Welcome to London!

As president of the British Transplantation Society I am delighted to welcome you to London to the BTS 13th Annual Congress.

We are very grateful to the members of the Programme Committee for putting together what promises to be a stimulating, innovative and diverse programme; and we hope there will be something for everyone. We again welcome our partner Societies and there will be joint symposia with BSHI, BASL and ISHLT.

Two pre-Congress symposia will be held on the Tuesday prior to the main meeting; a Science symposium on B lymphocytes and a Clinical symposium on the marginal graft. In addition to the regular Congress sessions, this year there will be also three concurrent postgraduate breakfast sessions covering immunosuppression, tissue typing and transplant surgery. We are also honoured to have Professor Sir Ian Kennedy giving the inaugural Hoffenberg memorial lecture.

We would also like to thank our corporate partners and other industry stakeholders whose support will help make our meeting possible.

The Annual Congress is always an excellent opportunity to meet with colleagues within an environment that is both educational and enjoyable.

With best wishes,

Keith Rigg

Tuesday 16 March

	Small Hall		**Council Chamber**
	Pre Congress Clinical Symposium **The Marginal Graft** *Chairs: Mr Vassilios Papalois & Prof Derek Manas*		**Pre Congress Scientific Symposium** **B Lymphocytes** *Chairs: Ms Lorna Marson & Prof Marlene Rose*
10.30	Registration & Coffee	10:30	Registration & Coffee
	What makes an allograft marginal and methods of evaluation		
11.00	Kidney: *Prof Rutger Ploeg*	11:00	Introduction & Welcome
11.30	Pancreas: *Prof Peter Friend*	11:10	Biochemical characterization of tolerance induction in developing B Cells: *Dr John Monroe*
12:00	Liver: *Mr Paolo Muiesan*	11:50	Induction of regulatory B cells: *Dr Claudia Mauri*
12:30	Heart/Lungs: *Prof Dirk Van Raemdonck/Mr Steven Tsui*	12:20	The role of apoptotic cells in inducing IL-10 secreting regulatory B cells: *Dr Mohini Gray*
13:00	Panel Discussion/Summary	13:00	*Lunch*
13:30	*Lunch*	14:00	B cell follicles in non-lymphoid tissue: *Dr Olivier Thaunat*
	Transplantation of the marginal allograft and outcomes		
14:15	Heart/Lungs: *Prof John Dark*	14:40	B cell markers in operational tolerance: *Dr Sophie Brouard*
14:45	Liver: *Prof Xavier Rogiers*		
15:15	Pancreas: *Prof David Sutherland*	15:20	*Tea*
15:45	*Tea*	15:40	B cells in renal transplantation: from bench to bedside: *Dr Menna Clatworthy*
16:00	Kidney: *Prof David Talbot*	16:20	Panel Discussion
16:30	Panel Discussion/Summary	17:00	Symposium Closes
17:00	Symposium Closes		

Wednesday 17 March

	Great Hall	Small Hall	Council Chamber	Committee Room 1
		Course 1.1: Transplantation Surgery Masterclass **Organ Retrieval** *Chair: Mr Vassilios Papalois*	**Course 2.1: Immunosuppression: a users guide** *Chair: Dr Adam McLean*	**Course 3.1: Histocompatibility & Immunogenetics for the Physician and Surgeon** *Chair: Prof Anthony Warrens*
08:00		Kidney: *Mr Geoff Koffman, Prof Rutger Ploeg*	Lecture: Corticosteroids – mechanism of action: *Prof Ian Adcock* Lecture: Calcineurin Inhibitors: *Dr Jack Galliford*	Introduction to HLA: *Prof Anthony Warrens*
08:20		Pancreas: *Mr Murat Akyol, Prof David Sutherland*		HLA Typing & data interpretation: *Dr Bob Vaughan*
08:40		Liver: *Mr Darius Mirza, Prof Xavier Rogiers*		
09:00		Panel discussion/summary		
09:30	**Plenary Session** *Chairs: Mr Keith Rigg & Mr Vassilios Papalois*			
	Where have all the donors gone. Will we achieve the 50% target? *Mr Chris Rudge*			
10.00	3 x Best Abstracts			
10.30	*Coffee*			

	Great Hall	Small Hall	Council Chamber
	Medical challenges in the transplant recipient *Chairs: Dr Chris Dudley & Dr Richard Baker*	**Solitary pancreas & live donor liver transplantation** *Chairs: Mr Murat Akyol & Prof Nadey Hakim*	**Basic Science: B Cells** *Chairs: Dr Menna Clatworthy & Prof Marlene Rose*
11:00	Proactive diagnosis and management of coronary disease in renal transplant recipients: *Prof David Taube*	Solitary pancreas transplantation: main stream treatment or still a big challenge? *Prof David Sutherland*	Importance and mechanism of action of B cells in transplantation: *Dr John Monroe*
11:25	Immunosuppressive strategies and the risk of malignancy: *Dr Chas Newstead*	Live donor liver transplantation: how far can we push the envelope? *Prof Xavier Rogiers*	Chronic rejection triggers the development of an aggressive intragraft immune response through recapitulation of lymphoid organogenesis: *Dr Olivier Thaunat*
11:50	4 x abstracts	4 x abstracts	4 x Abstracts
12:30	*Lunch & Exhibition*		
13:15		Wyeth/Pfizer Symposium **Optimising long term outcomes for Renal Transplant Patients** *Symposia Chairman: Prof Peter Friend* Speaker 1 – How and when to implement CNI minimisation strategy Speaker 2: How & when to implement a CNI elimination strategy	Novartis Symposium **One year Renal Function: could we do better?** - Chairman's introduction: *Prof Alan Jardine* - One Year Renal function: The State of the Nation *Dr Fergus Caskey* - Debate-CNI's have had their day-a new decade, a new paradigm? For: Dr Iain MacPhee Against: Prof Anthony Warrens

	Great Hall		Committee Room 1
	Medawar Medal 1 *Chairs: Mr Keith Rigg & Prof Anthony Warrens*		**BTS Transplant Nurses Symposium 1** *Chairs: Ms Jane Smith & Ms Jen McDermott*
14:15	**013:16** Global Survey Assessing Muslim Attitudes To Organ Donation		**"Hub and Spoke": The relationship between referring hospitals and transplant centres.**
14:30	**178:17** Allospecific B cells can receive help for generating anti-MHC I alloantibody through acquisition and presentation of additional graft antigens	14:15	Referring on…: from the perspective of a referring hospital: *Ms Helen Caldwell*
14:45	**166:18** Pancreas transplantation from non-heart beating donors in the United Kingdom	14:35	Hitting the target: The challenges of achieving pre-emptive living donor transplants in a referring unit: *Dr Michelle Webb*
15:00	**167:19** Macrophages mediate the Amelioration of Transplant Associated Injury by the novel Heme Oxygenase-1 inducer Heme Arginate	14:55	Distance learning: managing pancreas recipients on discharge back to the referring unit: *Dr Richard Smith*
15:15	*Coffee*		
	Medawar Medal 2 *Chair: Mr Keith Rigg & Prof Anthony Warrens*		**BTS Transplant Nurses Symposium 2** *Chair: Ms Moira Perrin & Ms Lisa Burnapp*
15:45	**174:20** Cytotoxic CD8 T Cells Receive Help From Indirect Pathway CD4 T Cells by Presenting Processed Alloantigen on Acquired MHC II	15:45	"Charting new territory": Translating the Organ Donor Taskforce recommendations into practice: - Differing solutions to taking the call; - Promoting organ donation through donation committees, clinical leads and embedding co-ordinators *Ms Christine Erdling, Mr Paolo Muiesan, Ms Julie Pascoe, Dr Paul Murphy, Ms Jen McDermott, Cash Ryan*
16:00	**094:21** Kidneys Donated after Cardiac Death have Equivalent Graft Function to those from Donors with Brain Death but a Short Cold Ischaemia Time is Critical		
16:15	**120:22** Blocking the Formation of Intra-graft Lymphoid Tissue Influences Effector Humoral Responses		
16:30	**012:23** Non Heart Beating (NHB) donor perfusion using Normothermic Extracorporeal Membrane Oxygenation (NECMO) in comparison to In-situ + Peritoneal (ISP+PC) cooling increases insulin production and decreases pancreatic cell damage and anaerobic metabolism		
17:00	*Welcome Reception & Moderated Poster session*		

Thursday 18 March

	Great Hall	Small Hall	Council Chamber	Committee Room 1
		Course 1.2: Transplantation Surgery Masterclass **Bench work preparation, pre transplant preparation of the graft**	**Course 2.2: Immunosuppression: a users guide** *Chair: Dr Adam McLean*	**Course 3.2: Histocompatibility & Immunogenetics for the Physician and Surgeon** *Chair: Prof Anthony Warrens*
08:00		Kidney: *Mr Geoff Koffman, Mr John Forsythe*	Lecture: Mycophenolate and azathioprine: *Dr Adam McLean*	Antibody Detection: *Dr Sue Martin & Dr David Briggs*
08:20		Pancreas: *Mr Murat Akyol, Prof David Sutherland*		Lecture and case studies
08:40		Liver: *Mr Darius Mirza, Prof Xavier Rogiers*	Workshop/coffee: Drug level monitoring: *Dr Gary Chusney*	
09:00		Panel discussion/summary	Lecture: mTORs: *Dr Paul Harden*	
	Chronic graft loss in renal transplantation *Chairs: Dr Chris Dudley & Dr Iain MacPhee*	**BTS/BASL Symposium** **PSC and Cholangiocarcinoma** *Welcome: Prof Derek Manas/Dr Mark Hudson*	**Basic science: Regulating the immune response to grafted tissue** *Chairs: Prof Paul Brenchley & Dr Wilson Wong*	**Joint BTS/ISHLT Symposium on Cardiothoracic transplantation** *Chairs: Dr Paul Corris & Prof John Wallwork*
09:30	Immunological aspects *Prof Mark Stegall*	*Chair - Prof Peter Hayes* Case 1: Presenter – *Dr Mark Davis* Responder – *Prof Andrew Burroughs* Case 2: Presenter – *Prof Derek Manas* Responder – *Mr Darius Mirza* Case 3: Presenter – *Dr Mark Hudson* Responder - *Dr Alex Gimson*	T cells: the answer to clinical operational transplantation tolerance? *Dr Andrew Bushell*	Multi-organ retrieval – state of the art 2010 *Mr Steve Tsui*
10:00	Histopathological aspects *Prof Terry Cook*		6 x abstracts	Multi-organ transplantation in cystic fibrosis *Dr Redha Soulimas*
10:30	Managing the failing transplant *Dr Paul Harden*			Allograft fibrosis and chronic lung dysfunction *Prof John Kirby*
10:40		*Chair Prof Derek Manas* Clinical dilemmas in Liver transplantation for PSC *Dr Mark Hudson*		
11:00	*Coffee*			
	Abstracts: Renal transplant outcomes *Chairs: Mr Bimbi Fernando & Dr Martin Raftery*	**BTS/BASL Symposium** (please note this session restarts at 11:15)	**Abstract: Immunosuppression 1** *Chairs: Mr Neil Parrott & Dr Simon Ball*	**Joint BTS/ISHLT Symposium on Cardiothoracic transplantation**
11.30		The science of PSC recurrence post Liver transplantation *Prof David Adams*	6 x abstracts	ABO incompatible cardiac transplantation in children *Prof Lori West*
11:45	6 x abstracts	Liver transplantation and Cholangio – carcinoma Case 1: Presenter – *Mr Raj Prasad* Responder: *Mr D Maguire* Case 2: Presenter – *Mr Steve White* Responder: *Mr D Maguire*		3 x abstracts

