compared to those aged less than 40. [HR 5.2, 95%CI 2.2, 12.6; $p<0.001$]

After adjusting for age and time after transplantation [Weibull survival model with Lexis expansion], South Asian patients had a 75% reduced risk of malignancy compared to Caucasians [HR 0.25, 95%CI: 0.09,0.71; $p=0.009$].

Patients who had renal failure due to vasculitis/GN who had received myeloablative chemotherapy had a 3.6 fold increased risk of malignancy [95%CI: 1.4,9.6; $p=0.011$]. Gender, monoclonal antibody induction, antibody incompatible transplantation and treatment of rejection was not associated with an increased risk of malignancy.

Time adjusted multivariable subgroup analysis of patients with skin cancer showed that Azathioprine was associated with a 3.4 fold increased risk, [95%CI 1.1, 10.0; $p=0.029$], compared with Mycophenolate Mofetil [MMF]. Male gender [HR 17.6; $p=0.006$] and previously treated vasculitis [HR 5.4; $p=0.025$] also increased the risk of skin cancer.

South Asians had a 90% reduced risk of skin malignancy [95%CI 0.01, 0.8; $p=0.03$]

This study shows that age, ethnicity and previous exposure to myeloablative chemotherapy were associated with malignancy. Skin cancer was associated with the use of Azathioprine [and not MMF], gender, previous exposure to myeloablative chemotherapy and rare in South Asians. Angiosarcomas of thrombosed AVFs have not been previously described. Formal surveillance strategies could be developed using these data.

18

Donor derived malignancy in renal transplantation: management dilemma

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Introduction: In this case report we highlight the management difficulties that we encountered when donor derived malignancy was identified in two transplant recipients from the same donor. We found, unsurprisingly, that management recommendations from the literature are based on case reports only.

Case:

The donor was a 60 year old man with myelodysplasia and interstitial lung disease who died after a prolonged intensive care admission with pneumonia. Both our recipients were on haemodialysis, Recipient 1 (R1) was a 64 year old man and Recipient 2 (R2) was a 42 year old woman. R1 had a wedge biopsy of the renal transplant during transplantation. This showed abnormal dysplastic cells in 2 glomeruli. Subsequently, both recipients had transplant nephrectomy 6 weeks post transplantation and discontinuation of immunosuppressant agents. Histology from both kidneys confirmed donor derived metastases considered to be small cell carcinoma of lung origin. Both recipients were offered chemotherapy although there is paucity of evidence for its benefit. Only R2 accepted chemotherapy. Eighteen months post transplant nephrectomy, R1 was found to have a unilateral lung lesion. He was an ex-smoker. The histology obtained suggests primary small cell carcinoma. R2 also developed abnormal CXR. A CT thorax was carried out 20 months post transplant nephrectomy and is currently undergoing further investigation. The major psychological impact is apparent, especially in R2.

Discussion:

Review of previously reported cases demonstrated that transplant nephrectomy with cessation of immunosuppressant therapy has been the usual management approach. Those cases where the transplant was continued subsequently developed evidence of malignancy and died within 6 months. Additional treatment with chemotherapy or radiotherapy varies widely depending on the type of malignancy. Some patients had good outcome despite no additional treatment. In our case, chemotherapy was offered based on assumption that micrometastases would have spread unchecked whilst the recipients were heavily immunosuppressed immediately post transplantation. The safe timing for the next transplantation for R2, if the upcoming CT is normal, remains controversial. Previous case reports had short follow up, mostly less than 2 years post transplantation at the time of publication. Rarely these included information on re-transplantation.

Conclusion:

We must be vigilant of donor derived malignancy as kidney transplantations from marginal donors is increasing. More robust recommendations for management of this rare and difficult complication of renal transplantation would be valuable.

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Correlation Of Everolimus Exposure With Reduced CsA Exposure To Efficacy And Safety Outcomes: Results From A Multicentre Study In Renal Transplantation

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Everolimus (EVR), allows for reduction in CNI exposure with preserved renal function (RF) without loss of efficacy in renal transplant recipients (RTs). Data from earlier studies suggests that targeting EVR C0 levels to >3ng/mL may provide optimal benefits in RTs. The A2309 study explores the optimal EVR C0 level by correlating trough levels of EVR at 12 months (M) with efficacy and safety parameters. This 24M, randomized, multi-centre, open-label, non-inferiority study compared 2 target trough levels of EVR (C0 3– 8ng/mL or C0 6–12ng/mL) with reduced CsA versus control group receiving enteric-coated mycophenolate sodium (MPA) 1.44g/day with standard CsA exposure. All RTs received basiliximab induction and steroids as per centre practice.

The objective of this post-hoc analysis was to correlate EVR C0 ranges with key efficacy and safety parameters including % of RTs with selected renal function events by 12M. Pooled analysis using the geometric mean of all measured EVR C0 levels up to the time of outcome or last study visit (12M) were used to correlate with key outcomes.

Results: Donor and recipient characteristics were comparable between groups. Both EVR groups were statistically non-inferior to the MPA control group for the primary composite efficacy failure (treated biopsy proven acute rejection [BPAR], graft loss, death or loss to follow up) and the renal function safety endpoints at 12M. Mean CsA C0 at 12M were 55, 49 and 137 ng/mL for 3–8, 6–12ng/mL EVR and MPA groups respectively, reflecting a 60% reduction in CsA levels for both EVR groups. Mean EVR C0 at 12M were 5.2 and 7.9ng/mL for 3–8 and 6–12ng/mL groups respectively.

Table: EVR C0 levels and efficacy and safety outcomes in patients

	EVR C0 < 3ng/mL	EVR C0 3-<8ng/mL	EVR C0 8-<12ng/mL	MPA 1.44g/day
Treated BPAR	18.2(6/33)	15.4(64/415)	10.5(9/86)	17.0(47/277)
Graft Loss	11.4(4/35)	3.7(15/410)	3.4(3/89)	3.2(9/277)
Death	2.7(1/37)	2.2(9/411)	3.4(3/88)	2.2(6/277)
Proteinuria	23.1(3/13)	12.1(45/373)	25.6(21/82)	12.6(31/246)
Wound healing	44.4(20/45)	30.2(114/378)	43.3(39/90)	25.6(70/273)
Hypercholesterolemia	70.9(39/55)	65.7(245/373)	78.1(75/96)	51.8(141/272)
Peripheral oedema	52.2(24/46)	46.4(167/360)	52.4(44/84)	44.0(120/273)

(
All values %incidence of event(n/N); #urine protein-creatinine ratio > 1G/G, excludes M1)
The probability of decreased glomerular filtration rate (GFR) correlates with CsA C0, but not with EVR C0 levels.

Conclusions: EVR C0 range 3–<8ng/mL during the first 12M provided similar efficacy and RF outcomes to MPA control. In addition, EVR C0 target of 3–<8ng/ml had less proteinuria and other adverse events compared to higher EVR C0 targets. EVR C0 range of 3–<8ng/mL appears the optimal EVR C0 target range in *de novo* RTs with reduced CsA.

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Lower Incidence Of CMV And BK Virus With Everolimus Vs. Mycophenolate In De Novo Renal Transplant Patients At 12 Months

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Cytomegalovirus (CMV) and BK virus infections are associated with acute and chronic graft rejections. Everolimus (EVR) in heart and renal transplant (RTx) patients is known to decrease the incidence of CMV.

Study A2309 is a 24-month, multicentre, randomised, open-label, non-inferiority study in *de novo* renal-transplant recipients. Patients were induced with basiliximab and received everolimus (EVR; 1.5mg/day targeting C_0 3–8ng/mL or 3.0mg/day targeting C_0 6–12ng/mL) with reduced-dose CsA *versus* mycophenolate sodium (EC-MPS) (1.44g/day) with standard-dose CsA (n=277). Corticosteroids were administered according to local practice. CMV prophylaxis was used in all high risk patients (donor positive/recipient negative). CMV and BK virus infections were reported as per local centre evaluations.

Results: Donor and recipient characteristics were comparable between the treatment groups. Both EVR groups were statistically non-inferior to the MPA control group for primary composite efficacy and renal endpoints at 12M. Overall, incidence of adverse events (AEs) was comparable between treatment groups over the 12M. Selected AEs (%) are listed in the Table

	EVR 3-8ng/mL (N=274)	EVR 6-12ng/mL (N=278)	MPA 1.44g (N=273)
Total AEs	98.9	99.3	98.9
Total Serious AEs	56.6	60.4	53.8
AEs leading to study discontinuation	18.1	20.4	9.4
AEs leading to study drug dose adjustments	22.3	27.0	34.8
Total Infections	61.7	64.0	67.8
- CMV infections	1.1	0.4	8.4
- BK virus infections	0.7	1.1	4.0
Any wound event	35.0	38.8	25.6
Neoplasms (benign, malignant, unspecified)	3.3	2.9	5.9

Lower incidence of CMV and BK virus was demonstrated in both the EVR groups as compared with the MPA control group. There was a lower incidence of laboratory haematological abnormalities and a higher incidence of lipid abnormalities in the EVR groups. There was a greater use of lipid-modifying agents in the EVR-treated patients.

In conclusion this study confirms there is a decreased incidence of CMV and BK virus infections in *de novo* renal transplant patients which translates as an additional benefit of EVR versus standard therapy.

12 Month Analysis Of Effects Of Graft Type, Donor Criteria And Gender On Improved Renal Allograft Function With Everolimus Facilitated CNI Reduction

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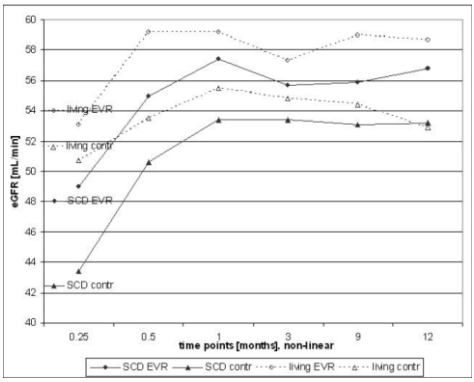
A number of factors have been shown to influence renal allograft function (RF) and outcome. In addition to immunologic variables and procurement or shipment related factors, these include donor criteria, allograft type, and presumably gender.

A2309 is a 24-month, multicentre, randomised, open-label, non-inferiority study comparing the efficacy and safety of three immunosuppressive regimens in *de novo* renal-transplant recipients: two regimens of everolimus (EVR; 1.5mg/day targeting C_0 3–8ng/mL [n=277] or 3.0mg/day [n=279] targeting C_0 6–12ng/mL) with reduced-dose CsA *versus* mycophenolate sodium (EC-MPS) (1.44g/day) with standard-dose CsA (n=277). All patients receive basiliximab induction therapy. Corticosteroids are administered according to local practice. Here, the impact of EVR facilitated CsA reduction on estimated GFR (eGFR) is assessed in (1) standard (SCD) *versus* extended (ECD) criteria donor, (2) deceased *versus* living donor allografts and (3) male *versus* female recipients in post-hoc analyses comparing EVR 1.5mg/day ($C_0$3-8ng/mL) to EC-MPS.

RESULTS: Immunologic variables, donor/allograft types and gender distribution between groups were comparable. Mean eGFR (MDRD) values at Month 12 of the on-treatment population (n=403) will be presented for SCD, ECD, decreased, living, male and female patients. Figure 1 displays evolution of renal function over time for SCD and living donors:



In each of the 6 subgroup analyses EVR treated patients showed numerically higher eGFR at Month 12. As expected, the recipients of kidneys from SCD did better than ECD, the same was observed for living compared to deceased donor allografts. Interestingly, female recipients achieved a higher eGFR compared to males. For the criteria SCD, living donors and female recipient the difference between EVR and EC-MPS control reached statistical significance ($p<0.05$). In conclusion, the A2309 patient subgroup analyses show that EVR in combination with reduced dose CsA leads to improved renal function in distinct subpopulations.

Cancer & Infection 2

Moderator: Rachel Hilton

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In *De Novo* Renal Transplant Patients Everolimus Significantly Reduces CMV Infection Incidence Vs. Mycophenolate: Pooled Analysis Of 3 Studies

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Cytomegalovirus (CMV) infections are associated with acute and chronic graft rejections. Everolimus (EVR) in heart and renal transplant (RTx) patients is known to decrease the incidence of CMV.

CMV data from 2004 *de novo* RTx from 3 EVR studies A2309 (N=833), B201(N=588) and B251(N=583) were analysed to identify differences between two EVR dosing groups and mycophenolate (MPA) control groups. In all studies, EVR groups received 1.5 mg/day, or 3 mg/day with either standard (SD-CsA) or reduced dose ciclosporin (RD-CsA). All control groups received (mycophenolic acid) MPA with ST-CsA. Steroids and CMV prophylaxis were given as per centre practice. CMV events (infection, syndrome, disease, viremia) were reported as per local centre evaluations.

Donor and recipient (D/R) CMV status at baseline were comparable between the treatment groups. Incidences of any CMV event by 12 months were 2.10 and 1.95% for EVR 1.5 and 3.0mg vs MPA of 4.34% (p<0.0001).

Incidence of CMV events by treatment group - n (%)

	EVR 1.5 mg/day, N=664	**EVR 3.0 mg/day, N=671**	**MPA,N=669**
CMV prophylaxis at baseline	201 (30.3)	199 (29.7)	205 (30.6)
CMV infection/syndrome - no prophylaxis	25 (5.4)*	22 (4.7)**	66 (14.2)
CMV infection/syndrome with prophylaxis	12 (6.0)	13 (6.5)	15 (7.3)
CMV viremia - no prophylaxis	18 (3.9)#	13 (2.8)*	40 (8.6)
CMV viremia with prophylaxis	10 (5.0)	6 (3.0)	12 (5.9)
CMV disease - no prophylaxis	9 (1.9)	5 (1.1)	10 (2.2)
CMV disease with prophylaxis	2 (1.0)	5 (2.5)	6 (2.9)
CMV infection/syndrome by serology status			
D+R-subgroup	17 (6.2)	19 (18.1)	27 (25.2)
D+R+subgroup	14 (4.9)^	10 (3.4)*	33 (12.0)
D-R-subgroup	1 (0.7)	2 (1.7)	6 (4.3)
D-R+subgroup	3 (3.0)	1 (0,8)***	8 (6.7)

*p<0.001 vs MPA; **p<0.0001 vs MPA; #p=0.004 vs MPA; ***p=0.036 vs MPA; ^p=0.0034
This pooled analysis documents significant reductions in incidence of CMV infection/syndrome and viremia in EVR-treated *de novo* RTx recipients, primarily those who did not receive CMV prophylaxis compared with the MPA control group.

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Prevalence And Implications Of EBV Detection And Viral Load In Stable Adult Renal Transplant Recipients

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Introduction The detection of EBV DNA in blood samples is an important clinical issue, due to the relationship of EBV and PTLD and the perceived clinical relevance of EBV infection. Interpretation and optimal management of EBV DNAemia in stable patients remains unclear. Prevalence data for EBV viraemia in stable adult renal transplant patients particularly in those many years after transplantation is lacking. We aimed to describe prevalence and viral loads in our transplant follow up population.

Methods We performed a prospective observational study in 501 consecutively recruited stable adult renal transplant patients attending routine outpatient follow up. Demographic, transplant, and immunosuppressive history data was recorded and symptom survey performed. Blood samples were taken for whole blood real-time EBV DNA PCR (copies/ml). Analysis of baseline prevalence of EBV viraemia was made.

Results 61% patients were male with a median age at recruitment of 52 years (range 19-80) and median time from transplant 6 years (range 0-32). 311/486 (64%) patients at recruitment had undetectable EBV viral loads while 175/486 (36%) were EBV positive. 19/486 (4%) had low viral loads <log 2, 92 (19%) log 2, 51 (11%) log 3, 12 (2%) log 4 and 1 (0.2%) log 6 (a patient with newly diagnosed PTLD). 22 patients recruited had a history of previous PTLD (n=12) or recently diagnosed PTLD (n=10). 16/22 (73%) PTLD patients had detectable viral loads including 6/12 of those with previous and all the current PTLD patients.

	Viral loads (EBV DNA)(copies/ml)						
Variable (no)	PCR -ve	PCR +ve	Log 1	Log 2	Log 3	Log 4+	Log ≥3
Age <39 (90)	55 (61%)	35 (39%)	3	18	12	2	14(16%)
40-49(127)	84 (66%)	43 (37%)	6	19	11	7	18(14%)
50-59(134)	83 (62%)	51 (38%)	7	27	13	3	17(13%)
>60 (135)	89 (66%)	46 (34%)	3	28	15	0	15(11%)
Time from Trsp. <1yr (80)	68 (85%)	12 (15%)	3	6	3	0	3(4%)
1-5ys (143)	101(71%)	42 (29%)	5	20	16	1	17(12%)
6-10yrs (121)	73 (60%)	48 (40%)	5	23	15	5	20(17%)
11-15yrs (77)	42 (55%)	35 (45%)	2	25	5	3	8 (10%)
>16yrs (66)	28 (42%)	38 (57%)	4	18	12	3	15(24%)

Discussion Up to 36% of adult renal transplant recipients attending routine clinic outpatient appointments have detectable EBV viral loads at any one time. 13% have log values of 3 or above but only a small number, approximately 1% without PTLD, have log values of 4 or above. Prevalence does not seem to increase with age but may rise with time from transplant. Further analysis of viral loads in relation to persistent infection and symptoms will be provided.

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A Single Centre Experience of Kidney Transplantation in HIV Infected Patients

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Background

With the advent of combination antiretroviral therapy (cART) there has been a dramatic reduction in HIV-associated morbidity and mortality. The incidence of end-stage renal disease (ESRD) in HIV-infected patients is, however, increasing. Kidney transplantation (KT) is considered a viable mode of intervention in this group of patients but there is paucity of data on outcomes and immunosuppression (IS) management.

Method

We carried out a review of HIV+ KT recipients at the UCL Centre for Nephrology Royal Free Hospital between November 2006 and November 2010. The pre-KT listing and work-up requirements were as per the collaborative BHIVA / BTS guidelines (2005).

Results

During the review period, 8 patients (6 male, 2 female) underwent KT with 11 on the transplant waiting list. HIV associated nephropathy (HIVAN) was reported as the cause of ESRD for 12/19 of the patients all of black ethnic origin. Of the 8 KT patients, 6 had a deceased, 1 live-related and 1 live-unrelated kidney donor. The median age at KT was 39.5 (29 – 67) years with a mean follow-up period of 16.25 months. All patients received induction IS therapy including basiliximab, mycophenolate, steroids and a calcineurin inhibitor (CNI). One patient died at the point of KT with cardio-respiratory arrest as the cause of death. The CNI ciclosporin A (CsA) was used in 6/7 patients, with significant dose reductions of 90-95% (range 30 – 100mg/day) required for 5/6 patients due to drug-drug interactions with ritonavir-boosted protease inhibitors (PI/r). One patient required minimal CsA dose adjustment on a non-nucleoside reverse transcriptase (NNRTI) based cART. The pre-KT CsA trial dose was an accurate predictor of post-KT doses. After dose adjustments, 6/6 patients achieved therapeutic T12 CsA levels with a mean of 325ng/ml at weeks 0 – 4 post-KT. One patient on a PI/r based cART received tacrolimus (FK) that required a 99% dose reduction (1mg once weekly) to maintain a mean pre-dose FK level of 8.3ng/ml. The graft survival for 7/7 patients was 100% with a mean eGFR of 56ml/min at maximal follow-up. Acute rejection (AR) occurred in 3/7 patients (median = 6 weeks) that responded to pulse corticosteroid therapy and with no recurrence compared to a 17% annual AR rate (n=110) in non-HIV patients at our centre. There were no chronic rejection episodes but 1 delayed graft function. All surviving patients maintained HIV viral suppression (VL<50cps/ml) and a mean CD4 count of 497cells/mm^3 post-transplant. There were no significant opportunistic infections or tumours recorded at maximal follow-up.

Conclusion

Our single centre experience reports favourable short and medium-term outcomes from kidney transplantation in HIV infected patients. However, the small patient cohort warrants a further large multicentre study with regard to optimal immunosuppression management and long-term patient and graft outcomes.

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Rejection: An Approach to PJP Prophylaxis Guidelines

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Pneumocystis jirovecii pneumonia (PJP) is a feared opportunistic infection in renal transplant patients. The unicellular fungus is ubiquitous in the environment but has an untreated mortality of 90-100% in non-HIV patients. This falls to 35% with treatment. Current European Best Practice Guidelines suggest 4 months of PJP prophylaxis post renal transplantation while KDIGO guidelines recommend 3 to 6 months.

There are three recent reports of outbreaks of PJP in renal transplant recipients. In Tokyo, there were 27 cases in a 1 year time frame in a centre which had seen only three cases in the previous 28 years. Over a similar 12 month period, 22 cases of PJP were identified in renal transplant patients in Leiden and recently the Royal Liverpool University Hospital reported 18 cases of PJP in their renal transplant population. None of these centres routinely used PJP prophylaxis after renal transplantation.

Our own renal unit performs approximately 50 transplants annually and PJP prophylaxis is not routinely given. In 40 years of kidney transplantation in this centre we can recall three patients with PJP and there have been none in the last decade. In the past 9 months, however, we have had three further confirmed cases of PJP. There has been no regional increase in PJP incidence. All cases occurred more than 6 months after transplantation. One patient had received anti-thymocyte globulin and plasma exchange for early acute rejection. The others had standard immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil at the time of transplantation with no antibody treatment. Two of the patients had also been treated for cytomegalovirus disease.

While the literature suggests that the peak susceptibility to PJP infection is 1 to 6 months post transplantation, all of our cases presented after this time and therefore outside the suggested window of prophylaxis. Similarly, in other outbreaks, a substantial number of affected patients presented beyond this standard 6 month period. The risk versus benefit ratio of routine prophylaxis may therefore be unfavourable, with potential exposure of transplant recipients to iatrogenic morbidity. We will continue with our current practice to not routinely prescribe PJP prophylaxis. There is a need for an up to date review of the evidence for PJP prophylaxis in renal transplant recipients.

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Antifungal Chemoprophylaxis Use In Kidney Transplantation During Major Demolition Work On A Hospital Site

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Introduction: Nosocomial outbreaks of invasive aspergillosis are a recognised complication of construction, demolition and renovation activities in or near hospital wards accommodating immunocompromised patients. There is no published guidance on when or how to prescribe antifungal prophylaxis in kidney transplant recipients during building work. We aim to report our experience of using itraconazole in a kidney transplant unit during demolition work.

Methods: 21 patients were prescribed itraconazole liquid 200mg bd for 1 month; 7 live donor recipients, 7 deceased cardiac death donor recipients and 7 deceased brain death recipients. 21 patients transplanted prior to the introduction of itraconazole and matched for donor type acted as controls. Length of initial hospital stay, incidence of diarrhoea, serum creatinine, eGFR, calcineurin inhibitor (CNI) levels, ALT, bilirubin and biopsy rate for the first 60 days post transplant were compared.

Results: Mean duration of itraconazole treatment was 21.43 days. 48% competed a 28 day course or longer of itraconazole. The most common reasons for discontinuing treatment early were high CNI levels n=5 and diarrhoea n=3. Overall more patients reported diarrhoea in itraconazole group 24% vs control 14%. Mean length of stay for transplantation was 14.5 days in itraconazole group vs 12.4 days in the control group (p=0.13). On days 3, 7, 14 and 21 the mean creatinine was higher, although not statistically significant, in the itraconazole group compared to the control. At day 60 mean creatinine and eGFR were similar for both groups. On days 3, 7 and 14 the mean tacrolimus levels were higher in the itraconazole group when compared to controls, reaching statistical significance on day 7 (16.45 vs 11.31, p=0.03). After stopping itraconazole the tacrolimus levels were significantly lower in the itraconazole group when compared to controls (day 21: 6.19 vs 12.35, p=0.0007, day 35: 7.81 vs 13.09, p=0.002, day 42: 7.37 vs 11.49, p=0.001 and day 60: 7.16 vs 11.53, p=0.009). The mean ALT was higher in the itraconazole group on days 3 and 7 but the differences did not reach significance. There was no difference in bilirubin results between the groups throughout the 60 days. One patient discontinued treatment due to a raised ALT. 13 Biopsies in 11 patients were performed in the itraconazole group and showed CNI toxicity (n=4), rejection (n=1), ATN (n=1), necrotic kidney (n=1), normal kidney (n=3), donor disease (n=1) and no renal tissue (n=2). 7 biopsies in 6 patients in control group showed ATN (n=1) and normal kidney (n=6). No cases of aspergillosis were reported in either group.

Discussion: We found itraconazole was poorly tolerated and interactions with CNI's were difficult to predict and manage despite significant CNI dose reductions. Despite initially higher mean creatinine and tacrolimus levels in the itraconazole group, eGFR and creatinine were comparable between the groups at day 60. Our experience only involved a small number of patients but highlights a number of problems. We hope our findings will be of use to other units experiencing similar building projects.

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Prophylaxis With 100 Days Of Oral Valgancyclovir Alone In The High Risk Group Is Not Sufficient To Control Cytomegalovirus Infection/Disease Following Kidney Transplantation

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Introduction.Cytomegalovirus (CMV) infection is a common cause of morbidity and mortality in Renal Transplant patients. Our current practice involves 100 days of oral Valgancyclovir prophylaxis to seronegative recipients of kidneys from CMV positive donors (D+/R-). The aim of this study was to audit the incidence of CMV infection and disease in our practice. The time of CMV infection in relation to the transplantation, immunosupression regimen, drug levels, biopsy-proven acute rejection, hospital stay and opportunistic infections were looked at retrospectively.

Method. The study group comprised of all patients receiving a new kidney only transplant performed in our unit between January 2007 and December 2009. The four CMV mismatch groups, D+/R+ (Donor positive/recipient positive), D+/R-, D-/R+, D-/R- were identified. CMV infection was defined as a positive result on PCR. CMV disease was defined as a positive CMV PCR result with symptoms.

Results. 183 kidney transplants were performed during the study period. (There was 100% prophylaxis in the D+/R- group with 100 days of oral Valgancyclovir). Sixty of the 183 (33%) patients had CMV PCR performed for symptoms in the post-transplantation period. Six patients were excluded (unknown donor status). Twenty four of the remaining patients had a positive PCR. The overall incidence of CMV infection/disease was 14% (24 in 177). The incidence of CMV in individual groups was: 9/53 (17%) D+/R+, 8/40 (20%) D+/R-, 7/41 (17%) D-/R+ and 0/46 D-/R-. The immunosupression regimen changed over the study period: in 2007 Cyclosporin, Azathioprine/MMF and Prednisolone, in 2008 and 2009 Cyclosporin/Tacrolimus, MMF and Prednisolone. The median time of infection in the different groups was 144 days in D+/R-, 70 days in D-/R+ and 67 days in D+/R+. 12 out of 24 patients needed hospitalisation for a median period of 12 days (range 1 to 86 days). Abnormal biochemical and haematological parameters did not corroborate with the diagnosis of CMV infection. Other opportunistic infections occurred in 8/24 patients. Biopsy proven acute rejection occurred in 10/24 patients (41%). There were 3 deaths and 4 graft nephrectomies.

Discussion. In this study, CMV disease post renal transplantation was found to be a significant cause of morbidity and mortality. The incidence of CMV after the 100 days of prophylaxis in the high risk group is of note. We suspect the incidence of CMV in the D-/R+ and D+/R+ group is high and related to over immunosupression. A PCR screening protocol in these two groups may be necessary to identify CMV viraemia prior to the patient becoming symptomatic and allow prompt outpatient management. As expected, there is a high rate of acute rejection associated with CMV along with hospitalisation and opportunistic infections. Only targeting the high risk group with 100 days of prophylaxis has not been sufficient to control CMV infection/disease after kidney only transplantation in our Unit.

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Vaccination post transplantation – are we doing enough?

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Introduction: All immunocompromised patients, including those post renal transplant are currently recommended to have annual prophylaxis against influenza and swine flu (H1N1) In addition, current United Kingdom guidelines suggest that concurrent vaccination for household contacts of these patients may have a beneficial effect on outcome. However, poor compliance as well as non-adherence by clinicians may result in these guidelines not being achieved with subsequent risk to a potentially susceptible patient cohort. We aimed to determine the vaccination uptake against influenza and H1N1 amongst a series of renal transplant patients.

Methods: Patients who had a renal transplant at a single tertiary unit over a 30 month period (January 2007 - July 2009) were included in a telephone based survey to determine if vaccination status for influenza and H1N1 influenza for the 2009-10 flu season. Demographic data including patient ethnicity, age and sex, and age of graft were assessed. Primary endpoints were assessed as uptake and vaccination for the two viruses with further details as to the source of provision and recommendation of the vaccinations established.

Results: 334 patients were transplanted over this period of which 201 were able to be contacted and included. Mean age at transplant was 49.3 years (range 16.8-78.8) and 114 (56.7%) patients were Male. There was a significantly greater uptake for the influenza vaccination compared to H1N1 vaccination (168 (83.6%) vs. 144 (71.6%) respectively; $p<0.001$; McNemar's test.) General Practitioners (GP's) were significantly more likely to recommend the influenza vaccination when compared to hospital doctors (126 (62.7%) and 97 (48.3%) respectively; $p<0.005$.) although this finding wasn't mirrored for the H1N1 vaccination (95 (47.3%) and 102 (50.7%) respectively; $p=0.55$.) GP's were significantly less likely to advise patients to have the H1N1 vaccination compared to the influenza vaccination; (95 (47.3%) and 126 (62.7%) patients respectively; $p<0.005$.) Only 60 (29/9%) of the questioned patients had household contacts who were vaccinated against H1N1.

Discussion: In the United Kingdom, renal transplant patients are currently significantly less likely to be vaccinated against H1N1 as opposed to the influenza vaccine despite the extensive publicity associated with this disease from the media in the recent past. In addition, few household contacts of transplant patients received the H1N1 vaccine despite recommendations to the contrary. This may reflect a lack of awareness of such guidelines amongst health professionals and patients alike. There appears to be many areas in which uptake of vaccination for both transplant patients and their household contacts can be improved thereby ensuring that potentially serious adverse events in these immunocompromised patients are avoided.

Cardiothoracic

Moderator: John Dark & Marlene Rose

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Outcome following treatment for acute antibody-mediated rejection caused by de-novo donor-specific HLA antibody after heart transplantation.

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Antibody-mediated rejection (AMR) may be caused by preformed or de-novo donor-specific HLA antibody (DSA); there are few data on the outcome of AMR caused by de-novo DSA after heart transplantation (HTx). Here, we report the outcome of all 13 patients treated for AMR, in association with de-novo DSA, since 2005 at our hospital. Of the 13, 8 were male, and the average age was 43.1 years with a range of 19.6 – 70.1 years. Diagnosis prior to HTx was dilated cardiomyopathy (N=6), ischaemic cardiomyopathy (N=4), congenital heart disease (N=2), rheumatic heart disease (N=1) and arrhythmogenic ventricular cardiomyopathy (N=1). Prior to treatment for AMR, immunosuppression was ciclosporin (N=6), tacrolimus (N=5) or sirolimus (N=2) and mycophenolate mofetil (N=11) or azathioprine (N=1) and prednisolone (N=1). Eight had undergone cardiac surgery prior to transplantation including a ventricular assist device in 1. Six had pre-existing cardiac allograft vasculopathy (CAV). In addition to biopsy and serologic evidence of AMR all had clinical and echocardiographic evidence of left ventricular systolic failure. The mean and median times between HTx and diagnosis of AMR were 7.1 and 4.5 years respectively with a range of 1.5 – 21 years. Twelve of the thirteen patients were treated with immunoadsorption (IA - Therasorb, Miltenyl-Biotech), while a single patient received plasma exchange alone because of the severity of his clinical condition. Antibody removal was followed by intra-venous immunoglobulin (IVIg) and rituximab between groups of treatments. Patients received an average of ten cycles of IA/PE with a range of 3-19 over a space of 56 – 220 days. There was frequently biopsy evidence of co-existing cellular rejection at the start of therapy and this was treated with IV methylprednisolone in 12 plus rabbit anti-thymocyte globulin in 9. Anti-infective prophylaxis consisted of low dose cotrimoxazole and aciclovir/valganciclovir as appropriate One patient also underwent total nodal lymphoid irradiation. Actuarial survival was 50% at 1 year and 26% at 2-years and 5 patients are currently alive. Five of the 8 deaths were cardiac in nature (heart failure/ arrhythmia/cardiac allograft vasculopathy/myocardial infarction), while two patients died following pulmonary embolism and one of multi-organ failure during the acute phase of treatment. There were no deaths caused by infection. Left ventricular systolic function had improved at 6 months following treatment in 4 of the 6 patients where measurements were available. The mean and median percentage reduction in DSA levels following treatment, as measured by mean fluorescent intensity (MFI) using Luminex technology, were 74.84% and 77.01% respectively with a range of 17.09% - 99.38%. In conclusion, acute AMR related to de-novo donor specific HLA antibody formation was an uncommon but serious late complication of heart transplantation and often occurred in the context of pre-existing CAV. Antibody removal treatment was often needed over a protracted period and, although cardiac function often improved, the mortality was high and most deaths were cardiac in nature. Better therapeutic approaches appear needed either through earlier diagnosis or with more effective methods of antibody- removal and suppression.

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Single Lung Transplantation With And Without Cardiopulmonary Bypass

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Introduction

Many transplant units avoid the use of cardiopulmonary bypass (CPB) for isolated lung transplant due to major concerns over aggravated lung reperfusion injury and excessive blood loss. We reviewed our 23 years experience of single lung transplantation to determine any adverse outcome

Methods

A retrospective study of all single lung transplants performed at our institution between 1986 and July 2010 were reviewed to examine differences in allograft function and post operative complications between cases undertaken with or without cardiopulmonary bypass.

Results

259 single lung transplants were undertaken between August 1986 and July 2010. 53(20.5%) were performed on bypass. The mean CPB time was 135.2 minutes. There was no difference in demographic data or primary pulmonary pathology between 2 groups. Donor ischaemic time was not significantly different in bypass and non-bypass groups (256.7m vs 241.9m ; p=0.18). Pre-op PO2/FiO2 was also not different in both groups. At 1 hour and 24 hours, post-op PO2/FiO2 ratio was no different (mean 2.95 and 3.24 in NCPB cases; 3.53 and 3.75 in CPB pts, p= 0.34 and p=0.75 respectively). Similarly extubation time was not influenced by the use of CPB. Mean blood loss, however was greater post operatively in CPB group (1254ml versus 968ml), although this was not statistically significant (p=0.002). The use of fresh frozen plasma and platelets was similar in the two groups (p= 0.64 and 0.41 respectively). More blood was transfused during post-op care of patients undergoing single lung transplantation performed on bypass (p=0.02).

Discussion

In conclusion, fears of poor post-op lung graft function after operation involving cardiopulmonary bypass appear unfounded. We could detect no difference in function at 1 or 24 hours, nor was there any difference in extubation time. It is clear, however that the use of CPB, appears to increase post-op bleeding and the need for transfusion. CPB may be used safely to facilitate lung transplantation.

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NKT cell migration into the transplanted lung: air-liquid interface model

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Introduction: Graft rejection is a major caveat to patient survival following lung transplantation. NKT cells are part of the adaptive immune system which have demonstrated tolerogenic effects yet the process is still unclear. One potential mechanism is via the CD200:CD200R signalling cascade. This study was designed to assess if peripheral blood NKT cells can migrate into the alveolar space of the transplanted lung and to characterise their phenotype following diapedesis do determine their functional state.

Methods: An *in vitro* lung model was used consisting of a cell biolayer of alveolar epithelial cells co-cultured over a bed of vascular endothelial cells. Peripheral blood mononuclear cells (PBMCs) were collected from lung transplant recipients (N=5) and were cultured into the vascular side for 24 hrs at 37ºC in 5% CO2. NKT cells from the alveolar and vascular side were characterised by flow cytometry using CD3, CD16, CD56 CD69, CD161, CD314 CD107a, CD200 and CD200R. Cell migration and marker expression following diapedesis was compared using paired samples t-test. *P*-values of <0.05 were considered to be statistically significant.

Results*:* In this *in vitro* model, NKT cells readily diapedised through the vascular bed to the alveolar space (mean migration 20±13%, p=0.001), whereby migrated NKT cells expressed CD69, CD107, CD161, CD314, CD200 and CD200R. Following diapedesis, there was a significant upregulation of the inhibitory molecule CD200 (26432±4425 vs 18938±11079, p=0.002), the marker of activation and cytotoxicity CD161 (47846±18878 vs 17861±5915) and downregulation of the receptor CD200R (46110±10167 vs 64006±17808, p=0.004).

Conclusions: This *in vitro* study suggests that peripheral NKT cells have the capacity to migrate into the airway of the transplanted lung where they can become activated in preparation for cytotoxicity. However, the upregulation of both CD200 and CD200R on NKT cells suggests that these cells may also provide inhibitory immunologic signals which could act towards inhibiting inflammatory responses.

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Moderator: Gavin Pettigrew

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Non heart beating donor in kidneys transplantation

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Although non heart beating donor [NHBD] organs are becoming more widely used in renal transplantation, there is a concern that their use may be associated with inferior outcomes, particularly in the long term.

In this study, we examine the outcomes of patients receiving NHBD kidney transplants and compare them with patients receiving organs from heart beating donors [HBDs] in our centre.

60 patients [13f, 47m; mean age 51.5+12.4 yrs] who received NHBD kidneys from 1st November 2005 were included in this study. 215 patients [82f, 133m; mean age 48,8+13.7 yrs] received HBD kidneys during the same time period were act as control.

All patients received Campath induction [30 mg iv perioperatively], low dose Tacrolimus [0.1mg/kg; target level 5-8 ng/mL] and a steroid sparing regime [prednisolone 60mg daily day 1-3; 30mg daily day 4-7 and then stopped].

5 year patient survival [NHBD: 89.3% vs HBD: 95.3%] and censored allograft survival [NHBD: 88.5% vs HBD: 89.3%] were similar in both groups.

The incidence of delayed graft function [DGF, defined as the need for dialysis post transplant]] was significantly higher in the NHBD group [43.6% vs 26.6%, p=0.02] and associated with a 5.7 fold increase risk of graft loss [95%CI 2.2, 15.0; p<0.001]. However, after adjusting for DGF, NHBD did not increase the risk of allograft failure.[HR 1.3, 95%CI 0.5, 3.6; p=0.539 Cox].

The incidence of rejection was similar in both the groups at 5 years [NHBD: 79.6% vs 74.3%].

Although allograft function, determined by MDRD eGFR, was 5.7 ml lower in the NHBD group [95%CI 0.3,-11.6; p=0.062] to start with, function did not deteriorate at a greater rate than in the HBD group [0.06 ml/month, 95%CI: -0.16, 0.29; p=0.580; Mixed effect model]

This study shows that DGF is more common in NHBD kidney recipients and associated with inferior outcomes and after adjustment for DGF, outcomes in recipients of NHBD kidneys were similar to those receiving HBD kidneys.

Prevention of DGF should therefore be a priority in non heart beating kidney donation.

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Predicting donor death and organ utilization after DCD donation: a decade of experience at King's College Hospital

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INTRODUCTION: The ever-increasing shortage of organs for transplantation has led to the reintroduction of donation after cardiac death (DCD) with the hope to increase the donor pool.

AIMS: 1.- To describe the trend of DCD offers and compare this with brain death (DBD) donor trends. 2.- To analyze the differences between accepted and declined offers. 3.- To find predictors of cardiac arrest and usability among the accepted DCD offers.