12:15		Liver transplantation for Hilar CC *Mr D Maguire*		
12:30	*Lunch & Exhibition*			
13:15		Astellas Symposium **"Improving Patient Adherence in 2010"** Presentation 1 – Medication adherence – an update for 2010 Presentation 2 – Moving from BD to OD Presentation 3 – Should we let the patient choose?	Roche Symposium **'Contemplating CMV'** *Chair- Mr John Forsythe* Speaker - *Prof Mark Pescovitz*	
	Abstracts – Ethics, Law and Public policy *Chairs: Mr Paolo Muiesan & Dr Antonia Cronin*	**Abstracts – Immunosuppression 2** *Chairs: Prof Peter Friend & Dr Nick Torpey*	**Abstracts – Histocompatibility** *Chairs: Prof Phil Dyer & Mr Nizam Mamode*	
14:15	4 x abstracts	5 x abstracts	4 x abstracts	
	Great Hall			
	Ethics Symposium **Religion and Organ Donation: Beliefs and Misconceptions** *Chair: Prof Genevra Richardson*			
15:00	Welcome and Introduction *Dr Antonia Cronin*			
15:05	Organ Donation Taskforce: faith work stream findings *Prof Gurch Randhawa*			
15:25	Organ Donation Campaign: key findings and action plan *Ms Komal Adris*			
15:45	Panel Discussion *Ms Komal Adris (Director Organ Donor Campaign), Prof David Katz (University College London, Board of Deputies of British Jews)* *Rev Dr Brendan McCarthy (Church of England's National Adviser on Medical Ethics and Health and Social Care Policy)* *Dr Indarjit Singh – Director, Network of Sikh Organisations* *Dr. Shuja Shafi. Shuja - chair of the Health and Medical Committee, the Muslim Council of Britain* *Prof Janet Radcliffe-Richards – Prof of Practical Philosophy, University of Oxford.*			
16:30	*Coffee*			
17:00	**Hoffenberg Memorial Lecture** *Introduction & Chair: Prof Robert Sells* **The Current Ethical Landscape of Transplantation** *Prof Sir Ian Kennedy*			
20.00	*Gala Dinner & The Floe*			

Friday 19 March

	Great Hall	Small Hall	Council Chamber	Committee Room 1
		Course 1.3: Transplantation Surgery Masterclass **Implantation / Post Transplant** *Chair: Mr Vassilios Papalois*	**Course 2.3: Immunosuppression: a users guide** *Chair: Dr Adam McLean*	**Course 3.3: Histocompatibility & Immunogenetics for the Physician and Surgeon** *Chair: Dr Sue Fuggle*
08:00	**Annual General Meeting**	Kidney: *Mr Geoff Koffman, Mr John Forsythe*	Lecture: Induction therapies Workshop/coffee: New & emerging therapies: *Dr Adam McLean* Lecture: Tolerance inducing regimes in human solid organ transplantation: *Dr Alan Salama*	Crossmatching *Dr Sue Fuggle & Dr Craig Taylor*
08:20		Pancreas: *Mr Murat Akyol, Prof David Sutherland*		
08:40		Liver: *Mr David Mayer, Prof Xavier Rogiers*		
09:00		Panel discussion/summary		
09:30	**What's Hot; What's New** *Chairs: Mr Chris Watson & Dr Rachel Hilton*			
09:30	Scientific *Prof Graham Lord*			
10:00	Clinical *Dr Richard Baker*			
10:30	BTS Astellas Clinical Research Fellow *Dr Sarah de Freitas*			
10:45	*Coffee*			

	Great Hall		Council Chamber
	NHSBT ODT Session *Chairs: Mr Nizam Mamode & Dr Peter Rowe*		**Basic Science** *Chairs: Ms Lorna Marson & Dr Eleanor Bolton*
11:15	Overview of activity and allocation in organ transplantation *Prof James Neuberger*	11:15	Anaphylatoxins: the salt and pepper of the immune response *Prof Steven Sacks*
11:30	Factors influencing waiting time to kidney transplant for paediatric patients *Mrs Rachel Johnson*	11:45	Improving on nature: antibody engineering *Prof Andrew George*
11:40	Does the 50% five-year transplant survival rule ensure a balance between the number of donor livers available and number of recipients? *Mrs Kerri Barber*	12:15	4 x abstracts
11:50	Pancreas transplantation: A UK and US comparison *Mr Alex Hudson*		
12:00	Incidence and outcome of short-term ventricular assist device support for early cardiac allograft failure *Mrs Helen Thomas*		
12:10	Eye donation from solid organ donors *Mr Mark Jones*		

12:20	Factors influencing long-term outcome of kidney transplantation *Mrs Rachel Johnson*		
12:30	Reporting on Donation Activity *Mrs Claire Counter*		
12:40	Variation between centre outcomes *Mrs Sue Madden*		
13:00	*Lunch/Exhibition*		

	Small Hall		**Council Chamber**
	Chapter of Surgeons Symposium		**BSHI Symposium: Desensitisation** *Chairs: Prof David Taube & Dr Paul Sinnott*
14:00	Welcome *Prof Derek Manas*		
	Session on service provision and training	14:00	HLA antibody incompatible transplantation: What should we be doing in 2010? *Prof Mark Stegall*
14:05	Opening Remarks *Mr Peter Veitch*		
14:15	How to runs a NORS and be EWTD compliant, Rep from BMA (tbc)	14:30	ABO incompatible transplantation: What should we be doing in 2010? *Dr Jack Galliford*
14:30	How are we going to train all the juniors under NORS? *Mr John Asher (Carrel Club)*		
14:45	Discussion	15:00	Domino and pooled live donor kidney transplantation: an effective replacement of the desensitization programmes *Prof Andrew Bradley*
15:05	A harrowing tale "Securing the fate of the donor before surgery commences": Emotional insights from a failed donor nephrectomy- *Mr. Thomas Lee*		
15:25	Clinical scenario session *Chair Mr Nizam Mamode* Presenter Responder Liver case: *Mr Murat Akyol & Mr Gavin Pettigrew* Kidney case: *Mr Afshin Tavakoli & Mr Geoff Koffman* Pancreas case: *Mr Sanjay Sinha & Mr Neil Parrott*	15:30	Panel Discussion: How do we get there? *Prof Mark Stegall, Dr Jack Galliford, Dr Rob Higgins, Dr Susan Fuggle, Prof Andrew Bradley*
16:00	*Congress Ends*		

Acknowledgements

A formal thank you to the West London Renal and Transplant Centre Local Organising Committee, chaired by Mr Vassilios Papalois and Prof Anthony Warrens, and the BTS Congress Organising Committee, Mr Chris Watson (chair), Mr Vassilios Papalois, Prof Anthony Warrens, Ms Lorna Marson, Dr Chris Dudley and Mr Keith Rigg.

The Symposia on Tuesday 16 March have been organised by Mr Vassilios Papalois, Prof Derek Manas, Ms Lorna Marson and Prof Marlene Rose. The training courses each morning of the congress have been organised by Mr Vassilios Papalois, Dr Adam McLean and Prof Anthony Warrens.

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

Clinical
Dr Richard Baker
Mr Nizam Mamode
Dr Adam McLean
Mr Nadey Hakim
Mr Murat Akyol
Dr Nick Torpey
Dr Menna Clatworthy

Laboratory
Ms Lorna Marson
Prof Marlene Rose
Prof John Kirby
Dr Eleanor Bolton
Prof Andrew George

Coordinator/Nursing
Ms Jane Smith
Ms Lisa Burnapp
Ms Liz Waite
Ms Gill Matthews

H &I
Prof Phil Dyer
Dr Paul Sinnott
Dr Sue Fuggle
Prof Anthony Warrens
Dr Craig Taylor
Dr Robert Vaughan

Ethics
Dr Antonia Cronin
Mr Vassilios Papalois
Dr Peter Rowe
Ms Laura Buist
Prof John Dark

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

Astellas	Lunchtime Symposia Conference Lanyards
Novartis	Lunchtime Symposia
Roche	Lunchtime Symposia
Wyeth/Pfizer	Lunchtime Symposia

The British Transplantation Society

Company and Charity Annual General Meeting

Friday 19 March 2010 08:00 to 09:30hrs

Great Hall, Kensington Town Hall, London.

1. Welcome
2. Apologies
3. Minutes of AGM on 24th April 2009, Liverpool Conference Centre, Liverpool (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. 13th Annual Congress
9. Any other business
10. Next meeting: Friday 11th March 2011, Bournemouth Conference Centre
11. Closure of meeting

By order of the Board of Directors

Date 8th February 2010

BRITISH TRANSPLANTATION SOCIETY

Minutes of the Annual General Meeting - *Reg. Charity 1098584 & Reg. Company 4691176*

Friday 24th April 2009 at 08.30, Hall 1, Arena & Convention Centre, Liverpool

1.0) PF welcomed the members present to the Annual General Meeting.

2.0) No apologies had been received. 43 members were in attendance.

3.0) The minutes from the last AGM of the charity held on 18th April 2008 at the SECC were approved and accepted as a true record of the meeting.

4.0) President's Report

4.1) ESOT 2011
The meeting will be held in Glasgow. The Executive Organising committee has ben created and a general conference organising committee is being developed. The co chairs from the BTS are Alan Jardine & John Forsythe.

4.2) RCS/BTS Post CCT Transplant Fellowships
The Department of Health has agreed to fund a number of Post CCT Transplant Fellowships. Fourteen posts have been advertised, located at several major transplant hospitals throughout England. Three posts in paediatric liver transplantation, three in laparoscopic donor nephrectomy and eight in abdominal multi organ retrieval. Current funding is for one year but it is hoped that the scheme will be renewed at the end of the first year.

4.3) Retiring Members of Council
Nizam Mamode, Colin Short, Nick Jones and Jacqui Spencer have all served their term on council, and thanks were given to their commitment. Chris Watson, General Secretary is also retiring from this post however is taking the position of Vice President, thanks was also given for all his hard work.

4.4) Bill Hoffenberg Memorial Lecture
A substantial grant has been received to support an annual Bioethics Lecture, in memory of Bill Hoffenberg. The council have met with Robert Sells and will come to a decision as to whether this should be held within the Congress or as a stand alone meeting.

5.0) Vice President's Report

5.1) Congress strategy
KR presented the future congress strategy. It has been decided to fix the meetings for the next 6 years with alternate Northern and Southern venues, with a central organising committee. After looking at 27 venues, and visiting 14, the following venues have been negotiated on a fixed price:

- 9-11 March 2011, 13-15 March 2013, 11-13 March 2015, Bournemouth International Centre.
- 22-24 February 2012, 26-28 February 2014, 24-26 February 2016, SECC, Glasgow

5.2) BTS Website

The Council agreed that communication needed to be improved internally & externally. Luke Devey was appointed as public engagement/web developer for the BTS. The website will incorporate a public area and a member only area, with a go live date in May. A flyer will be sent to all members when this is launched.

6.0) General Secretary's Report

6.1) Elections

603 voting codes were distributed with 206 votes cast. More online votes were received this year than last year but not as many as paper votes in 2007. As a result of this the following positions have been filled:

General Secretary - Chris Dudley

Councillor without portfolio – Richard Baker

Councillor representing coordination and transplant nursing – Jane Smith

Councillor representing transplantation surgery – Nizam Mamode

Councillor representing cardiothoracic transplantation – John Dark

Elected unopposed:

Vice President - Chris Watson

Member of the standards committee – Peter Andrews

Member of the transplant training & education committee - Susana Fernandez

Co-opted:

Councillor representing basic science – Marlene Rose

6.2) A list of new members was presented at the AGM. There were no objections to the proposed names.

6.3) Congress Abstracts

A total number of 255 Abstracts were submitted for the congress of which 189 were Clinical, 59 Laboratory and 7 Coordinator.

6.4) Awards, Fellowships and studentships

Roy Calne award – Manuela Carvalho-Gaspar, University of Oxford

Astellas Clinical Training Fellowship – Sarah de Freitas, Guys Hospital

Non Clinical PhD Studentship – Joseph Willett, Newcastle University

Radhika Chadha, University of Oxford

6.5) Rule 11: The Council

The role of the councillor representing Transplant Coordination and Nursing to be split into two roles. Donor Transplant Coordinator and Recipient Co-ordination and nursing. Both of the roles to serve a two year term on the council.

7.0) Treasurer's Report

7.1) The Finances of the Society are currently in good shape. The income over the last two years differs from 2007 mainly due to the loss of sponsorship for international meetings; however the expenditure remains static with more accumulated funds carried forward in 2008 than 2007.

7.2) The Corporate Partnership scheme was reviewed for 2009. There are now 2 levels of partnership. Corporate at a rate of £3K and senior at £25K. The Society currently has 3 senior members and 3 corporate members. Thanks were given to the Pharma companies for their continued support.

7.3) Membership rates will not change for the coming year.

8.0) 13th Annual Congress

Kensington Town Hall, London - 17-19 March 2010

9.0) AOB

There was no other business reported

10.0) Next meeting

Scheduled for Friday 19 March 2010, Kensington Town Hall, London

11.0) The AGM was closed at 09:05am

ABSTRACTS

Best Abstracts

Great Hall

17 March 2010

09:30-10:30

O1

Solving the kidney transplant crisis for minority ethnic groups in the UK: is being transplanted overseas the answer?

Antonia Cronin[1], Rachel Johnson[2], Rhiannon Birch[2], Robert Lechler[3], Gurch Randhawa[4]

[1]School of Law, University of Manchester, Manchester, United Kingdom, [2]NHS Blood and Transplant, Organ Donation and Transplantation Directorate, Bristol, United Kingdom, [3]MRC Centre for Transplantation, Kings' College London, London, United Kingdom, [4]Institute for Health Research, University of Bedfordshire, Bedfordshire, United Kingdom

Background Nearly 1 in 4 UK patients waiting for a kidney transplant are from a minority ethnic group. Organ shortage has prompted patients in need to source organs from overseas. We report a summary of demographic information held on the UK Transplant Registry about UK residents who have travelled overseas to receive a kidney transplant and returned to the UK for follow-up.

Methods Follow-up data were obtained on 210 living donor and 22 deceased donor transplants undertaken overseas between 01 January 2000 and 28 April 2009. Unadjusted (Kaplan-Meier) and risk adjusted (Cox regression modeling) analyses of five-year graft and patient survival, conditional on survival to one year, were carried out.

Findings Transplant recipients overseas were predominantly of South Asian ethnicity (62%). Overseas transplants took place predominantly in Pakistan (49%) and India (20%). 58% of transplants were from living unrelated donors. 28% were from living related donors, most of whom were recorded as cousins. Their mean age was 45·9 years (range 13-83 years, n=245). For those patients who return and are reported, there were significant differences in terms of five-year graft and patient survival ($p<0·01$ for both) for overseas transplants compared with patients transplanted in the UK.

Discussion

Minority ethnic communities appear more likely to travel overseas for a kidney transplant. This is perhaps not surprising, given they are least likely to receive a kidney transplant in the UK due to their greater propensity of kidney failure and shortage of suitable donors. Our analyses demonstrate a statistically significant inferior five-year patient survival and graft outcome in those patients transplanted overseas compared to those transplanted in the UK. It is essential that these patients are fully informed that transplant outcome from organs sourced overseas is significantly inferior and may relate to the quality of the organ transplanted.

O2

UK Registry of Antibody Incompatible Transplantation 2001-2009

Rob Higgins[1], Rachel Johnson[2], Susan Fuggle[2], David Taube[3], Jack Galliford[3], Nizam Mamode[4], Simon Ball[5], Rommel Ravanan[6], Nicholas Torpey[7], Andrew Bradley[2]

[1]University Hospital, Coventry, United Kingdom, [2]ODT, NHS Blood and Transplant, Bristol, United Kingdom, [3]West London Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom, [4]Guy's and St Thomas' Hospital, London, United Kingdom, [5]University Hospital, Birmingham, United Kingdom, [6]Southmead Hospital, Bristol, United Kingdom, [7]Freeman Hospital, Newcastle, United Kingdom

Antibody incompatible renal transplantation (AIT) is now widely practiced, but there remain uncertainties about outcomes. The UK Registry is the first comprehensive national registry for HLA and ABO AIT.

Comprehensive 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.

190 transplants were performed in 14 centres. 11 centres reported 109 HLAi transplants (range per centre 1-58); 9 centres reported 75 ABOi transplants (range per centre 1- 38), and 3 centres performed 6 transplants with simultaneous ABOi and HLAi.

ABO antibodies were removed with plasmapheresis in 76% of cases, antigen-specific absorption in 18%, and 6% had no antibody removal. In HLAi transplantation, 29% of cases had a pre-treatment positive complement dependent cytotoxic crossmatch (CDC), 49% negative CDC but positive flow cytometric crossmatch, 22% DSA detectable only by microbead or other solid phase assay. Centres used different combinations of IVIg and CD20 as well as plasmapheresis.

Three year graft survival (death and graft loss) was calculated on 190 transplants, and was 86 (95% CI 91-74)% in ABOi, 87 (79-93)% in HLAi, compared with 92 (91-93)% for all other living donor transplants, and 84 (83-85)% for all other deceased donor transplants.

In summary, over half the renal transplant units in the UK have performed AIT, and three year graft survival rates were comparable with the results of ‘antibody compatible’ deceased donor transplantation.

O3

5 Years of minimalist immunosuppression with Campath induction and Tacrolimus monotherapy without steroids or MMF in renal transplantation

Ka Kit Edmond Chan, Jack Galliford, Dawn Goodall, Tom DH Cairns, Rawya Charif, Nadey Hakim, Andy Palmer, Vassilios Papalois, Adam McLean, David Taube

Imperial College, London, United Kingdom

Although Campath induction is now widely used in renal transplantation, there are few medium term reports of its use with Tacrolimus [Tac] monotherapy without steroids or MMF.

In this study, we report our 5 yr experience with this minimalist regime.

372 consecutive patients transplanted from Aug 2004 [229m, 143f; mean age 47.0 ± 13.2yrs (1 SD); 179 live donors (LDs), 193 deceased donors (DDs)] received 30 mgs Campath iv, prednisolone for 1 week [60 mg daily for 4 days and 30 mg daily for 3 days] and Tac, 0.1 mg/kg/day [12 hr trough level 5 - 8 ng/L (LCMS)]

87 patients [45m, 42f; age 46.7±14.3 yrs (1 SD); 38 LDs and 49 DDs] receiving our previous immunosuppressive regime acted as historic controls. These patients received Daclizumab induction [2 mg/kg, day 0 and day 14], prednisolone for 1 week [60 mg daily for 4 days and 30 mg daily for 3 days], Tac, 0.15 mg/kg/day, [12 hr trough level 8 - 11 ng/L (LCMS)] and MMF 1.5g/day [12 hr target trough level 1.5 3.0 mg/L]

Rejection was diagnosed by allograft biopsy and treated with iv methyl prednisolone and reinstitution of oral steroids. Mean follow up in the Campath group was 22.1 ± 17.8 mths and 64.4 ± 21.5 mths in the control group

Patient survival at 1, 3 and 5 yrs in the Campath group was 98.9%, 96.7% and 96.9%, compared with 96.3%, 94.6% and 94.6% in the control group. Censored allograft survival was 94.8%, 91.3% and 87.8% at 1, 3 and 5 yrs in the Campath group, and 93.9%, 89.6% and 88.1% in the control group.

The incidence and nature of rejection were similar. Rejection free survival in the Campath group was 83.3%, 73.5% and 73.5% at 1, 3 and 5 yrs; and 94.8%, 78.5% and 75.8% in the control group. 23/69 [33.3%] rejection episodes in the Campath group were antibody mediated [AMR] and 6/20 [30%] rejection episodes were AMR in the control group.

Over 5 yrs, mean MDRD eGFR was 8.8 ml/min/1.73m^2 better in the Campath group [$p<0.001$; 95% ci: (4.8,12.8)]. eGFR at 1, 3 and 5 yrs was 54.8±1.2 vs 48.2±1.7, 51.9±1.8 vs 47.0±1.8 and 51.5±7.6 vs 47.5±1.9 in the Campath and control groups respectively.

NODAT free survival was similar [91.4% vs 96.5%, 86.9% vs 91.1% and 85.4% vs 91.1% at 1, 3 and 5 yrs in the Campath and control group].

This simple combination of Campath induction and Tac monotherapy produces similar medium term outcomes to a conventional immunosuppressive regime with no increase in late rejection and better allograft function

Medical Challenges in the Transplant recipient

Great Hall

11:00-12:30

O4

Comparison of outcomes of transplants from kidneys with small renal tumours, live unrelated transplants and dialysis wait-listed patients.

David Nicol[1,2], Nicholas Brook[4], Norma Gibbons[5], David Johnson[2,3]

[1]Royal Free Hospital, London, United Kingdom, [2]University of Queensland, Brisbane, Australia, [3]Princess Alexandra Hospital, Brisbane, Australia, [4]Queen Elizabeth Hospital, Adelaide, Australia, [5]Hammersmith Hospital, London, United Kingdom

We have previously reported the use of kidneys with small T1 renal tumours as a novel potential donor source for renal transplantation. After radical nephrectomy bench surgery is performed to excise the renal tumour and repair the parenchymal defect. These kidneys can be successfully transplanted into patients who may not otherwise have this opportunity for management of their end stage renal failure. In this study we analysed the outcomes of renal transplant patients (n = 43) who received grafts from donors (n = 41) with small (<3 cm) renal tumours removed before transplantation covering the period from May 1996 to September 2007. Patient and graft survival in this group were compared to the outcomes of conventional live unrelated transplants (LURTs) (n = 120) and to patient survival on the transplant waiting list for those who did not receive a kidney during this period (n = 153). Patients who had been removed from the transplant list due to co-morbidities were not included in the dialysis group. Patient survival at 1, 3 and 5 years were 92%, 88% and 88% for recipients of tumourectomized kidneys, 99%, 97% and 97% for LURTs, and 98%, 92% and 74% for dialysis patients waiting for a deceased donor kidney (log rank score 10.4, P = 0.005). One patient experienced a local tumour recurrence at 9 years following transplantation. This patient declined intervention and is currently under active surveillance. Transplantation of tumourectomized kidneys from patients with small, localized, incidentally detected renal tumours results in similar outcomes to conventional LURTs and confers a significant survival advantage for patients who would otherwise be unable to receive a transplant. The risk of tumour recurrence is extremely low and substantially less than death from co-morbidities in both dialysis and transplant populations.

O5

What are the outcomes for patients returning to dialysis after renal transplant failure in the UK?: Data from the UK Renal Registry

Lynsey Webb[1], Anna Casula[1], Charlie Tomson[1,2], David Ansell[1], Chris Maggs[1,3], Yoav Ben-Shlomo[1,4]

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Background: Around 22,000 patients in the UK have functioning renal transplants, 3% of which fail each year. Patients with established renal failure (ERF) who undergo successful transplantation have an improved quality of life and increased survival compared to those remaining on dialysis. However, there is increasing evidence from North American studies that graft failure is associated with significant mortality, particularly around the time of graft loss. This study is the first large UK study examining patient outcomes following transplant failure.

Patients and methods: Using the UK Renal Registry (UKRR) database, which collects baseline demographics and quarterly clinical data on all patients with ERF in the UK, two patient cohorts were identified. The control group consisted of patients commencing haemodialysis (HD) or peritoneal dialysis (PD) as an initial form of renal replacement therapy (RRT) between 01/01/2000 - 30/09/2008, that were wait-listed for transplantation within two years of starting RRT. Cases were patients commencing HD or PD after transplant failure between 01/01/2000 - 30/09/2008. Patients were followed until death, loss to follow up or the 31/12/2008, and were censored from the relevant cohort if transplanted or retransplanted. From both cohorts, patients were excluded if they were <18 years or had no recorded renal diagnosis. Hazard ratios (HR) and Kaplan-Meier survival were calculated. Cox regression modelling was performed, adjusting for age, sex, ethnicity and diabetic status.

Results: The total study cohort consisted of 11,280 controls and 3,417 cases. The adjusted HR for death within 30 days of starting dialysis post-graft failure was 10.6 (95%CI 4.3-26.1) compared to the control group. This fell to 5.4 (95%CI 3.5-8.4) at 90 days. The adjusted HR for death in the 1st year was 4.5 (95%CI 3.3-6.0) which steadily fell to a HR 1.2 (95%CI 0.3-1.6) at >5 years post-graft failure. For the first 2 years following graft failure, patients commencing on PD have a lower adjusted mortality than those on HD (HR 0.75, p=0.02).

Discussion: The initiation of dialysis following graft loss is associated with significant mortality, most pronounced in the first year after transplant failure. Patients commencing dialysis after graft failure do significantly worse than “fit” (i.e. suitable for transplantation) patients starting dialysis as initial RRT. Patients starting on PD have better outcomes; probably reflecting patient selection bias with fitter patients (fewer co-morbidities) opting for PD. The observation that the period of highest mortality risk is around the time of transplant failure suggests the cause is directly related to complications of graft failure and its management, rather than to underlying comorbidity causing both graft loss and increased mortality. Further analyses of the patient- and centre-level causes of this increased mortality risk are required, to inform the future development of risk-reduction strategies.