METHODS: We have performed a retrospective analysis of all the DCD and DBD offers to our Unit from 2001 to 2009. Accepted and declined offers were compared using descriptive statistics (T-test and chi-square). Accepted offers were divided among cardiac arrest and non-arrest patients. Those donors who arrested were divided into used and unused grafts. Descriptive comparisons and conditional step forward logistic binary regression models to assess predictors of cardiac arrest and usability were performed.

RESULTS:

Between 2001 and 2009, 982 DCD offers were referred to our Institution, of which 550 were accepted. Among the accepted offers, 315 patients had cardiac arrest and 155 liver allografts were used for transplantation.

During the analysis period, there has been a gradual decrease in the accepted DBD (95% in 2001 to 62% in 2009) and an increase in the accepted DCD offers (5% in 2001 to 38% in 2009). Declined offers have followed a similar pattern in the DCD (100% in 2001 to 31% in 2009) and the DBD (0% in 2001 to 69% in 2009) groups. Donor age (P=0.000), ITU stay (P=0.012), GGT (P=0.000), AST (P=0.000) and ALT (P=0.001) were statistically higher in the declined offer group.

In the DCD group, donor age >50 years (RR=1.786 [1,078 – 2,958]) and the use of inotropes (RR=0.159 [0,091 – 0,279]) were independent predictors of cardiac arrest and non-arrest in the regression model (Prediction capability=71,1%), respectively (P=0.024 and P=0.000, respectively).

Additionally, donor age >50 years (RR=2,823 [1,429 - 5,577]), BMI >30 (RR=6,095 [2,242 - 16,569]), warm ischemia time >25 minutes (RR=5,622 [1,721 – 18,365]), ITU stay >7 days (RR=3,526 [1,165 – 10,671]) and ALT ≥4x normal rates (RR=3,187 [1,019 – 9,971]) were risk factors for the usability of the graft.

The relative risk of non-usability was 20,97% (13,28% - 28,67%), 41,7% (28,27% - 55,13%), 58,29% (44,86% - 71,72%), 79,01% (71,32% - 86,72%) and 100% according to the accumulation of 1 to 5 risk factors, respectively.

CONCLUSIONS: DCD is a reliable source of grafts. We have developed models, which might be an useful tool as predictors of death in potential DCDs and graft usability and that may help to avoid unnecessary retrievals and healthcare expenditure.

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Short-term outcome following Donation after Cardiac Death (DCD) from Expanded Criteria Donors – A single centre experience.

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Introduction: Increasing gap between demand and supply of deceased donor organs has led to acceptance of kidneys from Expanded Criteria Donors' (ECD's). There is currently no clear evidence available to support this practice and longer term outcomes are still unclear. Our aim was to look at short-term outcome of donation after cardiac death (DCD) transplantation from ECD's.

Methods: Patients who underwent DCD transplantation between Sep 2008 and Oct 2010 were retrospectively studied. Donor demographic details, donor past medical history, cause of death, creatinine at retrieval, recipient demographic details and immediate/short-term outcome following transplantation were collected. Fisher's exact test was used to compare DCD's from ECD and non-ECD donors.

Results: In the last 26 months, 57 DCD renal transplants were carried out. 20 patients received organs from ECD's (all qualified >60 yrs criteria) (35.1%). Mean age of the ECD donors was 69.5 years (range 60-80 years) and majority were males (n=16). The cause of death was Cerebrovascular Accident (n=18) and Myocardial Infarction (n=2). 50% of ECD donors suffered hypertension previously (n=10). The average creatinine at retrieval was 80.6 umols/L (range 32-165 umols/L). Majority of the kidneys had good perfusion at retrieval (n=17, 85%). Mean age of recipients was 57.6 years (range 29-76 years) with equal number of male and female recipients (n=10 each). The average follow-up duration was 8.4 months (range 1-16 months). The delayed graft function rate was 50% (n=10) for ECD donors and 43.2% (n=16) for non-ECD donors (P=0.78). The mean Acute Tubular Necrosis (ATN) lasted 16 days (range 2-42 days) for ECD and 9.7 days for non-ECD (range 2-31 days), which was statistically significant (P=0.03). Two grafts were lost in ECD (Venous thrombosis , pseudoaneurysm of renal artery) in comparison to none in the other group. Though the rejection rate was higher in ECD (15%) in comparison to non-ECD (10.8%), it was not statistically significant (P=0.68). The average serum creatinine at 3 months was 184.6 umol/L (range 58-441 umol/L) for ECD and 128.8 umol/L (range 67-189 umol/L) for non-ECD, the difference was statistically significant (P=0.001). 100% of living non-ECD donors had functioning graft at the end of follow-up, compared with 90% for ECD donors (P=0.13).

Discussion: Although Expanded Criteria Donor increases the donor pool, the recipient selection should be done cautiously as the short term complications and graft function are less favourable in comparison with non-ECD donors. Analysis of data from all the centres in the UK will be helpful to validate these findings.

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Factors predicting Delayed Graft Function (DGF) following Renal Transplantation from Donation after Cardiac Death (DCD) donors – A retrospective single centre analysis

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Introduction: Delayed graft function (DGF) remains a common problem following renal transplantation and has been shown to be associated with less favourable long term outcome. The aim of our study was to identify any donor and recipient related factors leading to DGF following Donation after Cardiac Death (DCD) renal transplantation at our centre.

Methods: Patients who underwent DCD renal transplantation between Sep 2008 and Oct 2010 were included in the study. DGF was defined as requirement of two or more dialysis in the post transplant period in our unit Retrospective data collection was done comprising of the donor factors including demographic details, past medical history, serum creatinine at retrieval, allograft perfusion at retrieval and the recipient factors, type of induction agent, total ischaemic time, DGF and immediate complications. Univariate analysis was done using SPSS 16.0 to identify significant predictors of DGF.

Results: Over a period of 26 months, 57 DCD renal transplants were performed**.** The majority of the recipients were male (n=32, 56.1%). Mean age was 50.2 years (range 20 – 76 years) and mean follow-up duration was 14 months (range 1 to 26 months). 26 patients (45.6%) developed DGF. On univariate analysis donor factors including age, sex, cardiac disease, history of hypertension and diabetes, alcohol abuse and smoking history had no correlation with delayed graft function (p value >0.05). Similarly donor serum creatinine at retrieval ($\leq$ 100 versus > 100, OR=0.64 (0.17-2.40), P=0.74) and allograft perfusion (good versus fair/poor, OR=0.83 (0.21-3.29), P=1.00) had no impact on DGF. Recipient demographics and peri-operative factors like age, sex, mismatch score and type of induction agent used (Alemtuzumab (Campath) versus Basiliximab (Simulect) showed no correlation with DGF. Paradoxically our study showed no increase in DGF rate with increasing total ischaemia time ($\leq$ 12 hours versus >12 hours, OR=0.44 (0.12-1.66), P=0.34). Immediate post-operative complications (n=9, 15.8%) [bleeding needing exploration (n=3), cardiac event (n=1), lymphocele needing percutaneous drainage (n=1), early acute rejection (n=2), chest infection (n=2)] had no impact on DGF rate.

Discussion: From our single centre study no correlation could be made to donor and recipient factors for Delayed Graft Function post-DCD renal transplant, thereby emphasising the multifactorial nature of this common problem. Multivariate analysis of data from all the centres performing DCD in the UK will be helpful to identify DGF preventable factors.

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Extra Corporeal Memberane Oxygenation(ECMO) is superior than Cold Preservation(CP) for porcine DCDcat-2 donor livers: a histological analysis

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Aims:

Normothermic ECMO has been used by certain groups with success, in Donation after Cardiac Deaths (DCD's) for liver transplantation. We sought to compare the effects of ECMO on liver histological changes, with those from CP method of intra-vascular and -peritoneal cooling in n porcine model.

Methods:

11 cross-Yorkshire landrace pigs were studied as 2 groups; ECMO (n=5) and CP group(n=6). Under general anaesthesia, all animals underwent laparotomy for the cannulation of great vessels, placement of microdialysis catheters, followed by abdominal closure and euthanasia. After 30mins of warm ischaemia, abdominal aorta was isolated both proximally and distally, and thrombolysis administered. In the CP group, a peritoneal cooling circuit was established along with continuous aortic infusion of cold HTK solution for 2 hours. In the ECMO group, the circuit was commenced to perfuse the abdominal organs using pig's own oxygenated normothermic blood for 2hours. Liver was then retrieved, biopsied, cold stored and then re-perfused for 2 hours on an ex-vivo oxygenation circuit using a mixture of autologous blood and RS-I solution. Repeat biopsies were taken at the end of reperfusion. Tissue samples were then analysed using a semi-quantitative score by an expert liver histopathologist, blinded to the groups. Paired t-test or Mann-Whitney U tests were used to analyse the results, as appropriate.

Results:

After CP or ECMO preservation phase, no significant damage was noted in either of the groups. Some vacuolar changes were noted within the tissue parenchyma in both the groups and were comparable (p=ns).

But after cold ischaemia and re-perfusion injury, very noticeable histological differences were found in between the groups. Extensive damage was consistently noted in the CP group (mean damage - 72%, median 90%), with features such as hepatocytes with shrunken nuclei, sinusoidal dilatation and discohesive plates. While in the ECMO group, the liver parenchyma was significantly better preserved (mean damage – 16.6%, median 2.5%) (p=0.016).

The vacuolar changes noted in livers after ECMO preservation also did not get significantly worse on re-perfusion.

Conclusion:

The extent of vacuolation and histological changes has been shown to predict DCD liver graft viability in some studies. In our set of experiments, ECMO preserved DCD livers suffered much lesser damage. Therefore ECMO is probably better in preserving the tissue viability after reperfusion, in comparison to the CP method. This is in consistency with our biochemical results mentioned in our previous studies.

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Delayed Graft Function (DGF) In Renal Allografts From Donors After Cardiac Death (DCD) - Causative Factors And Influence On Outcome

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Background: The use of kidneys from DCD donors is a strategy that increases the number of available organs. Here, we report a significant experience of kidney transplantation from DCD donors and identify certain factors that may contribute to DGF and influence short to medium term outcome in this population.

Methods: Data was collected on all DCD donor transplants performed in a single unit during 5 years. Outcome measures included patient and graft survival, DGF, incidence of acute rejection (AR) and short to medium term graft function. Median follow-up time for recipients of DCD kidneys was 29.8 months (range 2-73.8 months). Chi square, Mann-Whitney and Student`s t tests were used to identify differences between groups. Kaplan-Meier estimates were used to assess graft survival and binary logistic regression was employed to identify factors associated with DGF.

Results: Between 20th September 2004 and 30th April 2010, 514 adult renal transplants were performed in our unit, of these 80 (15.5%) were from DCD donors. The median donor and recipient ages were 47 [17-68] and 51.5 [19-72] years, respectively. All patients received ATG for induction therapy and maintenance immunosuppression with tacrolimus (Tac), mycophenolate mofetil and prednisolone with an intention to withdraw it by 3 months. Median cold and primary warm ischemic times (CIT, WIT) were 13 [5-27] hours and 17 [8-24] minutes, respectively. Median number of HLA mismatches was 3 (mean 3.4). None of the patients experienced primary non-function, 55 (73%) had DGF. AR occurred in 7 (9%) subjects in the 1st year. Median eGFR at 1, 2, 3 and 4 years was 51.5, 53, 49 and 51 ml/min respectively. In patients who had at least 12 months of follow-up (n=61), one year patient survival rate was 95% (58/61) and one year graft survival rate was 92% (56/61). A higher proportion of males compared to females (85% vs 52%, p=0.003) developed DGF. Median 1st week average Tac level was 10.03 [2.4-25] µg/l. By logistic regression, none of the following factors were associated with occurrence of DGF: recipient diabetes, donor age, number of mismatches, average 1st week serum Tac level, CIT or WIT but female gender was protective factor against DGF (OR 0.181, 95% CI 0.059-0.554, p=0.002). 1-year (100% vs. 96%) and 3-year (93% vs. 93%) cumulative graft survival was not different (Log Rank p=0.85) in the presence or absence of DGF. As compared to patients with higher 1st week Tac levels (>6 µg/l), patients with lower Tac levels (<6 µg/l) had improved 1-year graft function (eGFR 59 [31-84] vs 47[14-95]; p=0.029). Lower average Tac levels (<6 µg/l) were not associated with any increase in episodes of AR (p=0.5).

Discussion: The proportion of DCD donor kidneys is increasing. In this analysis, gender but not ischemic times or donor age was associated with the occurrence of DGF. DGF in DCD kidneys does not affect medium term graft survival. DCD donor kidneys may be more vulnerable to calcineurin inhibitor toxicity in the first few days post-op therefore lower levels of calcineurin inhibitors from the beginning might be appropriate

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Introduction of a Virtual Crossmatch Policy Leads To A Reduction In Delayed Graft Function In Recipients Of Kidneys Donated After Brain Death

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Introduction: The virtual crossmatch (vXM) is a concept that allows omission of the pre-transplant XM test in patients when a negative XM can be reliably predicted from sensitization history and antibody screening. With the increasing use of organs from expanded criteria donors and donors after cardiac death (DCD) there is greater incentive to introduce a vXM, which may expedite transplant surgery. The vXM has been adopted by a number of transplant centres after initial implementation in Cambridge. The aim of the study is to assess the effect of a local vXM on cold ischaemia times (CIT), delayed graft function (DGF), and graft survival rate.

Methods: Between January 2009 and October 2010, 139 deceased donor kidney transplants were performed. Data was retrospectively collected from hospital databases. A vXM was performed in 52 (37%) transplants and in all cases a negative XM test was confirmed retrospectively. 111 (80%) of kidneys were donated after brain death (DBD) and 28 (20%) after cardiac death (DCD). DGF was defined as the necessity for dialysis in the first 7 days post transplantation, excluding patients who were dialysed for hyperkalaemia. Statistical analysis of data included Chi-Square contingency tests, Kaplan Meir survival plots and Cox proportional hazards regression with $p<0.05$ considered statistically significant.

Results: The mean CIT was 13.8 hrs with a prospective XM test and 9.9 hrs with a vXM ($p< 0.01$). A statistically significant beneficial effect of the vXM on DGF was apparent in recipients of DBD kidneys, where the DGF rate was 36% with a prospective XM test and 18% with a vXM ($p=0.046$). The corresponding DGF rate in recipients of DCD kidneys was 53% with a prospective XM test and 38% with a vXM. Logistic regression analysis of combined DBD and DCD data, after adjustment for variables that influenced DGF, showed that the vXM was not a predictor of DGF independent of CIT, but DGF was significantly lowered by reduced CIT ($p=0.002$). Omission of the prospective XM test neither influenced acute rejection nor graft survival.

Conclusion: The introduction of the vXM in this centre has within a short period shown a significant effect on CIT. In this analysis we have also seen an influence of CIT on DGF. The introduction of these practices merit consideration by other transplant centres.

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Moderator: Amanda Knight

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Comparison of Outcomes And Impact Of Delayed Graft Function (DGF) On kidneys From Donors After Cardiac Death (DCD) vs. Donors After Brain Stem Death (DBD)

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Background and objectives: Due to the growing demand for organs, the use of kidneys from DCD donors is increasing. Here, we compare graft and patient outcomes of DCD versus DBD donor kidney transplants performed at our unit.

Methods: All patients who received a renal transplant from a DCD or DBD donor in a single unit during a 5 year period were included. Patients transplanted with DCD donor kidney were administered ATG induction whereas those who received DBD donor kidneys were given basiliximab. Maintenance immunosuppressions for both groups were tacrolimus, mycophenolate mofetil and prednisolone with an intention to remove steroids by 3 months if no acute rejection had occurred. Outcome measures were graft and patient survival, incidence of DGF, incidence of biopsy proven acute rejection (AR), length of hospital stay and short to medium term graft function. Chi square, independent samples t-tests or relevant nonparametric tests were used to compare means. Kaplan-Meier estimates and Cox regression model were used to assess graft and patient survival.

Results: In the time period mentioned above, 514 adult renal transplants were performed, of which 208 (40.5%) were from living donors, 226 (44%) were from DBD donors and 80 (15.5%) were from DCD donors. Median follow-up time for recipients of DCD kidneys was 29.8 and for DBD recipients 39.6 months. There was no differences in donor age (median 47 [17-68] vs. 52 [2-78] years, p=0.2) or recipient age (51.5 [19-72] vs. 51[18-78] years, p=0.3), between DCD and DBD groups. More patients received re-transplantation in the DBD group (23% vs 9%, p=0.005). Median cold ischemic time was significantly shorter in the DCD group (13 [5-27] vs. 15 [6-32] hours, p<0.001) whereas number of HLA mismatches was lower in the DBD group (median 2 vs. 3, p<0.001). There was only 1 primary non function in DBD group and none in DCD group. There was significantly more DGF in the DCD group (74% vs 27%, p<0.001). Length of hospital stay post-transplant was also significantly longer for the DCD group (median 12 vs. 9 days, p<0.001). In the first year, AR was less common in the DCD group (9% vs 23%, p=0.005). Median eGFR at 1 year were similar in both groups (DBD 50 vs DCD 51.5 ml/min, p=0.6). Among patient with 1 year follow-up in both groups, one year patient survival rates (DCD 95% vs DBD 96%, p=0.8) and 1 year graft survival rates (DCD 92% vs DBD 90%) were similar. By Kaplan-Meier method, death censored graft survival was similar in both groups (p=0.6) as was patient survival (p=0.9).

Conclusions: In this analysis, medium term graft survival and graft function was similar for DBD vs. DCD donor kidney transplant recipients. The observed increase in DGF in the DBD group did not influence outcome (though it does contribute to an increased length of hospital stay). The lower incidence of biopsy proven AR in the DCD donor recipients probably reflects the use of ATG induction therapy in this group.

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Donor Kidney Disease and Transplant Outcomes for Kidneys Donated After Cardiac Death

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Background: Donation after Cardiac death (DCD) is becoming increasingly common and provides kidneys with comparable outcome to heart beating (DBD) kidneys. In recent years however, increasing numbers of marginal DCD kidneys from elderly donors (60+) have been used and long term outcomes are not yet known. Histopathological scoring systems have been developed to guide the use of marginal DBD kidneys but such scoring systems, based on the presence of chronic damage, have not been validated for DCD kidneys. Here we report how baseline damage impacts on outcomes of DCD kidneys.

Methods: Outcomes of all first time and single-kidney DCD (213) and DBD (100) transplants performed at our centre between 2006 and 2010 were analysed. Time zero biopsies were performed routinely and were scored histopathologically according to the presence of glomerular, tubular, parenchymal and vascular disease (summed total of 0-3 for each component) as described previously by Remuzzi et al. Multivariate analysis was performed to assess the association of a number of donor and recipient variables (donor age, donor type [DCD vs DBD], donor sex, donor hypertension, donor smoking, recipient age, recipient sex, cold ischaemic time and HLA mismatch level) on graft outcome of 90 day eGFR and death censored graft survival with an average follow up of 2 years.

Results: Multiple regression analysis revealed that only donor age and baseline score were independent predictors of reduced 90 day eGFR (Table 1). Univariate analysis confirmed that death censored graft survival for DCD and DBD kidneys was comparable. Levels of baseline disease were similar in DCD and DBD kidneys indicating that the deleterious impact of baseline disease on graft outcome was not greater for DCD kidneys than for DBD kidneys. Similar to DBD kidneys on univariate analysis, DCD kidneys scoring 4-6 had poorer graft survival than DCD kidneys scoring 0-3 though acceptable 2 year survival rates were achieved for these poorly scoring DCD kidneys.

Conclusion: Baseline disease in DCD kidneys impacts upon graft outcome but not to a greater extent than DBD kidneys. Kidneys with moderate baseline score (4-6) achieve satisfactory results when implanted singly.

Table 1: Multiple regression analysis of donor age, global score and donor type.

Variables (n=67)	Range	Estimate	Standard Error	P - value
Donor Age (years)	14 - 82	-0.29	0.13	0.0302*
Global Score (0-12)	0 - 6	-3.15	1.22	0.0124*
DCD vs DBD	-	2.44	3.84	0.5281

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Kidneys Procured from Deceased Post Cardiac Death Expanded Criteria Donors; Is our ambivalence justified?

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Introduction

Deceased Brainstem Dead (DBD) donors are considered Expanded Criteria Donors (ECD) if they are aged greater than 60 years or aged 50-60 years with 2 of 3 other adverse features (elevated terminal creatinine, past medical history of hypertension, and cerebrovascular event as the cause of death). Applying the same criteria to Deceased Cardiac Death (DCD) donors defines a new subgroup of donors. There is the fear that recipients of kidneys procured from such donors might have poorer outcomes. The aim of this study was to assess outcomes for kidney transplant recipients from DCD ECD and compare them with a contemporary group of recipients from standard DCD donors and also DBD ECD.

Methods

During a 5 year period a total of 306 renal transplants from deceased donors were performed in a single unit; 226 (74%) from DBD donors and 80 (26%) from Maastricht type III DCD donors. The DCD ECD and standard DCD were compared with respect to incidence of delayed graft function (DGF), primary non-function (PNF), 1 year patient and graft survival, and 1 year eGFR. The standard DBD donor transplants for the same period were used as a reference.

Results

Of the 226 DBD donors 85 (38%) were ECD and of the 80 DCD donors 21 (26%) were ECD. The median age of the DCD EC donors was 62 years. The Cold Ishaemic Time (CIT) was shorter for DCD ECD kidneys (10.5 hrs) than for standard DCD donors (13 hrs, p=0.03) whereas the median number of HLA mismatches was 3 in both. There was no PNF in the DCD group, and the incidence of DGF was the same in standard and ECD DCD donors. The 1 yr graft survival was 95% in both DCD ECD and standard DCD donors.

Donor Type		**N**	**DGF**	**PNF**	**1 yr graft survival**	**1 yr patient survival**	**Median 1 yr eGFR**
DBD	**standard**	141	22%	0%	94%	97%	52
	ECD	85	32%	1.2%	87%	97%	45
DCD	**standard**	59	68%	0%	95%	100%	52
	ECD	21	71%	0%	95%	97%	40

Discussion

A significant proportion of our DCD donors would be considered ECD according to criteria used in DBD donors. The recipients of such kidneys have the same rate of DGF with standard DCD donors when CIT is kept short. PNF is as low as in recipients of kidneys from both standard criteria DCD and DBD donors. 1 year graft and patient survival is excellent, although 1 year eGFR is less than for either kidneys procured from standard DCD donors or DBD ECD donors. These kidneys offer a good chance of medium term graft survival.

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Induction with ATG in DCD renal transplants improves patient outcomes and is cost effective compared to IL2 monoclonal antibodies (IL2Mab) at one year.

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Renal transplants from DCD are increasing in the UK; however such transplants have a greater risk of DGF and increased morbidity. Induction immunosuppression may contribute to reduce such risks but controversy remains as to the optimal regime. The aim of this study was to analyse outcomes and cost effectiveness of induction with ATG vs IL2Mab in DCD renal transplantation. **Method** We retrospectively analysed 45 consecutive DCD renal transplant recipients for 12 months. The first 24 received IL2Mab and following changes in policy the subsequent 21 received ATG induction. Outcome analysis was based on: patient and graft survival, DGF, BPAR, infections and serum Cr. Cost analysis included: hospital stay post transplant and for readmission, HD sessions, immunosuppression and clinic visits. **Results** Demographics, HLA mismatch, CIT and donor characteristics were comparable. At 12 months, patient survival was 90.5% vs. 87.5% (p NS) and graft survival was 90.5% vs 95.8% (p NS) respectively for ATG vs IL2Mab. Analysis was performed on all patients with a functioning graft at six months

Outcomes

Parameter(%)	**ATG**	**IL2Mab**	**P**
DGF	52	65	0.08
HD sessions	38	62	**0.0001**
BPAR	0	13	**0.003**
Infections requiring admission	17.6	43.4	**0.0001**
Patients readmitted	29.4	56.5	**0.0002**
Average serum Cr	133	168	NS
Average bed stay days post transplant	14	18	NS

Cost analysis results showed statistically significant savings in the ATG arm.

Cost analysis (£)

Parameter	**ATG**	IL2Mab	**p value**
Immunosuppression	47255	41508	NS
Bed stay days post transplant	95600	167200	**0.0004**
Bed stay days for readmission	19600	68800	**0.0001**
HD sessions	10384	20064	**<0.0001**
Clinic visits*	93760	167200	**0.007**
Total Cost			**0.002**
Average cost/patient	15659	19401	**0.002**

Conclusion

At 12 months, patients in both groups had similar patient and graft survival. BPAR and DGF was better in the ATG arm. Also, lower cost when compared to IL2Mab. Whilst this is a single centre study with small numbers, these results suggest that ATG is a cost effective induction agent and may contribute to improving patient outcomes and reduce morbidity in DCD renal transplants.

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ATB-346, a hydrogen sulphide releasing derivative of naproxen, reduces ischaemia reperfusion injury in a porcine model of donation-after-cardiac-death kidney transplantation

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Introduction

Hydrogen sulphide has been demonstrated to improve renal function and oxidative damage. Its administration is complicated by its short half-life and need for a donor. A novel hydrogen sulphide releasing drug, ATB-346, a derivative of Naproxen (NSAID) may address these problems. The objective of the study was to investigate the effects of ATB-346 in reducing renal ischaemia reperfusion injury (IRI).

Methods

Porcine kidneys were retrieved after 25 minutes of warm ischaemia and then preserved by static cold storage for 18 hours. After preservation the kidneys were reperfused with autologous blood using an isolated organ preservation system at 38-39°C and mean arterial pressure of 85 mmHg for 3 hours. Kidneys were randomised to 3 groups: control (n=6), ATB-346 (10μmol/l) (n=6) and Naproxen only (10μmol/l) (n=6). ATB-346 and Naproxen were added during priming of the circuit prior to *ex-vivo* perfusion. Functional parameters, serum and urine were measured. 3-way ANOVA measures with post-test comparisons were used.

Results

ATB-346 improved renal function with greater creatinine fall, with a significantly lower area under the curve (AUC) (ATB-346 (2063±143) *versus* Control (2261±169) *versus* Naproxen (2258±117) μmol/l.h; P=0.0112) and greater total urine output (P=0.0227). However, renal blood flow was significantly reduced by the administration of ATB-34 (AUC P=0.0123).

Discussion

ATB-346 ameliorates IRI with improved creatinine fall and total urine output. The reduced renal blood flow suggests that protection may also be conferred other than from its haemodynamic effects. As such, hydrogen sulphide releasing drugs shows promise in alleviating IRI.

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Donation After Cardiac Death Liver Transplantation Is Associated With Greater Renal Dysfunction

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The growing discrepancy between supply and demand for liver transplantation has precipitated a resurgence of interest in Donation after Cardiac Death (DCD). DCD liver transplantation offers acceptable graft and patient survival. Yet, the implications of suboptimal initial graft function for patient morbidity has not been established. The aim of this study was to determine whether DCD liver transplantation is associated with greater peri-operative and long-term post transplant renal dysfunction than Donation after Brain Death (DBD).

Methods: Single centre study of 66 patients who underwent elective DCD liver transplantation 01/2007-04/2010. The DBD controls (whole livers) were age-sex-MELD matched (1:1). Glomerular filtration rate (eGFR) was estimated by the MDRD4 equation. Chronic kidney disease was defined as eGFR <60ml/min/1.73m^2**.**

Results: DCD patients and DBD controls were well matched with regards to listing serum creatinine (p=0.762), eGFR (p=0.514) and the prevalence of ascites (p=0.117) There was no difference in the proportion of DCD and DBD patients who received renal sparing immunosuppression (p=0.315).

Peri-operative renal dysfunction: During the immediate post-operative period DCD patients compared with DBD controls had a greater change in serum creatinine from listing (+103% vs +40%, p=0.011), and a greater frequency of renal replacement therapy (32% vs 17%, p=0.042). In the DCD group, listing eGFR (p=0.177) was not predictive of the need for renal replacement therapy. Instead peak post transplant AST (p=0.003) and INR (p=0.042) were the only independent predictors. ROC analysis identified a peak AST >2800 U/l and peak INR >1.8 predicted renal replacement therapy with appropriate sensitivity and specificity.

Long-term renal dysfunction: At 12 months post transplant there was no difference in the proportion of DCD and DBD patients who had chronic kidney disease (55% vs 46%, p=0.398), and the mean change in eGFR from listing was also similar (-19% vs -14%, p=0.446). However, a multiple linear regression analysis in DCD patients adjusting for age, gender, listing eGFR and immunosuppression found that a higher peak peri-operative AST was predictive of greater loss of renal function (p=0.047).

Conclusion: DCD liver transplantation is associated with greater peri-operative renal dysfunction. Furthermore, in DCD patients peri-operative renal failure and long term loss of renal function are predicted by markers of initial graft function. Strategies are required to minimise the peri-operative renal 'hit' of DCD liver transplantation.

Histocompatibility

Moderator: Sue Fuggle

HLA specificity frequencies of UK renal waiting list patients - Claire Burt, Claire Cryer, Rachel Johnson and Phil Dyer (SNBTS and NHSBT)

Claire Burt[1], Claire Cryer[1], Rachel Johnson[2], Phil Dyer[1]

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Group	HLA - A2 Specificity	
	Number	Percentage
A	205	30.84
B	85	23.08
C	267	25.09
D	173	31.34
E	177	24.79
F	152	27.14
G	59	32.07
H	59	20.63
I	101	23.82
J	89	19.02
K	155	16.77
L	117	24.58
M	92	31.08
N	99	18.61
O	322	24.96
P	12	25.00
Q	57	23.75
R	124	28.70
S	122	23.64
T	170	25.53
U	133	27.37
V	69	30.80
W	189	26.25
X	67	23.59
Y	142	23.43
Z	145	28.54
AA	129	26.88

Figure1: HLA-A2 Frequencies

Introduction: This study reviews HLA specificity frequencies of all patients on the UK renal waiting list, in August 2009, and compares and contrasts the frequencies between 27 different centres. This data will be a useful resource for H&I labs UK wide to give an idea of which allele frequencies are rare and common in their particular area, and will be useful for training purposes providing information on local HLA frequencies. **Materials and Methods:** The data was obtained from NHSBT and contains the HLA-A, -B and -DR types of 7007 patients from 27 different registering centres, UK wide. Each centre was anonymised, with patient numbers ranging from 24 to 645 per group; the data was categorised according to centre. Any patient with a single specificity at any locus was homozygous, assuming that all patients were typed using "modern technology". As a result, frequencies were calculated as equivalent to genotype frequencies. The data has been analysed for allele frequencies using Excel and statistical analysis performed using the Graphpad Quick Calculator for analysing 2x2 contingency tables, with the Fishers exact test. The frequency of each allele is counted, and the Excel worksheet has in-built validation calculations to ensure that no data is omitted.

Results and Conclusions: Initial analysis of these data show that the most common HLA-A specificity is HLA-A2, with allele frequencies ranging from 16% to 32% (HLA-A2 positive patient numbers range from 12 to 322, with no significant differences between these groups, $p = 1.0$). The specificity frequencies of HLA-A2 for the entire data set are shown in figure 1. The most common HLA-B specificity is HLA-B44 (a split of HLA-B12), with allele frequencies ranging from 4% to 20% (HLA-B44 positive patient numbers ranging from 2 to 158, a difference which is not quite statistically significant, $p= 0.0865$). The most common HLA-DR specificity in this data set is HLA-DR4, with allele frequencies ranging from 8% to 23% (HLA-DR4 positive patient numbers range from 4 to 181, which is not statistically significant, $p = 0.2549$). This data may potentially be used for analysis of common haplotypes at two and possibly three loci, for example HLA-A1, -B8, - DR3, HLA-A2, -B44, -DR7 and HLA-A30, -B18, -DR3.

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TPMT genotype and Human Leukocyte Antigen (HLA) specificities: Is there any linkage disequilibrium?

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Background

Azathioprine is widely used as a cost-effective immunosuppressive agent following renal transplantation. It is metabolised by the enzyme TPMT. Inter-individual variations in the rate of metabolism of azathioprine can be a consequence of the presence of variant alleles in the TPMT gene, encoded on Chromosome 6 (6p22.3), which alter the level of enzyme present, or the functional quality of the enzyme. The TPMT variant alleles: TPMT*2, *3B, *3C, *3A (with G238C, G460A, A719G, both G460A and A719G mutations respectively), account for 75-80% of mutations in the TPMT gene. The Major Histocompatibility Complex, encoding HLA antigens, is also on the short arm of Chromosome 6 (6p21.3), and is a genomic region of extremely tight linkage disequilibrium spanning up to 8Kb. This study investigates whether linkage disequilibrium spanning the highly conserved MHC extends as far as the TPMT gene. The aim was to compare HLA specificities present with the patient's TPMT genotype to see whether it would be possible to use a patient's HLA type as a predictive indicator of their risk of experiencing toxicity to azathioprine.

Methods

In this study involving 186 individuals, TPMT genotyping was performed by allele specific PCR-SSP and PCR-RFLP typing for common TPMT variants (G238C, G460A, A719G) and HLA typing was performed prior to transplantation by PCR-SSP.

Results

Thirteen individuals had variant TPMT alleles. An increased association between common TPMT variant alleles was observed in patients who were positive for HLA-DR2, and HLA-A9. The presence of HLA DR2 was common in all 3 groups with variant alleles. However, this was not statistically significant ($p=0.0329$, 0.0256 & 0.1593 for A719G, G460A and combined A719G and G460A respectively) which may reflect the limited numbers in the study. For the variant G460A more people carrying the variant were HLA-A9 positive than those carrying wild type alleles, again this was not statistically significant ($p=0.138$). HLA-B27 was not increased in frequency in renal transplant recipients with either wild type or variant type TPMT alleles. Further studies with larger numbers would confirm whether there is any linkage disequilibrium between HLA specificities and TPMT variant alleles.

Discussion

Correlation between HLA-A and HLA-DR loci with the presence of variant TPMT alleles has been attempted in this study. There is some correlation identified between TPMT variant and HLA-A9, and HLA-DR2, but it does not show any strong correlation in this study population. This is a very first attempt for the number of individuals with available data to correlate. It will be interesting to look at possible linkage disequilibrium with inclusion of other non-functional TPMT variant alleles in a larger sample.

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Successful deceased donor renal transplantation despite the presence of pre-formed donor reactive HLA-DP antibodies

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Introduction. Sensitive solid phase HLA antibody assays are now routinely used to identify pre-formed HLA antibodies in patients listed for renal transplantation. Such assays are able to identify antibodies to HLA antigens whose clinical relevance remains uncertain, including HLA-DP antibodies. Here we describe successful deceased donor transplantation in 5 patients in whom donor-specific HLA antibodies (DSA) directed against donor HLA-DP were either prospectively identified or surmised.

Patients. Between August 2006 and November 2009 5 patients known to have multiple anti-DP antibodies were offered deceased donor organs. In all cases the pre-transplant B cell cross match (XM) was positive. Three patients were receiving second transplants. All were highly sensitized and were offered 000 A-B-DR mismatched grafts. All had HLA-DP DSA with a Luminex MFI >8,000 giving rise to a positive CDC B-cell XM in 1 case and strong positive flow cytometry B-cell XM in 2. Two patients receiving first grafts had low titre DSA (Luminex MFI 2-3,000) with weak positive flow B-cell XM. All received immunosuppression with basiliximab induction, tacrolimus, MMF and prednisolone. Two patients with high titre DSA who experienced delayed graft function (DGF) received, in addition, 5 post-operative 3L plasma exchanges (PEX) over 7 days and thymoglobulin (total dose 6mg/kg).

Results. 1 patient with high titre DP DSA had primary graft function with serum creatinine falling to 90μmol/L within 5 days of transplantation. Graft function has remained stable over 18 months follow up, with disappearance of DP DSA. All 4 other patients experienced DGF, with PEX and thymoglobulin administered to 2 with high-titre DP DSA. All underwent 1 or more transplant biopsies, with a single episode of Banff 1A acute rejection identified in 1 patient (low titre DSA). No biopsy was positive for C4d deposition. All were discharged from hospital with good graft function (serum creatinine 90-147μmol/L) and after 12-48 months follow up remain stable (serum creatinine 102-158μmol/L). In 2 patients DP DSA have disappeared, and in the other 2 have diminished.

Conclusion. In this small series, transplantation in patients with pre-formed HLA-DP DSA appears safe with good medium-term graft function.

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High Resolution Analysis of Renal Allograft Rejection – HLA typing

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Aims: To compare nucleotide sequencing of HLA alleles with standard antigen level HLA typing in 100 renal allograft recipients who lost their graft to rejection.

Methods: The donor recipient pairs in this study were originally HLA typed using the standard PCR-SSP antigen level methods currently used for renal transplantation matching and antibody assessment. We report the HLA typing of this cohort using nucleotide sequencing of exons 2,3 and 4 for HLA Class I and exons 2 and 3 of HLA-DRB1*,3*,4*,5*, -DQB1* and -DPB1* to define the allele level HLA type. In addition HLA-DQA1* and -DPA1* were typed using high resolution PCR-SSP.

Results: When assessing the HLA antigen mismatch of a donor/recipient pair it is normal to assume the most common HLA allele is present. For example the most common allele of HLA-A*02 is HLA-A*02:01 and a high resolution match for this allele is assumed if the HLA-A2 antigen is present. In our 100 pairs this form of assumed match was shown to be incorrect in 10.5 % of pairs at HLA-A*, in 19% of pairs at HLA-B* and in 28% of pairs at HLA-DRB1*. This resulted in an unexpected change of mismatch at the allele level of HLA-A*,-B* or -DRB1* in 47% of the donor recipient pairs when high resolution match was compared to the standard antigen level match. Lower levels of difference between antigen and allele level mismatches were detected for HLA-C, -DQ and -DP.

Conclusion: In total more than 50% of the donor recipient pairs in this cohort had a mismatch undetected by standard antigen level matching. This would result in an amino-acid mismatch that may induce direct and indirect T cell recognition and antibody production. High resolution HLA typing is not suggested for deceased donor HLA matching. Given the high level of “hidden” mismatches indicated in this study it may however be useful to take in to account the precise HLA alleles for accurate assessment of the HLA antibody produced when a renal transplant is rejected.

Immunosuppresion

Moderators: Sian Griffin & John Asher

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Low dose of ATG at induction immunosuppression for renal transplantation is associated with decreased incidence of CMV viraemia when compared to IL2Mab

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Introduction: CMV infection post renal transplantation is associated with increased morbidity and mortality. Use of ATG specifically has been associated with an increased risk of developing CMV and opportunistic infections. In our unit, to reduce the risk of developing CMV, all patients receiving ATG as induction immunosuppression receive CMV prophylaxis with valganciclovir except where the donor and recipient are both sero negative for CMV (D-/R-). For those patients receiving IL2Mab for induction, valganciclovir is prescribed only when the donor is sero positive for CMV and recipient is negative (D+/R-). The aim of this study was to determine the incidence of CMV in patients receiving ATG compared to IL2Mab for induction immunosuppression. All patients are monitored in follow-up clinic for CMV viraemia. The induction dose of ATG was 2.5 mg/kg on induction followed by 1.25 mg/kg on day 4 post-transplant. **Method:** We retrospectively analysed 84 consecutive renal transplant recipients from our unit who received valganciclovir prophylaxis post renal transplantation from April 2008 to March 2010. Data collected included patient demographics, source of organ, D/R status, induction therapy, duration of valganciclovir prophylaxis, days of under dosing and incidence of CMV. CMV viraemia was defined as count of > 3000 copies on PCR. **Results:** 44 patients received ATG induction immunosuppression and 40 IL2Mab. Patient demographics were similar in both arms although more patients in the ATG arm received a DCD renal transplant. The incidence of CMV viraemia was 31 % in the ATG arm and 45% in the IL2Mab arm (p= 0.04). Interestingly independent of course length, the time to CMV viraemia after completing valganciclovir prophylaxis was similar in both arms.