O6

Predicting Impending Hyperglycaemia in Normoglycaemic Renal Transplant Recipients

Adnan Sharif[1], Vinod Ravindran[2], Gareth Dunseath[3], Steve Luzio[3], David Owens[3], Keshwar Baboolal[2]

[1]Queen Elizabeth Hospital, Birmingham, United Kingdom, [2]University Hospital of Wales, Cardiff, United Kingdom, [3]Diabetes Research Institute, Penarth, United Kingdom

Introduction. Transplant-associated hyperglycaemia is a significant complication of solid-organ transplantation, with associated adverse patient and graft outcomes. The product of insulin secretion and sensitivity, termed the disposition index, is a mathematical constant in normoglycaemia. Declining disposition index implies a defect to these physiological components and anticipates impending hyperglycaemia. It would be valuable to detect the disposition index simply and non-invasively post-transplantation with fasting blood sampling. We explored the utility of a surrogate disposition index post-transplantation by three methods: physiological correlation, demonstration of a mathematical hyperbola and robustness across a heterogeneous group of renal transplant recipients.

Methods. First-phase insulin secretion and sensitivity was determined by mathematical minimal model analysis of 58 frequently sampled, intravenous glucose tolerance tests in 58 non-diabetic renal transplant recipients and correlated against surrogate indexes based on fasting blood samples. Insulin secretion indexes were validated against first-phase insulin secretion (validation of insulin resistance indexes has been previously performed). Products of insulin secretion/resistance indexes were then correlated against calculated disposition index, properly weighted regression analysis performed to ensure hyperbolic compatibility, auto-correlation studies conducted (against a duplicate set of metabolic investigations in 20 renal transplant recipients) and finally surrogates were tested in various sub-groups of renal transplant recipients to ensure robustness in a heterogeneous group.

Results. Insulin secretion surrogates correlated well with first-phase insulin secretion: fasting insulin/glucose ratio ($r = 0.501$, $p < 0.001$) and $HOMA_{sec}$ ($r = 0.586$, $p < 0.001$). From all evaluated surrogate products of insulin secretion and resistance, the best correlation was achieved with 'HOMAsec (first-phase insulin secretion) x McAuley's index (insulin resistance)' ($r = 0.594$, $p < 0.001$). Regression analysis was consistent with a mathematical hyperbola (ln HOMAsec vs. ln McAuley's index, $r = -0.639$ [95% CI -1.772 to -0.950]), statistical auto-correlation was excluded (by cross-analysing with the duplicate metabolic set) and the surrogate remained valid in different subgroups of transplant recipients.

Conclusion. Our surrogate 'HOMAsec x McAuley's index', which requires only fasting glucose, insulin and triglyceride measurements, is a simple and non-invasive surrogate for the disposition index. Its predictive utility for identifying impending hyperglycaemia post-transplantation should be investigated further to ascertain whether its experimental nature can translate to clinical validity.

O7

Mortality in Pancreas Transplantation: Is Surgery a High Risk Strategy for Severe Diabetics?

David van Dellen, Judith Worthington, Maria Mitu-Pretorian, Stephanie Trevelyan, Sarah Heap, Bence Forgacs, Abbas Ghazanfar, Babatunde Campbell, Ravi Pararajasingam, Hany Riad, Neil Parrott, Titus Augustine, Afshin Tavakoli

Manchester Institute of Nephrology and Transplantation, Manchester, United Kingdom

Background: Pancreas transplantation has evolved and in the 21st century successful transplantation in complicated Insulin Dependent Diabetes Mellitus (IDDM), is effective, improves quality of life, stabilises diabetic complications and increases longevity when compared to other modalities including the insulin pump. There is however a published associated mortality rate of 5-8% associated with the procedure. There is significant reticence among clinicians to refer suitable candidates of transplantation due to a perceived poor outcomes especially mortality for patients undergoing the procedure especially from the initial era. However, this cohort of patients undergoes transplantation whilst having significant co-morbidity, particularly cardiovascular impairment. IDDM per se may result in a high mortality rate even without the intervention of a transplant. We aimed to establish the mortality rates of patients on our waiting list compared to the rates after transplantation.

Methods: A retrospective analysis was carried out of all patients undergoing pancreas transplantation in our unit since the initiation of the programme in 2001 (SPK=148, PAK=33, PTA=11). This group was compared with the control group of patients accepted onto the waiting list for transplantation over the same period. The primary endpoint was patient mortality. In addition, risk factors such as medical history, diabetic complications, insulin requirements, age, type of transplant and waiting time were analysed.

Results: Mortality on the waiting list for those not transplanted over the study period was 30% (36/119) compared to a mortality of 9% (19/193) post-transplantation; ($p<0.001$) (8%(16/193) one year mortality). There were no differences between the two groups in terms of cardiological risk factors (mean ejection fraction >60%; myoview and echo results equivalent in both groups); duration of IDDM (21 and 24 years respectively; $p=0.26$) or dialysis requirements in those with nephropathy (26 and 23 months respectively; $p=0.73$.) Similarly there was no difference between age of death after surgery compared to age of death on the waiting list (46.7 vs. 43.7 respectively; $p=0.31$). There was also no difference in mean time from listing to death in the group with and without surgery (537 and 582 days respectively; $p=0.79$). However, there was a shorter median survival from listing in younger patients (<50) compared to older patients (525 vs. 933 days; $p<0.0001$.).

Conclusion: Mortality from pancreas transplantation whilst seemingly high, is far less compared to the mortality of patients awaiting pancreas transplantation ($p<0.001$). The cohort of patients who appear suitable to be listed for pancreatic transplantation are a hazardous group with a high mortality risk even in the absence of surgery, particularly in young patients with aggressive disease. Pancreas transplantation offers a protective effect both against mortality and for risk factor control, despite the concomitant risks of surgery and immunosuppression associated with transplantation. The risk of death from not having a pancreas transplant outweighs transplantation. In selected patients pancreas transplantation could be considered the benchmark treatment modality of IDDM.

Solitary Pancreas & Live Donor Liver Transplantation

Small Hall

11:00-12:30

O8

Pancreas allograft thrombosis in NHB and HB donor grafts: Incidence of venous vs. arterial thrombus & use of TEG-directed anticoagulation

Sushma Shankar[1,2], Anand Muthuswamy[2], Murali Somasundaram[2], Mohammed Rahman[2], Jens Brockmann[2], Sanjay Sinha[2], Anil Vaidya[2], Peter Friend[1,2]

[1]Nuffield Department of Surgery, Oxford University, Oxford, United Kingdom, [2]Oxford Transplant Centre, Oxford, United Kingdom

Background: Vascular thrombosis is the leading non-immunological cause of early pancreas graft loss. The pathogenesis of venous and arterial thrombus and measures to reduce incidence are thought be different. It is not known whether the incidence and pathogenesis of venous and arterial thrombus varies between Heart-beating-Donor (HBD) and Non-Heart-beating-Donor (NHBD) pancreas grafts. Thromboelastography (TEG) has been shown to predict hypercoagulability in a low-flow state. Previous data have supported the use of TEG directed anticoagulation in HBD pancreas recipients to reduce incidence of venous thrombus; its effectiveness has not been studied in NHBD recipients. **Methods:** From April 2004 to December 2009, 306 pancreas transplants were performed at the Oxford Transplant Centre (HBD n=272; NHBD n=34). All recipients received TEG directed anticoagulation with Dextran-40, aspirin and subcutaneous heparin in the post-operative period, and underwent post-operative duplex or MRI imaging as per protocol to exclude thrombus. These were retrospectively analysed for presence of venous and/or arterial thrombus (both partial and complete) within the 1st 28 days post-transplant. TEG Coagulation Index (CI) at time of thrombosis was noted. Recipients demonstrating no thrombus on imaging within 28 days post-transplant served as control for both HBD and NHBD groups. **Results:** Within the HBD group, 6.6% (n=18) recipients had venous and/or arterial thrombi on imaging, compared to 17.7% (n=6) recipients within the NHBD group. 0.4% (n=1) of HBD grafts and 8.8% (n=3) of NHBD grafts were lost to thrombosis ($p<0.05$). 4.8% (n=13) of HBD recipients had a venous thrombus component, compared to 11.8% (n=4) of NHBD recipients; 4.4% (n=12) of HBD grafts had venous thrombus only, compared to 2.9% (n=1) NHBD. Incidence of arterial thrombus was significantly higher in NHBD grafts with thrombus compared to HBD grafts (HBD 33.3%, NHBD 83.3%, $p<0.05$). Mean TEG CI in HBD recipients at time of venous thrombus was significantly higher than mean CI within HBD control ($p<0.05$) supporting previously reported association with hypercoagulability. However, mean TEG CI in NHBD recipients at time of venous thrombosis, was no different (-2.2 ±4.6) in comparison to NHBD control (-3.92 ±5.3). Median time to thrombosis from transplant was 4 days (range 1-17) in HBD and 3 days (range 1-24) in NHBD. There was no significant difference in cold ischemia between thrombus sub-groups in either HBD or NHBD populations. Transplant sub-groups (SPK/PTA/PAK/PASPK) with thrombus could not be stratified due to small numbers. **Conclusion:** HBD pancreatic grafts with venous thrombosis are associated with hypercoagulability within the first 28 days post-transplant, unlike the case in NHBD grafts. These findings support use of TEG in directing anticoagulation in HBD recipients. NHBD grafts with thrombus have significantly higher incidence of arterial thrombus compared to HBD pancreatic grafts and significantly higher incidence of graft loss. This suggests that the pathogenesis of thrombosis is highly likely to be different in NHBD compared to HBD grafts.

O9

Isolated Pancreas Transplants from Non-heart Beating Donors: the Oxford Experience

Anand Sivaprakash Rathnasamy Muthusamy[1], Murali Somasundaram[1], Anna Rizzello[1], Joseph Hughes[1], Mohammed Rahman[1], Helen Sansom[1], Jens Brockmann[1,2], Sanjay Sinha[1], Anil Vaidya[1], Peter Friend[1,2]

[1]Oxford Transplant Centre, Oxford, UK, [2]University of Oxford, Oxford, UK

Introduction: The comparative outcomes of pancreas only transplant (PA, including PAK and PTA) from non-heart beating donors NHBD and heart-beating donors HBD are unknown. This article summarizes a single-centre experience with these two cohorts.

Methods: From August '04 to October '09, 81 PA were performed, 53 from HBD and 28 from NHBD. NHBD pancreases were accepted based on donor age <50 years, BMI <32, and time to cardiac arrest from withdrawal <1 hour. UW solution was used in all cases, preceded by in-situ streptokinase pre-flush in 7 NHBD PA. All grafts had enteric exocrine and caval venous drainage. All patients received Campath induction and steroid-free maintenance with Tacrolimus & MMF. PA outcome was evaluated as incidence of graft, patient survival and complications.

Results: There were 31 PAK & 22 PTA from HBD; 15 PAK & 13 PTA from NHBD. Both groups had 15-month median follow up. Mean recipient age in HBD (43±7 years) was similar to NHBD (44±8 years). Recipient BMI was lower in HBD (25±4 vs. 26±3, $p<0.05$) than NHBD. Donor age (35±12 yrs vs. 31±11yrs, p=NS), donor BMI (23±3vs.23±3), cold ischemia duration (710±194mins vs. 764±143mins, p=NS), hospital stay (16±10vs.14±7 days) was similar in both groups. HBD & NHBD recipients had similar re-admissions (26% vs.21%) and re-operations (26% vs. 39%, p=ns). Overall pancreas graft (81% vs. 69%, p=0.1) and patient survival (98% vs. 96%, P=NS) was similar. HBD and NHBD PAK graft survival was similar (71% vs. 67%). Early graft loss due to thrombosis (11% vs. 0%, p=0.03) and pancreatitis (8% vs. 0%, p=0.1) in NHBD grafts resulted in inferior NHBD PTA outcome (69% vs. 96%, p=0.02). All NHBD grafts procured with streptokinase pre-flush are functioning to date. Primary non-function of the pancreas occurred in 3.5% (vs.0%) in NHBD. Delayed graft function of pancreas occurred more frequently in NHBD (18% vs. 2%, p=0.02). HBD pancreas graft recipients were more frequently treated for rejection (26% vs. 7%, p=0.03) and had majority of grafts lost to chronic rejection (17% vs. 7%, p=ns). One NHBD PAK recipient developed EBV associated PTLD treated successfully by immunosuppression reduction. Overall bacterial (4% vs. 3.5%), viral (4% vs. 3.5%) and fungal infection (2% vs. 0%) was similar.

Conclusions: Early graft loss in NHBD PTx is primarily due to perfusion related issues (thrombosis & pancreatitis). Role of thrombolytic pre-flush in avoiding early graft loss needs investigation. Immunological PAK losses emphasize difficulty in monitoring enterically drained pancreases.

O10

Liver Transplantation for Unresectable hepatocellular carcinoma in normal livers: Report from the European Liver Transplant Registry

H. Mergental[1,18], R. Adam[2], K. Hockerstedt[3], B.G. Ericzon[4], P. Kalicinski[5], F. Muhlbacher[6], J.L. Klempnauer[7], Ch. Broelsch[8], S. Friman[9], G. Mantion[10], C.F. Sellez[11], B. van Hoek[12], J. Fangmann[13], J. Pirenne[14], P. Muiesan[15], A. Koningsrider[16], D. Mirza[17], R.J. Porte[18]

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Background: Occurrence of hepatocellular carcinoma (HCC) within a non-cirrhotic and non-fibrotic liver (NC-HCC) is less frequent compared to cirrhotic livers. Patients with NC-HCC are usually healthy and free of symptoms, resulting in late tumour detection. Another group of patients suffer from intrahepatic NC-HCC recurrence after previous partial liver resection when another resection may be feasible. Historically it has been suggested that absence of cirrhosis was associated with poor outcome and regarded as a relative contraindication for liver transplantation (LT). We performed a multi-center survey to assess outcome of liver transplantation for NC-HCC.

Methods: Using the European Liver Transplant Registry (ELTR), we identified 109 patients transplanted for unresectable NC-HCC between January 1, 1994 and December 31, 2005. Detailed information about patient and tumor characteristics and posttransplant outcome was obtained by contacting the individual transplant centers. Predictors of outcome were identified using univariate Kaplan-Meier analysis with log-rank test and multivariate by Cox regression analysis.

Results: Of the 109 patients, 47 (43%) were male. Mean (range) age at time of LT was 38.9 (4-68) years. LT was the initial treatment in 65 patients (primary-LT group) and a rescue therapy for intrahepatic tumor recurrence in 44 patients (rescue-LT group). The median (range) of tumor size was 8 (0.5-30) cm for whole population, respective 12 (3-30) cm for prim-LT and 3.2 (0.5-12) cm for rescue-LT groups; $p<0.001$. The 5-year patient survival was 48%, respectively 43% for primary-LT and 58% for rescue-LT groups, $p=0.124$. The following variables correlated significantly with impaired 5-year survival: more than 4 tumor nodules (36% vs. 57%, $p=0.010$), macrovascular tumor invasion (15% vs. 54%, $p=0.005$), lymph node involvement (17% vs. 53%, $p=0.019$), transfusion of more than 6 units of red blood cells during LT (31% vs. 62%, $p=0.009$) age above 40 years (39% vs. 54%, $p=0.050$), in rescue-LT group it was also interval of less than 12 months between the initial liver resection and LT (22% vs. 71% $p=0.010$) and there was certain tendency for tumors larger than 8 cm (33% vs. 64%, $p=0.058$). Contrary, for primary-LT group there was not observed any tumor size limit predicting better posttransplant outcome. Multivariate analysis identified increased peroperative blood transfusion requirements (hazard ratio (HR) 2.18, 95% confidence interval (CI) 1.13 - 4.20, $p=0.02$) and macrovascular tumor invasion (HR 2.65, 95% CI 1.29 - 5.44, $p=0.008$) independent risk factors reducing 5-year survival.

Conclusion: The reported data indicate that LT may be a life-saving treatment option in a selected group of patients reaching 5-year survival rates of 50-70%. In contrast to HCC in cirrhotic livers, tumor size is not a predictor of posttransplant survival in patients when LT represent a primary treatment.

O11

1993-2009: Outcomes after intestinal transplantation – the Birmingham experience

Thomas Gelas, Girish L Gupte, Sharif Khalid, David Mayer, Jean deville De Goyet, Alaister Millar, Paolo Muiesan, Jane Hartley, Christophe Chardot, Deirdre A Kelly, Susan V Beath, Darius F Mirza

Birmingham Children's Hospital, Birmingham, United Kingdom

Late referral and deaths on waiting lists & post- transplant in our initial experience led to strategic changes to our ITx programme at the following timepoints: 1998 en-bloc combined reduced liver and bowel transplant (en-bloc rLSBTx); 2001 staged abdominal closure(SAC); 2002 dacluzimab / basiliximab as induction agent; 2005 modification of donor allocation criteria for ITx

Methods: Retrospective review of Liver Unit database to identify and report on the following variables in the 4 eras (’93-97;’98-01; ‘01-04; ‘05-09): number of children assessed, transplants performed, deaths on waiting list, type of transplant, survival.

Results: The strategy of SAC and en-bloc rCLSBTx has resulted in decrease in the number of children dying on the waiting list and more children <12 kg being transplanted. The use of basiliximab has not contributed to reduction in the incidence of rejection. Treatment of rejection has resulted in increased incidence of opportunistic infections. With the availability of EBV PCR monitoring, no mortality has been observed following PTLD due to early detection. Chronic rejection is associated with poor survival following re-transplantation. Haemolytic anaemia needs early recognition and aggressive treatment.

	1993-1997	1998-2001	2002-2004	2005-2009
No of children assessed	47	69	67	108
No of children with deaths on waiting list	10	3	9	17
No of ITx	4	17	9	31
Median weight at transplant in kg (range)	12.85 (10.2-21)	9.36 (8.8-34.8)	20.8 (7.1-52)	11 (5.7-53)
Number of combined liver ITx: isolated iTx	2:2	14:3	7:2	24:7
No of transplants in children <12kg	0	11	2	16
En-bloc rLSBTx	0	11	3	14
Staged abdominal closure (SAC)	0	2	3	18
Moderate - service rejection	1	1	2	9
Severe viral infections	1	2	1	15
EBV viraemia (PTLD)	1(1)	10(5)	7(1)	12(3)
Chronic rejection (deaths)	0	2(1)	2(2)	0
Hemolytic anaemia (alive)	0	0	0	5(3)
Survival	0%	0%	44%	70%

Conclusion: Combination of innovative surgical, medical strategies with increasing experience has contributed to 100 % survival in primary isolated ITx group (last 4 years) and overall survival of 70%. Early referral to ITx programme in future might lead to more isolated ITx being performed with improved prospects of survival in long-term.

Basic Science:
B Cells

Council Chamber

11:00-12:30

O12

Tertiary lymphoid organs in renal allografts can be associated with donor specific tolerance rather than rejection

Kathryn Brown, Steven Sacks, Wilson Wong

King's College London School of Medicine at Guy's, King's and St Thomas' Hospitals, London, UK

Tertiary lymphoid organs (TLO) are found at sites of chronic inflammation and can participate in the immune response similarly to secondary lymphoid organs. Thus far, their presence has invariably been associated with detrimental outcomes. In organ transplantation, there is a dynamic immune response similar to chronic inflammation. Indeed, the presence of TLO has been associated with chronic rejection. The main function of lymphoid organs is to amplify the immune response: in addition to a destructive alloimmune response, secondary lymphoid organs are also important in tolerance to antigens. We hypothesised that TLO may also form during tolerance as the tolerance process requires an active immune response. If so, their presence may enhance tolerance, resulting in better graft function, rather than chronic rejection.

DBA/2 kidneys were transplanted into C57BL/6 mice. Graft outcome in this model is either acute rejection (20%), chronic rejection (40%), or tolerance (40%). Kidneys harvested 14 days and beyond post transplantation contained lymphocytic infiltrates organised into clusters, with well-defined margins, unlike the diffuse infiltrate seen during acute rejection. Staining for PNAd revealed high endothelial venule formation (up to 0.48 ± 0.16 positive vessels per medium power field, mpf), a feature of tertiary lymphoid organs; and lymphatic neogenesis (up to 8.61 ± 1.94 positive vessels per mpf) also occurred in these allografts. The clusters of cells contained T cells, B cells, macrophages, dendritic cells, and $Foxp3^+$ regulatory T cells, with some segregation between T and B cell areas. This suggests that the cell clusters were TLO.

Correlation of the area of TLO within a kidney allograft, and its function as measured by blood urea nitrogen, revealed a significant association between large TLO and superior graft function ($r^2=0.3435$, $p=0.0106$). There were also significant correlations between the percentage of all the above cell types outside the TLO and graft function, with a high percentage of cells outside the TLO associated with poor graft function. For example, total $CD11c^+$ cell numbers did not correlate with graft function, although surprisingly there was a trend towards lower numbers being associated with poor graft function. However, a high percentage of $CD11c^+$ cells outwith TLO was found to correlate significantly with poor graft function ($r^2=0.66$, $p=0.0013$).

The ability of TLO to act as a site of antigen presentation was suggested by the presence of both intact donor MHC class II molecules, and recipient MHC class II molecules presenting donor peptides (2.26 ± 1 cells per hpf), within TLO. This indicates that TLO can act as a site of both direct and indirect allorecognition.

Formation of TLO and the presence of immune cells within them is associated with superior graft function in this model, suggesting that tertiary lymphoid organs can support a tolerant and beneficial immune response as well as the previously described destructive alloimmunity.

O13

A Novel Mechanism for Alloantibody Production.

Ines Harper, Tom Conlon, Chris Callaghan, Kourosh Saeb-Parsy, Eleanor Bolton, Andrew Bradley, Gavin Pettigrew

Department of Surgery, Cambridge, United Kingdom

Introduction

Donor CD4 T cells can provide help to recipient B cells through allorecognition of surface MHC II (Win TS et al 2009). Irrespective of BCR specificity, all B cells theoretically receive equivalent help, yet only autoantibody is produced 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.

Results

Upon injection of bm12 CD4 T cells into TCRKO mice, graft-versus-host (GVH) allorecognition of the disparate I-A^b MHC II on recipient B cells provoked strong autoantibody responses, but anti-OVA responses did not occur unless mice were immunized simultaneously with OVA. 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; in contrast injection with WT bm12 cells generated autoantibody only.

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 did not produce anti-K^d antibody. Self tolerance does not, nevertheless, prevent alloantibody-mediated destruction, because whereas bm12 CD4 T cells survived indefinitely in B6 TCRKO hosts, the development of anti-K^d alloantibody coincided with disappearance of bm12K^d CD4 T cells.

Interestingly, injection of BALB/c x bm12 F1 CD4 T cells into TCRKO B6 mice generated neither auto- nor alloantibody. This presumably reflects NK cell recognition and early killing of the more disparate F1 cells, because they were undetectable one week after injection into B6 $RAG^{-/-}$ mice, while bm12 and bm12K^d cells survived indefinitely.

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 the allo- and auto-antibody responses described recently in these patients.

O14

NKT cells play contrasting roles in the immune response to heart and skin allografts

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Background: NKT cells have been shown to rapidly produce a plethora of cytokines following activation, which can facilitate both immunity and tolerance, depending on the context of activation. However, whether specific activation of NKT cells with glycolipid ligands is beneficial or detrimental to tolerance to allografts remains largely unknown. To this end, we investigated the impact of glycolipids agonists on rejection and tolerance induction to fully MHC mismatched skin and heart allografts in wild-type (WT) and $NKT^{-/-}$ mice.

Results: Rejection of skin and cardiac allografts was identical in WT and $NKT^{-/-}$ mice. However, specific activation of NKT cells with glycolipid was found to significantly extend heart allograft survival (median survival time (MST) of 13 days with glycolipid compared to 7 days without) but surprisingly increased the rate of skin allograft rejection (MST of 10 days with and 15 days without glycolipid). This differential impact of NKT cell activation on alloimmunity was also found without the use of exogenous glycolipids. Costimulatory molecule blockade was found to result in a modest increase in skin allograft survival in WT recipients (median survival time (MST) of 32 days compared to an MST of 15 days for control rate rejection). However, allograft survival was found to be further extended in $NKT^{-/-}$ recipients (MST of 75 days). In contrast, heart allograft survival induced by costimulatory molecule blockade was reduced in $NKT^{-/-}$ mice compared to in WT mice (MST of 46 versus 60 days, respectively).