Parameter	**ATG**	**IL2Mab**	**p value**
CMV viraemia	31.8%	45%	0.04
Days post prophylaxis to CMV reactivation	41.3	44.4	NS
% of patients under dosed	59	30.5	0.0001

Further analysis of data showed that significantly more patients (59%) in the ATG arms were under dosed (i.e. > 7 days) compared to those in the IL2Mab arm (30.5%); p 0.0001

Conclusion: In our series, induction with low dose ATG and CMV prophylaxis is associated with lower incidence of CMV viraemia when compared to induction immunosuppression with IL2 Mab. This is despite more patients in the ATG arm receiving sub optimal doses of valganciclovir. Whilst this study is small in numbers, these results suggest that ATG induction can be used safely without concerns of increasing CMV.

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The Effect of Long-Term Maintenance Immunosuppressive Therapy on Th17 Cells in Alemtuzumab-Treated Patients

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Introduction: Leukocyte depletion at the time of transplantation with alemtuzumab (Campath-1H) has been demonstrated to be one of the ways of reducing immunosuppressive drug load without increasing the rate of acute rejection. While the impact of alemtuzumab treatment on the immune system has been explored, the effects of long-term immunosuppressive therapy in alemtuzumab treated patients still need to be elucidated.

Methods: In this study, we investigated the effect of long-term reduced immunosuppressive therapy on T effector and T regulatory (Treg) cell populations in 10 kidney transplant recipients treated with alemtuzumab induction. 7 patients were converted to sirolimus monotherapy at 12 months post-transplant while the remaining 3 patients with history of graft rejection were treated with sirolimus and mycophenolate mofetil (MMF). At > 3 years after transplantation Treg cells and Th1/Th17 responses were assessed by flow cytometry and real-time PCR. Additionally, we sorted and expanded IL17A-producing CCR6+CD4+ T cells and assessed their susceptibility to suppression by Treg cells *in vitro* suppression tests.

Results: 3 years of mTOR inhibitor monotherapy correlates with an increase in the number of IL-17A producing cells, compared to patients treated with sirolimus and MMF. In these patients, IL-17A expression was compensated for by an increase in Treg cell frequency and number. Additionally, we demonstrated that both proliferation and cytokine production by Th17 cells can be effectively regulated by Treg cells.

Discussion: Our results demonstrate that history of rejection and long-term maintenance immunosuppression has an impact on the number of circulating Treg and Th17 cells. But more importantly, we have shown that Treg can effectively regulate Th17cells both *in vitro* and *in vivo*.

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Delayed Graft Function is associated with an increased risk of renal allograft rejection and loss in patients receiving Campath and Tacrolimus monotherapy

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There are no published studies describing the effect of delayed graft function [DGF] in patients receiving Campath induction. We report the effect of DGF in a cohort of 500 consecutive kidney allografts [184f, 316m; mean age 48.2 years] transplanted from November 2005 in our unit.

All patients received Campath induction [30mg iv perioperatively], a steroid sparing regime [prednisolone 60 mg/d, days 0-3; 30 mg/d, days 4-6, then stopped] and low dose Tacrolimus monotherapy maintenance [0.1mg/kg/day, target 5-8 ng/mL]. DGF was defined as the need for dialysis after transplantation.

DGF occurred in 91/500 [18.2%] recipients.

Multivariable analysis demonstrated that every hour of cold ischemia time [CIT] increased the risk of DGF by 10% [OR 1.1; p=0.025; Logistic regression]. CIT together with recipient age [OR 1.06 per year; p=0.036] were strong predictors for DGF.

5 year patient survival was similar in the 2 groups [DGF+ 92.3%, DGF- 94.5%] whereas allograft survival was inferior in the DGF+ group [71.3% vs 93.5%; Logrank p<0.0001].

DGF was associated with a higher incidence of rejection [30.9% vs 25.9%; p=0.0446]. After adjusting for the effect of rejection and donor type, DGF was associated with a 4.8 fold increased risk of graft loss [HR 4.8; 95%CI:2.0,11.9; p=0.001; Weibull survival model with Lexis expansion].

Allograft function [MDRD eGFR] in the DGF+ group was 15.1 ml/min/1.73m2 [95%CI: -11.1, -19.1 p<0.001] lower before rejection than in the DGF- group. Whilst both groups experienced reduction in eGFR after rejection, the fall in eGFR in the DGF+ group was 6.2 ml/min greater than in the DGF- group [95%CI -1.0,-12.6; p<0.001; Mixed-effect model].

This is the first published study showing that DGF is associated with an increased risk of graft failure, rejection and impaired allograft function in patients receiving Campath induction and Tacrolimus monotherapy.

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The Effect Of CYP3A5 Expression On The Lipid-lowering Response To Atorvastatin In Renal Transplant Recipients

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Introduction: Statin therapy has been shown to reduce cardiovascular events in renal transplant recipients (RTRs). Atorvastatin is primarily metabolised by CYP3A4 and CYP3A5 to active metabolites which account for 70% of the inhibition of HMG-CoA reductase. It has been suggested that CYP3A5 polymorphism is responsible for the interindividual variability in response to Atorvastatin (Kvistio K, *et al. Pharmacogenetics* 2004; 14:523). The *CYP3A5*1* allele confers CYP3A5 enzyme expression while *CYP3A5*3* homozygotes are functional non-expressers. This study attempts to answer the question 'Is there a significant difference in lipid-lowering response (in total cholesterol and LDL) to Atorvastatin between RTRs who are expressers and non-expressers of CYP3A5?'

Method: 50 RTRs with good graft function, treated with Atorvastatin, were identified. Of the 17 expressers, 59% were male, 22% Caucasian, 35% Black, with a mean age of 55±12. Of the 33 non-expressers, 83% were male, 88% Caucasian, 3% Black, with a mean age of 52±11. A two-tailed t test was used to calculate the p values for the means. A responder analysis was done using the total cholesterol target of less than 5 mmol/L and the LDL target of less than 2 mmol/L with the two-tailed Fisher's exact test. **mean ± SD*

Results: The only difference identified between the two groups was that the expressers had a significantly greater mean creatine kinase than the non-expressers.

	CYP3A5 Expressers (n=17)	**CYP3A5 Non-expressers (n=33)**	**P-Value**
Atorvastatin dose	28.2 ± 12.8*	22.4 ± 14.1*	0.16
Total Cholesterol	4.25 ± 2.2*	4.23 ± 2.5*	0.70
LDL	2.3 ± 1.3*	2.02 ± 1.6*	1.00
Creatine Kinase	139 ± 41.0*	108 ± 43.8*	**0.02**
Alanine Transaminase	24 ± 6.4*	25 ± 4.2*	0.51
Ciclosporin	0%	0%	
Tacrolimus	88%	82%	0.70
Sirolimus	6%	9%	1.00
Prednisolone	59%	70%	0.53
Mycophenolate Mofetil	29%	12%	0.24
Azathioprine	12%	12%	1.00
Ezetimibe	12%	9%	1.00

Conclusion: Our data suggest that the CYP3A5 polymorphism does not affect clinical response to the lipid-lowering effects of Atorvastatin in renal transplant recipients. While higher creatine kinase in the CYP3A5 expressers may indicate greater susceptibility to myositis, it may just reflect the greater proportion of Black patients in that group.

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A survey to Determine the Patients' Views on Generic Substitution in the UK: Focus on Transplant Recipients

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Introduction: *Generic substitution* refers to switching between a branded and a generic version of the same drug (such as for ciclosporin switching from Neoral® to Dexcel). Patients might suspect that substitution has been done merely for financial reasons and that might compromise their quality of care. Others may believe that financially-driven drug substitution is fair as long as patients are well informed and allowed to choose freely between the available branded and its generic counterpart. A key concern is that both patients and physicians should be involved in the switching decision. This study examines the current patients' awareness and understanding of generic substitution in the UK. ***Method:*** A total of 163 renal patients were surveyed, using a questionnaire consisting of 36 multiple-choice questions at Barts and The London Renal Transplant Clinic, in the UK. Transplant recipients over 18 years, able to read and write English and willing to fill in the questionnaire were included in the survey. ***Results:*** Majority of patients (84%) were aware of the availability of generic medicines, 70% understood the terms "generic" and "branded" in relation to medicines and 54% were aware of generic substitution practice. However, 75% did not know if they were taking generic medicines and 84% felt that generics are not equivalent or only equivalent sometimes and they were uncertain that generics had the same quality as branded medicines. Of patients receiving generics, 66% were dissatisfied or uncertain about their satisfaction concerning generic medicines. Of these, 55% experienced noticeable differences between the branded and generic medicines mostly in the packaging, shape, colour or taste and felt that the branded medicines were more effective than the generics. In addition, 81% were uncertain and unaware that a generic form of ciclosporin is available in the UK and 77% would refuse generic substitution of ciclosporin. Almost half of patients (49%) believed that they would accept generic substitution with the agreement of both the general practitioner (GP) and the hospital specialist. Most patients (84%) stated that they were not monitored after switching to generic medicines; of these, 59% believed that substitution is promoted mainly to save the NHS money or because of the unavailability of branded medicines. Moreover, 28% of the highly educated and 46% of the less educated patients reported that they would refuse generic substitution. ***Discussion:*** Healthcare professionals and educational attainment could have a significant role on patients' acceptance of generic substitution. This survey clearly illustrates that many patients are un-informed and distrustful of generic medicines. They consider these drugs to be less effective and associated with increased adverse events. Thus, generic substitution in this group of patients necessitates patient education and additional clinician time to provide more information and reassurance.

Immunosuppression 2

Moderators: Iain MacPhee & Neil Parrott

Patients' Views on Generic Substitution in the United Arab Emirates (UAE): Focus on Renal Patients

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Introduction: In the last two decades healthcare cost has been rising globally. As a consequence, many countries were encouraged to limit their healthcare expenditures. It is often found easier to intervene on medications expenditures because of identifiable costs. A major strategy for lowering the cost of medications is with accepting generic equivalents of branded drugs into the global market. This strategy is proven to be effective. However, patients might suspect that substitution is based only on economic grounds and may compromise their quality of care. This study examines the renal patients' awareness and understanding of generic substitution in the UAE. ***Method:*** A total of 67 renal patients treated at the UAE General Hospital Renal Clinic were surveyed, using 36 multiple-choice questions. The questionnaire was written in English and translated into Arabic—the mother tongue language of the UAE. 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 (75%) were aware of the availability of generic medicines, 65% understood the term "generic" and "branded" in relation to medicines and 66% were knowledgeable of generic substitution practice. However, 81% did not know if they were taking generics and 53% felt that generics are not equivalent or only equivalent sometimes, and they were uncertain that generics had the same quality as branded medicines. In addition, 72% of the highly educated patients were aware of the generic substitution compared to 23% of the less educated patients. Of patients on generics, 62% were dissatisfied or uncertain about their satisfaction concerning generic medicines. Of these, 41% experienced noticeable differences between the branded and generic medicines mostly in the packaging, shape, colour or taste and felt that the branded medicines are more effective than generics. Nevertheless, 83% of patients stated that they would accept generic substitution if their physician agreed to do so. The majority of patients (91%) had stated that they were not monitored after switching to generic medicines; of these, 65% believed that substitution is promoted mainly because of the unavailability of branded medicines. ***Discussion:*** According to the results of this survey, education highly influences patients' acceptance of generic substitution. Healthcare professionals could also have a significant role in educating patients related to generic substitution. The lack of transparency related to generic substitution is of concern and might lead to confusion or worry for patients. Therefore, appropriate patient education and involvement in decision making related to medication management may reduce the number of patients dissatisfied with generic substitution.

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Tacrolimus Monitoring During Breastfeeding in Transplant Recipients

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Introduction:

At our centre, female kidney+/-pancreas transplant recipients whose immunosuppression includes Tacrolimus (Tac) and who plan pregnancy and conceive successfully, are advised to continue Tac during pregnancy. They are advised that data are slim on the safety of Tac when breastfeeding, but they are supported in choosing to breastfeed while on Tac, on the basis that maternal and neonatal Tac monitoring is available in our centre. We have sought to determine whether Tac is identifiable in breast milk and whether Tac levels in babies who are breastfed either fall post-partum or are sustained by breastfeeding.

Methods:

Seven mothers and 8 babies have been studied, where Tac was continued throughout pregnancy. Four babies were subsequently breast-fed. The aim was to collect samples from mother, baby and cord blood at the time of delivery and from mother, baby and breast milk, where relevant. Due to the very particular circumstances of the post-partum period, sample collection was not always complete.

Results:

At those deliveries with complete data sets [n=4], cord blood Tac levels were equivalent to maternal levels, range 2.0-10.3ng/ml and 1.6-7.8ng/ml respectively, cord blood being higher than maternal in 2 cases. A single reading gained from a baby at delivery was 12.0ng/ml (mother 5.7, cord blood 10.3).

In 2 babies who were not breast-fed, the Tac levels fell from 2.3 at day 3 to <1.0ng/ml by day 8, and from 4.6 at day 0 to 1.0ng/ml by day 5.

Breast milk Tac levels were <1.0ng/ml on 4 occasions, and 1.2 and 1.5 on 2 other occasions. In the 4 babies who were breastfed, Tac levels declined progressively from delivery despite breastfeeding: [d7:2.5, d10:1.4, d11:1.2]; [d4:3.0, d9:1.0], [d4:1.3; d12:<1.0]; [d72:<1.0], whilst maternal trough levels remained stable (range 2.8-6.8ng/ml).

Discussion:

Breastfeeding does not appear to retard the decline of Tac levels in babies from the high levels present in cord blood and presumably throughout pregnancy. Monitoring of babies and breast milk should be available for these patients.

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Mycophenolate Mofetil is well tolerated in a steroid avoidance regime and makes little impact on either GI symptoms or quality of life

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Background: We have recently completed a randomized controlled study comparing two steroid avoidance regimes. The control arm was treated with basiliximab induction followed by maintenance with tacrolimus and mycophenolate mofetil (MMF). The treatment arm received alemtuzumab followed by tacrolimus monotherapy. We hypothesised that avoiding MMF would yield economic advantages, reduce infection rates and improve quality of life by reducing gastrointestinal (GI) side effects. Here we present the results of these investigations.

Methods: 58 patients were recruited into each arm of the study and they were asked to fill in questionnaires at 6 and 12 months after transplantation. GI side effects were assessed using the gastrointestinal quality of life index (GIQLI) and the gastrointestinal symptom rating scale (GSRS). The overall quality of life was assessed by the SF36 health survey and the transplant quality of life scale. Patients were analyzed on an intention to treat basis.

Results: The scores were calculated and the overall results are shown in the table below:

	ALEM	**Control**	**P Value**
n	58	58	
GIQLI - 6/12	112	107.5	NS
GIQLI - 1 year	109	106.5	NS
Transplant QOL - 6/12	206	201	NS
Transplant QOL - 1 year	201	189	NS
GSRS - 6/12	1.53	1.37	NS
GSRS - 1 year	1.4	1.4	NS
SF36 - 6/12 - Physical component	47.5	44.4	NS
SF36 - 6/12 - Mental component	53.2	53.2	NS
SF36 - 1 year - Physical component	51.8	44.1	P=0.025
SF36 - 1 year - Mental component	53.4	51.2	NS

Conclusion: In this RCT comparing two steroid avoidance regimes there was no difference in either gastrointestinal symptoms or gastrointestinal quality of life irrespective of MMF administration. Overall there was a mild improvement in general physical well being for patients on tacrolimus monotherapy without MMF, but the cause for this is not clear. Overall MMF was well tolerated and did not appear to affect either GI symptoms or overall quality of life.

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Exploratory analysis of the interaction between maintenance steroid dose and the risk/benefit of steroid avoidance/withdrawal regimens following renal transplantation.

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Introduction

We have recently reported a meta-analysis of steroid avoidance/withdrawal (SAW) regimens following renal transplantation. This analysis demonstrated a significantly increased risk of acute rejection with SAW, offset by a reduction in cardiovascular risk factors including hypercholesterolaemia, hypertension and new-onset diabetes. The present study investigates whether the benefits are dependant on the maintenance dose of steroids used.

Methods

Methods for our meta-analysis have been reported previously. Randomised controlled trials comparing SAW regimens with maintenance steroids in renal transplant recipients were included. We re-analysed the data from this meta-analysis using a mixed effects model, incorporating maintenance steroid dose as a linear moderator variable. All data were analysed using the "metafor" package in the R statistical language. Statistical analysis within the model determined whether there was a significant interaction between maintenance steroid dose and reported outcomes (i.e. does the effect size seen vary with steroid dose used). Significance level for interaction was set at 95%.

Results

27 of 34 included studies reported the steroid dose used in the maintenance arm. No correlation was seen between year of publication and maintenance steroid dose. There was no significant interaction between maintenance steroid dose and graft function, risk of acute rejection or hazard for graft loss or patient death. Significant interaction was seen between maintenance steroid dose and risk of hypercholesterolaemia ($p=0.04$) and new onset diabetes ($p=0.01$), with lower doses associated with smaller benefits in these risk factors. No significant interaction between dose and serum cholesterol value ($p=0.16$) or risk of hypertension ($p=0.48$) was seen. There was an interaction between dose and serum triglyceride level, with higher doses associated with smaller benefit ($p=0.02$).

Conclusions

This exploratory, post-hoc analysis of meta-analysis data suggests a possible interaction between maintenance steroid dose and the potential benefits of steroid avoidance/withdrawal regimens. Withdrawal of lower-dose steroids appear to demonstrate smaller benefits in terms of the reduction in risk of hypercholesterolaemia and new-onset diabetes, with no effect on the increased risk of acute rejection. This study has limitations and these findings need to be confirmed in a prospective randomised controlled trial before firm conclusions can be made.

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High Tacrolimus levels during first 3 months post-transplantation are associated with subsequent post transplant CMV disease

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Introduction: Cytomegalovirus (CMV) infection is a major complication in transplant recipients. In spite of prophylaxis in high risk recipients (such as D+/R- cohort) incidence of CMV disease continues to be substantial. The factors leading to the incidence despite prophylaxis are not well delineated.

Methods: We retrospectively analysed 168 adult kidney transplant recipients during the year 2009 at our single centre. Of these 30 were D+/R-. 14 recipients developed CMV disease. We analysed the characteristics of recipients with CMV disease and compared with those who were free of CMV disease.

Results: 3 recipients were excluded from analysis (1 – died, 1 – graft nephrectomy, 1 – recurrent rejection within 3 months). High Tacrolimus levels were strongly associated with the development of CMV disease – 1 month (p=0.003) and 2-3 months (p=0.046).

	'CMV + group' (13)	'CMV – group' (14)	p
Age (Mean)	49	40.5	0.083932
Kidney only	10 (77%)	14 (100%)	NS
Grafts from DCD	1 (8%)	4 (29%)	NS
Mean Mismatch	2.76	2.07	NS
Mean Tac during 1st mon	11.2	7.6	0.003
Mean Tac during 2-3 mon	9.9	8.5	0.046

Discussion: Despite prophylaxis with Valganciclovir for 100 days, D+/R- recipients are at substantial risk of developing CMV disease subsequently. As reported in most series, disease in this group manifested 6 to 10 weeks after stopping prophylaxis. Recipients who developed CMV disease tended to be older. Tacrolimus levels during the early post transplantation period (during prophylaxis) that reflect potency of immunosuppression are strongly associated with CMV disease.

Conclusion: High Tacrolimus levels during early post transplantation period are strongly associated with subsequent development of CMV disease in D+/R- recipients. These recipients constitute a high risk group to develop CMV disease.

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Does Conversion From Cyclosporine To Tacrolimus As Secondary Prevention Provide Better Outcomes In Renal Allograft Recipients? A Meta-analysis

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Introduction. Suppression of allograft rejection remains the key element for successful organ transplantation. The calcineurin inhibitors (CNIs) tacrolimus and cyclosporine, often in combination with antiproliferative agents and corticosteroids, remain central to immunosuppression regimes.

A previous meta-analysis showed tacrolimus to be superior to cyclosporine in improving graft survival and preventing acute rejection when introduced de novo. However, it is unclear whether later conversion from cyclosporine to tacrolimus is beneficial for renal function, graft survival or biochemical parameters. In order to answer this question we performed a meta-analysis of randomised controlled trials in which a switch to tacrolimus was compared with cyclosporine continuation.

Methods. A literature search was conducted to identify published randomised trials. Six trials were identified. Follow-up periods ranged from six months to five years. Study end-point data from the trials was used in the analysis.

Meta-analysis was performed with the RevMan 5 software. Statistical heterogeneity between trials was assessed with the I^2 statistic. For low heterogeneity (I^2 <30%) data, a fixed effects model was utilised. A random effects model used for heterogenous data.

The primary outcomes of interest were comparisons of graft function, biochemical parameters (such as glucose and lipids) and graft survival.

Results. Creatinine was on average 36.5 μmol/L lower (95% Confidence Interval 7.2 – 65.9, I^2 72%, p = 0.01) in the tacrolimus conversion arm. Creatinine clearance was higher in the tacrolimus arm (mean 6.1 ml/min, 95% CI 0.5 – 11.7, I^2 56%, p = 0.03).

Diastolic blood pressure was lower in the tacrolimus conversion arm (2.3 mmHG, 95%CI 0.07-4.54).

No difference was identified in systolic BP, lipid or glucose profile or graft survival.

Conclusions. Conversion from cyclosporine to tacrolimus in prevalent renal allograft recipients is associated with improved renal function compared with remaining on cyclosporine. Diastolic blood pressure was lower in the tacrolimus conversion group.

No statistical significance was seen in graft survival, systolic blood pressure or biochemical (glucose and lipid) parameters.

Kidney Transplantation

Moderator: Will McKane

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An Old Conundrum: When Is The 'High-Risk' Elderly Kidney DonorToo High An Operative Risk To Take?

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Introduction: Increasing demand for live-donor kidneys, in parallel with national trends towards a more elderly population, make it important to consider the expansion of the donor pool to include older donors. Acceptance of those aged over 60 for nephrectomy is controversial, with a higher incidence of co-morbidity and a greater risk of post-operative complications often being sighted as reasons for caution. This study was performed to determine whether older age is in fact associated with greater risk of perioperative, as well as long-term, complications in donors undergoing nephrectomy.

Methods: This study assimilates nephrectomy data collected over the last five years at one of the United Kingdom's largest renal transplant units. We performed a retrospective analysis of the 389 'mini-open' technique living-donor nephrectomies conducted at the unit since 2005. All donors meeting the inclusion criteria were stratified into three groups by age ('elderly', 'senior', and control). The elderly and senior groups (age >60 years) included 65 donors. Extensive post-donation metabolic and renal function data, collected at 6-12 monthly intervals over a 5 year follow-up period, were analysed and compared to pre-operative data. Perioperative endpoints and surgical complications were also investigated and reported.

Results: As compared to the control group (<60 years), being elderly was shown not to impact significantly on intra-operative endpoints including mean operative time, and estimated blood loss. Post-operative complication rates were also not significantly different between groups, with pneumonia and wound infection constituting the commonest complications across the age ranges. Long-term follow-up (mean = 20 months) showed renal function and propensity towards hypertension, cardiovascular events and diabetes not to be significantly different between age groups. Readmission and reoperation rates did not differ across age categories and, similarly, the rate of major surgical complications was comparably low between groups.

Conclusion: Our unit's experience is that donor nephrectomy is safe in elderly donors and does not result in higher rates of major perioperative complications. Long-term follow-up data show good outcomes for donors of older age. It would be prudent to re-evaluate age's position as an exclusion criterion if we are to successfully expand the organ pool. While these results are encouraging, we advocate careful selection of elderly donors with appropriate pre-operative education and counseling, and can only recommend their inclusion in centres similar to our own, specialising in marginal donor transplantation.

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Small Renal Centres Contribute Significantly To The National Organ donor Pool

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Background and aim: Regional differences exist in access to renal transplantation in the UK. Here, we report on the transplant activity of a group of 3 renal units (non-transplant centres) in one region ("local") of the UK for the 10 year period of 1999-2008.

Methods: From local transplant databases, the following data was obtained for the 10 year period – 1. Number of cadaveric donors, 2. Number of cadaveric donor transplants,

3. Number of living donor transplants. Following data was obtained for the last 4 years –

1. Potential donor family consent rate, 2. Number of dialysis patients on the cadaveric donor transplant waiting list and 3. Prevalent number of dialysis patients. These figures were compared to a those of a transplant centre ("transplant") with similar number of dialysis patients and total population. National figures for these same data was obtained from NHSBT and the UK Renal Registry.

Results: The crude prevalence rate of RRT by dialysis was comparable between the 2 regions (452 per million population (pmp) per year in the local region compared to 446 pmp per year in the transplant region) for the last 4 years as were the total populations (local 675,200 and transplant 830,000). During the same period, the percentage of dialysis patients on the transplant waiting list per year was 14% for the local region compared to 31% for the transplant region (z-test $p<0.001$). In the local region over a 10 year period, there were 90 cadaveric donors compared to 106 from the transplant region. The consent rate from potential donors' family was 61%. During the same period, 84 patients from the local region received a cadaveric donor transplant and 19 received a living donor transplant, whereas in the transplant centre, 175 patients received a cadaveric transplant and 191 received a living donor transplant (z-test for both percentages $p<0.001$). On average per year, the percentage number of waitlisted patients receiving a cadaveric transplant was 26% for the local compared to 14% for the transplant region (z-test $p<0.001$).

Discussion: There is much scope for improvement in helping our region's ESRD patients access the transplant waiting list. Our living donor programme needs to be expanded. Small local centres like ours contribute significantly to the donor pool. It is expected that implementation of recommendations from the Organ Donor Taskforce across all 3 centres will help to improve donation services significantly.

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Successful Renal Transplantation Following Surgical Decortication Treatment For Encapsulating Peritoneal Sclerosis

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Encapsulating Peritoneal Sclerosis (EPS) is a contraindication to transplantation and it is a serious and potentially devastating complication of peritoneal dialysis (PD) treatment. It results in high rates of morbidity and mortality in the small percentage of patients who encounter it. Patients with EPS are often catabolic and can be severely malnourished as they present with features of bowel obstruction and are consequently unable to utilise nutrition enterally. In order to be considered for renal transplantation, these patients first need to undergo successful decortication surgery within an experienced EPS service.

We report on 4 patients who have received a deceased donor renal transplant (RTx) between August and November 2010, following successful surgical intervention for EPS. All patients required parenteral nutrition during their admission for the EPS surgery, but were able to take in adequate nutrition enterally by the time of discharge from hospital. One patient required stoma formation at the time of decortication surgery due to a perforation in the bowel. This was reversed after 12 months.

Case	Gender	Age	Time (yrs) on PD	Time (months) from EPS surgery** to RTx
1	Female	39	5.75	6
2	Male	45	6	4
3	Female	59	5	12 ** time from stoma reversal
4	Male	73	8.5	9

All four patients are now discharged from hospital with a functioning graft.

Case	Donor Type	Months post RTx	Current creatinine
1	DBD	3.5	128
2	DBD	2.5	129
3	DBD	1	125
4	DCD	0.75	188

Renal transplantation is possible in patients who have undergone previous surgery for EPS and patients should be activated on to the transplant list when they are recovered from surgery and maintaining good nutrition enterally. The current post transplant follow up period for these patients is short and we look forward to reporting on longer term results in the future.

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Is ethnic origin a barrier to uptake of vaccination in renal transplant patients?

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Introduction: Current published guidelines recommend that annual prophylaxis against influenza and swine flu (H1N1) is recommended in immunocompromised patients, including those following solid organ transplantation. Ethnic origin, including potential barriers with communication as well as inherent mistrust of a potentially poorly understood health system have previously proven to obstruct compliance to national guidelines within this cohort of patients. This may obviously prove detrimental to both patient and graft survival in view of the potentially serious adverse effects of infection with either organism in an immunocompromised host. We aimed to assess the effect of ethnic origin on uptake of these vaccines amongst a renal transplant population.

Methods: Patients who had a renal transplant at a single tertiary unit over a 30 month period (January 2007 - July 2009) were included in a telephone based survey to determine if vaccination status for influenza and H1N1 influenza for the 2009-10 flu season. The baseline demographic of the population served by this unit reflected a high incidence of patients from diverse ethnic backgrounds (70% White, 19.5% British Asian, 6% Black, 4.5% other). Demographic data including patient ethnicity, age and sex, and age of graft were assessed. Primary endpoints of the study were administration of the vaccine with potential differences in graft age and patient demographics forming secondary endpoints.

Results: 334 patients were eligible for inclusion in the study, of which 201 were able to be contacted and agreeable to answer the questionnaire. Mean age at transplant was 49.3 years (range 16.8-78.8) and 114 (56.7%) patients were Male. The mean time from transplant was 19.3 months (range 6-36). 154 (76.6%) patients were White, 32 (15.9%) were Asian, 13 (6.5%) were Black and 2 (1%) were classified as other ethnic group in keeping with known ethnic representation in the region. There was no difference between the mean age of patients who had the influenza vaccination and those that did not (49.8 and 46.6 years respectively; p=NS); and this finding was replicated for the H1N1 vaccination (50.2 and 47 years respectively; p=NS.)There were no differences in uptake of influenza vaccination amongst White, Asian or Black patients (128 (83.1%), 29 (90.6%) 9 (69.2%) respectively.) 121 (78.6%) White patients received the H1N1 vaccination, which was significantly greater than the uptake seen amongst Asian and Black patients (16 (50%; $p<0.005$) and 6 (46.1%; $p<0.05$) respectively).

Conclusion: Although ethnicity appears to not impact of uptake of Influenza vaccine, it does appear to be a critical factor in H1N1 vaccination uptake. This may result from cultural barriers. These groups should be specifically targeted to ensure adequate education as to the importance of vaccination to ensure adequate uptake of the H1N1 vaccine, especially in an immunocompromised population.

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Novel therapies for atypical haemolytic uraemic syndrome in renal transplantation

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Introduction Atypical haemolytic uraemic syndrome (aHUS) is a disease characterized by complement overactivation, in which defects in complement genes and acquired autoantibodies against complement regulatory proteins have been described. The key pathological lesion is thrombotic microangiopathy and identification of the underlying complement defect can both predict disease outcome and guide treatment. Plasmapheresis remains the mainstay of treatment, but the results are variable and often short lived. In those with factor H and factor I mutations that progress to end-stage renal failure, renal transplantation usually fails due to recurrent HUS. In this situation, combined liver-kidney transplantation has been suggested to correct the underlying genetic defect. An alternative new therapy is the complement inhibitor eculizumab (Soliris®; Alexion), which has been used successfully in the clinic.

Methods This presentation centres on two cases of aHUS; one treated with simultaneous liver kidney transplant and the other with eculizumab.

Results In the first case a 63 yr old male presented with aHUS, refractory to plasmapheresis, and developed end stage renal failure. He was identified as carrying a mutant factor H gene and quoted a 20% chance of graft survival with conventional single organ transplantation. After appropriate assessments he went on to have a simultaneous liver kidney transplant in 2009 and, one year later, he has excellent function of both allografts.

Our second case is a 46 yr old diabetic who received a simultaneous pancreas kidney graft in February of this year. He developed a thrombotic microangiopathy soon after transplantation which did not respond to withdrawal of calcineurin inhibitors or plasmapheresis therapy. After discussion with the relevant authorities consent was granted for eculizumab therapy and a dramatic, persistent response was seen to a course of only four infusions. Subsequent genetic testing has failed to identify an underlying complement defect.

Discussion The poor outcomes for patients with aHUS have proved barriers to transplantation in the past. Both of the new therapies presented here appear effective in either treating or preventing aHUS, in the right clinical setting, but have significant draw backs. Liver transplantation is a major surgical procedure and the donor pool is severely restricted. However, the alternative use of complement inhibitors may be associated with prohibitive cost implications. Who, when and how are questions that will need to be answered.

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A comparison between three donor scoring systems in predicting recipient and graft outcomes following deceased donor renal transplantation in adult patients

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Background: Deceased donor kidney quality is a risk factor for graft failure. Thus methods to quantify the quality of such kidneys, such as the use of deceased donor scores, would contribute greatly to the donor organ pool by reducing organ discard rates and preventing the need for re-transplantation. The existence of several deceased donor scores in the literature may have contributed to the uncertainty surrounding their use and their limited application in practice. The aim of this study was to compare the predictive utility of three validated clinical deceased donor scores; the Deceased Donor Score (DDS), the Donor Risk Score (DRS) and the Kidney Donor Risk Index (KDRI), in a single-centre study.

Methodology: Data on all deceased donor kidney transplants carried out in a single transplant centre between 2004 and 2009 were retrospectively collected from the centre's database as well as the national transplant registry. Multiple organ and paediatric transplants were excluded from the study. Using regression models and survival analyses, the scores were compared on their power to predict measures of early and late graft function as well as graft and patient survival. The scores were also compared in a subgroup of 'deceased after cardiac death' (DCD) transplants, given the steadily increasing contribution of this group of donors to the donor organ pool.

Results: The sample included 423 transplant recipients, of which 35.7% were recipients of DCD transplants (n=151). The overall incidence of delayed graft function (DGF) and primary non-function (PNF) was 24.7% and 0.5% respectively. Mean serum creatinine levels was 147.6 ± 58 μmol/L at 3 months and 150.9 ± 66 μmol/L at 12 months post-transplantation. The overall incidence of patient death and graft failure was 8.8% and 11.3% respectively. No score demonstrated significantly higher predictive power for any of the measures of early graft function (DGF and PNF). The KDRI showed significantly better predictive power for measures of late graft function (3- and 12-month creatinine levels), whereas the DRS was consistently superior to the other two scores in predicting survival outcomes in the overall cohort. No score was consistently dominant in predicting outcomes in the DCD cohort.

Discussion: Although both the DRS and KDRI were found to provide enhanced prediction, the DRS score was better at predicting graft and patient survival, which are the ultimate transplant outcomes of interest for clinicians. Application of the DRS in donor organ selection at the transplant centre would have potentially reduced the rate of organs rejected on subjective grounds by up to 18.4%. Based on these results, and taking into account the relative ease of applying the DRS compared to the KDRI, we would recommend the routine use of the DRS in clinical practice in order to optimise the donor organ pool and reduce patient morbidity and mortality.

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The effects of a 24 week exercise training programme on bone density, body composition and physical functioning in renal transplant recipients

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-Bone disease and abnormal body composition are major issues in renal transplantation. The tough immunosuppressive drug regime contributes towards increases in fat mass, poor physical functioning and loss in bone mineral density leading to increased fracture rates. Physical activity is encouraged for these individuals to address body composition balance and improve physical functioning; however, little support in safe access to exercise is given. The current study aimed to investigate the effects of a supervised 24 week training programme on bone density, body composition and physical functioning in renal transplant recipients.

Ten renal transplant recipients (Age 59.6 ± 10.3years, Mass 92.1 ± 30.6kg, Height 1.66 ± 0.12m) were recruited for the study. All patients were in a clinically stable condition and transplantation occurred at least 1 year prior to the study. Baseline measures of body composition were done using Bioelectric Impedance Analysis, Air Displacement Plesmography and Dual-energy X-ray Absorptiometry. A symptom-limited maximal incremental cycling test was completed to assess physical functioning. Patients then undertook 24 weeks of individualised progressive exercise completing three one hour sessions per week. Baseline tests were repeated at both 12 and 24 weeks.

Five patients completed the 24 weeks of training. Patients improved physical functioning with an increase in peak work rate on the exercise test from 73 ± 19.24 W at baseline to 99 ± 18.17 W at 24 weeks (P = 0.003). Peak oxygen consumption increased from 15.35 ± 4.02 $ml \cdot kg \cdot min^{-1}$ at baseline to 19.63 ± 4.39 $ml \cdot kg \cdot min^{-1}$ at 24 weeks. Body composition measured by all three methods were significantly correlated to each other ($R \geq 0.745$, $P \leq 0.001$). No significant change in total mass (mass baseline 80.1 ± 24.7 kg, 24 weeks 76.6 ± 23.3 kg) (P = 0.276) or body composition (% fat baseline 38.14 ± 6.81 %, 24 weeks 35.14 ± 6.68 %) (P = 0.126), as measured by DXA, was found. No change was found in bone mineral density over the exercise training period (P = 0.585).

Findings from the current pilot study suggest that a structured exercise program for those with functioning kidney allografts can bring about similar physiological adaptations and fitness improvements to those seen in the general population. However, despite large improvements in physical functioning, no significant improvement was seen in body composition balance or in bone health. It is possible that a 24 week period may not be sufficient to elicit any significant changes in these variables, but the results suggest that to improve these factors specifically a more targeted exercise regime possibly incorporating a larger element of resistance training may be needed.

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Cause of Death in Kidney Transplant Recipients: Results of the Scottish Mortality Audit in Renal Replacement Therapy (SMARRT)

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Background

Kidney transplantation offers the best outcomes for people with Established Renal Failure but is still associated with increased mortality. This retrospective cohort study investigates the factors associated with death in people with a functioning kidney transplant.

Methods:

All people who died In Scotland with a functioning kidney transplant between 01/01/2008 and 01/01/2010 are included. Patients were identified via Scottish Renal Registry data returns and linkage with death certification records. Data was extracted from the Scottish Renal Registry and additional information was obtained following a structured case review of care records by nominated nephrologists in each renal unit.

Results:

111 deaths were identified in the time period 01/01/2008-01/01/2010. The median duration of Renal Replacement Therapy before death (including time with a transplant) was 14.2 years (IQR 9.5-21.6). The median time between transplantation and death was 11.1 years (IQR 5.6-18.8). Significant factors associated with median duration of RRT before death were Primary Renal Diagnosis (Ranging from 19.5 years for Glomerulonephritis to 9.4 years for Diabetes, $p = 0.008$) and age at which RRT was commenced ($p<0.001$). The overall causes of death were as follows: Cardiovascular (27%), Infection (24%), Malignancy (22%), RRT complication (1.8%), Cessation of RRT after loss of graft function (0.9%), Miscellaneous (15%) and Unknown (9%). Infection is the commonest cause of death in those dying up to five years after transplant (46% of deaths), and malignancy accounts for a significantly greater proportion of deaths in those with more years of graft function before death. In total, 9% of patients died due to a healthcare associated infection and 33% due to a transplant complication (mainly infections or malignancies). Most patients (67%) died as inpatients, with only 12% dying at home.

Conclusions

Survival following a kidney transplant is significantly better than with other forms of renal replacement therapy. The most common causes of death overall are cardiovascular, but this varies according to total duration of renal replacement therapy, and healthcare associated infection remains an important cause of death in patients with kidney transplants.

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Proteinuria After Renal Transplantation: A Histological and Serological Study in 73 Patients

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Background: Proteinuria after renal transplantation is associated with poor outcomes even at low levels. Typically proteinuric patients have been thought to have "chronic allograft nephropathy" but recent evidence suggests that chronic allograft damage is actually heterogeneous. It has also been argued that most graft failure is due to immune-mediated microcirculatory injury. Here we sought to investigate a high risk group of proteinuric patients by performing renal biopsies and serological analysis for antibodies.