Conclusions: These studies show that the activation of NKT cells is beneficial to heart, but detrimental to skin allograft survival. Furthermore, the results suggest that whilst NKT cells may be manipulated to promote graft survival, the type of allograft and the site of NKT activation is critical to acquire the desired NKT response. Preliminary experiments suggest that there are intrinsic differences between lymph node and spleen NKT cells. This may account for these divergent responses, which we believe have important implications for attempts to manipulate NKT cell responses for the eradication of tumours, therapy for autoimmunity, as well as for transplant tolerance.

O15

Single Photon Emission Computed Tomography reveals novel patterns of lymphatic flow following heterotopic cardiac transplantation

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The lymphatic system channels the migration of antigen presenting cells to lymph nodes to initiate an immune response, and also acts as an exit route for activated T cells. Lymphatic vessels are not reconnected during transplantation, despite their importance in the immune process. We have used Single Photon Emission Computed Tomography-CT (SPECT-CT) to visualise the effluence of lymphatics from BL/6 donor hearts in syngeneic recipients 1 or 28 days after transplantation. Donor hearts were injected with Tc-99m labelled Nanocoll to visualise lymphatic flow using a nanoSPECT/CT *in vivo* preclinical imager. This acquired gamma camera images from different angles, allowing tomographic reconstruction of a 3-D image which is superimposed onto conventional CT images, giving detailed anatomical images of tissues that had taken up the radioactive tracer. Donor hearts were also injected with Evan's blue to allow identification and dissection of recipient lymphoid tissues for biodistribution studies and autoradiography. Heterotopic cardiac transplant in mice is usually performed in the abdomen; lymphatic drainage and antigen trafficking in the peritoneal cavity may result in an atypical immune response. We therefore compared hearts transplanted into the abdomen with those transplanted in the neck.

One day after transplantation of donor hearts in the neck, Tc-99m could be seen at the injection site within the transplanted heart, and at distinct "hot spots" in the surrounding tissue, suggesting that lymph from the donor organ was draining freely through severed ends of lymphatic vessels. At 6 hours after injection, the high intensity areas in the neck had subsided while the 2 "hot spots" on the chest wall intensified, suggesting that lymph from the transplanted organ had flowed out of severed lymphatic vessels and travelled to local draining lymph nodes. Scanning 28 days after transplantation revealed no lymphatic leak but demonstrated lymphatic flow from the donor organ to a deep cervical lymph node which emitted 6 times higher γ radiation than background in biodistribution studies, suggesting that donor lymphatics had reconnected with that of the recipient.

When transplanted into the abdomen, lymphatic leak could be seen into the peritoneal cavity 1 day after transplantation. Surprisingly, Tc-99m activity also migrated from the peritoneal cavity to 3 distinct hot spots in the thoracic cavity, suggesting that lymphatic leakage into the peritoneum flowed towards mediastinal lymph nodes. These nodes emitted 85 times higher γ radiation than background in biodistribution studies. Four weeks after transplantation, lymphatic leaks were no longer seen but lymphatic flow was detected into patches of lymphoid tissue within large and small bowel, which emitted up to 9 times higher γ radiation than background in biodistribution studies, suggesting that donor lymphatics had reconnected with the gut associated lymphoid tissue of the recipient.

Heart transplantation in the abdomen results in lymphatic flow towards colonic lymphoid patches; however, in humans most organs are transplanted extra-peritoneally, resulting in lymphatic drainage towards local lymph nodes. This discrepancy needs to be considered when using heterotopic cardiac transplant as a model of clinical transplantation.

Medawar 1

Great Hall

14:15-15:15

O16

Global Survey Assessing Muslim Attitudes To Organ Donation

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Introduction. There is an ever increasing disparity between the supply and demand of solid organs for transplantation. A complex array of factors influence refusal to donate organs, including religion. Of all religious groups, Muslims are acknowledged as resistant to organ donation despite theological approval from religious scholars and repeated initiatives promoting awareness. It is imperative for healthcare providers to explore Muslim opinion regarding organ donation and to identify these concerns we conducted a global population-based survey to look at this in greater detail. The aim of the project was to identify the causes of Muslim apprehension with regards to organ donation, thus allowing extrapolation into targeted, public health initiatives to increase awareness.

Methods. We conducted an international survey inviting voluntary completion of an anonymous, 41-part survey. No limitations on participation were made. Survey promotion was electronically conducted through Muslim groups/associations/internet forums and by hand distribution in local mosques. For a population target of approximately 1.5 billion, we targeted a completed sample size of 664 to achieve a 5% error margin and 99% confidence interval (assuming 50% response distribution). Logistic regression analysis was performed to assess multivariate associations with organ donation approval.

Results. 812 participants took the survey with 673 full completions (82.9% completion rate). 68.5% of respondents agreed with organ donation, despite only 36.2% believing it was compatible with Islamic belief (only 10.6% were registered organ donors). Only 2.2% of Muslims would categorically refuse an organ transplant if one were required, with the rest either happy to receive (72.8%) or undecided (25.0%). 9.9% of Muslims would prefer organ donation from a fellow Muslim alone, but a disproportionate 24.5% would only want to donate to another Muslim. Predictors for organ donation approval included younger age, lesser degree of self-rated religiosity, awareness of organ shortages, knowing someone with kidney disease/dialysis or respondent having kidney disease/dialysis (all $p < 0.05$). 76.7% of respondents stated advertisement of organ donation issues amongst Muslims was poor. The two biggest reasons cited by Muslims for reluctance to donate organs was interpretation of religious scripture (78.8%) and advice from their local mosque (70.8%).

Conclusions. Significant confusion remains amidst Muslims on the legality surrounding organ donation and this translates into poor donation rates. Due to their influence, failure to engage with religious scholars and mosques will prohibit initiatives to promote organ donation in the Muslim community. The results of this survey should be translated into a targeted and coherent engagement with the Muslim population to encourage organ donation in transplantation programmes for both the developed and developing world.

O17

Allospecific B cells can receive help for generating anti-MHC I alloantibody through acquisition and presentation of additional graft antigens.

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Introduction: Antibody specificity is restricted by the requirement for T cell help delivered through 'linked cognate' recognition of processed target antigen that is presented following BCR internalisation. Here we examine whether allo-MHC class I-specific B cells can receive help for generating anti-MHC class I alloantibody through acquisition and presentation of additional mismatched graft alloantigen.

Methods and Results: As expected, T cell deficient B6 (TCR KO) mice, when reconstituted with K^d-peptide-specific TCR Tg CD4 T cells, mounted strong anti-K^d alloantibody responses to a BALB/c heart graft. Surprisingly, anti-K^d antibody responses also developed when TCR KO mice were reconstituted with either B6 TEa CD4 T cells (that recognise donor IE MHC II peptide) or B6 Mar CD4 T cells (specific for H-Y peptide) and challenged with male BALB/c hearts. No alloantibody was generated when Mar-reconstituted mice received female BALB/c hearts, even when Mar CD4 T cells were activated by simultaneous challenge with male B6 APC, suggesting that help for anti-class I alloantibody responses provided through T cell recognition of an additional alloantigen requires co-expression of both antigens on the same graft cell.

To investigate the hypothesis that alloantigen-specific B cells capture neighbouring donor proteins when internalising target alloantigen and process this for presentation to helper T cells, bone marrow chimeric Mar mice were created that lacked MHC II expression only on B cells. These mice did not develop anti-K^d alloantibody responses to male BALB/c hearts; in contrast strong responses developed in MHC II^{+ve} control mice, confirming that provision of help by T cells that recognise additional alloantigen still requires cognate interaction with B cell MHC II. Next, donor hearts from mosaic B6.K^d/B6.IE mice (created by embryo aggregation of two transgenic strains to contain cells expressing K^d or I-E, but not both) were transplanted into TEa-reconstituted TCRKO mice. Compared to control K^{d+ve}/IE^{+ve} grafts, anti-K^d IgG alloantibody responses were reduced significantly. The residual antibody that developed probably reflects transfer, as demonstrable on flow cytometry, of small amounts of IE and K^d MHC antigens between chimeric cells in mosaic animals.

Finally, to examine whether this unusual mechanism of help for class-switched alloantibody contributes to graft damage, heart grafts were excised and analysed at day 50. Marked areas of scarring and significant vasculopathy (mean luminal stenosis 55%) were present in male BALB/c hearts transplanted into Mar-reconstituted TCR KO recipients, whereas female BALB/c hearts from Mar-reconstituted mice that were additionally challenged with male B6 APC had minimal parenchymal damage and only slight vasculopathy (12%).

Conclusions: Our demonstration, that help for anti-MHC class I effector alloantibody responses can be provided by CD4 T cells that recognise additional mismatched alloantigen, challenges the tenet of 'linked' antigen recognition between the BCR and helper TCR as a critical requirement for T-dependent antibody responses and provides a mechanism to explain how alloantibody specificities diversify after transplantation.

Alloantigen but is dependent upon acquisition and presentation of the additional alloantigen by the class I-specific B cell. This provides a mechanism whereby the generation of T cell reactivity to additional graft antigens late after transplantation could result in alloantibody production.

O18

Pancreas transplantation from non-heart beating donors in the United Kingdom

Anand Sivaprakash Rathnasamy Muthusamy[1], Lisa Mumford[3], Alexander Hudson[3], Jens Brockmann[1,2], Susan Fuggle[1], Sanjay Sinha[1], Anil Vaidya[1], Peter Friend[1,2]

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Purpose: To compare the early results of pancreas transplantation from non-heart beating donors (NHBD) and heart-beating donors (HBD) in the United Kingdom.

Methods: Data were obtained from the UK Transplant Registry on all pancreas transplants performed between 1 January 2006 and 30 November 2009. Of the 735 transplants performed in this period, 649 were from HBD and 86 from (Maastricht category 3 and 4) NHBD. Pancreases were retrieved if donor asystole occurred within 60 minutes of treatment withdrawal. There was no pre-mortem cannulation or pharmacologic intervention. 'No-touch' time varied between 5-10 minutes. In situ perfusion with University of UW solution was carried out via the common iliac artery in most cases. Kaplan-Meier estimates were used to compare 90-day graft and patient survival.

Results: Since 2006 there has been a significant increase of NHBD graft utilization in the UK. NHB donors were younger (median± interquartile range) (27(18-40) yrs vs. 37(24-46), $p<0.01$), had lower BMI (23(20-24) vs. 24(22-26), $p=0.003$), lower serum creatinine (μmol/l), (62(50-82) vs. 76(60-94), $p=0.01$), less cerebrovascular cause of death (27 vs. 59%, $p<0.0001$), but had similar gender, ethnicity and blood group as HBD. NHBD grafts tended to be utilized locally (74 vs. 65%, $p=0.08$) and resulted in more isolated pancreas transplants (PA) (48 vs. 15%, $p<0.0001$). Recipients had similar age, gender, ethnicity, BMI, HLA mismatch, sensitization and waiting time in both groups; NHBD grafts had longer cold ischemia (13h 49min vs. 12h33 min, $p=0.01$). Overall pancreas graft survival was similar in HBD and NHBD (85 vs. 83%, $p=0.5$), with comparable results in SPK (91%, (CI 88-93) vs. 84%(67-92), $p=0.2$) and PA (81%, (CI 70-88) vs. 76%(57-87), $p=0.5$), with more NHBD grafts lost to thrombosis (8% vs. 4%, p=NS). SPK survival was significantly better than PA in both cohorts. Patient survival was comparable (99% vs. 94% in SPK, $p=0.06$), 96% vs. 97% in PA, $p=0.9$).

Discussion: The NHBD cohort utilizes younger donors with lower BMI, less vascular cause of death and better renal function; this is offset by the longer cold-ischemia time despite more local utilization. The outcomes in the NHBD cohort were similar to the HBD grafts. The short follow-up, wide confidence intervals and low numbers limit the ability to draw strong conclusions and to perform robust multivariate analysis.