Methods: We identified 115 patients with significant proteinuria (24hr excretion > 0.5g or equivalent). Patients were excluded mostly because of poor graft function but 73 patients proceeded to transplant renal biopsy. Tissue samples were examined by light microscopy but EM was not performed. Contemporary serum samples were also analyzed for the development of HLA-specific antibodies using single antigen luminex beads.

Results: A summary of the morphological diagnoses made by a blinded histopathologist is shown in the table below:

Histological diagnosis	**Frequency**
C4D- Microcirculation Injury	27.5% (n=20)
C4D+ Microcirculation Injury	11% (n=8)
T cell Rejection	16.5% (n=12)
Glomerulonephritis	14% (n=10)
CNI toxicity	15% (n=11)
IFTA- non specific	11% (n=8)
Others	5% (n=4)

Microcirculatory injury was based on the findings of glomerulitis, peritubular capillaritis or transplant glomerulopathy on light microscopy ("g","ptc" or "cg" scores). Serum screening was completed for 68 patients at the time of the biopsy, 53% (36/68) of whom had HLA specific antibodies. 61% (22/36) of these antibodies were donor-specific (DSA). Of the 28 patients with microcirculation injury de novo HLA specific antibodies were detected in 71.4% (n=20/28) 70% of which were donor specific (n=14/20). In patients without microcirculatory injury antibodies were present in 35.6% (n=14/40) (p=0.003).

30 patients with proteinuria had a serum creatinine change <20% over the year preceding the biopsy. Even in this group 53% of the grafts had evidence of immunological injury (microcirculation injury, n=12; acute rejection, n=4).

Conclusions: The pathology of post-transplant proteinuria was heterogeneous but immunological graft damage was the dominant underlying cause (55% of cases). This finding extends to patients with seemingly stable graft function. Information based on graft biopsy and serological analysis in proteinuric patients should inform the design of trials for treatment in the future.

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Outcome Of Paediatric And Adult Patients Who Are Called In For Renal Transplantation But Do Not Receive A Transplant

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Introduction

Being called in for a transplant and being sent home on the same day is a traumatic event for patients and staff. There may be many reasons for this occurrence.

Methods

We investigated the outcome of adult and paediatric renal transplant waiting list patients called in for transplant, between 2005-2008 in a single transplant centre, who were subsequently sent home, without being transplanted.

Reasons for non-transplantation were divided into medical, surgical, donor-specific, allograft specific, crossmatch and other.

Results

In the paediatric practice there were 26 episodes of non-transplantation in 17 children over the four years. The commonest reason for non-transplantation was size discrepancy between donor and potential recipient (50%) with medical and surgical reasons accounting for 12% and 6% of episodes respectively. Overall, these children had a good outcome with 14 (82%) going on to be transplanted within two years of the episode of non-transplantation.

In the adult practice there were 145 episodes of non-transplantation in 125 patients. Overall, 83 patients (66%) went on to receive a renal transplant. The commonest reasons for non-transplantation were donor specific which included issues such as previously undiagnosed malignancy. This category accounted for 50% of non-transplantation episodes. Those potential recipients turned down as medically unfit (8%) had a particularly poor outcome, with 55% of them dying within two years and only 27% going on to receive a transplant within the same time period. In contrast, of those turned down for allograft-specific reasons (21% of episodes, 31 episodes in 27patients) 74% went on to be transplanted.

Conclusions

There is a marked difference in the reasons for non-transplantation between adult and paediatric practice. The main reason for non-transplantation in children is size discrepancy with the potential donor. In adults, non-transplantation is more commonly related to donor health issues. Non-transplantation related to recipient medical factors is associated with a poor outcome in adults, both in terms of mortality and successful transplantation. This information may be useful in the process of counselling future patients faced with being called in for renal transplantation but being sent home without receiving a transplant.

Kidney Transplantation 2

Moderator: Najib Kadi

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BK Virus Nephropathy-Associated Graft Loss in Post Transplant Recipients: A Single Centre Experience

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Introduction

The objective of this study was to, retrospectively, assess the incidence of BK virus nephropathy (BKVN)-associated graft loss in post transplant patients in our unit.

Methods

Transplant recipients (both kidney alone and simultaneous pancreas-kidney) with positive BK virus polymerase chain reaction blood tests were identified from microbiology records. If BKVN was diagnosed, immunosuppressive therapy was reduced accordingly until BK viral titres were negative. Statistical analyses showed positivity for Shapiro-Wilk's normality and so parametric *t* tests were used.

Results

Of the 58 consecutive BKVN-positive transplant recipients evaluated, 4 were simultaneous pancreas-kidney transplant recipients. 37 were men (63.8%). 42 recipients received cadaveric organs, with a mean of 3.6 HLA mismatches. Maintenance immunosuppressive therapy was with Prednisolone (70.7%); Mycophenolate Mofetil, (58.6%), Tacrolimus (56.9%), Cyclosporine (34.5%) and Sirolimus (5.2%).

The mean time period from the date of transplant until the date of first diagnosis of BKVN, was 47.9 months. The mean creatinine at the time of BKVN diagnosis, at 3 months, 6 months and 12 months post diagnosis was 160.8, 159.2, 162.8 and 165 respectively.

Graft loss function was defined as an estimated glomerular filtration rate (eGFR) of < 10mls/min/m^2. Only two cases of graft loss function were identified in our BKVN positive group (3.4%). These two cases suffered graft loss at 20 and 27 months post-BKVN diagnosis. Overall, eGFR at 12 months post transplant compared to 12 months post-BKVN diagnosis was significantly lower (P=0.025).

Discussion

Screening for BKVN results in lower incidence of BKVN-associated graft loss. Active surveillance with prompt reduction in immunosuppressive therapy was the gold standard of treatment, and, as evidenced here, can prevent graft loss.

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The Impact of BK Virus Nephropathy on Renal Graft Survival in a UK Transplant Center

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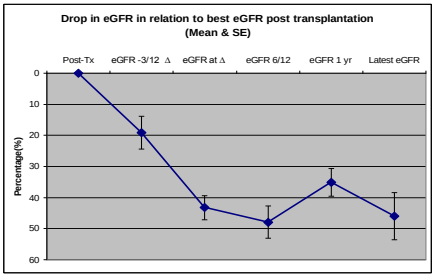
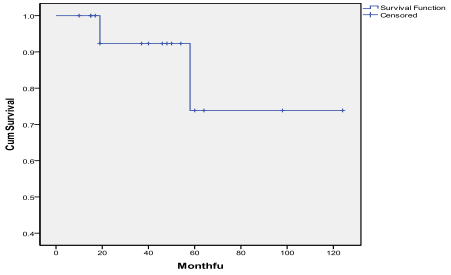
Introduction: The incidence of BK Virus Nephropathy (BKVN) is from 1.1% to 10.3%.[1] Graft loss due to BKVN is reported to be between 15 – 50 %.[2] Early diagnosis of BKVN improves graft survival.[3] KDIGO guidelines suggest routine screening in renal transplant recipients.[4] Currently in Leicester no formal screening program exists.

Method: We identified BKVN cases by retrospective review of Virology and Histopathology databases. We excluded cases of BK Viremia without histological evidence of BKVN.

Results: Between 01/03/2000 and 16/05/2010, 22 patients were identified and four were excluded. Of the 18 patients, 11 were male and 10 had a living donor transplant. 9 patients (50%) had previous rejection episodes with four receiving anti-thymocyte globulin. Baseline immunosuppression for 17 patients consisted of Mycophenolate, Tacrolimus and Corticosteroids. Following the diagnosis of BKVN, a majority had their baseline level of immunosuppression reduced, initially the anti-metabolite followed by the calcineurin inhibitor. Three had cidofovir therapy and three had conversion to sirolimus.

Incidence	2.9%
Median time of diagnosis of BKVN from Transplantation	11 months (range 3 to 91)
Median follow up time post transplantation	43 months (range 5 to 124)
Median follow up time post diagnosis of BKVN	14 months (range 3 to 111)





Three months prior to the diagnosis of BKVN, there was significant reduction in eGFR compared to baseline eGFR (p =0.004). After BKVN was diagnosed, graft function stabilized and there was no further significant eGFR reduction. (p =0.688). However there were two graft losses and one patient died as a result of multiple myeloma. The five year death censored graft survival was 74%. This is significantly lower when compared to five year graft survival at Leicester[5] (p=0.0064).

Conclusion: In our experience the decline in graft function occurred before diagnosis of BKVN was made and 5 year graft survival was significantly lower compared to our center's UK Transplant data. Following diagnosis, a reduction in immunosuppression stabilised graft function. We propose to prospectively study graft outcome following implementation of screening program with serum BKV PCR.

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BK Virus Associated Nephropathy (BKVAN) following renal transplantation – A single centre experience.

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Introduction: Diagnosis of BK Virus associated Nephropathy (BKVAN) following renal transplantation has recently increased in frequency due to a combination of increased awareness and use of more potent immunosuppressive agents. Our aim was to audit the outcome following BKVAN diagnosis.

Methods: We retrospectively studied patients diagnosed with BKVAN at our centre between January 2001 until October 2010. The patient demographics, diagnostic method, treatment modality used, monitoring post-diagnosis and graft function data were collected.

Results: Over the period of 10 years, 12 patients were diagnosed with BKVAN, of which 10 (83.3%) were diagnosed in 2010. The mean age of the patients was 44.3 years (range 22-69 years) and majority were male (n=9, 75%). 8 had cadaveric and 4 had live donor grafts. 6 patients were on dual immunosuppression with tacrolimus and mycophenolate and 6 were on triple therapy with additional steroids. The mean serum tacrolimus level at the time of BKVAN diagnosis was 8.5 ng/ml. Mean time to BKVAN diagnosis post-transplant was 14.1 months (range 3-33 months). Since we didn't have any protocol of BK Virus screening, only those patients with worsening serum creatinine were biopsied (n=8, 66.7%) or urine electron microscopy (EM) done (n=4, 33.3%). Histological confirmation was done in those with urine decoy cells. The average baseline post transplant serum creatinine was 143.8 umol/L (range 92-200 umol/L), which worsened to 252.5 umol/L (range 167-350 umol/L) at the time of BKVAN diagnosis (range 3.5-13). All patients were treated with reduction of immunosuppression which included stopping of mycophenolate (n=12, 100%), 1/3rd reduction of tacrolimus (n=1, 8.3%) and introduction of steroids (n=3, 25%). No antivirals were used in our patients. Following diagnosis of BKVAN, monitoring with plasma BK Virus DNA load was done in all patients, with majority being monitored till 3 months only. None of the patients achieved their baseline creatinine at the end of mean follow-up of 8.6 months (range 1-39 months), when the average was actually worse at 283 umol/L (range 170-421 umol/L). There was no episode of acute rejection or graft loss following immunosuppression reduction.

Discussion: BKVAN is an emerging problem and persistent graft deterioration was noted in 100% of our patients. Though it's a recognised clinical problem, there is no consistency in the literature Many centres have used different antivirals and immunosuppressive regimes with variable outcomes. Looking at the incidence and the results in our centre, a research project has been designed, with a screening and follow up protocol to address the problem.

Conclusions: BKVAN is an emerging problem and persistent graft deterioration was noted in 100% of our patients. Appropriate screening tool using urine electron microscopy should be a norm in all renal transplant units and post-BKVAN diagnosis should be followed by regular plasma BK virus DNA load monitoring to necessitate appropriate immunosuppression reduction regime.

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Potential of transplantation for kidneys removed electively for renal cell carcinoma.

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Introduction: Despite recent concerted effort at national level to increase organ donation in UK, there remains a gap between the number of patients on the waiting list and kidneys available. In view of this ongoing shortage new sources have been explored with variable success. Each year in the UK 7000 new cases of renal cell carcinomas (RCC) are diagnosed. Current data shows that around 50% of these newly diagnosed cases are T1a tumours (<4cm). These patients could safely undergo partial nephrectomy. However due to technical challenges only 20% undergo this procedure, the rest have radical nephrectomy. Evidence also exists to suggest that these radically removed kidneys can be transplanted after resection of small tumours. However there is a need to audit current practice in UK for management of small renal cancers in order to assess the real potential for using such restored organs. Therefore we looked at trends from one large urology centre in North East of England.

Methods: This is a retrospective analysis comparing the use of partial and radical nephrectomy for all the patients undergoing surgery for a T1a tumour in Freeman hospital, Newcastle, between 2004 and 2008. The National database from the British Association of Urological Surgeons (BAUS) was also analysed for mode of treatment of T1a tumour affected kidneys from 2004 to 2010.

Results: A total of 163 patients underwent surgery for small RCC (T1a) in Freeman hospital over the five years studied with an average of 32.6 cases per year. Percentages of partial nephrectomy have gradually increased from 14% to 38% with radical nephrectomy cases correspondingly reducing from 86% to 62% (Tab. 1). Data collection for BAUS has been started recently with only 15 recorded cases in initial years (2004 to 2007). With improved reporting there were 256 cases between 2008 and 2010. Although incomplete but still 61% of these underwent radical nephrectomy.

Year	Total Nephrectomy	Partial nephrectomy	Radical Nephrectomy
2004	21	3 (14%)	18 (86%)
2005	18	6 (33%)	12 (67%)
2006	49	12 (24%)	37 (76%)
2007	44	19 (43%)	23 (57%)
2008	31	12 (38%)	19 (62%)

Conclusions: Despite clear evidence, a significant proportion of patients with small RCC still undergo radical nephrectomy and potentially these kidneys could be used for transplantation after resection of tumour. A more robust national database would help in the estimating the real pool of kidneys from this source. It is however accepted that issues of patient safety and ethics would have to be overcome before this approach is widely adopted.

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24 Hours Ambulatory Blood Pressure Monitoring (ABPM) Permits Stratification of Apparently Hypertensive Kidney Transplant Recipients (KTRs)

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BACKGROUND: Previous work at our centre has demonstrated that more than half of all apparently hypertensive KTRs based on clinic readings, have acceptable blood pressure control when ABPM is performed. In this study we have followed KTRs identified as hypertensive in clinic to see whether ABPM readings predict clinical events and in particular if they can predict graft and patient outcomes better than routine outpatient BP recordings.

METHODS: 87 Patients were selected on the basis of high average BP readings (mean of 5 visits). A control group of patients who had suffered postural symptoms (n=11) formed group 1. A satisfactory ABPM reading was defined as an average systolic pressure (SBP) less than 130mmHg and a diastolic pressure (DBP) less than 80 mmHg. Patients were divided into three SBP groups. Group 1 SBP had both clinic and ABPM <130 mm Hg (N=11), group 2 had clinic SBP >130 mm Hg but ABPM SBP <130 mm Hg (N=47) and group 3 had both clinic and ABPM SBP >130 mm Hg (N=40). Similarly 3 DBP groups were created with a cut-off value of 80mm Hg. Patients were followed-up for a mean of 41 months. The primary outcome measure was the occurrence of a composite endpoint (Death, Graft failure, MI, and CVA/TIA). eGFR was also compared across the groups at yearly intervals for the duration of follow-up. Survival analysis was performed by the Kaplan-Meier method and e-GFRs were compared across the groups by ANOVA.

RESULTS: Kaplan-Meier analysis shows that patients in SBP group-3 had the worst outcomes and patients in SBP group-1 had the best outcomes (Primary event free survival: Group-1 100%, Group-2 91.6%, Group-3 70%, p=0.003). Similar trends were seen within the DBP groups but they were not statistically significant. Analysis of e-GFRs across the three SBP groups by ANOVA reveals that patients in group-3 have a significant decline in their eGFR when compared to the other groups **(Table-1).** Similar trends were not seen within the DBP groups.

	e-GFR Time-0	**e-GFR 1 year**	**e-GFR 2 years**	**e-GFR 3 years**	**e-GFR 4years**
Group-1	50ml/min	51ml/min	49ml/min	51ml/min	53ml/min
Group-2	48ml/min	48ml/min	46ml/min	46ml/min	45ml/min
Group-3	45ml/min	42ml/min	42ml/min	38ml/min	35ml/min
P-value	ns	ns	ns	0.03	0.05

DISCUSSION: ABPM provides significant additional information compared to clinic readings in apparently hypertensive patients. Selective use of ABPM identifies a high risk subgroup of KTRs who should be targeted for intervention.

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Access to Renal Transplantation at Nottingham University Hospitals

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Introduction: Early referral and transplant listing confers distinct advantages in terms of life expectancy, quality of life, graft survival and time accrued on the waiting list. In the UK, equity to access and activation appears largely centre specific rather than case mix dependent. The NSF framework recommends eligible patients are listed within 2 years of RRT and, if pre-dialysis, listed when eGFR ≤15. A previous poster from our unit had suggested that fewer than expected patients were active on the national renal transplant waiting list.

Aims: To determine the timeline for referral and listing in our prevalent transplant waiting list population and identify reasons for delay. Additionally, determine if transplantation has been considered in patients not listed.

Methods: We performed a retrospective analysis of all adult prevalent pre-dialysis (eGFR <15), those with failing transplants and dialysis (HD, PD) patients at Nottingham City Hospital. In those listed for transplantation we analysed demographics, time from first doctor meeting (FDM) and RRT to referral, assessment and list activation. Data were derived from the renal database and electronically held clinic letters. Patients with missing data and transferred from paediatrics were excluded.

Results: Of 658 prevalent patients, (160 pre-dialysis, 390 HD, 108 PD), 160 are listed for transplantation (84 HD, 51 PD and 25 pre-dialysis). 15 patients have diabetes mellitus, 57% are male and 42% aged ≥50. The table illustrates the median times. Despite 74% HD and 88% PD patients with a FDM >90days, only 11% and 26% patients respectively were listed pre-dialysis.15% pre-dialysis patients are listed. Delays were identified in 21 patients, mainly relating to investigations. Within the cohort not listed, 37 (19% pre-dialysis) are being assessed, 19 have been referred (26% pre-dialysis). All patients not listed had an appropriate reason documented.

Conclusions: Timeline for referral and listing is suboptimal. However, data is retrospective and median times may be skewed due to historic long waits. Delays were mainly related to cardiology investigations, and many of the pre-dialysis patients were seen in advance of the need for listing. Pre-dialysis listing has improved from 9 to 15% in 2yrs and work continues with prospective audit showing further significant improvements in the last 12 months

Modality	Listed (n=)	Referral to surgeon (wks)	Surgeon to list (wks)	Referral to list (wks)	Referred pre-dialysis (n=)	Listed pre-dialysis (n=)	FDM > 90 days to RRT (n=)
Pre-dialysis	24	11	3.5	14.8	NA	NA	NA
HD	84	10.8	5.4	16.5	20	7	62
PD	51	13	3.4	14.1	23	12	45

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Pre-transplant Markers for Post-transplant Kidney Function Based on Transcript Isoforms of Bioageing Marker CDKN2

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Introduction and Aims:

Pre-transplant prediction of post-transplant renal function and outcome is extremely challenging and this is especially apparent with older or marginal donor allografts. We have demonstrated previously that allograft bio-age, as determined by CDKN2A expression level, is a superior prognostic and predictive marker to donor age in this context. The CDKN2 locus, however, displays complex spatio-temporal and epigenetic regulation of at least five transcript isoforms. We have sought to dissect the relative contributions of these individual transcript isoforms to determine their capacity as pre-transplant makers of post transplant allograft function.

Methods:

Blinded analysis of zero hour donor biopsies was undertaken for the expression of CDKN2 transcript variants, by real-time PCR. Linear regression analysis was performed to establish any associations between the individual transcript variants and donor age, cold ischemic time, serum creatinine (SC) levels and urinary protein to creatinine ratio (UPCR) at six months post transplant. Additionally, methylation of CDKN2 promoter was assayed to assess epigenetic status in relation to the allograft functional parameters.

Results:

Our analysis confirmed a strong association between the CDKN2A and donor age (p=0.0001), SC level (p=0.02) and UPCR (p=0.002) at 6 months post transplant. In contrast, no association was observed with either p14 or p15 transcript variant 2 expression for any clinical parameters investigated. Expression of p12 and p15 transcript variant 1 was not detected in renal allografts. Additionally, no overt changes in CDKN2 promoter epigenetic status were detected.

Conclusions:

These data indicate that CDKN2 isoforms can be used as a valuable pre transplant marker for the clinical evaluation of post-transplant renal allograft function. The epigenetic stability of the CDKN2 promoter suggests that other regulatory mechanisms (e.g. RNA stability, histone modifications or miRNAs) are involved in the regulation of this locus.

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Standardising Practice in Screening for Prostate Adenocarcinoma in Renal Transplant Recipients

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It is widely accepted that the incidence of cancer in renal transplant recipients (RTR) is higher than that in the general population. It has also been shown that RTR are at risk of early occurrence and locally advanced Prostate Adenocarinoma (PAC). However, there is very little literature looking at the screening, presentation and diagnostic methodology of PAC in patients on the transplant waiting list (TWL). European Best Practice Guidelines (EBPG) published in 2000 recommend screening males over 50 on the TWL with a Prostate Specific Antigen (PSA) level and prostate echography.

The aim of this study is firstly to establish how many of our patients on the TWL have an elevated PSA. The second aim was to establish whether other renal units in the UK followed EBPG, and how they managed TWL patients with an elevated PSA. We suspected that this was an area of controversy which may need further study to establish robust UK guidelines.

According to the UK Prostate Cancer Risk Management Programme, the recommended practice in the general population in whom a higher than normal PSA value is detected is a prostatic biopsy. In our experience, however, most urology centres recommend 2 recorded elevated PSA levels a few months apart, which have been compared against an age specific reference range, as well as a full history and clinical examination before subjecting patients to a transrectal ultrasound-guided biopsy.

There is anecdotal evidence that most renal units in the UK do not screen male TWL patients for PAC and, of those that do, there is no consensus or protocol in place regarding how to act upon an abnormal result.

Of the 256 patients that are currently active on the renal TWL, 103 (40%) are men over the age of 50. Fourteen (14%) patients had raised PSA levels (3.5 – 17.7). Of these, one has been investigated by the Urologists and no malignancy has been found. The remaining patients are still to be investigated.

In order to objectively measure current practice with regards to screening for prostate cancer in TWL patients, we conducted a telephone survey of all renal transplant units in the UK. We found the majority of units did not routinely screen for prostate cancer. The few that did screen did not have a protocol in place for following up their abnormal results.

Despite the good evidence that there is an increased incidence of PAC in male RTR, there is no standardised protocol for screening the target population on the UK's renal TWL. In fact there is often no protocol at all. This may be due to a lack of clarity on how to manage these patients once an abnormal PSA has been detected.

We would therefore recommend consultation with and guidance from our urological colleagues and then establishment of a screening programme and a UK-wide guideline to be constructed. Alternatively, it may just be easier to ignore the EBPG as we may be about to "open a can of worms", which was one of the helpful comments made when embarking on the study!

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Does Urinary Tract Infection Have An Impact In Renal Transplantion To Patients With Diseased Lower Urinary Tracts

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Introduction

Approximately 6-8% of patient on dialysis has lower urinary tract abnormality. These patients are often considered as high risk for transplantation. The commonest complication being Urinary tract infection (UTI) has serious morbidity related to urosepsis.

Method

We retrospectively analysis the prevalence of UTI and urosepsis in patients undergoing transplantation with abnormal lower urinary tract from January 2000 to June 2010. Statistical analysis was limited due to numbers in groups when classified either according to underlying abnormality or type of reconstruction performed

Results

There were 83 patient which included 38 vesicouretic reflux(VUR), 12 posterior urethral valves(PUV), 5 neuropathic bladders, 9 augmented bladders, 5 with urostomy There was 8 miscellaneous which included urethral strictures, prune belly syndrome etc.69% were males .Reconstructive surgery, where required, was undertaken prior to transplantation. Six cases were lost to follow-up or transferred. Median follow-up period was 51 months (range 2-123). Overall 547 episodes of UTI were treated in this patient group with an average of 1.4 UTIs/patient/year. Patients with urostomy (4.09) and neuropathic bladders (3.39) had significantly more UTIs/year compared to PUV (0.58) and VUR (1.45) groups. Urinary conduits experienced more UTI's/patient/year than those with augmented bladders (4.09 vs 1.56) although urosepsis was similar in both groups. Graft loss occurred in 7 cases all of which were UTI related and spread across all groups. One patient died of an unrelated cause with a functioning graft.

Discussion

Urinary tract infection is a common complication in patients with abnormal urinary tracts mainly in patients with urostomy and neuropathic bladders following transplantation. Better strategies to reduce the incidence and impact of UTI are required in all patients with abnormal urinary tracts to minimize the significant impact this has on graft survival. Single institution analysis is limited by case numbers in evaluating strategies related to management of lower urinary tract abnormalities in renal transplantation

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Borderline Rejection In Renal Allografts – Management Strategies and Outcomes for Kidney Transplants in 2008.

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Introduction: Borderline changes are frequently identified in renal allograft biopsies. The relationship between borderline change and acute renal allograft rejection is unclear and optimal clinical management remains uncertain.

Method: We retrospectively studied patients who received a kidney allograft at our centre between January 1st and December 31st 2008 and who underwent an allograft biopsy within the first year. We identified 40 renal allograft biopsies in 33 patients that showed borderline change as the principal finding. We assessed the degree of allograft dysfunction pre-biopsy and the change in graft function post biopsy, quantified as a percentage change in serum creatinine. We arbitrarily defined a significant change in graft function as a percentage change in serum creatinine greater than 10% above or below pre-biopsy baseline. Treatment was allocated to one of 3 categories: 'Anti-rejection therapy', 'No Treatment' and 'Treatment for other diagnoses'. In further analysis, the 'No Treatment' and 'Treatment for other diagnoses' groups were combined into a 'No Treatment for rejection' group. Outcomes for each category of treatment were assessed in terms of the percentage change in serum creatinine above or below the pre-biopsy baseline.

Results: 27 biopsies (68%) were for allograft dysfunction, 7 (18%) were protocol biopsies and 6 (15%) were for delayed graft function (DGF), and these were excluded from further analysis. Of the remainder, 20 (59%) were treated for rejection. Of these 19 (95%) achieved a final serum creatinine within 10% of the pre-biopsy baseline and 10 (50%) achieved a significant improvement in serum creatinine, as previously defined. 8 (24%) received no treatment; all of these achieved a serum creatinine within 10% of baseline and 4 (50%) achieved a significant improvement in creatinine. 6 (18%) were treated for alternative diagnoses such as CNI toxicity. Of the 14 episodes that were not treated for rejection, 12 (86%) achieved a serum creatinine within 10% of the pre-biopsy baseline, 4 (29%) had a significant improvement in serum creatinine and 2 (14%) had continued deterioration in function. Overall, in 14 cases (41%) there was improved graft function, in 17 cases (50%) there was no significant change in function and in 3 cases (9%) there was a significant deterioration in function. 4 patients subsequently developed unequivocal T cell mediated rejection between 1 and 4 months later.

Discussion:

In this single centre observational study, borderline change was non-progressive in the majority (91%) of cases, though some patients (12%) later developed unequivocal T cell mediated rejection. A favourable outcome was seen both in patients who received anti-rejection therapy and in those who did not. This demonstrates that our individualised treatment strategy based on clinical assessment of each case is successful. The favourable outcomes seen in those patients not treated for rejection suggests that a more conservative approach may be appropriate, and that this should be an area for future study.

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Histological parameters in transplant glomerulopathy: distribution and effect on outcome

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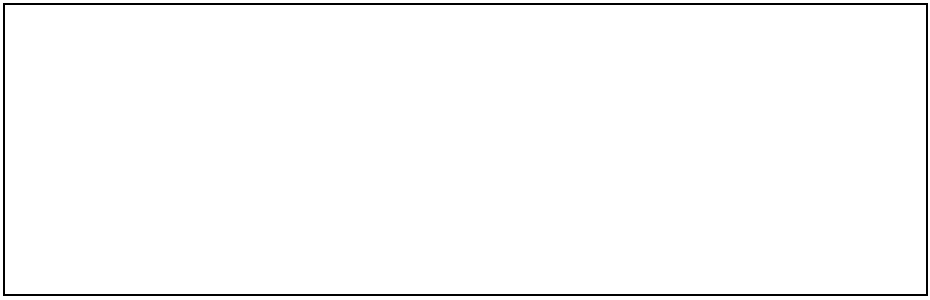
Transplant Glomerulopathy [TG] is a common cause of late allograft failure. TG generally has a poor response to treatment and a poor outcome, although some cases do better than others. We reviewed the histology of our cases with TG in order to describe the association with other histological features, and their effect on outcome. We analysed all cases of TG diagnosed at our institution between 2006 and end 2009. Histopathological features were classified according to Banff criteria, and related to graft outcome. There were 56 patients with TG [32M, 24F, mean age 47.1±12.0 years], defined as double contours in glomerular capillary walls in the absence of immune complex disease. The mean age of the allograft at diagnosis of TG was 8.6 +/- 7.4 (median 6) years. 41% had class II DSAb, 27% had class I+II DSAb and 7% class I alone. All patients with TG were established on Tacrolimus and Mycophenolate Mofetil without the use of steroids. Fifteen patients also got Rituximab, and 18 patients also received courses of plasma exchange with ivIg.

The graph illustrates the frequencies of Banff scores 0 to 3 (1-mild, 2-moderate, 3-severe) for glomerulitis (g), TG (cg), interstitial fibrosis (ci), total inflammation (ti), peritubular capillaritis (ptc) and C4d staining. Peritubular capillary basement membrane multilamellation (PTCBMML) was analysed by electron microscopy in 54 patients and was present in significant amounts in 63% of cases. Allograft survival was 17% overall at 4 years after diagnosis of TG. After adjusting for graft age, there was no effect of histopathological variables on outcome. There was a trend for worse graft survival in those with higher interstitial fibrosis and total inflammation. Interestingly, there was also a trend to better outcome in those with moderate glomerulitis (g2).

In our experience, TG overall has a bad prognosis. There were no histological features at the time of diagnosis of TG that helped predict outcome. As could be expected, there was a trend to worse outcome in those with extensive scarring and tubulointerstitial inflammation.



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Moderator: TBA

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Outcomes of live kidney donor work-up: a single centre experience

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Introduction: Many potential donors are referred for live kidney donation (LKD), but only small percentage actually become donors. The aim of this study was to assess the outcomes of LKD work up at our centre and to identify factors which could be modulated to increase the number of LKD.

Methods: A review of departmental database and case notes of all potential live kidney donors (PLKD) referred between January 1995 and November 2010 was carried out and data analysed to establish the outcomes of LKD work up.

Results: Of the 667 PLKDs evaluated, 152 (22.8%) proceeded to actual kidney donation. The reasons for non-donation are shown in table below.

Donor-related reasons	291 (57%)
Recipient-related reasons	109(21%)
ABO-incompatibility	72(14%)
Positive cross-match	43(8%)
Total	515

The donor-related reasons for non-donation were medical causes (n=96, 18.6%), donor withdrawal (n=55, 10.7%), renal vascular abnormalities (n=30, 5.8 %), low glomerular filtration rate (n=22, 4.3%), urological abnormalities (n=21, 4%), and high body mass index (n=5, 1%). Although the PLKDs were suitable, donation was declined for recipient-related reasons such as existing cardiovascular co-morbidities (n= 44, 8.5%), a kidney transplant from a deceased donor (n=42, 8.1%), refusal by recipients (n=10, 2%), and patients transferred to other centres (n=6, 1.2%).

Discussion: Twenty-two percent (n=115) of the donor evaluated could not proceed to kidney donation from ABO incompatibility and positive cross match, which is a potential future source of donors to utilise. Increasing number of transplant centres, including our own centre, have recently adopted desensitisation and paired organ donation programmes. Importantly, thorough evaluation of the recipients is mandatory to exclude unsuitable recipients at a very early stage of live donor work-up. It is also important to remove recipients from the deceased donor transplant waiting list once the donor is fully worked up and theatre date scheduled in order to avoid disappointments.

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A Service Evaluation On Long Term Risks of Living Kidney Donation, A Local Experience.

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Introduction

Living donor kidney transplantation (LDKT) has superior graft and recipient outcomes over deceased donor kidney transplantation (DDKT). There is emerging evidence from centres worldwide of the long-term safety profile of living kidney donation, however, more locally in the United Kingdom this information is somewhat lacking.

This is a retrospective study of a cohort of local regional living kidney donors to evaluate the long-term risks of developing chronic kidney disease (CKD), hypertension (HTN) and proteinuria following living kidney donation.

Method

Donor characteristics and follow-up data of all living kidney donors between 2001 and 2008 were compiled. Their pre-donation eGFR (MDRD 4 variable), blood pressure and proteinuria were compared with post-donation follow-up data using non-parametric 'Wilcoxon signed rank test' to identify any significant differences in these factors as evidence of potential long term risks.

Results

A total of 59 donors were identified. Three lost to follow-up and the remaining 56 donors were followed-up for a median of 3 years since donation (range 1 - 7 yrs). 57.2% of donors were women. Median age at donation was 46.1yrs (range 19-71 yrs). Mean body mass index (BMI) was 26.8±2.7kg/m^2. None of the donors were diabetic but one developed diabetes 2 years after donation. Three donors were recorded as having +1 proteinuria. During post-donation follow-up 12.5% developed new proteinuria (6 donors developed +1 and one developed +3 proteinuria). Mean systolic (SBP) and diastolic (DBP) blood pressure at donation were 125.3±13.9mmHg and 76.6±8.4mmHg respectively. 3 years after donation no significant changes in BP was noticed (SBP 124±24.7mmHg, p=0.59; DBP 76.7±8.9mmHg, p=0.75). 5 years later a non-significant rise from baseline was noticed (SBP 130.4±27.9mmHg, p=0.95; DBP 79±17mmHg, p=0.77). Median eGFR and creatinine at donation were 82.5 ml/min/1.73m^2 and 81.5 µmol/l respectively. 3 years after donation eGFR fell significantly to 57±16ml/min/1.73m^2 (p=0.001), however at 5 years eGFR stabilized to 47.5±10.9ml/min/1.73m^2 with no significant further deterioration (p=0.85).

Discussion

These findings of local experience confirm that long-term risks of development of CKD, HTN and proteinuria following living kidney donation from carefully screened donors remain acceptably low indicating that potential future donors can be offered reassurance based on local data.

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Living Kidney Donation And Pregnancy; A Survey Of Practice In The UK

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Introduction

Whilst there are well documented effects of pregnancy on the kidney in the UK there are no strict guidelines on the use of female donors of reproductive age. We performed a survey to assess practice across the UK.

Methods

A telephone survey of live donor coordinators at 29 units across the UK was performed in November 2010. For the purpose of the survey 45 was considered the upper end of reproductive age.

Results

We received a 100% response rate. No units have a departmental policy on the management of these patients. The majority of units, 16 (55%) work potential female donors up as they would work up a male donor, whilst 11 units (40%) defer assessing them until other "more suitable" donors have been considered. Three units say that their practice varies between consultants.

If these women are used as donors there is a wide variation in the advice offered regarding time before they can conceive, with seven units (25%) offering no advice whilst other units suggest anything from six months up to one or two years.

There is also varying advice provided about antenatal care. One third of units (10, 34%) provide no specific advice, whilst 9 units (31%) tell the patients to inform the obstetricians of their donation. In the last 10 years twenty five units (86%) have used more than 10 female donors of reproductive age with 16 units (55%) estimating that between 1-5 of these donors have gone on to have children post donation.

Conclusions

There is a wide variety in practice in the use of female donors of reproductive age as kidney donors in the UK. The subsequent advice about pregnancy and antenatal care is also variable.

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Is radionuclide assessment of renal function an essential component of the kidney donor work-up?

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AIM

NHSBT guidelines state that where potential living donors have significantly different split renal function, the least functioning kidney should be donated in order to ensure adequate donor renal function at age 80. It has been suggested that USS and CT findings be utilised as a marker of renal function, with formal functional assessment only where indicated. We aim to analyse USS, CT and DMSA findings for living donors at a busy regional transplant centre to determine the utility of DMSA in routine assessment for living donation.

METHOD

A prospectively maintained database of living donor nephrectomies performed between 2004 and 2010 was interrogated. Ultrasound, CT and Tc-DMSA scans are performed routinely in living donor assessment. The results of these investigations were analysed and compared for efficacy in estimating split renal function.

RESULTS

169 nephrectomies were performed, 145 (86%) had available preoperative USS results, 158 (93%) had CT results and 149 (88%) had available DMSA results. Of those with available DMSA results, 15 donors (10%) had a clinically significant difference in split renal function on DMSA. All of these patients had undergone USS and CT scanning. In these patients, there was no correlation between split function and renal size on USS. 8 of these 10 (53%) had a smaller kidney on the side of poorer function, 3 (20%) were equal in size and 4 (27%) had a larger kidney on the side with poorer function. When compared to those who had a normal DMSA scan, there was no significant difference in mean kidney size (11.02 vs 10.93) or mean size difference between right and left kidney (0.49 vs 0.40) as determined by USS. Only 1 of these donors had renal scarring on CT evaluation, and no patients had undergone volumetric assessment.

CONCLUSION

Kidney size on USS and CT angiogram did not correlate to DMSA-determined split renal function prior to donation. The resolution and reliability of these investigations must therefore be questioned. Reliance on one investigation to highlight potential discrepancy may lead to false reassurance, or even indicate the wrong side. In order to facilitate accurate and ethical donor counselling and ensure donor safety, definitive prospective investigation is needed.

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Pre-emptive immunosuppression using tacrolimus for living kidney transplantation

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Introduction

Recent clinical practice guidelines advocate the use of pre-emptive immunosuppression in live donor kidney transplantation without a clear evidence base. This analysis compares the efficacy of pre-emptive immunosuppression with Tacrolimus mono therapy versus standard immunosuppression commenced at the time of transplantation.

Methods

Prospectively collected data was used to compare the outcome of a series of live donor kidney transplants in which 99 patients received pre-emptive Tacrolimus mono therapy for two weeks (PE) and 100 patients received standard immunosuppressive therapy beginning on the day of transplantation (control). The main outcome measures were the incidence of biopsy-proven acute rejection (BPAR) at three months, allograft function and allograft survival.

Results

Pre-emptive immunosuppression with Tacrolimus mono therapy did not decrease the incidence of BPAR at three months (PE 13/99 vs. Control 6/100; P=0.097). There were no differences in allograft function measured by serum creatinine at one year (PE 130±36 vs. Control 142±69μmol/L; P=0.6829). One-year graft survival was equivalent in the two groups (PE 96.9 vs. Control 97.0%; P=0.9915). There were no differences in Tacrolimus levels at one week post-transplantation in the two groups (PE 13.6 ± 3.6 vs. Control 11.1 ± 5.8; P=0.1276).

Conclusion

This study suggests that pre-emptive immunosuppression with Tacrolimus mono therapy has no effect on the outcomes of live donor kidney transplantation.

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Change in serum creatinine in immediate post donation period in live kidney donors correlates with 3-year post donation creatinine.

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Introduction: The proportion of kidney transplantation from living donors is increasing in the UK. There is evidence of better graft and recipient outcome after living kidney transplantation. Serum creatinine rise in the immediate post operative period in live donors, starting in the 1st postoperative day. This trend however reverses 3 - 5th days post operatively. Published data suggest that most donors should recover 75% of their pre-donation renal function. We serially analysed the observed change in post donation renal function in a cohort of our patients. Our analysis showed a clear relationship between the extent of this rise in creatinine and future creatinine values at 3 years after donation.

Methods: We carried out an initial analysis of anonymised data of 69 donors from the database of living kidney donations carried out in our centre between 1997 and 2008. We noted peak serum creatinine in the post donation period and expressed this as a proportional change in donor's preoperative serum creatinine – calculated as [(peak creatinine – baseline creatinine) ÷ baseline creatinine]. We calculated the correlation of this initial change in serum creatinine with the creatinine at 6 weeks, 1 year and 3 years to assess associations.

Results: There was an average of 44 μmol/L increase in serum creatinine over baseline value [range 12-96 μmol/L], representing a change of 59% [range 14-148%]. The mean time to peak creatinine was 2.02 days in the cohort and median was 2 days. We found a significant correlation between the proportional change in peak post-op creatinine and creatinine at 3 years [n21, R^2 0.71]. Correlation was not significant between the proportional change in peak post-op creatinine and the creatinine at 6 weeks [n69, R^2 0.49] and at 1 year [n32, R^2 0.52]. This poor correlation remains even for donors with a high proportional change in creatinine.

Discussion: It is well established that live donor kidney recipients benefit in terms of better graft survival, function, and patient outcomes. It is expected that donor serum creatinine will rise in the immediate post donation period. We found a correlation between this initial rise in creatinine and future creatinine from the 3rd year post donation. We believe that this correlation can be used to risk stratify donors, allow an early prediction of poor renal outcome and need for closer donor monitoring.

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Poster Moderator: Lisa Burnapp

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Failure to complete the Live Kidney donation process: Racial & Cultural variations

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Introduction:

Over a 3 year period 173 live renal transplant donors who failed to proceed to donation were reviewed-55% White British, 24% Overseas, 11% Asian British, 10% Black British.

Methods:

Data was collected retrospectively from our database.

Results:

Overall, 58% failed to donate due to medical reasons and 42% due to non-medical reasons. The majority (75%) ceased the donation workup process at an early stage.

The commonest medical aetiologies were -Immunological incompatibility (35%), Low GFR (11%) and Obesity (10%). Non -medical reasons were -More suitable donor found (32%), Donor elected to withdraw (21%) and Donor failed to materialize to complete process (14%).

Significant differences in reasons for failure to donate are seen between Overseas and British donors. Racial differences in non-donation amongst the British are also noted.

Conclusions:

Completion of the donation process is only 17%. Early identification of modifiable barriers to donation may improve the yield, especially in ethnically diverse communities.

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Barriers to living donation: a qualitative study of recipient anxieties

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BACKGROUND: Although living donation is increasingly common, many recipients express reluctance to accept a living donor, and some have difficulty in relationships after transplantation. Few data are available regarding the specific psychosocial anxieties potential and past recipients may experience. We performed a detailed semi-qualitative study of living donor recipients, in order to determine the anxieties experienced by living donors, and to understand how these might inhibit living donation.

MATERIAL AND METHODS: 14 participants who had undergone living kidney transplantation, took part in a semi-structured qualitative interview at the Renal Outpatient Department, Guy's Hospital. The interview explored their journey of renal transplantation. It was then transcribed verbatim and analysed using framework analysis.

RESULTS: Four themes emerged from the framework analysis: 1. The decision for living donation: All patients expressed hesitancy to approach donors directly. The main barrier to accepting donations was fear for the donor's health. 2. Relationship change: Donor-recipient relationships rarely suffered post-transplantation except when the relationship was previously unstable. Amongst relationships in general, some recipients had difficulty disclosing information about their transplant, and some found friendships strained after disclosure. 3. Post transplantation: Many patients felt dependent on others following the operation and complained of side-effects from medication. This was worse in pre-emptive compared to dialysis patients. 4. Perceptions of self, health and the future: Few participants regretted the choice of living donation, many saying it was a life-changing experience. Complications or inadequate support were related to a more negative outlook.

INTERPRETATION: Living donor kidney recipients remain understandably anxious about the donor, and this may inhibit acceptance of donation. Transplant programmes may need to consider placing greater emphasis on informing the recipient about donor risks and outcomes, and this reassurance may need to continue after transplantation has taken place. Donor-recipient relationships which are unstable prior to transplantation are often worse following donation. Pre-emptive recipients experience a greater sense of dependency after transplantation and may require additional psychosocial support.

KEYWORDS: Renal transplantation, Psychosocial concerns, Kidney Recipients, Decision-making, Social relationships; Self-perception; Recovery

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Estimated glomerular filtration rate and long-term outcomes following live kidney donation: a single centre experience

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Introduction: Renal transplantation from live donor source provides best short and long-term outcomes. Following kidney donation, there is significant reduction in glomerular filtration rate (GFR), which may categorise them into stage 3 chronic kidney disease (CKD) according to the K/DOQI NKF guidelines, which raises concerns among both donors and the care-takers, particularly the general practitioners. The aim of this study was to examine the changes in the renal function (serum creatinine, GFR and proteinuria) and the long-term outcomes following kidney donation.

Methods: Over a period of 32 years commencing 1978, 164 live kidney donors were included in the study. Data was collected from a prospectively maintained database. The estimated glomerular filtration rate (eGFR) was calculated by using Modification of Diet in Renal Disease (MDRD) formula. Serum creatinine, eGFR, proteinuria, body mass index and blood pressure were measured before and after (3, 6, 12 and 36 months) kidney donation. The pre-donation parameters were compared with post-donation parameters for the analysis purpose.

Results: The average age at the time of donation was 43 ± 11 years, with 50% being male donors. The mean pre-donation serum creatinine and eGFR were 76 ± 14 µmol/L and 85 ± 15 ml/min/1.73m^2, respectively. The serum creatinine increased to 108 ± 24, 109 ± 22, 109 ± 21 and 106 ± 21µmol/L and the eGFR decreased to 56 ± 10, 51 ± 18, 56 ± 17 and 57 ±12 ml/min/1.73m^2 at 3, 6, 12 and 36 months, respectively. There was 34 ± 9, 35 ± 11, 33 ± 9 and 35 ± 18 % fall in eGFR at 3, 6, 12 and 36 months, respectively, compared to the pre-donation level, which were statistically significant ($P<0.001$). At the end of 1 year 67 % of the donors had a median eGFR of 50 ml/min/1.73m^2 (range, 35-59), thereby falling into the category of stage 3 CKD. However there was no significant proteinuria and hypertension post-donation. One donor developed kidney failure 16 years post-donation requiring haemodialysis and two had died after 2 and 9 years.

Discussion: Although significant increase in serum creatinine and reduction of eGFR occurred after kidney donation, which led 67% of the donors to fall into the category of stage 3 CKD at 1 year, there was no significant proteinuria or hypertension in long-term follow-up. In a survey carried out at our centre three years ago, we had observed that the quality of life in these donors were not significantly different from that of healthy controls despite reduction in the eGFR noticed in this study.[1] Therefore, we conclude that the reduction of eGFR after kidney donation should not raise any concern and live kidney donation should be encouraged.

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Quality of life after live donor kidney transplantation compared with cadaveric donor transplants: a prospective study

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Introduction: Renal transplantation is the best treatment for most patients with end stage renal failure. It improves the recipient quality of life. We compared prospectively the quality of life of living and cadaveric transplants recipients over twelve month period post transplantation.

Subjects and Methods: All patients undergoing either living donor or cadaveric renal transplantation at our institution were included in this prospective study between January 2005 and June 2009. They were compared to a healthy control group. The standard short form (SF-36) health related quality of life (HQOL) questionnaire was used at four time points over one year including pre transplantation, 6 weeks, 6 months and one year after transplantation.

Results: This study included 508 subjects. Of these, 186 controls, 188 living transplant recipients and 134 cadaveric transplant recipients with a mean age of 46.7±11.3, 47.1±11.5 and 46.5±15.2 years respectively. Males constituted 47.8%, 52.2% and 64.9% of the groups' population respectively. The total SF-36 scores prior to surgery were significantly higher in the control group (mean score 90.6±8.77) compared with those who subsequently had living (58.1±20.1) or cadaveric transplants (54.7±18.7) ($p<0.001$)). Significant difference was observed in the physical function, role-physical, body pain, general health, vitality, social functioning, role emotional and mental health SF-36 domains and also in the calculated physical health and calculated mental health dimensions. There was no significant difference between recipient groups pre-transplant in SF-36 domains and dimensions. There was stepwise improvement in QOL scores over the period in each time point post transplant in both recipient groups. The SF-36 total scores at one year has improved significantly compared with pre-transplant score with 86.3±14.9 ($p<0.05$) in the living transplant group and 77.5±19.4 ($p<0.05$) in the cadaveric group compared with the pre-transplant scores. The difference in total SF-36 scores and the physical health dimension were significantly higher in live kidney recipient group compared to cadaveric recipients ($p<0.05$)

Conclusions: Living and cadaveric kidney transplants offer a significant improvement in the quality of life of the recipients. Living transplant recipients enjoy a significantly higher improvement in quality of life compared to the cadaveric kidney transplant recipients.

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Weight Management in living kidney donors – how can we help?

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BACKGROUND: A healthy body mass index (BMI) is classified as 20-25kg/m². Local guidelines recommend a BMI of 30 kg/m² or less prior to living kidney donation. Historically dietetic support has not been available for living donors; encouragement to achieve and maintain a healthy weight had been provided by the live donor transplant co-ordinators (LDC's). Weight loss of between 5-10% reduces risk of cardiovascular disease, improves blood pressure control and improves respiratory function (National Obesity Forum, 2010). A reduction in BMI may also decrease wound complications, reduce length of hospital stay and reduce long term risk of diabetes or glucose intolerance. A collaborative approach between the dietetic service and LDC's was established to address this.

AIM: To provide an effective weight management service for living kidney donors prior to donation.

METHOD: In February 2009 the renal dietitians and LDC's produced a protocol whereby patients with a BMI >30kg/m² were referred to the dietitian for weight management advice prior to commencement of live donor work up. Over a period of one year twenty seven patients were referred to the dietitian for weight management advice. The type of intervention available to the patient included; an out-patient appointment, telephone conversation or email contact. Duration of intervention was dependent upon patient need and compliance to intervention. All patients had their BMI calculated and a detailed assessment of their current dietary intake and lifestyle during each consultation. Individualised written and verbal dietary information and advice was provided to each patient. Each patient had the option to withdraw from intervention with the dietician at any time, allowing their input from the LDC's to continue as before.

RESULTS: Twenty seven patients were referred to the dietitian for weight management advice. Of the 27 patients, 6 patients did not respond to referral. Of the 21 remaining patients, all had initial contact with the dietitian, followed by 1 patient choosing follow up intervention through phone contact only and the remaining 20 via outpatient appointments. On referral 1 patient had BMI <29kg/m², 13 patients (59%) had BMI 30-35kg/m², 32% had a BMI 36-40kg/m² and 1 patient had a BMI greater than 41kg/m². Of the 20 patients who received outpatient dietetic intervention, 13 patients lost weight (0.6-13kg), 5 patients gained weight (0.9-1.4kg) and 2 remained stable. Of those patients that lost weight, the average weight loss was 5.4kg (6%). Average weight loss for the 20 patients was 4kg (4%).

CONCLUSION: Not all potential donors accept dietetic intervention. Following dietetic intervention patients achieved an average of 4% weight loss. Average weight loss achieved nears the parameters known to infer health benefits.

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Heroism, paternalism and autonomy in living donation

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Introduction

Autonomy has been a dominant feature of medical ethics since the advent of principlism some forty years ago. Transplant teams are often faced with the need to limit autonomous choice when potential living donors seek to donate despite increased perioperative risks. Limiting autonomy in this context may be justified on the basis of beneficence, but some might argue that refusing donation may cause significant harm. Heroism is applauded in the context of other risky activities, such as war or rescuing victims from a fire, but is not often considered as relevant in transplantation

Methods

4 case histories were considered in order to attempt to understand the appropriate response to high risk situations:

A 79 year old with a previous CVA presented as a non-directed donor and was turned down.

A 30 year old overseas donor with a renal stone and no local urology service wished to donate to his brother, and was turned down.

A 45 year old with a BMI of 35 kg/m^2 wished to donate to her husband and was accepted.

A 19 year old wished to donate to his mother, in the context of antibody incompatibility, and was accepted.

Results

Study of these cases suggests that principlism may no longer suffice as the basis for medical ethical decisions. The best of interests of the donor are difficult to quantify-many 19 year olds later regret decisions taken at that age, whilst at 79 years decisions may be more thoroughly considered. The potential for moral, emotional and psychological benefit after donation is uncertain, but may be significant. Limited and explicit paternalism may have a place.

Conclusions

Living donation is a highly charged emotional act. Heroism and profound moral benefit are important considerations. Paternalism has a place but should be explicit. Autonomy can no longer be considered the overriding ethical principle.

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A Weighty Problem: When Is The 'High-Risk' Obese Kidney Donor Too High An Operative Risk To Take?

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Introduction: Increasing demand for live-donor kidneys, in parallel with national trends towards a more obese population, make it important to consider the expansion of the donor pool to include obese donors. Acceptance of obese individuals is controversial due to the possible increased risk for surgical complications and concern that obesity may contribute to long-term renal disease. This study was performed to determine whether obesity is in fact associated with greater risk of perioperative and long-term complications in donors undergoing nephrectomy.

Methods: This study assimilates nephrectomy data collected over the last five years at one of the United Kingdom's largest renal transplant units. We performed a retrospective analysis of the 389 'mini-open' technique living-donor nephrectomies conducted at the unit since 2005. All donors meeting the inclusion criteria were stratified into quartiles by baseline body mass index (BMI). Of these 116 were obese (BMI >30 kg/m^2). Donors of high BMI (>35 kg/m^2) were compared with controls of normal BMI, and a number of subgroup analyses were also conducted. Extensive post-donation metabolic and renal function data, collected at 6-12 monthly intervals over a 5-year follow-up period, were analysed and compared to pre-operative data. Perioperative endpoints and surgical complications were also investigated and reported.

Results: As compared to the control group, a high BMI (>35 kg/m^2) was shown not to impact significantly on intra-operative endpoints including mean operative time, and estimated blood loss. Post-operative complication rates were also not significantly different between groups, with pneumonia constituting the commonest complication across the BMI range. Long-term follow-up (mean = 20 months) showed renal function and propensity towards hypertension, cardiovascular events and diabetes not to be significantly different between BMI quartiles. Readmission and reoperation rates did not differ across donor BMI categories and, similarly, the rate of major surgical complications was comparably low between groups.

Conclusion: Our unit's experience is that donor nephrectomy is safe in obese donors and does not result in higher rates of major perioperative complications. Long-term follow-up data show good outcomes for donors with elevated BMI. It would be prudent to re-evaluate obesity's position as an exclusion criterion if we are to successfully expand the organ pool. While these results are encouraging, we advocate careful selection of obese donors with appropriate pre-operative education and counseling, and can only recommend their inclusion in centres similar to our own, specialising in marginal donor transplantation.

Live Donor Surgery

Poster Moderator: Alun Williams

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Implications and management of incidental adrenal swelling in patients undergoing laparoscopic donor nephrectomy

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Introduction: Potential living donors undergo thorough investigation before the process of donation. This may lead to unexpected pathologies. One of these pathologies is adrenal swelling, or incidentaloma. We report our experience in the management of incidentaloma diagnosed in potential living kidney donors.

Methods: A retrospective review of the first 424 laparoscopic donor nephrectomy (LDN) carried out in our institution was performed. 4 cases with pre-existing adrenal swellings were identified. No donors with adrenal masses were refused LDN. The 4 patients with an adrenal mass on imaging underwent extensive evaluation to exclude malignancy and determine whether the adrenal mass was functioning. CT represents the base line investigation to exclude malignancy. Measurement of 24-hour urinary fractionated metanephrines was used to exclude phaeochromocytoma. Absence of hypertension and hypokalemia excluded primary hyperaldesteronism. A low dose dexa-methasone test was used to exclude subclinical Cushing syndrome. All cases underwent multidisciplinary discussion (MDM), including an opinion from an endocrine surgeon. The side of the nephrectomy was decided according to the side of the adrenal mass irrespective of the vascular anatomy. Comparison of the operative parameters of LDN alone and with adrenlectomy was performed. Recipient outcome was recorded.

Results: 4 patients (3 males & 1 female, age range; 46-63 years) had an incidentaloma. Two were left, 1 right and 1 bilateral. Size ranged between 1.8 x 1.4 to 3x1.7 cm. The patient with bilateral incidentaloma did not have adrenelectomy with LDN after discussion in the MDM which suggested the other adrenal might enlarge after unilateral adrenelectomy. He underwent a right LDN, based on anatomical considerations. The remaining 3 patients underwent simultaneous LDN and adrenalectomy. Operative time ranged from 200 to220 minutes. Estimated blood loss (EBL) was 100 ml. Warm ischemic time (WIT) was 3 minutes. No significant difference was found between the operative time, EBL, WIT or postoperative stay between patients who had LDN with adrenelectomy or those who had LDN alone. All grafts are functioning well.

Discussion: Incidentalomas present a particular problem when discovered during work-up for living kidney donation & will be a problem faced regularly by transplant centres. There are additional issues to consider in presence of an incidentaloma including exclusion of malignancy and function and the management of bilateral incidentaloma. Our approach is, for tumours below 4cm, to exclude malignancy, phaeochromocytoma and other endocrine abnormalities, then to proceed to simultaneous adrenalectomy and LDN, without waiting for frozen section. In the case of bilateral tumours, adrenalectomy is not performed. During LDN the kidney with the adrenal mass is removed irrespective of anatomy.

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Live Donor Nephrectomy – Right side, Obesity, Complex Anatomy – Does it matter?

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Introduction:

The number of live donor transplants is increasing within UK year on year. Such transplants offer superior results in comparison to donation after brain death and after cardiac death. Live donor nephrectomy can be performed using various techniques. In our unit we have adopted the Hand Assisted Retroperitoneoscopic (HARS) approach since 2005. Right side nephrectomy, complex anatomy and donor obesity give rise to more difficult procedures. The aim of this study was to review these subgroups further.

Methods:

Between 2/2005 and 9/2010, 229 HARS nephrectomies were performed. Prospectively collected data were reviewed and analysed using SPSS v17.

Results:

There were 115M and 114F donors. The mean age was 48 (min 18, max 76) and the mean BMI was 26 kg/m2 ± 3.5 (SD) [18 kg/m2 - 38 kg/m2]. 41 (18%) donors had BMI >30 kg/m2. There were 199 (87.3%) left side and 27 (12.7%) right side neprhectomies. Some 109 cases (48%) had complex anatomy. The mean operative time for all cases was 136 ± 45 min (SD), for simple anatomy cases 128 ± 44 min (SD) and for complex anatomy cases 144 ± 45 min (SD). Warm ischaemia time (WIT) was 97 ± 43 seconds (mean ± SD), cold ischaemia time (CIT) was 63 ± 35 min (mean ± SD) and the median blood loss 20 ml (IQR=50). The median postoperative stay was 2 days (IQR=1). The incidence of minor and major complications was 5.2% and 2.6% respectively. There was no significant difference between left and right side nephrectomies with respect to age, sex, BMI, operative time, blood loss, WIT, CIT, complex anatomy and post-operative length of stay. Similarly, there was no significant difference in these parameters between donors with a high BMI (>30kg/m2) and those with a low BMI (<30kg/m2). Complex anatomy operations had a significantly higher blood loss (median 10 versus 20 ml, p=0.042) and CIT (56 ± 26 versus 72 ± 42 minutes [mean ± SD], p=0.003) than those with simple anatomy.

Discussion:

HARS live donor nephrectomy is a safe technique, offering low incidence of complications to donors and a short hospital stay. This technique is suitable for complex anatomy, right side nephrectomy as well as obese donors.

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Impact of donor kidney size on allograft functions in living donor renal transplants: does size matter?

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Background: Nephron mass has been identified as one of the non-immunological factors that may have some impact on long-term graft survival and function. In addition, the impact of recipient weight on patient and graft survival has been the subject of some controversy, particularly with the evolving obesity epidemic within the United Kingdom. Data with regards to body mass index (BMI) has demonstrated conflicting results with some studies suggesting that pretransplant obesity is a significant risk factor, whilst others have refuted this association. We aimed to analyze the impact of the size of donor kidney, an indirect marker of nephron mass on short and long term renal allograft function following live donor transplantation.

Methods: A retrospective analysis was performed of all living donor transplants in a single unit over a 5 year period (Jan 2005 – Dec 2009; 241 patients.) Patients receiving second or subsequent grafts were excluded from analysis. The influence of renal size on graft survival and function in all living donor transplants was assessed. Graft survival was determined as independence from dialysis requirement, irrespective of serum Creatinine. Renal size was determined by pre-operative assessment at the time of donor evaluation (Computed tomography (CT), Magnetic Resonance (MR) scanning or ultrasound scan (USS.)) Kidney size was defined as standard if between 10 and 13cm and 5 to 7.5cm wide as per pre-determined standard, Whilst smaller or larger kidneys were classified into separate groups for the purposes of analysis. BMI (kg/m^2) was calculated in all recipients and classified according to the World Health Organization (WHO): under weight (16.5-18.4), normal (18.5-24.9), over weight (25-29.9), obese class I (30-34.9), class II (35-39.9) and class III (>40). Graft survival was used as a primary endpoint.

Results: 222 patients were eligible for inclusion. Patients excluded from analysis included second or subsequent allografts (n=19).

Graft Survival Results are demonstrated below:

	Small size kidney			**Standard size kidney**			**Large size kidney**		
	Recipient	**1 yr %**	**3 yr %**	**Recipient**	**1 yr %**	**3 yr %**	**Recipient**	**1 yr %**	**3 yr %**
Under weight	5	40	20	13	85	69	1	0	0
Normal BMI	18	89	83	103	96	84	5	100	100
Over weight	4	75	75	36	91	86	3	100	67
Obese class I	2	100	50	13	85	70	2	100	100
Obese class II	1	100		10	80	50	3	67	33
Obese class III				1			2	50	50

	Small size kidney Mean GFR			**Standard size kidney Mean GFR**			**Large size kidney Mean GFR**		
	90 days GFR	**1 yr GFR**	**3 yr GFR**	**90 days GFR**	**1 yr GFR**	**3 yr GFR**	**90 days GFR**	**1 yr GFR**	**3 yr GFR**
Under weight	52.6	57.4	41.8	55.2	53.3	49.2			
Normal BMI	66.6	55.4	51.3	68.2	62.1	59.7	61.2	63.2	53.3
Over weight	49.8	41.7	39.3	57.3	51.5	50.2	51.4	41.5	43.6
Obese class I	49.5	45.2	36.6	49.6	48.6	47.4	52.6	39.8	38.4
Obese class II	20.7	16.2		48.9	42.2	45.2	38.9	38.3	33.6
Obese class III				19.3			41.4	36.3	32.1

Summary: The above data indicates that the short and long term graft survival is poorer in recipients with extremes in body habitus (both low and high BMI) irrespective of the size of the donor kidney. There is also a trend towards improved graft survival in patients who receive larger kidneys. This may suggest a role for careful consideration in patients with higher BMI's who may be receiving kidneys from small donors, and therefore with associated smaller allografts, or in those in which there is a large BMI disparity between donor and recipient.

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Proposed Model for Patient Response Outcome Measures (PROM) in Live Donor Nephrectomy Based on Donor Responses.

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Introduction

Patient Response Outcome Measures **(**PROMs) are a means of collecting information on the clinical quality of care delivered to NHS patients as perceived by the patients themselves. The aim of this study was ascertain key questions that may affect the outcome for donors at the time and following donation.

Method

An anonymous questionnaire was sent to all donors who had undergone donor nephrectomy at our unit from January 2004 to December 2009. Using a modified SF-36 questionnaire peri-operative and post-operative care was evaluated by quantitative and qualitative means.

Results

There were 98 donors in the given time period with 51 returning the questionnaire. The most common symptom post operatively was constipation affecting 76% of donors. Pain relief was affective with 55% of donors reporting no to mild pain. By 1 month 70% of donors felt no pain but 63% of donors felt mild to moderate tiredness. Moderate to severe sleep disturbance was experienced by 90% of donors with noise accounting for most complaints.

More than half of donors had returned to their normal daily activities by 1 month however there was a small group (9%) that had not by 6 months. 5 patients had returned to work by 2 weeks however the most (51%) donors returned to work at 3 months.

Donors rated nursing and doctor attitudes towards them as excellent or good in 72% and 81% cases respectively. 1 in 3 felt nursing care was excellent.

Emotionally most donors felt that this was a positive experience (n>30) with comments used as feeling proud, delighted and brilliant, however 1 in 5 felt weepy, let down and isolated after surgery.

Conclusion

This questionnaire has identified resolvable post operative symptoms and issues. Most donors are happy with the care and the outcome but this has identified a group of patients who feel isolated and upset following donation and emotional support is required for donors not just pre but also post donation.

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The effects of Urokinase on early graft function in live donor kidney transplantation

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Introduction

Thrombolytic agents have been used to enhance the preservation condition and improve graft outcome in deceased kidney donation. However, there is no evidence for the routine use of such agents in living donor kidney transplantation to improve early graft function.

Methods

A pilot study of 100 live donor kidney transplants was performed. Fifty cases with Urokinase added to the preservation solution and fifty without Urokinase representing the control group. Slow graft function (SGF) was defined as a less than 10% fall in serum creatinine within the first 24 hours, and early graft function measured by area under the curve serum creatinine (AUC Cr) over the first 7 days after transplantation.

Results

The incidence of SGF was 24% in the control group compared to 8% with the addition of urokinase (p=0.054). However, there was no difference in AUC Cr between the urokinase and control groups (1666 ± 687 vs 1676 ± 692 μmol/L.day respectively; p=0.883). There were no incidences of intravascular thrombi and no adverse events reported from the use of Urokinase.

Conclusion

The addition of Urokinase to the kidney preservation solution reduced the incidence of SGF in a cohort of live donor kidney transplants. SGF has a negative impact on patient and graft survival, and occurs more frequently in live donor kidney transplantation than is often realised. This study shows the use of Urokinase warrants further investigation in this field.

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Use of Living donor kidney that could not proceed toward transplantation. Survey of donor wishes.

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Background: Although Living Donor Kidney Transplantation is highly successful, rare complications can be extremely challenging. The rare scenario where a kidney donated by a living donor can not be transplanted because of unexpected clinical findings at time of transplant poses enormous pressure on the transplant team

In this study we assessed the wishes of living donors should this scenario had happened. We also included questions to assess our donors' awareness of organ shortage and if they were informed in clinic of this rare but possible complication

Methods: We sent a questionnaire to living donors who underwent donor nephrectomy in our unit between 2000 and 2010. We gave an imaginary scenario where their donated kidney could not be implanted into the proposed recipient after living donor nephrectomy

The donors had to choose one of five answers if they were put in that position: discard the kidney, re-implant it back in the donor, offer it to research, or offer it to another donor on the local or national waiting list

We also asked if they were made aware of this scenario by the operating surgeon and if knowing this would have influenced their decision to progress towards donation

Other questions were targeted to assess donors' awareness about altruistic donation, number of people on the transplant waiting list and number of transplants performed in our unit and nationally

Results: We received 90 questionnaires out of 227; 40% response. For the given scenario the majority (80%) has chosen to offer the kidney locally or nationally; 3.4% chose to offer it to research. Only 14.7% have chosen to have it re-implanted and 1.1% chose to discard it ($p < 0.0001$). More than two third of the patients (69%) were aware of this rare complications and were all consented in clinic. Also 92% of all the donors would still be happy to donate their kidneys including those who were not informed prior to the procedure during the consent process ($p < 0.0001$). The questionnaire also showed that the donors had a rather significant underestimation of the shortage of organs; similarly, there was underestimation of the number of renal transplants performed annually both locally and nationally. 41% of the respondents heard about altruistic donation

Conclusion: From our survey the majority of donors are happy to proceed with donation despite the risk of not being able to transplant. It appears that in our series most donors do not wish to undergo autotransplantation, however in a questionnaire all the implications of this procedure could not be explained fully

Despite being a selected group of individuals where higher level of awareness could be expected, it appears that there is a chronic underestimation of the shortage of organs

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"Bench" Ureteroscopy in Living Kidney Donors With Kidney Stones: Maximising Donor Kidneys

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Introduction: An increasing renal failure population requires maximising living kidney donation. In our growing living-donor programme we diagnose incidental stones in 5% of potential donors and consider these to be "extended criteria" donors. We look for alternative donors, but if there are none, we proceed to kidney donation, provided that stones are unilateral, ≤1cm and neither infection or cystine stones. We consider the role of (ex vivo) bench ureteroscopy immediately after living donor nephrectomy to permit use of these kidneys.

Methods: Prospective analysis of potential donors with asymptomatic stones on non-contrast phase of CT angiogram

Results: 42 potential kidney donors had asymptomatic stones (size 1 - 8.5mm) of whom 7 with bilateral, 1 with possible medullary sponge kidney and 1 with a contra-lateral angiomyolipoma were excluded from donation. In 15 cases the donor was unsuitable for other reasons or an alternative donor was available. 2 overseas potential donors with stone were excluded because of the high risk of stone recurrence and lack of appropriate urology follow up in their home country. 6 people are currently progressing through donor assessment.

10 people with small asymptomatic stones have donated a kidney. None underwent pre-donation stone treatment. 6 had right-sided calculi: 5 had right nephrectomy (1 to 4mm stones) and one (1mm stone) had left nephrectomy. 4 patients with left-sided calculi had left nephrectomy. Bench (ex-vivo) ureteroscopy was attempted in 7 explanted living donor kidneys - 1 unsuccessful, 1 negative ureteroscopy (no stone seen) and 5 successful – 3 with Holmium laser fragmentation of kidney stone and 2 with zero-tip basket retrieval. Donor and recipient follow up (2 months-3 years) - no stone related complications or detrimental effect to graft outcome.

Conclusion: Incidental stones in potential kidney donors are common. When a unilateral small stone is detected, donors and recipients should be fully counselled of the potential risks. Potential donors from overseas need special consideration both of environmental stone risk factors and ease of access to specialist urology services in their home country. For UK potential donors, donating a small (≤4mm) stone in situ may be appropriate but needs a larger patient cohort and longer follow up for firm conclusions. Bench ureteroscopy allows safe removal of stones before implantation and the donor does not need any extra procedure to remove the stone.

Live Donor Surgery 2

Moderator: Gaby Oniscu

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Outcomes in live kidney Transplantation: Can Trainees 'Cut' it?

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Introduction: The constraints of the European Working Time Directive upon a Surgical Trainees operative exposure are well documented. Transplantation offers significant stressors in terms of patient expectation which are heightened in the context of live kidney transplantation. This has resulted in a traditional reticence amongst transplant units to allow Trainees to perform allograft implantation, further compromising operative exposure. However, Senior Trainees with Vascular competencies and previous cadaveric implant experience should benefit from the live donor implant training. We assessed the outcomes of live kidney implantation by Surgical Trainees and potential deleterious effect on graft outcomes.

Methods: A retrospective analysis was performed of living donor renal transplant implantation procedures over a 76 month period (Jan 2003 to April 2010; 277 patients; M=168, F=109; mean age 36.1±1.01 (range 2-71)). Outcomes were compared between Consultant and Surgical Trainees subjectively assessed by Consultants and with cadaveric implantation competency, operating both with and without supervision. There were no patient exclusions, including paediatric patients (<16 y.o.) Primary endpoints were defined as Surgical complications (vascular, urological and wound). In addition, Creatinine and Glomerular Filtration Rate (GFR) at 3 months were analysed as secondary endpoints.

Results: 147 patients (120 adults, 27 children; M=93, F=54; mean age 33.6±1.49, range 2-70) had transplants performed by Consultants whilst 130 were performed by Trainees (124 adults, 6 children; M=75, F=55; mean age 38.8±1.29, range 3-71**,** p=NS).There were a total of 3 vascular complications (1 renal artery thrombosis in the Consultant group; 2 episodes of bleeding requiring re-exploration in the Trainees group (p=0.49)) 5 patients had urological complications (stenosis) requiring intervention (2 Consultants, 3 Trainees, p=0.56.) In addition, there were 4 wound infections requiring antibiotics (1 Consultant, 3 Trainees, p=0.26) There were no differences between the Consultant and Trainee group in terms of either mean Creatinine (135.5±7.6 and 128.5±5.1 respectively, p=0.46) or GFR (54.5±2.8 and 54.9±2.2 respectively; p=0.91)

Conclusions: Donor organ shortage coupled with constraints on available time will place an increasing importance on live donation as a potential training opportunity. Emotional implications of graft failure coupled with perceived technical challenges have historically limited Trainee exposure to live donor implantation. However, outcomes for Senior Surgical Trainees can replicate those of Consultants, with good transplant outcomes coupled with minimal complications. The challenges facing Surgical training will require a paradigm shift to ensure that capable Surgical Trainees are offered exposure to this procedure ensuring that they achieve the competencies to satisfactorily complete Surgical training.

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Early ultrasound after living donor transplantation allows immediate correction of arterial obstruction in recipients with a native urine output.

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Introduction:

Between Jan 2008 and Oct 2010, 278 adult living donor kidney transplants were performed in our institution. Our protocol included an ultrasound scan (US) in recovery to assess perfusion of the transplanted kidney. The purpose of this study was to assess whether this scan led to a change in management.

Methods:

We retrospectively collected data from our database and from the case notes. We collected information on whether the transplant was pre-emptive and, if not, the modality of renal replacement therapy and whether the recipient had a native urine output. We looked at the reports of all the scans that were done and consulted the notes to see whether any abnormality was found and, if so, whether any action was taken.

Results:

272/278 (98%) had an US in accordance with protocol and of these 11% were abnormal.

Of the abnormal scans:

21 showed localised abnormalities of perfusion which were not re-explored (100% rescanned without progression).

8 showed global poor perfusion or abnormal flow in the main transplant artery or vein.

Of these 6 were re-explored and 2 were not.

The 2 that were managed conservatively had hypotension leading to global poor perfusion (1 secondary to MI, 1 secondary to longstanding adrenal insufficiency).

Of those that were re-explored: 1 had a negative re-exploration.

3 had poor flow secondary to position and were re-positioned in theatre; 1 of which had delayed graft function (DGF) as a result.

2 had arterial thrombus and underwent thrombectomy, of which 1 had DGF and ITU care

All of the patients with positive operative findings had a native urine output.

Of those with a normal USS in recovery, 2 patients subsequently lost the kidney during that admission. 1 suffered renal vein thrombosis 12h post-op, and 1 lost the kidney as a result of haemorrhage at day 4.

Conclusion:

2% of live donor recipients had a change in their management as a result of an US in recovery. All of these patients had a native urine output, and so malperfusion was occult. They all left hospital with a functioning graft. We recommend immediate post-op US as a non-invasive potentially graft saving procedure and we plan to extend it to our deceased donor kidney transplants.

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Early USS after paediatric living donor renal transplant allows immediate correction of perfusion problems and maintained primary graft function.

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Introduction:

70 paediatric live donor kidney transplants have been performed at our institution since 2005. Our protocol dictated that the recipients should receive ultrasound (US) assessment of renal perfusion before leaving recovery or on arrival in Paediatric Intensive Care (PICU) or renal ward. This study aims to determine whether these scans have directly affected patient management in the immediate post operative period.

Methods:

We performed a retrospective review of the case notes and investigation results. We recorded the indication for transplant, mode of Renal Replacement Therapy (RRT), and pre-operative native urine output.

We then looked at the post operative scan reports and recorded subsequent interventions in any cases with abnormal perfusion on ultrasound.

Results:

63/70 (90%) had US in recovery / PICU. 4 did not have US in recovery and 3 cases results were not available.

2/63 (3%) of cases had abnormal graft perfusion on ultrasound; both had native urine output; and both were immediately returned to theatre.

Case one was reported as no arterial flow on US. At operation a large renal artery thrombus was identified requiring thrombectomy and re-implantation

Case two, US showed minimal intra-renal blood flow. This improved following exploration and repositioning of the graft.

Both cases had global perfusion on subsequent US, primary graft function and were well on discharge.

Conclusion:

Early postoperative ultrasound identified perfusion problems in 3% of paediatric live donor renal transplants allowing immediate graft saving intervention. All cases had native urine output and may not have been identified by urine output measurement alone. We recommend US in recovery / on arrival in PICU or renal ward in all paediatric renal transplants.

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Looking Through The Keyhole. Is Laparoscopic Donor Nephrectomy Really A Cut Above The Rest?

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INTRODUCTION

It has previously been established that laparoscopic donor nephrectomy is associated with less pain and a shorter post-operative stay; thus it has been advocated as the procedure of choice. Few studies have compared the inflammatory stress response induced by open and laparoscopic donor nephrectomy. The neutrophil to lymphocyte ratio (NLR) is one easily measurable parameter that can be used to measure stress induced by major surgery and correlates well with organ dysfunction scores.

METHODS

105 laparoscopic donor nephrectomies were undertaken at our institution between October 2006 and June 2010. For comparison data were compared with the last 105 consecutive open donor nephrectomies at the same hospital. Data were collected on patient demographic, length of stay and complication rate. Day one post-operative albumin, haemoglobin and haematocrit drop and pre- and post-operative NLR were compared between the two groups. An unpaired T test was used for statistical analysis.

RESULTS

	LAP	OPEN	
Female (%)	51.4	60.0	
Average age (years)	46.5	48.4	ns
Average length of stay (days)	5.18 +/- 1.29	6.83 +/- 1.55	p<0.00001
Average albumin change (g/L)	-10.65 +/- 4.08	-10.34+/-7.67	ns
Average haemoglobin change (g/dL)	-1.86+/-0.96	-2.46+/-1.21	p=0.0001
Average haematocrit change	-5.33+/-3.16	-6.83+/-4.09	p=0.004
Pre-op NLR	1.95+/-0.72	2.58+/-2.6	p=0.02
Post-operative NLR	8.77+/-6.09	7.53+/-5.81	ns
Complication rate-major and minor (%)	19	27	
Data complete (%)	95.2	84.7	

DISCUSSION

This study concurs with other series published in showing a shorter post-operative stay, less blood loss and fewer post-operative complications when laparoscopic and open donor nephrectomy are compared. However, the lack of significant difference in the post-operative albumin drop and NLR between the two groups would suggest that the physiological insult of both methods of donor nephrectomy are comparable. The shorter post-operative stay may be due predominantly to less incisional pain or perception that a more minor procedure has taken place.

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Impact of Renal Vessel Multiplicity on Perioperative and Long-Term Donor Outcomes Following Living-Donor Nephrectomy

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Introduction: Live donor kidney transplantation is consistently superior to deceased donor transplantation. Multiple renal vessels present a technical challenge to the operating surgeon and might, it is hypothesised, herald greater risks of perioperative and long-term complications for the donor.

Methods: This study assimilates nephrectomy data collected over the last five years at one of the United Kingdom's largest renal transplant units. We performed a retrospective analysis of the 335 'mini-open' technique living-donor nephrectomies conducted at the unit since 2005. Intra-operative data and post-operative outcomes (up to 5 years) for multiple and single vessel donors are analysed, compared and reported.