Conclusions: These early results suggest that carefully selected NHBD are a feasible source of donor pancreases with acceptable graft and patient outcomes. Risk factors determining adverse early outcome need to be identified, to improve these results. Further efforts at reducing cold ischemia time could contribute to improving the early outcomes in the NHBD cohort.

O19

Macrophages mediate the Amelioration of Transplant Associated Injury by the novel Heme Oxygenase-1 inducer Heme Arginate

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Introduction Ischaemia reperfusion injury (IRI) is an important cause of delayed graft function, a negative prognostic factor for renal allograft survival. Heme Oxygenase-1 (HO-1) is reported to improve outcomes in animal models of transplantation. We have demonstrated a capacity for pre-treatment with the novel HO-1 inducer Heme Arginate (HA) to protect in an animal model of renal IRI. It remains to be shown in which cell types HO-1 expression is important and whether HA can provide protection in models of transplantation. Methods *IRI Model* Laparotomy and right nephrectomy followed by non-traumatic clamping of the left renal pedicle for 20 minutes was performed in 6-week-old FvB/FVB-CD11b-DTR mice. Renal function was determined by serum Creatinine at 24h. We compared PBS treated animals with those given 30mg/kg iv HA. Macrophage depletion was induced by administration of 10ng/g Diptheria toxin (DT) ip to CD11b-DTR mice *Transplant model*. After 24h pre-treatment with 30mg/kg iv HA or PBS, kidneys were transplanted from FvB donors into untreated FvB recipients. Recipients were sacrificed 24 hours after surgery and acute tubular necrosis (ATN) scores were determined. Results *IRI model* HA pre-treatment provided both functional (creatinine) and structural protection (ATN score). The serum creatinine rose to 132±44.4µmol/l in controls vs. 78±24.3 µmol/l in HA treated animals (n=8, $p<0.05$, Normal mouse creatinine ~50µmol/l). HA pre-treated animals also exhibited reduced ATN (69.6±10.2% in control mice vs. 36.5±7.8 % in HA pre-treated animals, n=8 vs. n=5, $p<0.05$). Interestingly, this protection was associated with significant numbers of HO-1 positive macrophages (Mϕ) at the site of maximal injury. The renal tubules at this anatomical site do not up-regulate HO-1 in response to HA treatment, suggesting a potentially protective role for these cells. To clarify this, selective deletion of Mϕ was induced via DT administration to CD11b-DTR mice, Mϕ ablation abrogated any structural or functional protection from HA (Creatinine 43.0±2.7 vs. 75.3±11.6 vs. 74.2±11 vs. 103.2±22.0µmol/L HA+PBS vs. HA+DT vs. PBS vs. DT+PBS; $p<0.05$ HA+PBS vs. HA+DT). This implicates HO-1 positive Mϕ as key mediators of HA derived protection. *Transplant model* HA pre-treatment of the donor failed to protect against ATN when compared with PBS treated controls (ATN score 53.7±7.0% in HA treated donors vs. 58.9±12.8% in PBS controls; $p>0.05$). There were no significant differences in the numbers of HO-1 positive Mϕ at the site of maximal injury between the groups. Conclusion The results demonstrate that renal Mϕ mediate the protective effects of pharmacological HO-1 induction. Lack of protection after donor pre-treatment has implications for the use of preconditioning agents in the context of organ transplantation. HA pre-treatment of recipients and consequent up-regulation of HO-1 in circulating monocytes may represent the most effective way of ensuring the delivery of sufficient numbers of these protective cells to the site of injury within transplanted organ. This is the focus of ongoing work.

Medawar 2

Great Hall

15:45-16:45

O20

Cytotoxic CD8 T Cells Receive Help From Indirect Pathway CD4 T Cells by Presenting Processed Alloantigen on Acquired MHC II.

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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.

Female Mar (B6 RAG2$^{-/-}$) recipients, whose monoclonal CD4 T cells recognise self-restricted male H-Y peptide (i.e., indirect allorecognition), rejected male BALB/c heart grafts acutely (MST 12d, n=6), but only if reconstituted with 10^6 effector female B6 CD8 T cells. Female BALB/c grafts survived >50d, confirming that CD8 T cell-mediated rejection was dependent on indirect help from Mar CD4 T cells. Surprisingly, although the epitopes for Mar CD4 and CD8 T cell recognition are on different APCs (recipient vs donor), CD8 T cell-reconstituted Mar recipients challenged with male B6 APCs (causing effective Mar CD4 T cell activation) mounted minimal cytotoxic CD8 T cell responses and did not reject female BALB/c grafts. Effective help was thus only generated when H-Y and MHC I alloantigens were co-expressed on graft cells.

We hypothesised that, analogous to the provision of cognate T cell help to B cells, this requirement for co-expression reflects acquisition of H-Y antigen from graft cells by allospecific CD8 T cells, with subsequent processing and presentation in the context of MHC II for Mar CD4 T cell recognition. In support, Mar recipients reconstituted with MHC II$^{-/-}$ CD8 T cells rejected male BALB/c grafts more slowly than when reconstituted with WT CD8 T cells (MST 21d, n=6 vs 12d, n=6), and reconstitution with CD8 T cells from H-2DMa mice (which are unable to process antigen) resulted in indefinite graft survival (n=4). In contrast, male B6xBALB/c F1 grafts (which enable 'linked' help via direct allorecognition of both Mar CD4 and CD8 T cell epitopes on donor APCs) were rejected rapidly when reconstituted with WT (MST 8d, n=4), MHC II$^{-/-}$ (MST 8d, n=4) or H-2DMa (MST 10d, n=4) CD8 T cells, indicating that antigen processing and MHC II expression by CD8 T cells is necessary only for indirect CD4 T cell help. Finally, although mouse CD8 T cells do not normally express MHC II, flow cytometric analysis revealed acquisition of MHC II by activated CD8 T cells upon culture with WT (but not MHC II$^{-/-}$) APCs.

Our data suggest 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.

O21

Kidneys Donated after Cardiac Death have Equivalent Graft Function to those from Donors with Brain Death but a Short Cold Ischaemia Time is Critical.

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[1]University of Cambridge, Cambridge, United Kingdom, [2]NHSBT, Bristol, United Kingdom

Background: Recipients of kidneys from DCD (donation after cardiac death) donors have a higher incidence of DGF (delayed graft function) than recipients of DBD (donation after brain death) kidneys but equivalent graft survival. We determined whether graft function (eGFR) is also equivalent for DCD and DBD kidneys and identified factors influencing graft function and transplant survival.

Methods: A comprehensive analysis of all adult recipients of kidneys from controlled DCD and DBD donors performed in the UK between 2000-2007 was undertaken and multiple regression analysis performed to identify variables that influence transplant outcome.

Findings: Graft survival was very similar for recipients of DCD (n=748) and DBD (n=6889) kidneys with an unadjusted 5 year graft survival rate of 76% for both groups and a hazard ratio for DCD kidneys (after correction for variables influencing outcome) of 1.01 ($p = 0.97$). Although the eGFR at 3 months was lower for DCD than for DBD kidneys ($p = 0.03$), by 12 months the eGFR in the two groups was equivalent ($p = 0.57$). As expected, DGF was more common in recipients of DCD than DBD kidneys (49 vs 24 %, $p < 0.0001$). However, for DCD kidneys, DGF was not a predictor of graft loss ($p = 0.39$), but for DBD kidneys DGF correlated with inferior graft survival ($p < 0.0001$). Surprisingly, the incidence of acute rejection within the first 3 months of transplant was lower in DCD than in DBD kidneys (16% vs 24 %, $p < 0.0001$). For recipients of DCD kidneys the factors found to adversely influence graft survival, using Cox regression analysis, were increasing donor age (age > 60 yrs, HR 2.3, $p= 0.001$), greater recipient age (age > 60 yrs, HR 2.03, $p=0.01$) and cold ischaemic time of >12hrs (HR 1.9, $p = 0.06$). Multiple linear regression analysis showed that the eGFR in recipients of DCD kidneys was adversely influenced by increasing donor age, non-trauma donor death, donor hypertension, greater recipient age, and longer cold ischaemic time.

Conclusion: Although DCD kidneys have a slower return to function than DBD kidneys, both graft function and graft survival are equivalent in the longer term, and reducing cold ischaemia time is critically important for maximising transplant outcome.

O22

Blocking the Formation of Intra-graft Lymphoid Tissue Influences Effector Humoral Responses

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Introduction

Tertiary lymphoid organs (TLOs) and intra-graft lymphatic vessel (LV) proliferation have been described in allografts and may contribute to rejection. The lymphotoxin-β receptor (LTβR) signalling pathway is essential for lymph node development in ontogeny and vascular endothelial growth factor receptor (VEGFR-3) signalling is required for lymphangiogenesis. Here we study the effect of blocking these pathways on TLO and LV formation in a model of allograft vasculopathy (AV).

Methods

The presence of TLOs in day 50 bm12 heart allografts in B6 recipients was confirmed by: discrete aggregates of B and T cells associated with high endothelial venules. LV density was assessed by staining with anti-LYVE-1 mAb. LTβR signalling was blocked by weekly intra-peritoneal injection of 100μg LTβR-Ig fusion protein (n=5), and VEGFR-3 signalling by injection of 25□g/g mF4-31C1 mAb three times per week for 3 weeks. Control recipients received rat IgG (n=5). Donor T cells within bm12 heart allografts provoke, in B6 recipients, anti-nuclear autoantibody (Win TS 2009); this was quantified by binding test sera to nuclear antigen expressing HEp-2 cells and by anti-ds DNA ELISA.

Results

All bm12 heart allografts from control-Ig treated B6 recipients contained TLOs, composed predominantly of B cells. Although LV density was reduced in recipients treated with mF4-31C1 (1884.6μm^2 vs control 3368μm^2, p=0.03), TLO formation was unaltered. In contrast, treatment with LTβR-Ig resulted in fewer TLOs (median/heart=0 vs 2, p=0.01), less dense LV (1427.4 μm^2, p=0.008), and a non-significant reduction in severity of AV. However, autoantibody responses were significantly diminished. To address whether the reduction in autoantibody following LTβR-Ig treatment is due predominantly to blocking TLO formation (rather than influencing signalling in conventional lymphoid tissue), a further group of B6 mice were challenged with bm12 CD4 T cells. The autoantibody response that this provoked was reduced by LTβR-Ig treatment but much less so than in heart-grafted mice.

Conclusions

Blocking VEGFR-3 signalling prevented LV, but not TLO, formation within allografts. In contrast, LTβR-Ig treatment blocked TLO development and was associated with a reduction in autoantibody. Although LTβR-Ig treatment influences responses within conventional lymphoid tissue, our results suggest that this reduction was due predominantly to the prevention of TLO formation and confirm that the lymphoid microenvironment of the allograft plays an important role in chronic rejection.

O23

Non Heart Beating (NHB) donor perfusion using Normothermic Extracorporeal Membrane Oxygenation (NECMO) in comparison to In-situ + Peritoneal (ISP+PC) cooling increases insulin production and decreases pancreatic cell damage and anaerobic metabolism

Soroush Sohrabi[1,3], Susan Stamp[2], Brian Shenton[2,3], Chris Ray[1,3], Aditya Kanwar[1,3], Stephen Ray[2], Noel Carter[1], David Talbot[1,3]

[1]Sunderland University, Sunderland, UK, [2]Newcastle University, Newcastle upon Tyne, UK, [3]Freeman Hospital, Newcastle upon Tyne, UK

Aims: NECMO has been successfully used for donor perfusion in liver and renal transplantation. In this study we compared the effects NECMO and ISP+PC on pancreas retrieved from NHB donors.

Methods: 11 landrace pigs were grouped into NECMO (n=5) and ISP+PC (n=6). Under general anaesthesia microdialysis catheters were placed followed by euthanasia. After 30mins of warm ischaemia NECMO and ISP+PC were initiated for 2 hours followed by pancreas retrieval. The pancreata were stored in UW solution over night and re-perfused on an ex-vivo oxygenation circuit for 2 hours. Microdialysis (MD) and perfusate samples were taken during 2 hours re-perfusion. MD samples were analysed for tissue glycerol, lactate and pyruvate and perfusate samples were analysed for insulin, amylase and lipase.