Results: Of the 232 donors satisfying the inclusions criteria, 27 (12%) had multiple renal arteries in the kidney to be removed. Total operation time was not significantly different between those with a single vessel (125 +/-49 minutes) and those with multiple vessels (120 +/- 48 minutes $p<0.05$). Warm ischaemia time and estimated blood loss were also found not to vary significantly between groups. Total length of hospital stay was not significantly longer for those with multiple vessels (4.8 +/- 1.3 days) as compare to single vessel donors (5.3 +/- 1.4 days $p<0.05$). Peri-operative and long-term (mean = 19 months) complication rates were also not significantly different between groups, with pneumonia and wound infection constituting the commonest postoperative complications for both.

Conclusion: Our unit's experience is that donor nephrectomy is safe in donors with multiple vessels and does not result in higher rates of major perioperative complications. Long-term follow-up data show good outcomes for these donors. While these results are encouraging, we advocate careful selection of multiple vessel donors with appropriate pre-operative education and counselling, and can only recommend their inclusion in centres similar to our own, specialising in marginal donor transplantation.

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Right Laparoscopic Donor Nephrectomy: A Safe Method For Laparoscopic Donor Nephrectomy

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Introduction:

Laparoscopic donor nephrectomy (LDN) is accepted as a standard method of living donor nephrectomy. Left sided LDN (L-LDN) is preferred to right sided LDN (R-LDN) due to longer length of the left renal vein and there is a reluctance to perform right-sided nephrectomy laparoscopically. The purpose of this study was to establish the safety and efficacy of R-LDN at a single transplant centre.

Methods:

All laparoscopic nephrectomies performed from between December 2004 and October 2010 were analysed using a prospectively maintained database. The decision on laterality was based on renal anatomy and split renal function determined by CT-angiography and DMSA renography. R-LDN was compared with L-LDN for donor and recipient outcome measures.

Results:

A total of 167 LDN were performed comprising of 65 (39%) R-LDN (group 1) and 102 (61%) L-LDN (group 2). The groups were matched for age, gender, pre-operative creatinine and GFR.

Peri- and post operative complications occurred in 3 (5%) and 6 (6%) patients of group 1 and 2 respectively. Two cases in group one required open conversion and one case in group 2. Blood transfusion was necessary for two patients in group 1 and for one patient in group 2. None of the patients required re-operation.

There was no significant difference between R-LDN and L-LDN in terms of initial warm ischaemic time (3:36 vs 4:09 min, p=0.099), duration of inpatient stay (3.7 vs 3.3 days, p=0.13) or 6-week postoperative creatinine (118 vs 117, p=0.70).

When compared for recipient outcome, there was no significant difference between the two groups in 6 months postoperative creatinine (138 vs 131, p=0.44), incidence of rejection or graft failure at one year.

Conclusion:

In our experience R-LDN is equivalent to L-LDN in donor safety and outcome, and does not affect recipient outcome measures. R-LDN should be offered routinely when pre-operative imaging demonstrates the right kidney is the preferred donor organ.

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Anterior Extraperitoneal and hand assisted laparoscopic donor nephrectomies: do outcomes differ?

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Introduction: Live kidney donation to increase the potential donor pool has caused the advent of novel approaches to replace the traditional loin procurement method with its high morbidity and post-operative pain incidence, with both laparoscopic and anterior extraperitoneal approaches becoming frequently performed. Enthusiasts have advocated laparoscopic approaches quoting perceived improvements in patient recovery time associated with minimal complications. However, potential adverse effects to the donated kidney, specifically delayed graft function (DGF) due to the pneumoperitoneum during the procedure have not been evaluated. We aimed to compare outcomes in open anterior extraperitoneal and laparoscopic donation techniques.

Methods: A retrospective analysis was performed of renal transplant donors over a 76 month period (Jan 2003 to April 2010; 268 patients). Outcomes were assessed in both anterior extraperitoneal and hand assisted laparoscopic (HALD) approaches. All operations were carried out by consultant surgeons and paediatric recipients and organs donated or exported to other centres were excluded. The primary endpoint was DGF, defined as dialysis required on 2 occasions. Outcome measures including donor complications, length of stay and recipient Creatinine at 3 months were analysed.

Results: 108 patients donated using an anterior extra-peritoneal approach over the study period (Male: 63, Female: 45; mean age 45.3±1.2, range 20-69) whilst 158 patients underwent HALD (M:101, F:57, mean age 44.8±0.9, range 19-71, p=NS). There were more episodes of DGF in the anterior approach compared to the HALD donor group (9/108 (8.3%) vs 5/158 (3.1%), p=0.06). Glomerular filtration rate was equivalent in the 2 groups (53.25±2.76 and 53.4±1.68 respectively, p=0.94) Donor complications were equivalent across open and HALD groups respectively (chest infections: 7.4% and 7.5%; urinary tract infections: 3.7% and 2.7%; neuralgia: 4.6% and 1.3%; and requirements for blood transfusion 2.7% and 2.5% respectively; p=NS for all.) Wound infections were higher in the HALD group (3.7% vs. 8.2%, p=0.14) and neuralgia in the anterior extraperitoneal approach (4.6% vs. 1.3%; p=0.09.) Mean length of stay was significantly shorter in the HALD group (3.7±0.18 vs. 4.4±0.27 days; p=0.01)

Discussion: The requirement and frequency of live kidney donation has heightened interest in the benefits of varying methods with advocates of both anterior extraperitoneal and laparoscopic approaches developing. Although both methods appear safe, the potential adverse effects of the pneumoperitoneum on DGF appear unfounded. Our series suggests a tendency towards higher rates of neuralgia with the anterior approach although other complications did not differ between the two groups and recipient renal function was equivalent. Length of stay, however, was significantly shorter demonstrating potential economic benefits to the health service. Enthusiasts for both approaches should therefore be able to justify their approach. In the future patient preference will undoubtedly alter surgical approach although both techniques should be offered in suitable donors.

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Hand assisted laparoscopic donor nephrectomy – are hand ports really necessary?

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Background: Hand port devices (HPD) are used routinely for Hand-Assisted Laparoscopic

Surgery including Hand-Assisted Laparoscopic Donor Nephrectomy (HALDN) allowing for decreased morbidity, shorter hospital stays and improved cosmesis. HALDN also provides perceived advantages over total laparoscopic donation including the ability to use tactile feedback, easier and rapid control of bleeding by digital pressure, better exposure and dissection of structures, rapid kidney removal and a shorter learning curve. However HPD's remain costly and may be a limiting factor in the adoption of a hand-assisted technique, particularly in the developing world where resources are limited, resulting in surgeons utilising alternative methods to allow procurement. We have developed experience in performing HALDN without the aid of any HPD ('device free') and we aimed to establish whether there were any adverse effects to performing donor surgery in this manner.

Methods: A retrospective analysis was performed of patients undergoing left HALDN at our unit over a 3 year period (2007-2010, 164 patients). 84 patients underwent device free HALDN whilst in 80 patients a HPD (Gelport™) was utilized. Procurement was performed utilising a standardised protocol in both groups. The primary endpoint was duration of operation, with secondary endpoints of post-operative wound infections and incisional hernias.

Results: There was no difference in duration of operation for the device free (98 minutes;

range 43-215 minutes) compared to HPD group (94 minutes; range 36-180 minutes; p=0.37). A device was required in 3 (3.6%) patients in which device free approach was attempted. There was no difference in either group in terms of rates of postoperative wound infections (0% vs 2.5% respectively; p=0.24), all of which settled with conservative management. In addition, there was no differences with respect to incisional hernia incidence (2.4% vs 1.4% respectively; p=1.00)

Conclusion: HALDN has revolutionised the process of donor organ procurement, whilst device free HALDN can be performed with no discernable compromise in operating time or patient outcome as demonstrated by the inherently low complication rate. Fears of adverse operating conditions, due to potential compromise of the pneumoperitoneum proved unfounded, which is obviously of paramount importance in live donation. This approach has significant implications in both cost benefit and translation of this technique to developing units as the cost of the Gelport™ is over £350 per single use. This important modification may be the key to providing HALDN to the wider population and potentially developing nations ensuring that this valuable source of potential donor organs is maximally utilized.

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Inferior Epigastric arteries provide a useful conduit allowing successful transplantation of kidneys with multiple arteries.

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Background: The current paucity of donor kidneys has led to the increased use of organs with aberrant vascular anatomy, especially multiple arteries. However, this may result in increased technical challenges and potential pitfalls including thrombosis, especially in the clinical setting of small accessory arteries. This issue has particular resonance in the scenario of lower polar arteries, due to the vessel's critical role in providing a blood supply to the ureter, necessitating preservation of these vessels if possible. This should not be performed with any potential compromise to the vascular supply from the main renal artery. Novel techniques have therefore been utilised to revascularise lower polar renal arteries. We aimed to assess the results of anastomosis of the accessory lower polar arteries to the inferior epigastric artery (IEA), a branch of the external iliac artery.

Methods: A retrospective analysis was performed of all patients undergoing renal transplantation utilising the IEA for inferior polar arterial anastomosis over a 10 year period (2001 to 2010; 1269 adult patients). All patients underwent renal transplantation with the main renal artery anastomosed to common, external or internal iliac artery, and accessory inferior polar artery to IEA. Primary endpoints were urinary complications. Secondary endpoints included graft and patient survival, Creatinine at 1 year and post-transplant arterial complications (hypertension) due to renal artery stenosis.

Results: 19 patients underwent accessory polar renal arterial anastomosis to the IEA over the study period (10 live donors kidneys, 9 cadaveric; median age 49 (range 23-66)) None of the patients were diabetics or had pre-existing peripheral vascular disease. 18 patients had 2 renal arteries and 1 patient had 3 arteries. Median anastomotic time was 38 minutes (range 30-70) In terms of primary endpoints, there were no urinary complications. In addition, there was only 1 episode of post-transplant hypertension due to renal artery stenosis of the polar artery in the series. 2 patients (2/15 time censored at 1 year, 4 within last year and grafts functioning) suffered graft loss with no mortalities. Creatinine at 1 year was 135.5 umol/l (median, time censored to 15 patients; range 91-354) with a median Glomerular Filtration Rate of 52.5ml/min (range 15-80).

Conclusion: Alternative strategies to allow successful revascularisation of aberrant arterial anatomy will allow safe utilisation of a larger donor organ pool. The use of inferior epigastric arteries has proved in our case series, the largest to date, to be safe with excellent graft and patient outcomes. In addition, there were no associated ureteric complications and an associated low incidence of post operative arterial stenosis. This novel surgical approach in adults therefore offers an alternative which ensuring optimal graft outcomes in the face of potential significant technical challenges.

Liver Transplantation

Moderator: Murat Akyol

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Clinical impact of hepatic arterial injuries in deceased donor livers with aberrant anatomy

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Background: Hepatic arterial injury is a rare complication of deceased liver procurement. It usually occurs when arterial anatomy is aberrant, thereby making the utilisation of the graft more challenging. Arterial reconstruction is often required under these circumstances, potentially increasing the risk of hepatic artery thrombosis (HAT). The aim of this study is to investigate whether arterial injury in the presence of aberrant anatomy requiring reconstruction increases the incidence of HAT and biliary complications within 3 months of liver transplantation.

Methods: Of 844 adult first single-organ liver transplants performed in our centre between 1994 and 2007, 654 had normal anatomy and single arterial anastomosis (Group 1) and 87 (10%) grafts had aberrant anatomy requiring multiple arterial anastomoses. Among the 77 grafts with aberrant hepatic arterial anatomy and complete operative records, 14 had evidence of hepatic arterial injury during procurement (Group 3) whilst 63 did not (Group 2). The incidence of HAT and non-thrombotic biliary complications within the first 3 months was compared among the 3 groups using the Chi-square test.

Results: HAT within the first 3 months after transplantation in Group 1, Group 2 and Group 3 was 2.9 %, 5% and 14%, respectively. This difference was statistically significant (p=0.01). The incidence of non-thrombotic biliary complications at 3 months in Group 1, Group 2 and Group 3 was 6.8%, 9% and 14%, respectively (p=0.11).

Conclusion: This is the first study describing the clinical impact of arterial injury during liver procurement in donors with aberrant anatomy requiring bench reconstruction. We conclude that arterial injury repair in the presence of aberrant anatomy is associated with a higher incidence of HAT.

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Induction Therapy With Basiliximab And Delayed Introduction Of Tacrolimus Is Associated With A Reduced Requirement For Post-Operative Renal Replacement Therapy In High-Risk Patients Undergoing Orthotopic Liver Transplantation

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Introduction: Early renal impairment following orthotopic liver transplantation (OLT) is a frequent occurrence often aggravated by the use of nephrotoxic calcineurin inhibitors (CNI). Induction therapy with the IL-2 receptor antibody basiliximab has the potential to protect renal function by allowing the delayed the introduction of calcineurin inhibitors.

Aims: To examine the need for renal replacement therapy (RRT) in the immediate post-transplant period in patients undergoing OLT with pre-operative renal impairment. RRT rates in patients who received induction therapy with basiliximab and delayed introduction of tacrolimus were compared to those receiving immunosuppression involving tacrolimus from the outset.

Methods: A retrospective review of patients undergoing OLT at the Scottish Liver transplant unit between Dec 2005 and October 2009 with creatinine levels of 120mmol/l and above at the time of transplantation was undertaken.

Patients were treated with standard immunosuppression of steroids, azathioprine and tacrolimus (control group) or basiliximab on day 0 & 4 with steroids and azathioprine from day 0 and tacrolimus introduction delayed until day 7 (study group). The use of basiliximab was at the surgeon's discretion.

Statistical analysis was undertaken using Graphpad Prism and SPSS. Parametric and nonparametric tests were used as appropriate including Pearson correlation and Mann Whitney U tests.

Results: 35 patients underwent OLT with a preoperative creatinine >120mmol/l, 18 patients received basiliximab induction and 17 patients received standard immunosuppression. One patient receiving combined kidney/liver transplantation was excluded from analysis. Patient demographics were similar between the 2 groups. Cold ischaemic times (CIT) and transfusion requirements were comparable. MELD score was higher in the study group (27 vs. 23)

Two deaths occurred within 60 days of transplantation in the study groups with no mortality in the control group.

Postoperative RRT was associated with increasing age, MELD ($p<0.001$) and intra operative blood transfusion requirements ($p<0.008$).

The study group had significantly higher preoperative creatinine levels compared with the control group ($p<0.05$). Despite this the study groups had lower rates of post transplant RRT (18% vs. 47% $p=0.035$). At day 30 and 60 post transplant there was no significant difference in renal function between the two groups.

Discussion: In a high risk group of patients, in spite of higher serum creatinine levels and higher MELD scores, those receiving basiliximab and delayed introduction of tacrolimus had a significantly reduced incidence of post-operative renal dysfunction requiring RRT when compared to those receiving standard immunosuppression.

Conclusion: This study shows a beneficial effect of induction therapy with basiliximab and delayed introduction of tacrolimus in the context of patients with renal impairment who undergo OLT.

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Patient outcome following portal venous and hepatic arterial reconstruction in orthotopic liver transplantation

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Introduction. Portal venous and hepatic arterial inflow is frequently insufficient to allow adequate arterial and venous inflow to the liver graft. Donor iliac artery and vein are most commonly used as conduits from aorta and superior mesenteric vein to overcome this problem. In this study we describe the outcome of patients in the Scottish Liver Transplant Programme who underwent cadaveric OLT where arterial and venous grafts were required.

Methods. All patients who underwent OLT at The Royal Infirmary, Edinburgh between 1996 and 2010 were identified from the transplant unit database. Data regarding outcome of patients requiring vascular reconstruction were gathered from the database, hospital case notes and operation notes and compared to those with standard vascular reconstruction. All liver transplants except split grafts were included in the analysis. Data analysis was performed using Microsoft excel and graph pad prism.

Results. Eight hundred and twenty three consecutive patients were analysed. Of these, 66 patients (8%) required a vascular conduit. Fifty of these were arterial and 19 were portal venous (3 patients required both). Mean red cell transfusion was significantly higher in patients who underwent portal venous reconstruction (7 vs 11 units, $p<0.05$). 30 day mortality was almost double in the venous reconstruction group (10.5% vs 5.8%, $p<0.001$). The need for arterial reconstruction did not significantly increase morbidity or mortality. Cold ischaemic times, warm ischaemic times and operative times were similar in all groups.

Conclusion. The need for portal venous reconstruction results in significantly increased morbidity and mortality in OLT graft recipients. This highlights the essential requirement of pretransplant vascular assessment in order to provide informed consent to the patient and be able to chose suitable grafts for the recipient, potentially avoiding extended criteria donors if a venous conduit is required.

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Outcomes and Diagnostic Challenges Posed by Incidental Cholangiocarcinoma After Liver Transplantation

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Introduction

Liver transplantation in the presence of cholangiocarcinoma (CCA) generally carries a poor prognosis. However, the outcome of patients found to have incidental CCA on explanted liver histology is less clear. We have evaluated the outcomes of incidental CCA in our liver transplant population.

Methods

A retrospective search was made of the transplantation and histopathology databases for patients fulfilling our definition for incidental CCA. All records, including archived histopathological slides were retrieved and analysed.

Results

Of 1288 patients undergoing liver transplantation over the twenty year period 1988-2008, nine were found to have incidental CCA (0.70%). Seven of the nine patients underwent liver transplantation for primary sclerosing cholangitis. Three additional patients who were transplanted for presumed hepatocellular carcinoma which subsequently turned out to be CCA were identified, but excluded from survival analysis.

The majority of tumours were early stage (T2 or below), but five (55.6%) had positive biliary transection margins. Median follow up was 51 months. Five patients (55.6%) developed recurrence of CCA after a median interval of 25.8 months, giving a disease-free survival of 100% at 1 year, and 66.7% at 3 years. There was no demonstrable difference between patients who experienced recurrence and those who have not in median follow-up, age, sex, CA 19-9, MELD score, tumour stage, tumour grade or tumour margin status. Three patients have died of recurrence, with a median interval from transplantation of 25 months. The overall 3 year survival was 66.7%.

Discussion

Incidental CCA's highlight the challenge of diagnosing this elusive disease. Although they tend to be early stage tumours, in keeping with the aggressive nature of the disease, the recurrence rate is high, and prognosis relatively poor. Prospective liver transplant recipients, especially those with PSC, should be investigated rigorously to exclude CCA.

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Deterioration of Renal Function Is Worse In Patients Transplanted With NASH Cirrhosis

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Introduction: Non-alcoholic steatohepatitis (NASH) cirrhosis is an increasing indication for liver transplantation (LT) worldwide. The impact of LT on renal function in this at risk group is not known. Our aims were to compare the post-LT renal function and survival of this cohort with a matched comparison group

Methods: 48 patients transplanted for NASH between 2000 to 2008 in a single UK centre were compared with 48 patients (matched for age, sex, Model for End-Stage Liver Disease (MELD) and estimated glomerular filtration rate (eGFR)) transplanted for other types of chronic liver disease during the same time period.

Results: Reduction in eGFR was significantly greater in the NASH versus comparison group at first 2 years post-LT (mean difference 6.15 ml/min, p=0.004) years post-LT. At 2 years 29% of NASH patients had developed stage IIIb chronic kidney disease (CKD) as opposed to only 11% in the comparison group. Tacrolimus levels were similar in the two groups. Furthermore NASH patients were considerably more likely to start mycophenolate mofetil (MMF) compared to non-NASH patients during the follow-up period (Hazard Ratio 2.33, $P<0.05$). The survival of NASH patients was similar to the comparison group at 1-year (88% v 86%) and 5-years (82% v 82%) post-transplant.

Conclusions: Patients undergoing LT for NASH develop greater renal dysfunction compared with patients transplanted for other types of chronic liver disease. In our experience many more patients with NASH require rescue therapy with MMF for renal dysfunction compared to matched control patients. The potential therapeutic benefit of renal sparing immunosuppression in NASH patients undergoing LT merits further investigation.

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Improved Cryopreservation Strategy for Liver Cell Spheroids towards development of a Bioartificial Liver

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Aim: Acute liver failure has high morbidity and mortality, with unpredictable presentation and a challenge for transplant resources in an era of donor organ shortages. There is considerable interest in a Bioartificial Liver (BAL) which could either bridge the gap to transplantation or support host liver recovery. We have focused on alginate-encapsulated liver cell spheroids (ELS) as the functional unit for BAL. For clinical translation, a robust cold chain with ability for long-term storage is essential to deliver an "off-the-shelf" therapy to the point of need with good immediate function. Cryopreservation of ELS is problematic because of the random nature of ice crystal formation. Cholesterol crystals are known to be ice nucleators in nature and we have investigated crystalline cholesterol during cryopreservation of AELS to improve post-thaw outcome.

Materials and Methods: HepG2 cells were encapsulated in 1% alginate and cultured for 7 days to form ELS. ELS were exposed to cryoprotectant solution (12% v/v DMSO/Celsior) and cooled cooled in cryo-vials with or without 1 mg solid cholesterol using a controlled rate freezer (Planer Kryo10). Sample temperatures were monitored by immersed thermocouples and recorded by a data logger. Cryopreserved samples were stored in the vapour phase of liquid nitrogen. ELS were recovered by rapid warming and washed free from cryoprotectant. Viabilities were assessed using fluorescein diacetate and propidium iodide staining in conjunction. Cell numbers were quantified by nuclei count. Liver-specific function was quantified using an albumin ELISA. Viability, number and function of ELS were assessed at 24, 48 and 72h post-warming. Results are expressed as fold change compared to unfrozen ELS. Statistical analyses were made by ANOVA and students t-test.

Results: Sample supercooling (an index of random ice nucleation) was reduced by 11°C by inclusion of cholesterol (n=2). Viabilities were significantly improved at all time points ($p<0.01$) with cholesterol, except at 72h by which time new cell division would replace dead cells. Minimum viabilities occurred at 24h for both cryopreserved groups (84% with cholesterol, 43% without). Viable cell numbers were also significantly improved ($p<0.01$) when cholesterol was included, whilst cell numbers never recovered beyond about 40% without cholesterol, even by 72h post-thaw. Without cholesterol, viable cell numbers were 25%, 34% and 41% at 24, 48 and 72h respectively. Albumin production (µg/24h) was reduced cf. unfrozen ELS in both cryopreserved groups but was higher with cholesterol at 24 and 72h timepoints.

Conclusion: Crystalline cholesterol is an effective ice nucleator during cryopreservation of ELS which reduced sample supercooling and improved both cell recoveries and function. Controlled ice nucleation is an important strategy in devising cold chain delivery of BAL based on ELS components.

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Surgical Outcomes after Colorectal Resection in Patients with Orthotopic Liver Transplantation

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Background: Liver transplanted patients are immunocompromised and at an increased risk of developing de novo malignancies, particularly in the setting of PSC and UC. Indications for colorectal resections in these patients commonly include UC or colorectal cancer. We present data on patient outcomes from colectomy during and after liver transplantion.

Patient and Method: A retrospective review of 40 colectomies performed on 37 liver transplant patients between June 1998 and July 2010 was undertaken.

Results: 28 patients had colectomies for UC, of which 27 had PSC and 1 had hepatitis. 15 patients had colectomies for malignancy, of which 9 were on the background of UC. 3 patients had a colectomy at the same time of their liver transplant and 34 patients had colectomies post transplant. Length of stay ranged from 5 to 31 days with a median of 10 days. 30 days mortality was 0. There were 8 deaths with survival ranging from 2 to 150 months. Overall median survival was 60 month (5 years). In the cancer cohort, there were 2 deaths and median survival was also 60 months. Overall 1, 3 and 5 year survival was 86.5%, 75.7% and 48.7 % respectively. Survival in the cancer and non-cancer cohort was 80% vs 86%, 73% vs 77% and 53% vs 41% respectively.

Operation	Panproctocolectomy	Subtotal colectomy	R hemi colectomy	L hemi colectomy	AR	APR	Pouch
Patient nos	17	7	5	2	2	1	3
Cancers	4	2	5	1	2	1	0

Of the 3 patients who underwent an IPAA, only 1 kept the pouch. 1 pouch were lost because of fistula formation and the other because of a malignancy at the ileoanal margin resulting in a proctectomy.

Time to diagnosis of CRC post OLTX (years)	PSC-UC	Non PSC-UC
Range	0 – 9 years	0 – 17 years
Median	5 years	8 years

Conclusion: Surgical outcomes after colorectal resections in liver transplanted patients when undertaken in a tertiary referral and transplant centre are acceptable and compare favourably with general population. The timing of colectomy in liver transplanted patients with PSC is debatable but our data would support undertaking colectomies earlier.

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Who gets the liver transplant? The use of responsibility as the tie breaker

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Is it possible to invoke the use of moral responsibility as part of the selection criteria in the allocation of livers for transplant? Criticism has been applied to the difficulties inherent in including such a criterion and also the effect that employing such a judgment might have upon the relationship between the physician and patient. However, these criticisms rely on speculation and conjecture and, I believe, do not relate to all the arguments put forward in favour of applying moral responsibility. I believe that none of the present arguments against using moral responsibility in the allocation of livers for transplant are good enough to warrant its dismissal.

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Peri-venous and not peri-portal human hepatocytes are the targets of ischaemia-reperfusion injury following liver transplantation.

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Introduction: Ischemia-reperfusion injury (IRI) is known to cause allograft dysfunction in 10% of patients following orthotopic liver transplantation. IRI culminates in hepatocyte injury and predisposes to both acute and chronic rejection. The liver acinus, the functional unit of the liver, consists of both peri-portal (PP) and peri-venous (PV) hepatocytes. IRI can be mimicked in vitro by using models of hypoxia and hypoxia-reoxygenation (H-R). Rodent studies of hepatic IRI suggest that there may be differential susceptibility of PP and PV hepatocytes to hypoxia and H-R. The increased susceptibility of some hepatocytes is thought to be due to their propensity to generate Reactive Oxygen Species (ROS). Whether PP and PV human hepatocytes exhibit differential responses to hypoxia and H-R is not known. The differential response of hepatocytes to hypoxic injury would have strong implications for potential therapeutic strategies. Moreover, it would improve the understanding of the pathogenesis of hepatic IRI. We therefore assessed the responses of PP and PV human hepatocytes to hypoxia and H-R.

Methods: Human hepatocytes were isolated from human liver tissue using a collagenase perfusion technique. Fluorescent Activated Cells Sorting (FACs) was utilised to distinguish between PP and PV human hepatocytes. Hepatocyte ROS production, apoptosis and necrosis were determined by using the fluorescent dye 2',7'-Dichlorofluorescin, Annexin-V and 7-Actinomycin D (7-ADD) respectively in a three-colour reporter assay and subjecting cells to FACs analysis.

Results: PP and PV human hepatocytes could be clearly distinguished by FACs analysis. PV human hepatocytes significantly increase intracellular ROS accumulation during hypoxia and H-R with a concomitant increase in apoptosis and necrosis. Previous studies in rodent hepatocytes have shown that the mitochondrion is the main cellular generator of ROS. Indeed, inhibition of mitochondrial function, with the complex I inhibitor, rotenone, significantly reduces PV human hepatocyte ROS accumulation. Furthermore, inhibition of the mitochondrial function almost completely ameliorated PV human hepatocyte apoptosis and significantly reduced necrosis during hypoxia and H-R. In contrast, PP human hepatocytes do not increase ROS accumulation. Furthermore, PP human hepatocytes do not undergo any cell death during hypoxia and H-R.

Conclusion: Our data clearly demonstrates that PV and not PP human hepatocytes have increased susceptibility to cell death during hypoxia and H-R. These findings have important implications for both the understanding of hepatic IRI and the targeting of therapeutic strategies for liver diseases.

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The development of a nurse led transplant assessment process in liver transplantation

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Liver transplant patients are usually admitted as an in-patients for 5 days, where they are assessed and undergo an education programme as part of the informed consent process prior to be accepted onto the waiting list. With the move to the new hospital, there has been a reduction in bed capacity leading to a need to review the assessment process.

We began by reviewing our current practice and looked internationally how this worked at other centres. Key to the whole process was the development of an initial clinic to perform basic investigations to identify co-morbidities i.e. Hepato Pulmonary Syndrome, Pulmonary Hypertension, etc, which would require an in-patient assessment. This also gave the Transplant Coordinators the opportunity to identify patients with complex psycho educational needs who would require more intensive input, more suited to an in-patient assessment .In order for this to work a pathway and protocol was written with an inclusion/exclusion criteria.

Once the patient has attended the initial clinic their results are reviewed with their Consultant and a decision is made as to how to proceed. If they are deemed suitable as an out-patient they attend a further two days in which they are reviewed by a Hepatologist, Surgeon and Anaesthetist and they undergo intensive education by the Transplant Coordinator. They also have opportunity to meet with patients who have undergone liver transplantation via our support group. The patients are then presented at the transplant MDT by the Liver Transplant Coordinators.

Results

To date, we have assessed 43 patients as an outpatient. Of these 22 have been placed onto the waiting list. We have referred 5 to the in-patient assessment pathway, 9 are currently awaiting further investigations, 1 patient chose not to proceed, 1 patient was not surgically suitable, 3 patients were too early. 1 patient went for alternative therapy, and 1 patient beyond listing criteria. From informal feedback patients have expressed their satisfaction as it takes less time, although more intensive, they avoid an in-patient stay and build a close relationship with their Coordinator. With advancement of nurse practice this system lends itself to the coordinator being more autonomous and gaining new skills, which in turn increases job satisfaction.

Conclusion

Although in its' infancy the process does work, however, there needs to be a degree of flexibility. The key to its' success is the appropriate selection of patients to undergo this format of assessment

Miscellaneous

Moderator: Steve Powis

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Responses to non-polymorphic HLA Class 1 derived peptides are mediated by $CD4^+$ T effector memory cells

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We have recently described that renal transplant recipients' peripheral blood mononuclear cells produce γ-interferon in response to peptides derived from the non-polymorphic α3 domain of class 1 HLA. These responses to cryptic self-epitopes are associated with chronic allograft dysfunction. The cell surface phenotype of responding cells was shown to be $CD3^+CD4^+CD25^+CD127^+$.

We now further refine this phenotypic definition by demonstrating that $CD4^+CD25^+CD127^+CD45RO^+CCR7^-$ T lymphocytes added to γ-interferon ELISPOT assays containing $5x10^5$ PBMC's, result in an upward titration of response in the presence of specific (HLA derived) but not control peptide ($n=10$, $p<0.005$). This was not observed when titrating equivalent numbers of $CD4^+CD25^+CD127^+CD45RO^+CCR7^+$ or $CD4^+CD25^+CD127^-CD45RO^+CCR7^{+/-}$ T lymphocytes, into these cultures ($n=10$, $p<0.005$).

The responses to HLA derived peptides were then further investigated using two agents (Shk peptide and PAP-1) that inhibit kv1.3 K^+ channels. kv1.3 channels play a role in T effector memory cell activation. γ-interferon production measured in the ELISPOT assay was significantly inhibited by both Shk ([50nM], $n=20$, $p<0.0001$) and by PAP-1 ([1 & 5 mM], $n=20$, $p<0.001$). There was however no significant inhibition of responses to PPD antigen or anti-CD3.

If responses to HLA derived cryptic self-epitopes that are associated with chronic allograft dysfunction are also representative of pathogenic T lymphocyte responses to transplantation antigens, then our observations suggest that targetting T effector memory cells may have therapeutic utility in countering chronic rejection.

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In vivo imaging of T-Regulatory cell mediated transplant tolerance

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Naturally occurring $CD4^+CD25^+Foxp3^+$ T-regulatory cells (Tregs) are known to be key players in preventing autoimmunity and limiting immune responses to non-self molecules such as alloantigens. Where Tregs suppress *in vivo* is still unclear. One way to study this *in vivo* is via whole body imaging. As direct *ex vivo* radiolabelling of leukocytes with radiotracers and imaging, via Single Photon Emission Computed Tomography (SPECT), is a routine clinical procedure within Nuclear Medicine, we decided to utilise this technology to image Treg lines *in vivo*.

In order to non-invasively track Tregs *in vivo* over time, we retrovirally transduced Treg lines (generated from $CD4^+CD25^+$ T cells isolated from C57BL/6 mice and stimulated *in vitro* with autologous BL/6 Dendritic Cells) to express Sodium Iodide Symporter (NIS), a protein symporter required for cellular radiolabelling and mCherry Red Fluorescent Protein. We demonstrated that NIS/mCherry expressing Tregs uptake Tc99m *in vitro* while maintaining their phenotypic and suppressive function when compared to NIS/mCherry unlabelled Tregs. Whole body SPECT imaging of the NIS/mCherry expressing Tregs *in vivo* following adoptive transfer into C57BL/6 mice and injection of Tc99m showed accumulation of Tregs within the spleen. Organ biodistribution studies confirmed this.

We will use a similar approach to image alloantigen-specific Tregs in an animal model of skin transplantation to determine location (lymph node, spleen or skin transplant) and kinetics of Treg accumulation during an allograft response. The data from these experiments will assist in optimising the use of human Treg lines for adoptive cell therapy to prevent graft rejection.

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Vascular access surgery: do transplant surgeons still have a role?

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Background: Vascular Access Surgery (VAS) has traditionally been performed by both Vascular and Transplant Surgeons. However, Vascular Surgery's imminent devolution is likely to provide challenges in both service provision and training. Multidisciplinary teams may be projected as best working practice but current delivery remains largely unknown due to the absence of a UK registry. In addition, VAS training has been placed under the remit of the General Surgical curriculum whilst the training parameters have appeared under Vascular Surgery on the Inter-Collegiate Surgical Curriculum Programme (ISCP), potentially excluding Transplant trainees in the future. The aim of the study was to establish national views and the role of Transplant Surgeons in the current and future training and service provision of VAS in the United Kingdom.

Methods: An online survey (Surveymonkey™) was distributed to consultant and trainee societies in transplantation and vascular surgery (British Transplantation Society (BTS) and Carrel Club; Vascular Surgical Society (VSS) and Rouleaux Club respectively) and members of the Vascular Access Society of Great Britain and Ireland (VASBI). The survey concerned issues regarding current and future training and service provision in VAS.

Results: 218 surgeons responded with a 93% completion rate and were predominantly Consultants (66.6%). Vascular surgeons (72.9%) constituted the majority with 90% performing less than 100 procedures annually. Only 50.5% of respondents' deemed current training opportunities sufficient although 32% felt that this could be improved. Divisions occurred between who should provide future training although 70.7% felt that combined vascular and transplant surgeons should provide service. Only 17% felt that full endovascular training was essential for training and currently only a minority of trusts had provision for training in this field. With regards to service provision, VAS is currently performed by transplant surgeons (43.4%) or vascular surgeons locally (43%) ensuring appropriate patient accessibility. Dedicated vascular coordinators were employed in only 62.7% of trusts, whilst 80.6% had nephrology services available on site. Interventional radiology was available on an emergency basis in only 57.9% of respondents.

Conclusion: VAS is currently delivered on an *ad hoc* basis with both vascular and transplant centres providing service and training exposure. National guidelines remain vague with regard to VAS. With the imminent separation of the sub-specialities there is potential for dilution and inadequacy of training, which will impact on service provision in the future. A coalition of vascular and transplant surgeons will be imperative to establish and achieve standards thereby maximising opportunities. A national registry is required to audit and maintain standards. However, it is encouraging that the majority view remains that Transplant surgeons have an important role to play in VAS delivery in the future.

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Creation of Neo- Intestine For Transplantation

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Introduction: Diseases of the small and large intestine carry significant morbidity and mortality. Creation of neo- intestine for the purpose of successful transplantation could improve post - operative outcomes in patients where extensive small and/ or large bowel resection has occurred. Creation of neo- intestine was attempted in a large animal model using tissue engineering methodology.

Methods: Heart beating donor retrieval of swine colon with intact vascular arcade was performed under general anaesthesia. Explanted specimen vasculature was perfused on bench with 25,000U Heparin in 1L N. Saline to achieve adequate thrombolysis. Following colonic lavage, decellularisation was performed by peristaltic pump perfusion of colonic and vascular lumens using a series of reagents: SDS, trypsin & EDTA and DNase I. Adequate decellularisation was demonstrated by routine histological techniques and quantification of nuclear material. Following protocol optimisation, biocompatibility was assessed by transplantation of en- bloc specimens into swine using a variety of vascular approaches. Reperfusion was assessed macroscopically, by routine histological techniques and immunohistochemistry. Potential cell sources for seeding decellularised scaffolds were investigated. Isolation of colonic organoid units (cellular aggregates within a villus core of epithelial cells and mesenchymal tissue) was attempted using cell culture techniques. Clinically feasible alternative cell sources for seeding were investigated. Similar principles were applied in relation to the small intestine.

Results: Colonic specimens were explanted and thrombolysed successfully with variable quality of perfusion noted. Decellularised colonic extra- cellular matrix (ECM) was produced and decellularisation demonstrated by H&E staining. ECM architecture of colon and vasculature with elastin and collaged preservation was demonstrated by picrosirius/ miller's elastin staining. Reperfusion of decellularised ECM scaffolds was limited by small vessel vascular thrombosis. At the time of submission, the isolation of colonic organoid units was being characterised further.

Discussion: The production of decellularised ECM intestinal scaffolds with intact vascular arcades can be achieved in a large animal model with potential for transplantation. Successful cell seeding of such ECM scaffolds by appropriate sources may be possible resulting in the potential of large scale growth neo- intestine for clinical use.

Paediatric Kidney Transplantation

Moderator: TBA

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Paediatric Renal Transplantation In A Single Centre: The Changing Demographic Of The Last Decade

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Introduction

There have been many changes in practice over the last 10 years that could affect paediatric renal transplantation. These include improved neonatal care, changes in organ allocation and the introduction of DCD and living donor programmes. We aimed to assess the demographic of paediatric transplant recipients in a single centre over the last 10 years to see what impact these changes may have had.

Method

Prospectively recorded data about paediatric renal transplant recipients from 1st January 2000 to 31st December 2009 was collated retrospectively and analysed. For the purpose of analysis data from the first half of the decade (1.1.2000 to 31.12.2004) was compared with the second half (1.1.2005-31.12.2009).

Results

In the first half of the decade 63 transplants were performed with 46 of these (73%) being from DBD donors and the remainder from living donors. This compares with 55 donors in the second half of the decade, of which 33 (60%) were from DBD donors, 2 (4%) from DCD donors and 20 (36%) from living donors.

Of those who received a kidney from a living donor 4 (23%) had also been on the waiting list in the first half of the decade, whilst 10 (50%) were during the second half.

The average age of recipients was 4433 days in the first half of the decade, and 3857 days in the second half ($p=0.039$). There seems to be a trend to perform transplantation in smaller children with 13 transplants performed in children under 20kg in the second half of the decade (eight of which were from living donors) compared to five in the first half (one of which was from a living donor). Average time on the waiting list was 359 days in the first half compared to 397 days ($p=0.97$) in the second.

There were no noticeable changes in the causes of renal failure in this population over the decade.

Conclusions

In our unit the children being transplanted are significantly younger in the second half of the decade compared to the first. The changes in organ source do not mirror the changes in the adult population over that time; although the proportion of organs transplanted from living donors has increased a successful local adult DCD programme has not greatly influenced paediatric practice.

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Native Nephrectomy in Paediatric Renal Transplantation – Less is More!

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Introduction

Historically, the indications for pretransplantation native nephrectomy included chronic renal parenchymal infection, infected urolithiasis and vesico-ureteric reflux, heavy proteinuria, intractable hypertension, symptomatic cystic disease and malignancy.

Our aim was to establish the frequency of, and indications for, native nephrectomy in a cohort of children who underwent renal transplantation at our institution.

Methods

Details of all children who were listed for renal transplant between January 1990 and January 2010 were retrieved from our prospectively maintained database. Children who underwent pretransplantation nephrectomy were analysed. Underlying aetiology of established renal failure, indication for nephrectomy, timing in relation to renal transplant, survival, transplant –related complications, current renal function, were documented.

Results

17 /101 children listed for transplant (16.8%) underwent pretransplant native nephrectomy (26 nephrectomies in all). Indication for nephrectomy were heavy proteinuria with frequent albumin infusions (7 children), obstructive uropathy with severe recurrent UTIs (4), vesico-ureteric reflux (VUR) with recurrent infection (1), bilateral Wilms` tumour or Denys-Drash syndrome (3), autosomal dominant polycystic kidney disease and multicystic dysplastic kidneys (2).

Median age at nephrectomy was 3.0 years [range 0.2 – 14.7 years]. 6 nephrectomies were left sided, 4 were right. 8 children underwent bilateral nephrectomies, 6 at the same sitting. No kidneys were removed at the time of renal transplant. 6 kidneys were removed laparoscopically, all during the last 5 years of the series. 3 children are awaiting their first transplant. Median time interval between (first) nephrectomy and transplant was 2 years.

1 child died of pneumonia. 4/16 children required a further renal transplant, 2 for thrombosis and 2 for late allograft rejection. All transplanted children (except 1 with poor adherence to immunosuppressant regimen) have stable graft function. Median follow-up was 4.5 years.

Discussion

The indications for pretransplant native nephrectomy may be declining. When absolute indications (malignant conditions) were excluded, this procedure was performed in only a small minority (13.9%) of children.

This may be an important factor in reducing the overall morbidity of these children, who already may be undergoing multiple surgical procedures. This more conservative approach did not adversely affect graft function in our series.

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Integrated Paediatric to Adult Transition Coupled with a Dedicated Young Adult Clinical Service reduces Kidney Transplant Failure Rates

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Adolescence is a time of increasing independence, experimentation and rebellious behaviour that may manifest as non-adherence to immunosuppression in transplant recipients. Transfer from paediatric to adult care has been associated with a 35% graft failure rate in the UK within 12 months of follow-up in adult care. We have assessed the impact on graft survival of introducing an integrated paediatric to adult transition service coupled with creation of a dedicated young adult clinic.

Prior to 2006 paediatric transplant recipients were transferred to our centre by a single letter from a paediatric nephrologist. In 2006 we introduced a joint paediatric-adult transition clinic in 2 paediatric renal units with multidisciplinary clinicians from both the paediatric and adult centres. Paediatric patients were seen jointly in the transition clinic for 1-2 years before transfer to the adult service. All transplant patients who transferred from paediatric care were pooled into a dedicated young adult clinic managed by a single nephrologist, transplant nurse specialist and youth worker. Patients who transferred directly between 2002-2006 (Group 1) were compared to a second cohort from 2006-2010 (Group 2) who went through integrated transition from paediatric care into the young adult clinic service.

9 (3m;6f) teenagers transferred in group 1 at a median age (range) of 18(16-18) to 6 different Consultant Nephrologists. In contrast 12 (7m;5f) teenagers in Group 2 transitioned aged 17.5(16-18) through the integrated clinic to the Young Adult Clinic service.

In Group 1 , 6 of 9 (67%) developed transplant failure at a median of 40(1-62) months post-transfer; and 1 patient died of systemic sepsis 3 years post-transfer. In Group 2 there have been no transplant failures/ deaths at a median follow-up of 18 (7-46) months post-transfer. At 12 months post-transfer there were 2/9 (22%) graft failures in Group 1 and no graft failures in group 2 ($p=0.08$) and when Group 2 is compared against a UK published rate of graft loss of 35% ($p=0.04$) . Late acute rejection occurred in 33% of Group 1 and 0% of Group 2 ($p=0.04$). Patients managed in the Young Adult Clinic had a median blood pressure of 130/75 and serum cholesterol of 4.1mmol/L. At a median age of 19 (18-23); 17% are in full-time employment; 25% undertaking a University degree; 17% studying for an NVQ at a local college; 25% in special needs education and only 17% are unemployed.

The introduction of an integrated transition service for teenage transplant recipients transferring to adult care has led to a major reduction in the rate of transplant failure and risk of late acute rejection. This is apparent in comparing outcome at 12 months post-transfer against a historical cohort and confirmed against published UK data of 35% graft loss. Preserved continuity of care by a small young adult clinic team is associated with good cardiovascular risk factor control, immunosuppression adherence and a low level of unemployment.

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Extraperitoneal Renal Transplantation in Small Children Results in Early Improvement in Graft Function.

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Abstract

Renal transplantation is considered more technically challenging in small children compared to adults, especially using live donor adult kidneys. Traditionally, kidneys were placed intraperitoneally but over the last decade extraperitoneal positioning has been attempted. The aim of this study was to establish whether there is a difference in kidney function and outcome dependent on the position of the kidney.

Method: The medical notes of all children under the age of 6 who received a renal transplant at our unit between January 1998 and October 2009 were reviewed. Demographic data, operation details, mismatch, immunosuppression regime, complications and function of the graft were analysed.

Results: A total of 30 transplants were performed in children under six years of age. The one-year patient and graft survival were 97% and 93%, respectively. Eighteen were undertaken via an intraperitoneal approach, with the remaining being placed extraperitoneally. There were no significant differences in the number of complications observed between the two groups and median length of stay was comparable (19.5 days versus 20.5 days for the intraperitoneal group).

The plasma creatinine values for the two groups were compared using multivariate linear regression analysis and adjusted for age, weight, gender and baseline plasma creatinine. Between day 2 and 14 post-operatively, patients who underwent extraperitoneal renal transplantation had an adjusted change in plasma creatinine which was significantly lower throughout this period.

Conclusion: Extraperitoneal approach of kidney transplantation in small children is safe and technically feasible. From our series, there appears to be early improved function, although there is no long-term difference in function between approaches.

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Supporting Young Adults With Chronic Kidney Disease

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Introduction: Young adults with chronic kidney disease (CKD) have been identified as a vulnerable group for poor treatment outcomes. A significant number of kidney transplants have been lost unexpectedly following transfer from paediatric to adult renal care. Recognition has increased that having CKD as a young adult can impact on many areas of life. Recommendations have been developed to aid the implementation of an effective transition from paediatric to adult renal care. However, the needs of young adults once they enter adult renal care have not yet been addressed. As one of five projects funded by NHS Kidney Care to support young adults with CKD, this project aimed to address the needs of young adults with CKD in adult renal care.

Methods: A youth worker was recruited to develop a support service for young adults aged 18-25 with CKD. A pathway was developed in which individual and group interventions were provided depending on the needs presented. Baseline and ongoing measures of health were recorded to enable an audit of the service to be conducted. The project was underpinned by qualitative research undertaken by an assistant psychologist, exploring the needs of young adults with CKD. Focus groups and interviews were held to explore their experiences in adult renal care and identify their support needs. The research aimed to establish whether their needs differed depending on the type of treatment undertaken and the entrance (direct or transition) to adult renal care. Thematic analysis was undertaken with the findings used to enhance the development of this service.

Results: The audit of the newly developed service showed that it had impacted positively on those who accessed it. It was felt that with time these positive outcomes would become more apparent. The feedback received from both patients and staff suggested that the service was highly valued with its tailored approach appreciated.

The research identified that young adults with CKD have support needs in many areas. Differences were found to exist between the needs of those undertaking different forms of treatment. It was highlighted that those who entered adult renal care directly had additional support needs to those who experienced a transition from paediatric renal care. This led to the identification of ways that the support service could develop to meet these needs.

Discussion: The project identified the need for ongoing tailored support to be provided for young adults with CKD. Initial findings suggested that providing this service helped to enhance the quality of life experienced by young adults with CKD. The service was also thought to provide value for money, as it acted as a preventative factor reducing the likelihood of treatment non-concordance and resulting poor health outcomes occurring. It is thought that if continued implementation of the service can occur, a reduction in the loss of transplanted kidneys due to treatment non-concordance may be noted.

Pancreas & Islet Transplantation

Moderator: Derek Manas

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Improved Pancreatic Islet Isolation Methods To Optimise The Use of Donor Pancreata for Islet Transplantation

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Introduction: Pancreatic islet transplantation is a relatively new component of NHS transplant services in the UK. Islet transplantation is currently reserved for severe, labile, Type I diabetics, who exhibit hypoglycaemic unawareness but has been used for the management of total pancreatectomy patients in both allogeneic and autologous settings.

Methods: Islet isolation from cadaveric pancreata involves the enzymatic digestion of a whole organ, and density gradient separation of Islets of Langerhans from exocrine tissue. Purified islets are cultured in preparation for release as an Investigational Medicinal Product, to cGMP standards, to recipients identified on the national waiting list. We have optimised each element of the isolation process by examining the activity of the enzymes used to digest organs. Using the Wunsch reaction, by spectrophotometry we determined optimal enzyme reaction conditions to be 35.5C and 2mMol CaCl, with a Collagenase concentration of ~ 1.8U/ml in a tightly controlled digestion circuit flowing at 150ml/min. To enhance the purification of islets we developed a new continuous gradient designed to extract islets across a range of densities between 1.06 and 1.07 g/ml, taking into consideration local factors in islet isolation such as room temperature and elutable volumes from the Cobe 2991 cell processor. The culture of islets was also enhanced by the addition of Human AB serum as a supplement to culture media.

Results: The organs that are directed for islet isolation are generally those considered unsuitable for whole-organ transplant, e.g., from donors with BMI >30kg/m^2, anatomically compromised for vascular transplantation, or otherwise declined for whole-organ transplant after offering, and therefore may endure a less than optimal cold-ischaemic time before release to the islet transplant program. Very few are optimal in all respects. Since January 2009 we have processed 35 cadaveric pancreata, 10 of which achieved a yield and purity sufficient for release as a medicinal product, of which 5 were transplanted into 4 patients. Of the 5 transplanted products, mean number of Islet Equivalents was 368,000 with a purity of >50%. Mean cold ischaemic time of donor organs was 6 hours and mean organ weight was 99g. Amongst the 4 transplant recipients with a median follow up of 410 days (14 – 493) post transplant, all have seen a reversal of hypoglycaemic unawareness, and median daily requirement for exogenous insulin has decreased from 36IU to 12.5IU.

Conclusions: The local improvement in isolation protocols is intended to advance the field of islet transplantation. Of the 5 donor pancreata processed and transplanted, one weighed 63g, the product of which resulted in insulin independence, and one had a cold ischaemic time of $9^1/_2$ hours. Both of these donor organs lay outside optimal acceptance criteria but their successful use suggests that with optimised methods of isolation, the use of marginal donors could be extended. Our optimised methods support our aim to produce transplantable islet preparations from donor organs more successfully, but also to render marginal organs less marginal and so further optimise the use of organs that can be considered suitable for pancreatic islet transplantation.

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Clinical Allogeneic Islet Transplantation: A single Centre Update.

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Introduction: We previously presented our experience of islet transplantation in 4 recipients using the Edmonton protocol. Since April 2008, islet transplantation in England and Wales has been funded by the National Commissioning Group of the Department of Health. The principal recipients of allogeniec pancreatic islets are patients with labile Type I diabetes and repeated episodes of hypoglycaemic unawareness. The original Edmonton protocol focussed on islet transplant alone (ITA) recipients, although an increasing number of Islet After Kidney (IAK) recipients may also benefit from improved glycaemic control without incurring the additional risk from immunosuppression. We now describe our experience of islet isolation and transplantation in a further 4 recipients.

Methods: Donor pancreata were allocated to our islet isolation facility under the national scheme with a general BMI cut off of 30Kg/m^2 for allocation to islets or whole organ transplantation. Islets were isolated using collagenase digestion and purified by continuous density gradient separation. All islet preparations were cultured prior to infusion into the portal vein via a percutaneous transhepatic approach. All patients received Tacrolimus or Cyclosporin A and Mycophenylate Mofetil with induction by Basiliximab or Campath.

Results: Between January 2009 and September 2010, we were offered 81 donor pancreases and accepted 45 for processing. From the 45 accepted organs, 12 were not suitable for processing. Out of the 33 processed organs, 9 (27%) met release criteria with a mean Islet Equivalent (IEq) yield of 295,289 and 50% purity. Four local recipients with hypoglycaemic unawareness (3 IAK and 1 ITA) received a total of 6 islet infusions with a mean dose per patient of 9,286 IEq/Kg. Five infusions were isolated locally and a single infusion transported from another centre. All patients had return of hypoglycaemic awareness with a reduction in exogenous insulin requirement at a median follow up of 410 days (14 – 493) post transplant. Median insulin dose reduced from 36IU/day to 12.5IU/day with one patient achieving sustained insulin independence. Median HbA1c reduced from 8.7% to 6.9%, at last follow up. There were no infectious complications or fatalities. One patient required transfusion of 2 units of blood following a puncture site bleed after transplantation which has prompted a change to our peri-transplant anti-coagulation protocols. There was no significant change in overall renal function after transplantation.

Conclusion: Our data suggest that allogenic islet transplantation is a safe and effective treatment for hypoglycaemic unawareness with the ability to achieve sustained insulin independence without the significant procedural risks associated with whole organ transplantation. In addition to improving metabolic control in brittle type 1 diabetic patients, it is hoped that recipients will benefit from an improvement in quality of life and, in the case of IAK patients, a contribution to the longevity of their pre-existing kidney transplant. Continuing improvement in isolation techniques should enable a greater utilisation of donated organs and subsequently increase the number of patients who can benefit from this life enhancing therapy.

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Oxygenation during pancreas digestion improves islet isolation outcomes

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Background: During isolation of pancreatic islets, normothermia is restored without adequate re-oxygenation of the tissues. Indeed, it has previously been reported that during the pancreas digestion phase, a transient, but rapid and significant decrease in oxygen partial pressure occurs. This is likely to have significant consequences for islet graft quality and islet engraftment following transplantation. We postulate that supplementation of isolation media with oxygen and adenosine, as substrates for ATP production, will result in improved islet yields and better islet function.

Materials and Methods: In this pilot study, Lewis rats were used in size-matched pairs. Islets were isolated using well-established and standard techniques. The following 3 experimental groups were investigated: 1) standard isolation medium (Control Group), 2) hyper-oxygenated isolation medium (O2), and 3) adenosine supplemented medium (ADO). In the O2 group, the isolation medium was saturated with oxygen by bubbling clinical grade O_2 at 4ºC for 20-30 minutes until pO_2 exceeded 120kPa. In the ADO group, adenosine was added to the digestion solution to achieve a final concentration of 0.5mM. Following isolation and purification on a Histopaque gradient, islets were handpicked, counted, and evaluated metabolically. Results were reported as the number of islets isolated from the donor per kg BWt, the % viability using Fluorescein Diacetate / Propidium Iodide fluorescence test, and the glucose stimulation index (GSI).

Results: In the Control Group, isolation yielded a mean of 1166±168 islets/kg BWt. The viability was in excess of 95%, and the mean GSI after overnight culture was 2.6±0.4. Oxygenation of the isolation media resulted in a significantly higher pO_2 than in control group (134.2±13.8kPa vs. 27.9±1.1kPa). Use of hyper-oxygenated medium resulted in 30% increase in islet yield (1513±211 islets/kg BWt). No change in islet viability was recorded. Islets isolated in this O2 group had better GSI (5.5±1.7) compared with controls. Addition of adenosine to the digestion medium increased the number of isolated islets by almost 40% (1603±517 islets/kg BWt), but only produced a moderate improvement of their secretory function (GSI 4.2±1.8).

Conclusions: This pilot study suggests that supplementation of isolation media with oxygen and adenosine, may help to prevent the deleterious effects of hypoxia during islet isolation. Optimisation of pancreas digestion by a means of simple pharmacological interventions may therefore improve islet yields and function, resulting in an increase in the number of pancreases yielding transplantable preparations.

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Collagenase Does Not Persist In Human Islets Following Isolation

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Introduction: Optimal islet isolation requires the delivery of collagenase to the pancreatic islet-exocrine interface, in order to digest the extracellular matrix to release intact islets. However, we have previously demonstrated the presence of collagenase within human islets immediately following intraductal collagenase administration. The aims of this study were to determine if collagenase becomes internalized into islet spaces and cells during the isolation procedure, and remains within the islet post-isolation.

Methods: With appropriate consent and ethical approval, human pancreases (n=14) were retrieved from multiorgan donors (age range 34–66 years, BMI range 21-37; cold ischemia times 3.5-10 h) and islets isolated by standard methods. Specimens were fixed in 4% paraformaldehyde at various stages throughout the isolation process: during digest collection, following University of Wisconsin solution incubation, immediately post-isolation, and after 24 h of culture at 37°C. Islets were embedded in agar, cryo-sectioned and immunolabelled for collagenase and insulin.

Results: Immunoreactivity for collagenase was not observed in isolated islets in any of the preparations analysed. Collagenase labelling was detected in one sample taken at the digest collection phase in one islet preparation only. No collagenase-specific labelling was seen in islets sampled at any of the other time-points, in any of the 14 islet preparations. Islets labelled with a control, species-matched antibody showed no specific fluorescence. As a positive control, isolated islets were incubated with collagenase for 1 h at 37°C and then processed as above. Collagenase labelling was detected, indicating that islets are able to take up or bind collagenase.

Discussion: Collagenase that enters islets during intraductal administration is washed out of the islets during the collection phase of the isolation process and thus does not remain in islets after isolation. This observation negates safety concerns that collagenase remains within islet grafts for transplantation. However, collagenase within islets during and following intraductal administration may cause damage to islets during the digestion process and therefore have a negative impact on islet yield, integrity and graft survival.

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Pancreas Allograft Rescue Using The Damaged Donor Superior Mesenteric Artery

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Introduction: We describe a case report of a patient who developed a superior mesenteric artery thrombosis following simultaneous pancreas kidney (SPK) transplantation as the result of a technical error during the retrieval process, which was not detected on back-table preparation and during implantation. We review the steps of the procedure and make suggestions to prevent such complications from occurring in the future.

Methods: We retrospectively reviewed the case of a patient who developed an unexplained metabolic acidosis following SPK transplantation. We describe a technique for revascularisation using the gastroduodenal artery (GDA) as an alternative to the superior mesenteric artery (SMA).

Results: Following non heart beating donor SPK transplant the recipient developed an unexplained metabolic acidosis and hyperkalemia, whilst demonstrating primary kidney function and achieving glycemic control. Emergency magnetic resonance angiography was suggestive of SMA thrombosis to the donor pancreas, which on immediate re-laparatomy was discovered to be due to an occlusion caused by the mesentery staple line applied during retrieval. By resecting the thrombosed segment of the Correl Y graft to the donor pancreas, removing it of clot and interpositioning this remnant between the graft and the previously ligated GDA it was possible to save the donor pancreas.

Discussion: Some studies have concluded that patency of either the SMA or splenic artery alone is sufficient to supply the pancreaticoduodenal graft. Due to intraparenchymal vasculature abnormalities and variations however, occlusions of one of these grafts, as in the case of our patient, may lead to segmental graft infarction. Checking the patency of both the SMA and the splenic artery with heparainised saline and retrograde perfusion of the GDA from SMA injection at the back-table may alert the surgeon to a problem.

Revascularization of the GDA is not performed routinely, however evidence exists that this can improve the blood supply to the head of the pancreas and to the donor duodenal segment lowering the incidence of duodenal complications. In our case the GDA provided alternative perfusion to the head of the pancreas and duodenum following technical SMA occlusion.

During graft implantation, inspection of the graft on revascularization is crucial in allowing the surgeon to assess perfusion. In our case the slow perfusion of the pancreatic head and duodenum should have alerted us to a potential vascular problem.

The first 48 hours post operatively is when the majority of arterial and venous thromboses occur. A meticulous approach and regular checks during the retrieval, at the back-table and also at implantation would help to prevent such a complication from reoccurring. Persistent acidosis with hyperkalemia in the presence of adequate glycemic control and primary kidney function should also lead the team to suspect a possible problem with the pancreatic graft. In our case attempting anything other than surgical re-exploration would have likely to have been futile and may have necessitated an eventual graft pancreatectomy.

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Beware the pancreas transplant recipient with elevated fibrinogen and hypotension

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Introduction

Thrombotic complications remain a significant challenge in pancreas transplantation, and with treatment of established thrombosis notoriously difficult, early detection is paramount. Noting that many patients with complications in our series had elevated fibrinogen levels, we reviewed our series to determine whether there was a genuine association.

Methods

We retrospectively reviewed the case records of consecutive patients receiving whole-organ pancreas transplants in our centre from 2005 to 2009, noting serum fibrinogen levels on routine coagulation screens, whether there were episodes of hypotension, and whether a thrombotic complication arose in the graft.

Results

There were 10 patients with thrombotic complications (6 pancreatic, 1 renal), all of whom had full data in their records. There were 45 other patients without thrombosis, of whom 14 had missing blood pressure data, leaving 31 to be included in the study. Patients with fibrinogen levels >7g/dl and hypotension were significantly more likely to experience a thrombotic complication (odds ratio 16.7, p=0.001, Fisher exact test), but fibrinogen levels alone were not an independent predictor of thrombosis.

Conclusions

The combination of elevated fibrinogen level and hypotension appears to be a harbinger of thrombosis in pancreas transplantation. Fibrinogen, as an acute phase protein, may simply be a marker of underlying event predisposing to thrombosis, but as a coagulation protein it may also be an independent causative agent.

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DC Donor organs give comparable results to DB donor organs in SPK transplantation.

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Introduction:

Our unit has performed 10 DCD simultaneous pancreas and kidney (SPK) transplants since first performing this procedure in early 2007. During the same 4 year period we have performed 80 DBD SPKs. This study aims to compare graft and patient survival outcomes in DCD and DBD SPK recipients.

Methods:

Data from all of SPK patients is recorded in a prospective database. We performed a retrospective review of this data for cold ischaemic time (CIT), initial graft function and 1 year graft survival for both pancreas and kidney grafts. We also compared donor and recipient age at transplant and the recipient's previous mode of dialysis and 1 year recipient survival.

Results:

	DCD (n=10)	DBD (n=80)
Donor Age (Median, yrs)	30 (range 15-49)	35 (range 12-52)
Recipient Age (Median, yrs)	41 (range 26-61)	42 (range 27-61)
Pre-emptive	90% (9/10 patients)	44% (35/80 patients)
Pancreas CIT (Median, hrs)	12.8	12.9
Kidney CIT (Median, hrs)	15.0	14.6
Kidney Delayed Graft Function	50% (5 cases)	22.5% (18 cases)
1-year Pancreas Survival	100%	87.5% (70 cases)
1-year Kidney Survival	100%	87.5% (70 cases)
1-year Patient survival	100%	98.75% (79 cases)

Conclusion:

DCD organs were used in significantly more cases of pre-emptive kidney transplant ($p<0.01$). Delayed kidney graft function was 2 times more prevalent in the DCD group however there was no significant difference in 1-year graft and patient outcomes ($p>0.1$). With appropriate selection of donor and recipient, DCD SPK transplantation appears to be a safe and promising option that helps maximise the use of DC donor organs.

Pancreas & Islet Transplantation 2

Moderator: Nadey Hakim

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Severe Pre-transplant Proteinuria Can Be A More Reliable Determinant Factor For Renal Function Deterioration After Pancreas Transplant Alone Than eGFR

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Introduction: The level of renal function is an important parameter determining the type of pancreas transplant offered to patients with life threatening complications of type 1 diabetes, as this may indicate the risk of a clinically important post-transplant deterioration. However, this risk is poorly understood and this retrospective, single-centre analysis has been performed to assess potential risk factors affecting renal function after pancreas transplant alone (PTA).

Methods: 24 patients, with a mean age of 43.2±10.1 years at the time of transplant, who received a PTA over a 4-year period, were follow-up for a mean period of 25.1±8.1 months (range: 16-40). All cases had a systemic venous drainage with an enteric exocrine drainage. All patients received induction immunotherapy with alemtuzumab and steroid-free maintenance with tacrolimus and mycophenolate mofetil. Only patients with functioning pancreatic grafts were included in this analysis. eGFR levels were used to evaluate renal function pre- and post-operatively. Various pre- and post-transplant parameters and characteristics were included in the risk and time-to-event analysis.

Results: Multivariate risk analysis indicated that the only pre-transplant characteristic, including low pre-PTA eGFR (<40 ml/min/1.73m^2), that significantly affected the development of substantial deterioration in renal function was severe proteinuria (Urine Pr/Cr ≥100) (OR=14.000, CI=1.057-185.492, p=0.045). Postoperatively, preservation of native renal function was significantly worse in patients with high tacrolimus levels (>12 mg/dl) at 6 months after-PTA (p=0.026), which was also identified as an independent risk factor after Cox regression analysis (HR=14.300, CI=1.271-160.907, p=0.031). A trend was identified with the presence of severe pre-transplant proteinuria (p=0.062).

Discussion: Our results suggest that PTA is appropriate even in patients with borderline renal function, provided that (i) they do not suffer from severe proteinuria and (ii) careful monitoring and tailoring of immunosuppression is ensured.

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Risk Analysis For Deterioration Of Renal Function After Pancreas After Kidney Transplant

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Introduction: Pancreas after kidney (PAK) transplantation is appropriate for the treatment of selected patients with diabetes and a functioning renal transplant. There are concerns about the risk of renal allograft deterioration (previously shown to be associated with kidney to pancreas transplant interval >1 year, pre-PAK eGFR <45 ml/min/1.73m^2, kidney rejection and proteinuria), but a full risk analysis has still to be conducted. This retrospective, single centre study has been carried out to clarify which patients are likely to benefit from pancreas after kidney transplantation.

Methods: Thirty-three patients, with a mean age of 43.1±7.9 years at the time of transplant, who received a PAK over a 5-year period, were followed-up for a mean period of 30.4 months (range: 2-62). All cases had a systemic venous drainage with an enteric exocrine drainage. All patients received induction immunotherapy with alemtuzumab and steroid-free maintenance with tacrolimus and mycophenolate mofetil. Only patients with functioning pancreatic grafts were included in this analysis. eGFR levels were used to evaluate renal function pre- and post-operatively. Various pre- and post-transplant parameters and characteristics were analyzed.

Results: Multivariate risk analysis identified a trend for substantial deterioration in renal function among patients who suffered from CMV disease post-PAK (p=0.090) and those with rejection before the pancreas transplant (0.078). On univariate time-to-event analysis, preservation of renal allograft function was significantly worse in patients suffering from gastropathy (p=0.040) and in those with high (>12 mg/dl) tacrolimus levels at 12 months post-PAK (p=0.040), but neither achieved significance as independent prognostic factor.

Discussion: Although this study is limited by small sample size and is single centre and retrospective, it nonetheless suggests that a substantial deterioration of renal allograft function is more likely in patients suffered from prior renal allograft rejection, symptomatic gastropathy, CMV disease post-PAK, and high tacrolimus levels 1 year post-transplant.

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'Timing the Implant': Outcomes in Pancreas Transplantation and its relation to the time of Surgery

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Background: Pancreatic transplantation is a demanding procedure in diabetics who have significant co-morbidity and higher risk of death with majority of what are performed during out of hours (preparation and transplantation). Though the recommendation of National Confidential Enquiry into Peri-operative death (NCEPOD) outlined the risk operating during night time in terms of increased number of complication and mortality

Aim: To evaluate if performing pancreatic transplants within out of hour time represent an intrinsic risk toward the patient and the organ, thus trying to establish whether the pancreatic transplant should be performed as soon as possible, aiming to reduce the CIT, or it should rather be rescheduled to day time, offering a better result and a safer surgery to the patient

Methods: A retrospective analysis of 201 patients received was pancreatic transplantation in our unit between 2001 and 2010 was carried out, Complete data was available on 175 patients (SPK 133, PAK 30, PTA 12). This cohort was subdivided and contrasted according to the time of surgery was initiated (Group I: 8am-4pm; Group II: 4pm to 10pm; and Group III: 10pm to 8am)
101 patients operated between 8am-4pm, (60 Males), with a median age of 43 years, (81 SPK, 15 PAK, 5 PTA) and a median CIT of 803 minutes. The group II were 56 patient, (34 Males), with median age of 42 years, (41 SPK, 11 PAK, 4 PTA), and a median CIT of 924 min. Group III was of 18 patients, (12 Males), with a median age of 44years, (11 SPK, 4 PAK, 3 PTA) and a median CIT of 915 min. There were no significant differences in terms of donor or recipient demographics across the groups. The primary endpoint utilised was patient mortality at 30 days and one year, with secondary endpoints of graft failure and surgical complications analysed.
Results: There were no differences in types of transplants or demographic data across the groups (Median ages: I: 42.7 years ; II: 42.9 years; III: 44.4 years; p=NS

Time started	No	CIT	30d graft failure	30d mortality	1yr Mortality
I: 08:00–16:00	101	821m	22 (22%)	2 (2%)	4 (4%)
II: 16:00-22:00	56	929m	10 (18%)	2 (3.5%)	5 (9%)
III: 22:00-8:00	18	898m	3 (17%) **p=0.63**	0 (0%) **p=0.55**	1 (5.5%) **p=0.65**

Major surgical complications	Group I	Group II	Group III	p value
Graft thrombosis	**16 (16%)**	**6 (11%)**	**4 (22%)**	**NS (0.51)**
Bleed/Haematoma	**12 (12%)**	**6 (11%)**	**2 (11%)**	**NS (0.93)**
Wound infection	**18 (18%)**	**7 (13%)**	**2 (11%)**	**NS (0.49)**
Radiological collection drainage	**10 (10%)**	**7 (13%)**	**0 (0%)**	**NS (0.17)**
Major intestinal fistula	**11 (11%)**	**2 (4%)**	**0 (0%)0**	**NS (0.14)**
Peritonitis / Abdominal Abscess	**18 (18%)**	**12 (21%)**	**3 (17%)**	**NS (0.91)**

Conclusion: Based on ours experience pancreatic transplant during out of hours per se doesn't seem to represent a risk factor for the life of the patient nor for the success of the operation. The main factors for a successful transplant are the careful selection of donor and recipient in terms of age, BMI, PMH and more importantly the CIT.

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Glycated haemoglobin and fasting plasma glucose fail to detect abnormal oral glucose tolerance in whole pancreas transplant recipient

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Background: HbA1c and fasting glucose are routinely used in clinical practice as a means of monitoring metabolic pancreas graft function. It is widely accepted that HbA1c and fasting glucose within the normal, non-diabetic range implies normal glucose homeostasis and thus normal graft function. However, not all patients achieve normal oral glucose tolerance (based on the WHO criteria) and published literature suggests 20-40% of patients will exhibit abnormal oral glucose tolerance (AbNGT) after transplantation. We examined the rate of AbNGT within our pancreas transplant population in relation to FPG and HbA1c values.

Methods: 24 whole pancreas transplant recipients underwent a standard 75g oral glucose tolerance test (OGTT), FPG and HbA1c measurement at 3 months after whole pancreas transplantation.

Results: All patients had FPG and HbA1c values within the normal non-diabetic range (Mean FPG 5.0mmol/L range 4-5.7 mmol/L, Mean HbA1c 5.1% range 4.4 – 6%). In our cohort 21% (5/22) of patients had AbNGT (3/24 IGT, 2/24 DGT) on OGTT. Both FPG and HbA1c tended to be higher in patients with AbNGT as compared to NGT and reached significance for FPG (4.8 mmol/L vs 5.5 mmol/L p=0.013) but not for HbA1c (5.0% vs 5.4% p=0.17).

Conclusions: These data suggest that a significant proportion of patients demonstrate AbNGT after pancreas transplantation and that the OGTT can identify patients with suboptimal graft function whereas FPG and HbA1c within the normal, non-diabetic range fail to do so. Although a difference in FPG was demonstrated between patients with NGT and AbNGT, the sensitivity and specificity of FPG is too poor to be of clinical use based on this data but further data is needed. These data suggest that AbNGT will only be reflected by very small changes in FPG and HbA1c in these patients. Clinicians should be aware that FPG and HbA1c at the higher end of the normal range might highlight patients with suboptimal graft function and further data is needed to determine whetherthe noral range needs further stratification in this patient group. We would recommend routine OGTT at defined intervals after pancreas transplantation to identify patient with suboptimal graft function and monitor patients' graft function over time. This will allow graft function to be further stratified within this population. Identification of patients with suboptimal graft function is essential for ongoing clinical care and possible future trails of therapeutic interventions to improve and prolong graft function (such as gut hormone analogues).

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Abnormal oral glucose tolerance in whole pancreas transplant recipients is characterised by a delayed peak insulin response, greater glucose area under the curve and lower insulinogenic index during oral glucose tolerance test

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Backgroud: Pancreas transplantation aims to restore endogenous insulin secretion and normalise glycaemic control in patients with type 1 diabetes (T1DM). However, a significant proportion of whole pancreas transplant recipients exhibit abnormal oral glucose tolerance (AbNGT) after transplantation suggesting suboptimal graft function. In order to consider potential interventions to improve graft function it is essential determine the characteristics of AbNGT.

Methods: We performed a standard 75g OGTT in 24 patients at 3 months after pancreas transplantation. Samples were taken at 0, 10, 30, 60, 90 and 120 minutes for determination of glucose and insulin levels.

Results: 5 of 22 patients exhibited AbNGT. Although total insulin secretion during OGTT was not significantly reduced in patients with AbNGT, time to peak insulin response was significantly delayed as compared to patients with normal glucose tolerance (NGT) (96 min vs 45 min p=0.02). The delay in early insulin response was accompanied by significantly higher glucose levels at 30, 60, 90 and 120 minute time points as well as significantly higher glucose area under the curve (AUC_{GLUC}) in the AbNGT group as compared to patients with NGT. Furthermore, the insulinogenic index (II), which expresses the ability of glucose to stimulate an appropriate early phase insulin response was significantly reduced in patients with AbNGT (7.6 vs 32.3 p=0.004).

Conclusions: Taken together these findings suggest patients with AbNGT after pancreas transplantation have an altered pattern of insulin secretion and glucose disposal in response to an oral glucose load leading to postprandial hyperglycaemia. This suggests that the ability of glucose to stimulate an insulin response and the timing of that response is of greater importance than the overall magnitude of the insulin response itself.

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ASA Physical Status Classification System in Pancreas Transplantation outcomes; Does it accurately predict risk?

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BACKGROUND: The American Society of Anaesthesiologists Physical Status Classification system (ASA) was adopted as a surrogate marker to aid in the assessment of preoperative physiological status. There have been no previous reports of the association between ASA scores and subsequent morbidity and mortality outcomes in pancreas allograft transplantation. We aimed to characterise whether higher ASA scores predicted potential negative sequelae to pancreas transplantation, both in terms of associated morbidity and mortality but also with regard to length of hospital stay.

METHODS: A retrospective analysis was carried out of 203 consecutive patients undergoing pancreas transplantation in our unit since the initiation of the programme in 2001 (SPK=155, PAK=36, PTA=12), in 20 cases ASA status was not documented. Primary endpoints included patent mortality and graft loss. Secondary endpoints included associated morbidity and length of hospital stay. Statistical analysis was performed using Chi-Square and ANOVA tests.

RESULTS:

	Overall	**ASA 2**	**ASA 3**	**ASA 4**	**P VALUE**
Sample size	183	27	152	4	
Median Age (yrs)	42	44.7	41.6	45.1	0.8170
BMI	25.5	27	25.3	25.5	0.1261
Pancreas Graft failure (%)	18	7.7	19.1	0	0.5539
Pancreas Graft survival (months)	28.6	30.5	27.16	28.08	0.9634
One year Mortality (%)	13.1	18.5	14.5	0	0.7048
Patient survival (months)	37.6	34.06	37.93	28.08	0.6282
Median hospital stay (days)	17	20	17	49	0.1703
Median CIT (hours)	14.1	13.61	14.3	16.06	0.3737
Wound infection (%)	14.3	18.5	15.1	25	0.7969
Minor/Major Fistula (%)	7.9	3.7	8.5	50	**0.009**
Respiratory infection (%)	14.7	18.5	7.9	0	0.5473
Cardiac complications (%)	3.9	7.4	4	0	0.6559
DVT/PE (%)	8	3.7	4.6	0	0.8940

CONCLUSIONS: ASA has proven to be a reliable indicator of peri-operative anaesthetic morbidity and mortality risk. However, there appears to be no correlation between ASA status classification and outcome data in pancreas transplantation with regards graft outcomes. There was a trend towards longer post-operative stays in patients with ASA 4 and appeared to be a higher rate of intestinal fistulae in high ASA status. Pancreas transplantation, by necessity is performed in patients with poor cardio-respiratory reserve but perceived anaesthetic risk should not be an obstacle to successful transplantation.

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Pre-transplant thromboelastograph (TEG) and thrombophilia screening do not predict thrombosis following pancreas transplantation.

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Introduction

In spite of improvements in surgical technique and immunosuppressive practices, technical failures early after transplant remain a common cause of pancreas loss. Of the technical failures thrombosis is the most common cause with an incidence of around 5 to 10%. Thrombosis may be caused by factors in the pancreas (e.g. reperfusion injury), immunological factors (e.g. rejection), or may be a manifestation of an underlying pro-coagulant state. In order to investigate this we prospectively screened all the patients assessed in Cambridge to see if we could predict thrombosis, and thus institute more aggressive prophylaxis as appropriate.

Methods

Of the 115 patients transplanted in Cambridge between 2001 and November 2010, 105 patients underwent screening at assessment with a thromboelastograph (a measure of clot formation kinetics) and thrombophilia screen (including factor II and V polymorphisms, levels of protein C, S, AT/Hep binding, APC sensitivity ratio, DRVVT & silica clotting time).

Prophylaxis against thrombosis comprised enoxaparin 40mg/day till discharge, followed by aspirin 75mg/d. Since August 2009 epoprostenol infusion has been given intra-operatively and continued for 5 days.

Results

46% of patients had both a normal TEG and normal thrombophilia screen.

49% had an abnormal TEG and 19% an abnormal thrombophilia screen, with 14% where both tests were abnormal.

In the same period 8 (8%) pancreases were lost due to thrombosis at a median 9.5 days post transplant (range y to z), with two patients losing both kidney and pancreas at the same time. A further 7 patients had a thrombotic event in the pancreas that was successfully managed by anticoagulation

Of the 16 patients (15%) who had a thrombotic event (8% lost their pancreas to a thrombus);

- 3 had an **abnormal** TEG and **abnormal** thrombophilia screen.
- 5 had a **normal** TEG & a **normal** thrombophilia screen.
- 1 had an **abnormal** thrombophilia screen and **normal** TEG.
- 6 had a **normal** thrombophilia screen and **abnormal** TEG.

Conclusion

Diabetic patients being assessed for combined kidney and pancreas transplant are commonly prothrombotic, as determined by thromboelastography. However neither TEG, nor the routine thrombophilia screen, predict post transplant thrombosis in the pancreas.

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Mycotic Pseudoaneurysm Occurrence Following Kidney And Pancreas Transplantation

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Introduction: Mycotic pseudoaneurysms in transplant patients may lead to life-threatening complications including hemorrhage. Some authors advocate the elective removal of grafts from recipients, who have received a transplant from which candida sp. has been cultured in the perfusion fluid. Other authors advocate a conservative approach with symptom monitoring, anti-fungal therapy and radiological surveillance.

We retrospectively reviewed the last 140 transplants carried out at our centre to see whether there is a correlation between perfusion fluid positivity for candida sp. and the risk of life threatening vascular complications in kidney and pancreas transplantation. As part of the existing centre protocol all patients who received an organ which had a positive culture for candida sp. were treated with 14 days of intravenous caspofungin and a subsequent four week course of oral fluconazole.

Method: 140 transplant were retrospectively reviewed. Perfusion fluid samples were taken at the back-table and cultured for 10-15 days. We analysed and compared the results of positivity between pancreas and kidney transplants. For patients positive for candida sp. from the perfusion fluid we reviewed their notes and subsequent follow-up to identify whether they were treated with anti-fungal therapy and whether they developed vascular complications.

Results: Our results from the last 91 kidney transplants failed to grow candida sp. No patients in this cohort developed pseudoaneurysms. However, perfusion fluid samples from three out of the last 49 pancreas transplants fluid cultures were positive for candida albicans. Despite a treatment course of caspofungin followed by maintenance fluconazole treatment, all of these patients eventually developed pseudoaneurysms involving the Y graft or the common iliac artery onto which the graft was anastomosed. All three of these patients developed life-threatening bleeds requiring salvage pancreatectomies. One pancreas transplant recipient failed to grow candida sp. from the perfusion fluid, but later went on to develop a pseudoaneurysm requiring graft pancreatectomy. Culture of the graft itself grew candida.

Discussion: Candida sp. is a common commensal of the gut flora, hence it is not surprising in pancreas transplantation, where donor duodenum is kept and anatomosed to the recipient's small intestine, that there is a higher incidence of fungal contamination compared to kidney transplants. Candida sp. are thought to predispose to the development of pseudo-aneurysms by causing an inflammatory arteritis of the vasa vasorum, a phenomenon also observed in intravenous drug users.

In our experience, the culture of perfusion fluid is of value in identifying patients at risk of developing complications. There are cases of false negative results however. Great caution is required in patients in whom the perfusion fluid is positive for candida sp. Conservative management should only be considered in those patients in whom early anti-fungal treatment has been started and where regular radiological follow-up is possible. In an attempt to reduce the incidence of fungal contamination in pancreas transplantation, all donors now receive bowel decontamination during procurement and the recipients receive a single dose of intravenous caspofungin intraoperatively.

Post Transplant Complications

Moderator: Martin Drage

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Complications And Their Association With Delayed Graft Function (DGF) In Kidney Transplantation From Donors After Cardiac Death (DCD)

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Background: The growing demand for renal transplants has resulted in the increased utilisation of organs from DCDs. Although there is an abundance of data on short to medium term outcome in DCD transplants, there remains a paucity of specific data on the incidence of complications (both medical and surgical) in this patient group. Here, we report a single unit experience of kidney transplantation from DCDs, the rate of medical and surgical complications and their association with DGF.

Methods: Eighty patients who received DCD renal transplant in a single unit over a 5 year period were included. All of these patients received ATG according to body weight for induction and maintenance immunosuppression with tacrolimus, mycophenolate mofetil and prednisolone which was withdrawn by the 3rd month if not more than 1 acute rejection had occurred. Subcutaneous sodium heparin was administered in the majority of patients for 1 week post-transplant and they all received valgancyclovir prophylaxis. Infectious, surgical and medical complications occurring within 6 months after transplantation were analysed. Chi square and Mann-Whitney tests were employed to compare factors between patients with and without DGF.

Results: In the time period mentioned above, 514 adult renal transplants were performed of which 80 (15.5%) were from DCDs. Median follow-up time for recipients of DCD kidneys was 29.8 [2-73.8] months. The median donor and recipient ages were 47 [17-68] and 51.5 [19-72] years. 55 (73%) patients experienced DGF.

The following infectious complications were identified amongst DCD recipients (n=80): urinary tract infections: 47(58.8%); pneumonia: 11(13.8%); clostridium difficile associated diarrhoea: 4(5%); wound infection: 26(32%); bacteraemia: 5(6.3%); CMV infection-PCR positive: 8(10%). Identified medical complications were: acute cardiovascular: 12(15%), cerebrovascular: 1(1.3%) and venous thrombo-embolic events: 0. Occurrence of surgical complications were: fluid collections 20(25%), ureteric leak: 3(3.8%), ureteric obstruction (hydronephrosis: 5(6.3%), renal artery stenosis: 4(7.2%), including 1 requiring dilatation, renal vein thrombosis 1(1.3%). There was no association between the occurrence of DGF and the incidence of any of the above complications. All the 8 re-transplanted patients experienced UTI (p=0.03) and they had a tendency to develop more frequently hydronephrosis (p=0.044). Older recipients experienced urine leak (p=0.05). Longer cold ischemic time was associated with increased incidence of renal artery stenosis (p=0.003).

Conclusions: In this preliminary analysis a significant number (>50%) of DCD recipients experienced an infectious complication during the first 6 months post transplant. We also demonstrate that both surgical and infectious complications are higher in the re-transplanted patients and that longer cold ischemic time may contribute to renal artery stenosis. Though preliminary in nature we feel that this study has highlighted some important correlations which warrant further investigation in a larger patient cohort and correlation with recipients of organs from brain dead donors.

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Continuous Doppler Blood Flow Monitoring after Kidney Transplantation.

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Introduction

After kidney transplantation, surveillance of graft blood supply is critical. A delay in detecting compromised graft perfusion impacts on organ survival. Current practice utilises doppler ultrasound to monitor vessel patency and graft perfusion and is performed repeatedly following kidney and pancreas transplantation. We have used an implantable probe that has allowed for easy vessel attachment and safe continuous audible monitoring of vascular anastomoses. It has been used in the observation of microvascular tissue transplants, free flaps and paediatric liver transplants but as yet, not in monitoring kidney allografts. We feel a transplanted kidney could benefit greatly from continuous blood flow monitoring.

Methods

To assess feasibility of the probe in renal transplantation, we used the probe in 18 consecutive renal transplants with good results.

Results

Much fewer doppler ultrasound scans were ordered during the 18 admissions and the probe obviated the need for a surgical re-exploration in a situation whereby the ultrasonographer cound not visualize the kidney in an obese patient. There were no complications and all probes were removed easily.

Discussion

This probe has the potential to identify transplanted organs threatened due to flagging or cessation of blood supply allowing immediate intervention. It can also obviate the need for unnecessary surgical re-exploration. This aim of this feasibility study is to enable a controlled clinical trial to assess the use of the probe in routine transplant practice.

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Skin Cancer In Renal Transplant Patients

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Introduction: It is well known that organ transplant recipients are at a higher risk of non-melanoma skin cancer compared to the general population. Established risk factors include UV exposure, fair skin type, HPV infection and duration of immunosuppression. As graft survival improves, prolonged immunosuppression is inevitable. Emphasising the importance of sun protection and skin surveillance is vital to reducing the morbidity associated with skin cancer.

Methods: We carried out a questionnaire study to identify the perception of skin cancer risk in renal transplant patients, to identify (i) if patients are informed of the increased risk of skin cancer and (ii) patient behaviours.

193 questionnaires were distributed in the general transplant follow-up clinic. 95% were returned (184 questionnaires). 58% of respondents were male; mean age was 52 years (range 17 - 80 years) and the median time from transplantation was 20 months (0 - 401 months). 65% of respondents were skin type 3 or fairer.

Results: 87% of patients are aware of the increased risk of skin cancer in transplant recipients. This was discussed post transplant in 90% of respondents, but in only 70% and 62% before and during the immediate transplant period respectively. In over 50%, this information was provided by either a nurse or transplant co-ordinator. Renal physicians advised regarding skin cancer risk in 43%. Surprisingly this information was most often provided by only one health professional (in 40% of cases). 75% of respondents received written information regarding skin cancer.

74% of patients specifically avoid sun exposure during the summer, and a quarter always protect their skin by wearing long sleeves or a hat. 88% of respondents use sunscreen, although the majority only use this in the summer. 45% use sunscreen on all exposed areas, and 50% use an SPF greater than 30.

26% of patients do not examine their skin regularly, but 65% have increased their sun protection measures following their transplant. **All patients attend an annual nurse-led screening clinic for skin checks,** and 29% have seen a dermatologist following transplantation for assessment of their skin. Although this subset of patients employ sun-protective measures more frequently than those who have not had subsequent skin problems, this did not reach statistical significance. Female respondents used sunscreen more frequently than male patients (94.6% v 84.6%, $p < 0.05$) but there was no statistical difference in sun-protective behaviour with regards to duration of immunosuppression.

Discussion: Previous work cites patient awareness of skin cancer between 30 - 68%, with better awareness in dedicated transplant skin clinics. Our data provides higher levels of awareness in a general transplant clinic population. Although the majority of patients adopt sun-protective behaviours – which may influence the risk of skin cancer in the future – these practices remain variable; so continued reinforcement and patient education remain a necessary part of the follow-up process in this particular patient group.

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Management of primary symptomatic lymphocele after kidney transplantation: a systematic review.

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Background: Post transplant lymhocele is a collection of lymphatic fluid around a transplanted kidney which may compromise the transplant or its adjacent structures. Management of post-transplant lymphocele varies between units and the best treatment options are undefined.

Aims: To evaluate and compare the different approaches of lymphocele management among recipients of kidney transplants.

Methods: Studies were identified by searching Medline and Embase for articles from January 1954 to January 2010. Data was extracted regarding the incidence, treatment and treatment outcomes of primary symptomatic lymphoceles after kidney transplantation (deceased and live donation). Primary outcomes included rates of lymphocele recurrence and rates of conversion from laparoscopic to open surgery. Secondary outcomes included the total length of hospital stay, intra-operative (defined as complications occurring during the surgical procedure) and post-operative complication rates (defined as complications occurring after the surgical procedure.)

Results: Fifty-two retrospective case series reports with 1,113 cases of primary lymphocele were selected for review. Primary treatment modalities included: aspiration (n=218), sclerotherapy (n=155), drainage (n=219), laparoscopic surgery (n=333), and open surgery (n=188). Of the 218 cases of lymphocele treated with aspiration alone, 141 recurred associated with a recurrence rate of 0.593 (95%CI: 0.515 - 0.667). Of the 333 cases of lymphocele treated with laparoscopic surgery, 19 recurred, with a recurrence rate of 0.082 (95%CI: 0.055 - 0.121). Of the 188 cases of lymphocele treated with open surgery, 18 recurred, with a recurrence rate of 0.163 (95%CI: 0.106 - 0.242). The conversion rate from laparoscopic to open surgery for the management of post kidney transplant lymphoceles was 0.116 (95%CI: 0.083 - 0.160).

The intra-operative complication rates of laparoscopic and open surgery were 0.075 (95%CI: 0.048 - 0.117), and 0.080 (95%CI: 0.039 -0.159), respectively. The post-operative complication rates of laparoscopic and open surgery were 0.058 (95%CI: 0.030 - 0.107) and 0.224 (95%CI: 0.109 -0.407), respectively. The mean (SD) hospital stay was 2.5 (1 - 5) days for laparoscopic surgery and 5.5 (3.8 - 8) days for open surgery.

Conclusions: Compared with open surgery and aspiration therapy, laparoscopic surgery appears to be the better option for the management of post transplant lymphoceles. However, the evidence base to support or refute the current available treatment decisions is poor. Our study findings highlight the need for better comparative data to inform clinical decision making for the management of this common and important complication after kidney transplantation.

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Transplant Renal Artery Stenosis: Incidence, Management and Outcomes in 897 Transplants at a Single Centre Over 15 Years

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Introduction:

Transplant Renal Artery Stenosis (TRAS) is a recognized complication following renal transplantation, with a reported incidence of up to 23%, depending upon definition. We present our experience over a 15-year period, reporting the incidence, investigation, management and outcomes in the treatment of patients who developed Transplant Renal Artery Stenosis. Although balloon angioplasty and stent placement are recognized in the management of this condition, the effect of stent placement on graft survival has not been reported, and therefore attention is given to this aspect of treatment.

Methods:

A study using a prospective database was performed of patients undergoing renal transplantation at a Renal Transplant Unit from 1994 until 2009. Of these patients, those with findings in keeping with Transplant Renal Artery Stenosis on ultrasound examination, underwent angiography with angioplasty and stent placement if appropriate. Data analysis included age of donor and recipient, transplant characteristics, incidence of Transplant Renal Artery Stenosis, morphology, intervention, transplant function, systolic blood pressure, incidence and timing of transplant failure.

Results:

A total of 897 renal transplants were performed with 30 patients (3.34%) being found to have developed Transplant Renal Artery Stenosis. Twenty-two of these patients (73.33%) underwent a single angiographic procedure, with 8 (26.67%) requiring multiple interventions. 8 patients (26.67%) underwent stent insertion. Ten patients (33.33%) suffered delayed graft function. Nine of the recipients (30%) suffered at least 1 episode of acute rejection. Nineteen patients (63.33%) experienced a fall in creatinine levels seven days post angioplasty with 21 (70%) showing improvement at one month. None of the patients diagnosed with Transplant Renal Artery Stenosis suffered graft loss due to this condition.

Discussion:

The incidence of Transplant Renal Artery Stenosis at our unit is in keeping with findings reported in the literature. The results from this study suggest that the use of percutaneous angioplasty with or without stent placement is a safe and effective treatment of Transplant Renal Artery Stenosis and, when preceded by early diagnosis, results in the preservation of transplanted organs in which this disorder occurs. The use of endovascular stents in treating Transplant Renal Artery Stenosis did not adversely affect graft survival in this study.

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Transplant Ureteric Stent Trial (TrUST): Early versus Standard removal. A Randomised Controlled Trial - Pilot Data.

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Introduction:

The introduction of transplant ureteric stents (TUS) has significantly reduced the incidence of major urological complications (i.e. urinary leak and ureteric obstruction) post renal transplant from 9% to 1.5%. However ureteric stents themselves can cause complications of pain, haematuria, infection, migration, fragmentation and infection. The incidence of TUS complications ranges from 14-46% and has been associated with length of time they remain in situ. Optimal time for stent removal has not been established and no systematic comparison between early (<7 days) and standard removal (1-3 months) has been made.

Aims & Objectives:

A randomised control trial to compare the current standard of cystoscopic TUS removal at 6 weeks to early removal on day 5 (achieved by attaching the stent to the catheter). Primary objective is to determine the effect of early TUS removal on stent related complication rates. The secondary objectives are to determine the effects of early TUS removal on ureteric complication rates; patient acceptability; procedural costs and resource availability and allocation.

Methods:

A randomised control trial. Guy's & St Thomas' adult and paediatric patients (≥2 yrs) listed for either living or deceased donor renal transplant were screened. Randomisation via an online system to either standard TUS removal or Early TUS (stent attached to catheter). Required sample size – 88 patients per group *(80% power, 5% type 1 error with aim of 15% reduction in complications)*. Multi-centre ethics approval in 2009.

Results:

Between April and October 2010, 23 patients screened for eligibility. 12 met the inclusion criteria, consented and were randomised into trial (early arm n = 6, standard arm n = 6). There have been no serious adverse events. There have been no reports of urinary leaks or ureteric obstruction in either arm. There have been no stent complications reported in either arm. Of those allocated to the early arm, 2 did not receive the allocated intervention due to technical difficulties in attaching the stent to the catheter. There was a 1 day delay in one patient for stent removal in the early arm (catheter balloon required percutaneous needle puncture due to stent suture). In the standard arm one patient had a 6 week delay for stent removal due to varicella zoster.

Conclusion:

It appears feasible to remove TUS on day 5 after transplant without cystoscopy through a non invasive technique with the potential benefits of better patient acceptability, reduced stent complications, reduced costs and resources associated with cystoscopy. This study now has a NIHR Research for Patient Benefit grant and multi-centre recruitment will permit required sample size and determine safety and benefits of early TUS removal.

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Is there a role for routine ultrasound examination of the kidney transplant following transplantation?

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Introduction

Ultrasound examination (USS) of the transplanted kidney is a simple and safe method for assessing the general morphology, vascular perfusion and peri-transplant space of the transplanted kidney. It is, however, operator dependant. In times of financial constraint is this a test we can justify when the indications for it and the information gleaned from it potentially add little or anything to the management of patients following transplantation?

Methods

We reviewed the patient records for all kidney transplants done in our unit in the financial year 2008/09. Indications for USS were documented as well as abnormalities detected and the need for intervention based on these results.

Results

64 patients underwent 106 USS in the first 2 weeks following their transplant. There were 21 live donor transplants, 27 DBD and 16 DCD transplants performed. 44 of these scans were done as "routine" post transplant scans. 48 of the 64 recipients had immediate graft function with all but 2 patients receiving "routine" scans, and 18 of them receiving >1 scan despite a falling creatinine. Delayed Graft Function was seen in 16 patients, 7 of whom received >1 scan. Abnormalities were detected in 18 of the 106 scans, all of which were due to collections or haematomas. No abnormalities detected resulted in intervention. There were no perfusion issues identified.

Discussion

This study demonstrates that there is no indication to perform post transplant USS in the majority of patients. It is simply there as a method of reassurance for the transplant team. USS is simple and easy to perform, but does cost approximately £40 per study. Avoidance of a superfluous investigation therefore has the potential to save the NHS a significant amount of money.

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Early Approach To Renal Artery Stenosis Following Transplantation; Single Unit Experience

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Introduction

Renal artery stenosis is a well reported potentially curable complication of renal transplantation associated with hypertension, allograft dysfunction and graft loss.

The prevalence range from 1-23%. Aggressive definitive diagnosis has not generally been pursued due to concerns regarding contrast exposure and the technical complexity and risks associated with surgical repair.

Method

In this study we review our experience with renal artery stenosis(RAS) utilizing magnetic resonance angiography(MRA) as the initial diagnostic tool with selective use of formal angiographic pressure gradient assessment and angioplasty of confirmed stenoses.

Results

During the period April 2006 to August 2010 a total of 370 transplants were performed. Of these 137(37%) underwent MRA based on the clinical parameter of an unexplained rise or persistently elevated serum creatinnine. Associated clinical features included significant or worsening hypertension in 55%, fluid retention in 27% and bruit in 11%. Based on an MRA study demonstrating or suggesting arterial stenosis 35 patients proceeded to formal angiography. Of these patients 17 had no further procedure as the interventional study demonstrated an inaccessible lesion (n=2) or no significant stenosis based on imaging or minimal pressure drop across a suspected or demonstrated lesion. The remaining 18 (3 live donor, 15 deceased donor including one peadiatric enbloc) underwent angioplasty of a stenotic lesion without use of indwelling stents. Twelve (66%) of these were within 6 months of transplantation and 16(88%) within a year. The location of the stenoses all three live donors were juxtra-anastomotic in the internal iliac artery (IIA). There were 2 multi focal stenosis in 2 patients. All patients had radiological and clinical improvement although 6 patients required 2 or more procedures before this was achieved. Hypertension was significantly improved (based on discontinuation of medications or reduction in dosage) in only in 22%.

Discussion

In conclusion MRA appears an effective initial screening tool for the early development of RAS following renal transplantation. Its use allows an aggressive approach to diagnosis whilst minimizing use of more invasive techniques and risks of contrast exposure. Angioplasty within this selected group resulted in only modest improvements in hypertension, overall but substantial improvement in graft function. This improvement in renal function contrasts to the reported results of endovascular intervention in native renal arteries. In the transplant setting angioplasty alone is associated with a high retreatment rate. A multi-centre randomized trial comparing our current approach to stenting appears warranted.

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Povidone-iodine sclerosant therapy for post-renal transplant lymphocele

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Introduction

Lymphoceles post renal transplantation are a relatively common complication occurring in between 5 to 15% of all renal transplants. They represent a potentially serious hazard to the survival of the graft and the recipient. Serious complications of lymphocele include infection and renal artery and vein compression resulting in thrombosis. The standard treatment for symptomatic lymphoceles is ultrasound-guided percutaneous drainage with open drainage techniques reserved for recurrent or large lymphoceles. Sclerosing therapy using iodine is well known technique for managing lymphoceles.

Methods

A prospectively maintained database of renal transplant recipients at a single centre was examined retrospectively to identify all patients with lymphoceles between 1996 and 2010. Statistical analysis with Mann-Whitney U test was used to compare those patients treated with iodine therapy and those treated without. Outcome measures included requirement for open drainage, rate of infection and mortality.

Results

Between 1996 and 2005, a total of 512 renal transplants were performed. Lymphoceles were diagnosed in 20 patients, none had iodine therapy. Between 2008 and 2010, 186 renal transplants were performed. 12 patients developed lymphoceles and several underwent iodine sclerotherapy. The outcomes are represented in the table below:

	No-iodine	Iodine	Significance (p-value)
Transplants	512	186	
All lymphoceles	20	12	
Treated lymphoceles	14	7	
Percutaneous drainage	14	7	
Outcomes			
Open drainage	2	0	0.305
Infection	1	0	0.480
Mortality	0	0	0.480

Discussion

This is the first study to compare iodine sclerotherapy against no sclerotherapy for post transplant lymphoceles. We have shown that since the introduction of iodine sclerotherapy there has been no need for open drainage of lymphoceles, there have been less infections and no mortality. There have not been any adverse reactions to this technique. We feel it is therefore safe and effective in the management of post transplant lymphoceles.

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A Single Centre Audit of Cold Ischaemia Time, and It's Impact on Renal Transplant Outcomes

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Introduction Cold Ischaemia Time (CIT) is thought to have important implications for both immediate graft function and long term graft survival. At a time when demand for transplants continues to increase it is important to identify areas for improvement which may prolong graft survival. Minimising the risk of delayed graft function by minimising CIT is likely to have important impact not only on patient morbidity and length of hospital stay but also on cost effectiveness of transplantation and the need for post transplant dialysis.

Methods data was analysed from 110 renal and or pancreas transplants that took place between December 08 and November 09 at Manchester Royal Infirmary. We reviewed the cold ischaemia times for kidney and kidney/pancreas transplants during the period of introduction of virtual crossmatch; broke down the stages that contribute to CIT and identified areas for improvement. We also undertook a review of eGFR at 1 week following renal transplant in 53 of the patients to assess if initial renal function at 1 week in kidneys with CIT <18hrs and >18hrs were significantly different.

Results on data analysis we found that the median CIT for all transplants at our unit during the aforementioned period was 17 hours and 10mins, a figure above national average at the time. Following introduction of virtual crossmatch this figure was significantly decreased to 14hrs 46mins (P=0.0002). The component parts that contribute to CIT were broken down to identify potential areas for increased efficiency in future.

We also found the difference in eGFR between those with CIT <18hrs (33.6mls/min) and >18hrs (15.3mls/min) at one week to be statistically significant (P=0.0006). Furthermore, the audit revealed the difference between eGFR at 1 week in HB vs NHBD kidneys which was also found to be significant (P=0.01).

Conclusion the introduction of virtual crossmatch has made a significant difference to the CIT in our programme. The importance of CIT in reducing the risk of delayed graft function was further highlighted by the difference in eGFR at one week in those with shorter CIT (<18hrs). This has implications not only on a patient level but also on health economics.

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Transplant Kidneys From Donors After Cardiac Death Have A Distinct Pattern Of Evolution Of Renal Function

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Introduction

Deceased Cardiac Dead (DCD) Maastricht III donor transplants have an excellent outcome comparable with DBD donor transplants despite a higher proportion of slow or delayed graft function (DGF) in the DCD group. Applying the same criteria of DBD extended criteria (EC) donors to the DCD donors defines a new subgroup of DCD EC donors.

The aim of this study was to assess the change of renal function for kidney transplant recipients from DCD ECD and compare it with a contemporary group of recipients from standard DBD donors.

Methods

During a 5 year period a total of 306 renal transplants from deceased donors were performed in a single unit out of which 80 (26%) were from Maastricht type III DCD donors. The change of kidney function of 21 kidneys procured from DCD ECD and the 59 standard DCD transplants were compared with the function of DBD donors at 3 months, 6 months and a year after transplant.

Results

Of the 226 DBD donors 85 (38%) were ECD and of the 80 DCD donors 21 (26%) were ECD (p=0.05). The median age of the DCD donors was 62. The CIT of DCD kidneys (10.5 hrs) was lower than this of DBD donor kidneys (13 hrs, p=0.03) whereas the median number of HLA mismatches was higher. The 1 year graft survival was comparable.

Donor Type		**N**	**DGF**	**3mo eGFR**	**6mo eGFR**	**1 yr eGFR**
DBD	**standard**	141	22%	53.6	53.8	52
	ECD	85	32%	43.1	46,3	45
DCD	**standard**	59	68%	48	50	52
	ECD	21	71%	32.8	36.5	39.5

There was a continuous improvement in function in DCD kidneys between month 3 and 1-year post transplant. The 1-year eGFR had a tight correlation with the 3 months eGFR in DCD kidneys (correlation coefficient=0.74).

Conclusion

DCD transplant kidneys show a continuous improvement in their function over the first year. ECD DCD kidneys have inferior but still very acceptable function compared to ECD DBD kidneys.

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Effect Of Giving Set/Cannula Variables On Preservation Fluid Flow: An Ex Vivo Analysis

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Introduction: Despite the introduction of a National Organ Retrieval Service, significant differences in cadaveric organ perfusion techniques remain. There is little evidence to show which perfusate flow rate achieves optimal organ preservation. In addition, the giving set/cannula arrangements needed to achieve this rate are unknown. Type of perfusion fluid, cannula size, tubing length, height of the perfusate bag, and external pressure applied to the bag all influence flow. We therefore examined the impact of these variables on perfusate flow in an ex vivo system.

Methods: One litre bags of ViaSpan™ (UW) or Soltran™ (Marshall's) solution were attached to a Y-connector (Fast-Flow™, Baxter), which in turn was connected to either a 3 m or 1.5 m length of Flexi-rib™ tubing (Pennine Healthcare, internal diameter 7 mm). This was attached to a cannula, varying in diameter between 14-20 Fr (Terumo™). The cannula was either 0.4 m or 0.8 m below the bottom of the fluid bag. In addition, the preservation fluid was either non-pressurised (gravity alone), or had 100 mmHg pressure applied to the bag via a Medex pressure infusor (continuous or initial pressure only). The time for 500 mL of perfusate to flow was measured, and, after re-filling, was repeated. A mean flow rate was then calculated. All combinations of the above variables were examined. Perfusate temperature was kept between 5-9 ^{o}C.

Results: Surprisingly, under gravity pressure, increasing the cannula size from 14 to 20 Fr caused decreased flows in some set-ups. However, with ViaSpan™ height of 0.4 m, and full length tubing, increasing the cannula size from 14 to 20 Fr increased flow from 172 mL/min to 219 mL/min (27% rise). Overall, flows were at least 15% faster for Soltran™ compared to ViaSpan™; the percentage increase was more marked when the perfusates were driven by gravity rather than pressurised infusor (80-100% increase). Halving the length of the tubing increased flows by approximately 10% across all set-ups (e.g. 20 Fr cannula, ViaSpan™, 0.8 m height, 3 m tubing: 269 mL/min, vs 301 mL/min for 1.5 m tubing). With a 20 Fr cannula, raising the ViaSpan™ or Soltran™ bag from 0.4 to 0.8 m results in ~20% more flow; initial pressurisation to 100 mmHg doubles flow. Continuous pressurisation leads to further doubling.

Discussion: Despite Poiseuille's equation, altering the cannula size from 14Fr to 20Fr did not consistently increase flow, possibly due to turbulence. Cannulas can be chosen more on the basis of ease of cannulation than on perceived impact on flow. The viscosity of ViaSpan™ limits flow, especially under gravity feed; tubing length is less important. The major ex vivo determinant of perfusate flow is bag pressure; continuous pressurisation is superior to initial pressurisation. These data provide a rational basis for designing experiments to measure perfusate flow in vivo and determine its clinical significance.

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Poster Withdrawn

Ischemia-reperfusion injury of transplanted kidney: Histopathological analysis of disease progression

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Background: In the clinical settings, renal graft inevitably undergoes various periods of hypothermic storage prior to engraftment. Ischemia-reperfusion injury (IRI) following the prolonged cold storage is responsible for the delayed graft function and has been considered to contribute to the progression of end-stage graft failure. The aim of this current study is to obtain a deep understanding of the pathophysiology of IRI through identification and quantification of histopathological changes as the disease progresses.

Methods: The syngeneic Lewis-to-Lewis (RT1I) rat renal transplant model was used. The grafts were stored in the 4°C Soltran preserving solution for 0-24 hrs and morphology was assessed before and shortly after transplantation. The histopathology, function and survival of grafts with 16 and 24 hr cold ischemia were followed up to day 28 post-transplantation.

Results: Prolonged cold ischemia (>16-24 hrs) induced tubular necrosis, which was aggravated after reperfusion. In grafts treated with 16 hr cold ischemia, high level of tubular necrosis was found within 2 weeks post-transplant. $CD68^+$ macrophage emerged 24 hr after reperfusion (45.1± 16.2 under x 40 magnification) and infiltrated heavily in the kidney on day 4 (63.1.± 7.3) until day 12 (74.7.± 7.1). These changes gradually resolved and were replaced with tubular fibrosis. Inter-tubular α-SMA staining was detected (7.1± 1.4% on day 8) and steadily increased on day 28 (10.3 ± 2.8%, $p< 0.01$ compared with day 8). Substantial inter-tubular collagen deposition was found after first week post-transplantation (9.6 ±3.0% on day 8) and the accumulation persisted afterwards (8.1 ±3.1% on day 12) until day 28 (13.2 ±4.2%). 24 hr cold ischemia induced acute graft failure shortly after 2 weeks post-transplantation.

Conclusion: Prolonged cold storage led to ischemia-reperfusion injury, which was characterized as progressive tubular necrosis, vascular inflammation and macrophage infiltration. Tubular fibrosis and tubular atrophy were found in grafts during recovery, which might contribute to long-term impairment in renal function.

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Short term hypothermic machine perfusion in a model of kidney preservation

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Introduction

Hypothermic machine perfusion is emerging as an improved method of preservation compared to static cold storage techniques for donation after cardiac death (DCD) kidneys. Nonetheless, combining hypothermic techniques using the ease of static cold storage to transport the kidney and hypothermic machine perfusion on arrival at the recipient centre may enhance the preservation condition and also be a more practical approach to preserving DCD kidneys.

Methods

Porcine kidneys were retrieved after 10 minutes *in situ* warm ischemia, then preserved by either 18 hours of static cold storage (CS), hypothermic machine perfusion for 18 hours (HMP) or 14 hours CS followed by 4 hours of HMP (4 HMP). Kidneys were reperfused for 3 hours with oxygenated autologous blood on an isolated organ perfusion system to assess renal function and injury parameters.

Results

Intrarenal resistance (IRR) was significantly higher in the 4 HMP group [Area under the curve (AUC) IRR; 4 HMP 8.48 ± 2.97, CS 3.41 ± 1.80, HMP 3.78 ± 1.68mmHg/min.h; P = 0.011] and creatinine clearance (CrCl) lower compared to HMP (AUC CrCl; 4 HMP 2.3±0.6, CS 2.2 ± 1.7, HMP 9.8 ± 7.3ml/min/100g.h; P = 0.022). Levels of endothelin-1(ET-1) were higher in the 4 HMP and CS groups (ET-1; 4 HMP 21.6 ± 4.0, CS 24.2 ± 2.3, HMP 11.4 ± 4.6pg/ml; P = 0.002) and morphological injury was increased in the 4 HMP group (P = < 0.05).

Conclusion

This porcine kidney study demonstrated no advantage of the addition of 4 hours of HMP after a significant period of CS. There was also some indication of an additional loss of cellular integrity.

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Machine-perfused Kidneys: What are the optimum times and perfusion parameters for improved graft function?

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Introduction

Machine perfusion (MP) has been used successfully to prepare kidneys pre-transplantation. Previous work done at this centre has suggested that the incidence of delayed graft function (DGF) can be reduced with MP in Non Heart-Beating Donor (NHBD) kidneys, but little data is available regarding optimum perfusion time and parameters with relation to patient outcome.

Methods

MP data from NHBD renal transplants performed between 13th March 2009 and 10th November 2010 (n=56) was analysed retrospectively at a single-centre. Protocol for MP utilised the Lifeport system in all cases.

Specific MP variables collated included total time on MP, delay from retrieval to MP (i.e. initial static cold storage time), dynamic resistance and flow rate (measured every 10s for duration of MP). Markers of graft function were Serum Creatinine (Cr) at days 0, 1, 7 and 30. In addition, the requirement for dialysis post-operatively was also noted. Cohorts were divided according to total time on MP [0-2hrs (n=4), 3-5hrs (n=12), 6-8hrs (n=12), 9-11hrs (n=15), 12-14hrs (n=3), 15-17hrs (n=7), 18-20hrs (n=3)]. Subject end points were at day 30 and percentage decrease in resistance, flow rate and Cr were calculated for each specific cohort.

Results

Of the 56 subjects, there was one case of primary non-function. 3 patients died with functioning grafts past day 30 post-operatively. Kidneys functioning post-operatively by day 30 showed mean percentage falls in Cr of 51.9% (0-2 hrs MP), 63.5% (3-5 hrs MP), 75.8% (6-8 MP), 72.2% (9-11 hrs MP), 76.3% (12-14 hrs MP), 74.9% (15-17 hrs MP) and 59.2% (18-20 hrs MP). The mean percentage falls in dynamic resistance were 29.6% (0-2 hrs MP), 48.6% (3-5 hrs MP), 44.0% (6-8 hrs MP), 47.6% (9-11 hrs MP), 55.9% (12-14hrs MP), 66.5% (15-17 hrs MP) and 25.0% (18-20 hrs MP).

Discussion

Our results showed the greatest percentage fall in Cr in post-operative recipients was seen in kidneys on MP for 6-17 hrs. MP times outside of this interval (<6hrs or >17hrs) showed comparatively less reduction in Cr. The greatest percentage reduction in resistance was seen in kidneys on MP for 3-17 hrs. This data is limited by sample size but suggests that there may be an optimum time for MP prior to transplantation and substantial reductions in resistance on MP may contribute to improved graft function.

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Correlation between pulsatile machine perfusion parameters of kidney grafts from donors after cardiac death and post transplant kidney function

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Introduction: Kidneys from DCD donors are an important source of organs for transplantation. Compared with kidneys from brainstem dead donors, they have increased rates of primary non-function, delayed graft function and reduced graft survival. Preservation of such organs after retrieval may be by cold storage or by hypothermic pulsatile machine perfusion (HPMP). Recent evidence of the benefits regarding the use of HPMP is controversial. The time taken for normalization of perfusion parameters may provide an indicator for graft function and may allow for early intervention.

Subjects and Methods: All machine-perfused DCD kidney transplants performed at a single unit between 2002 and 2009 were examined retrospectively. The creatinine levels at one and three months post transplantation and the number of days to graft function were compared against the time to reach ideal flow (≥80ml/min) and ideal resistance (≤0.25Ω) when placed on the LifePort© machine. Linear regression analysis was used to compare the data. Results were expressed as the coefficient of determination, R^2, to give a best fit value from 0 to 1.

Results: During the study period, 84 kidneys from 47 donors were machine-perfused before transplantation. The mean donor age was 39±14 years. The warm ischaemia time was 10±24 minutes and cold ischaemia time was 16±4.4 hours. The 84 recipients had a mean age of 52±11.5 years. Re-warming time was 32±15.3 mins. Kidney graft reperfusion was good in 87%, fair in 12% and patchy in 1%. Serum creatinine (SCr) at one month and 3 months was positively correlated with the time to normalisation of flow (R^2 = 0.4236 and 0.4812 respectively). SCr at one month and 3 months was positively correlated with the time to normalisation of resistance (R^2 = 0.5261 and 0.4714 respectively). The longer the time to normalisation of flow, the longer the time to graft function (R^2 = 0.3563).

Discussion: There is a correlation between the time to normalisation of flow and the time to normalisation of resistance and the creatinine at 1 and 3 months. The longer it takes to reach ideal flow and resistance, the worse the creatinine at 1 and 3 months. The longer to ideal flow and resistance, the longer the time to graft function, however, the correlation is weak. Overall, the time to normalisation of these parameters may have implications on the long-term DCD kidney transplant function.

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A novel perfusion fluid for DCD donor kidneys; better as a flush or a storage medium?

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Aims

Aqix® RS-I is an innovative non-phosphate pH buffered solution with proven benefit in tissue preservation. Its role in renal organ perfusion and preservation in the context of donation after cardiac death (DCD) transplantation is unclear. In particular whether it confers better protection of the organ as a flush or storage medium is to be determined.

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.
• All organs were flushed with 250mls of ambient room temperature (18-23°C) Aqix® RS-I solution followed by 250ml cold (4-8°C) Aqix® RS-I solution.
• Kidneys were then subjected to static cold storage for 24hours in either RS-I solution (n=6) `RS-I Storage group' or UW solution (n=5) `RS-I Flush group'
• Organs were then 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 similar performance between the groups
• Mean lactate at 2hours reperfusion was 2.6mmol/L +/- 0.79 in the RSI-Storage Group vs 1.08+/- 0.33 (SE) RSI Flush group.
• Mean serum creatinine fell by 160µmol/L +/-20 in RSI Storage vs 210µmol/L +/- 20 in RSI Flush group.
• Renal vascular resistance was higher in the RSI flush group finishing at a mean of 1.19mmHg/ml/min +/- 0.24 in the RSI storage group vs 1.29 +/- 0.1 in the RSI flush group

In all cases the trends were compared using repeated measures ANOVA and were not found to be statistically different in any parameter.

Conclusion

Whether storage in RS-I confers an additional protection from the deleterious effects of cold storage and ischaemia-reperfusion injury requires further investigation, ideally in the form of a transplant model.

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Marginal allograft viability assessment in the preservation period utilising rapid sampling microdialysis.

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Viability assessment of the marginal allograft during the preservation period is imperative to avoid unnecessary discarding of marginal organs and maximising graft survival outcomes. To address this need, we have developed a system that allows continuous tissue monitoring with rapid measurements of the metabolic markers of ischaemia. This abstract reports the results from our ongoing study. Our aim is to develop a tool that allows for accurate organ viability assessment in the preservation period. The system is based on a rapid sampling microdialysis analyser that has previously been validated in clinical studies monitoring tissue viability in brain injuries and bowel ischaemia.

Kidneys were retrieved from large Landrace Crossed Breed pigs after termination. 12 unperfused kidneys were monitored at room temperature for 48 hours post-retrieval in the control group. In the preservation group 4 kidneys have been monitored to date. These kidneys were flushed with cold University of Wisconsin solution after retrieval and stored on ice at 4^{o}C, followed by continuous tissue monitoring for 48hrs. A microdialysis probe was tunneled 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. The microdialysis system sampled 200nL of dialysis fluid from the probe, this was injected into a distributed enzyme based biosensor system, resulting in a current (*A*) peak at the detection electrode proportional to the dialysate lactate concentration.

On commencement of microdialysis monitoring stable levels were achieved within 10 minutes, with quantifiable lactate concentrations in the control group. The 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 preservation group there was no detectable concentration of lactate within the extracellular fluid.

This fall in concentration in the control group was not caused by the microdialysis process but rather reflected ongoing tissue processes, specifically a reduction in anaerobic metabolism as ischaemia worsened and cells died. The absence of identifiable lactate within the parenchyma of the kidneys in the preservation group is likely due to a significant reduction in anaerobic metabolism as a result of hypothermia.

This preliminary study provides the baseline ischaemic profile for porcine kidneys whilst validating the technique of microdialysis as a tool for organ viability assessment, and will allow appropriate comparison when examining the effect of organ preservation via simple cold storage, hypothermic or normothermic pulsatile perfusion.

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