Results: After 30 minutes of warm ischaemia and 2 hours of donor perfusion, the ISP+PC group had higher tissue lactate/pyruvate ratio (p=0.007). After re-perfusion the ISP+PC group had higher %weight increase /100g tissue although the difference was not significant. Perfusate analysis showed that the ISP+PC group had significantly higher amylase than the NECMO group (p=0.014). Insulin measured in the perfusate was significantly higher in the NECMO group (p=0.018). Although oxygen consumption was higher in ISP+PC group then NECMO group this difference was not statistically significant.

Discussion: Pancreata retrieved in the NECMO group had less anaerobic metabolism during donor perfusion compared to the ISP+PC group presented by their lower tissue lactate / pyruvate ratio. Re-perfusion of pancreas in the NECMO group showed better beta cell function presented by higher insulin release and lower amylase as sign of cell injury compared to the ISP+PC group. NECMO could potentially be a better method for non heart beating donor perfusion for pancreas transplantation than cold perfusion.

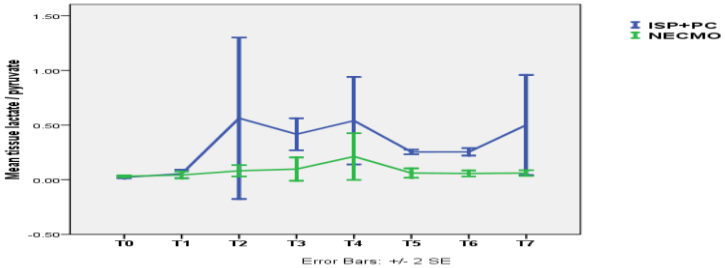

Figure: Mean tissue Lactate/Pyruvate ratio during 2 hours of reperfusion (T1-T7)

Basic Science

Regulating the immune response to grafted tissue

Council Chamber

18 March 2010

09:30 – 11:00

O24

Rapid recruitment of Foxp3+ regulatory T cells into cardiac allografts following the induction of specific unresponsiveness to alloantigen *in vivo*

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University of Oxford, Oxford, United Kingdom

Introduction: The aim of this study was to determine the kinetics for Treg entry into cardiac allografts following the induction of specific unresponsiveness to alloantigen *in vivo* and to assess the impact of such cells on the expression of pro-inflammatory genes associated with the development of operational tolerance.

Methods: C57BL/10 (B10, $H2^b$) cardiac allografts were transplanted into either naïve CBA ($H2^k$) mice (grafts rejected with a median survival time (MST) of 8 days) or CBA mice that had received anti-CD4 mAb and a donor-specific blood transfusion (DST) i.v. ('pretreated mice') 28 days before transplantation (MST >100 days). Cardiac allografts transplanted into $RAG^{-/-}$ recipients (no functional T or B cells) were used as controls for activation of the innate immune system after transplantation. Cardiac allografts were analysed 2, 5, 8 and 10 days after transplantation by real-time PCR analysis to determine the relative mRNA expression of CD3, Foxp3 and a panel of different pro-inflammatory and cytoprotective genes.

Results: Analysis of cardiac allografts from pretreated mice revealed an early infiltration by Treg (10-fold increase in the expression of both CD3 and Foxp3) and an associated increase in chemokine and chemokine receptor mRNA intragraft expression by 2 days after transplantation compared to controls. In particular, the expression of CCL5, CXCL9, CXCL10 and XCL1 was dramatically increased (64, 116, 186 and 276 fold, respectively) compared to that expressed in allografts transplanted to naïve recipients. Early Treg infiltration also correlated with an enhanced intragraft mRNA expression of genes associated with Treg phenotype and/or function such as CCR5, CCR8, IL-27p28, CD103, IDO, IL-10. By 10 days after transplantation, the difference in gene expression between grafts from pretreated and naïve recipients was found to persist but was not as marked as 2 days after transplantation. This data indicates that Treg had infiltrated cardiac allografts earlier and in greater numbers in pretreated mice compared to naïve recipients. The importance of Treg for the induction of tolerance in this model was demonstrated as depletion of Treg by injection of anti-CD25 mAb (PC61) 14 days before transplantation of a cardiac allograft in pretreated recipients resulted in the rejection of the grafts that otherwise would be accepted (MST=27 versus 100 days).

Conclusions: We propose that under conditions leading to long-term graft survival, regulatory T cells that have been generated by anti-CD4 + DST pretreatment are recruited to the graft before the priming and infiltration of alloreactive effector T cells. The earlier and increased expression of intragraft chemokines in pretreated recipients may be important for the early recruitment of regulatory T cells that, by expressing CCR5 and CCR8, infiltrate the graft and suppress T cell mediated effector mechanisms within the graft itself.

O25

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

Ines Harper, Chris Callaghan, Kourosh Saeb-Parsy, Eleanor Bolton, Andrew Bradley, Gavin Pettigrew

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Introduction - We have recently reported a role for autoantibody in the development of mouse heart graft vasculopathy; autoantibody that surprisingly was dependent upon donor CD4 T cells within the heart graft for its development. Regulatory T cells (T-regs) 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 T-regs in the development of autoantibody and allograft vasculopathy (AV).

Methods - The contribution of T-regs 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 (YTS antibody given i.p. on day -1, 1, 3, 5,7) or anti-IL-17 antibody (50µg i.v. on day 1,2,5,7, and weekly thereafter) and by adoptive transfer the day after transplant of naturally occurring T-regs (nT-regs) (purified from either the donor or recipient strains). Graft survival was assessed by daily palpation and autoantibody production assayed by staining nuclear-antigen-expressing HEp-2 cells.

Results - Unexpectedly, anti Il-17 treatment of B6 recipients of bm12 hearts did not affect the development of autoantibody. In contrast, T-reg depletion markedly exacerbated autoantibody production and accelerated graft rejection (MST 21 n=5 vs. WT 95d). Heart grafts from bm12 donors that were depleted of CD4 T cells prior to retrieval provoked significantly less autoantibody and survived longer (MST 32d) in the T-reg-depleted B6 recipients, suggesting that accelerated rejection following T-reg depletion is at least partly due to exacerbation of humoral autoimmunity. Surprisingly, whereas autoantibody production after transplantation was unchanged following transfer of nTregs of recipient (B6) origin, the response was almost completely abrogated by adoptive transfer of donor (bm12) nTregs. We hypothesise that bm12 nTregs are more effective because they share the same target ligand ($I\text{-}A^b$ on host autoreactive B cells) as is recognised by the helper population of bm12 CD4 T cells within the heart graft.

Conclusions - Our results demonstrate a previously unrealized mechanism whereby T-regs contribute to graft survival by preventing effector autoantibody responses. The use of donor, rather than recipient, T-regs may be particularly effective at preventing graft-versus-host mediated autoimmunity.

O26

Identification of non-gal antigens targeted by antibody induced after cardiac xenotransplantation

Guerard Byrne[1,2], Paul Stalboerger[1], Zeiji Du[1], Christopher McGregor[1,2]

[1]Mayo Clinic, Rochester, Minnesota, United States, [2]University College London, London, UK

The development of Gal knockout (GTKO) pigs homozygous for a targeted mutation in the GGTA-1 galactosyltransferase gene has eliminated expression of α-Gal in these donors and thereby reduced the significance of anti-Gal antibody in delayed xenograft rejection (DXR). These new donor pigs have not however eliminated DXR which remains an antibody and complement-induced process. This suggests that undefined endothelial cell non-Gal antigen(s) are the remaining antibody target(s) in GTKO rejection. In this study we define the specificity of non-Gal antibody induced after pig to primate heterotopic cardiac xenotransplantation (CXTx) using a proteomic and expression library analysis.

Methods: Heterotopic CXTx using Gal-positive (GT+ n=4) and GTKO (n=1) hearts was performed without T-cell immunosuppression. Sensitized serum was collected on necropsy. Graft specific antibody was also recovered from GTKO transplants performed with standard immunosuppression (n=8). Proteomic analysis of induced non-Gal IgG used 1 and 2 dimensional Western blotting, protein recovery and nanoLC/MS/MS analysis to identify non-Gal antigens. Retrovirus encoded GT+ and GTKO porcine aortic endothelial cell (PAEC) cDNA libraries were produced and screened with sensitized serum by fluorescence activated cell sorting. Retroviral encoded genes were recovered by PCR from isolated clones and sequenced to identify the non-Gal antigens.

Results: Antibody induced after GT+ heterotopic CXTx without T-cell IS and antibody eluted from rejected GTKO hearts transplanted with full IS detected intense IgG binding to a complex of GTKO PAEC membrane antigens greater than 150kDa and to bands at 140, 130, 35, 27, and 19kDa in 1D Western blots. Immunoreactivity to the 150kDa complex was due to antibody binding to fibronectin (FN) and MG-160. An induced immune response to FN was confirmed by ELISA. Western blotting of GTKO antigens separated by 2D electrophoresis and nano-LC/MS/MS spectroscopy identified a series of stress response proteins consisting of heatshock family members and inflammation associated proteins made up of annexin family members. Expression library screening was performed using sera from 3 different xenograft recipients. A total of 199 and 317 clones were analyzed from GT+ and GTKO libraries respectively. After sorting, PCR positive clones showed 3 fold or greater binding of sensitized IgG compared to control HEK cells. Sequence analysis of the recovered cDNA identified 7 independent target genes involved in glycosylation, complement regulation, thrombosis and inflammation.

Conclusion: This is the most comprehensive analysis of induced non-Gal antibody responses to specific endothelial cell membrane proteins to date. The identified proteins cover a range of cellular functions, including the possibility of additional non-Gal carbohydrate antigens. The identity of these non-Gal antigens suggest that in addition to direct complement-mediated damage and EC activation, induced antibody responses may compromise certain cell functions and thereby contribute to DXR.

O27

Perioperative cardiac xenograft dysfunction: a barrier to clinical xenotransplantation?

Christopher McGregor[1,2], Guerard Byrne[1,2], Michal Vlasin[1], Randall Walker[1], Henry Tazelaar[1], William Davies[1], Krishnaswamy Chandrasekaran[1], Elise Oehler[1], Barry Boilson[1], Barry Wiseman[1], John Logan[1]

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A milestone of ninety-day median survival after orthotopic cardiac xenotransplantation in non-human primates is a likely preclinical requirement for clinical application. We have achieved this benchmark using heterotopic cardiac transplantation. We now report on our initial studies using orthotopic cardiac xenotransplantation.

Methods: Twenty-two orthotopic transplants were performed in two series, Series 1 (n=16) and Series 2 (n=6). Donors in Series 1 were Gal-positive and expressed high levels of the human complement regulator CD46. Recipients in this series were treated with intravenous anti-Gal therapy (TPC) to block preformed anti-Gal antibody and to stop the induced anti-Gal antibody response. Donors in Series 2 were Gal knockout pigs (GTKO) homozygous for an engineered mutation in the GGTA-1 galactosyltransferase gene. Donors in Series 2 also expressed the human complement regulator CD55. In Series 2 remote and central cardiac preconditioning was performed prior to organ collection and recipient antibody was decreased by plasmapheresis immediately prior to transplant. Immunosuppression in both groups consisted of ATG induction, tacrolimus, sirolimus, and tapering steroids. Heart function was monitored biochemically, echocardiographically, and by intramyocardial electrocardiography. Changes in intragraft gene expression were studied at cardiac death.

Results: In Series 1, 75 percent of recipients could be weaned from cardiopulmonary bypass, 19 percent from the ventilator, with 19 percent operative survival. In Series 2, 100 percent of recipients could be weaned from cardiopulmonary bypass, 66 percent from the ventilator, with 50 percent operative survival. Hearts that failed early showed essentially normal histology and no evidence of hyperacute rejection. Perioperative failure was due to an inability to maintain sufficient cardiac output, despite inotropic support. Six recipients made a healthy recovery and survived 2, 14, 23, 34, 40 and 57 days (the latter two recipients being the longest survivors to date in the literature). Operative survivors showed early diminished cardiac function compared to normal hearts but their function recovered to normal levels within 5 to 10 days. Rejection was not a major factor in recipient mortality as no survivor died due to delayed xenograft rejection. Histology of some recipients showed evidence consistent with ongoing rejection and analysis of intragraft gene expression was consistent with ongoing cardiac injury.

Conclusions: Perioperative cardiac xenograft dysfunction after orthotopic cardiac xenotransplantation is unacceptably high. Fortunately, early cardiac function was improved through a combination of cardiac preconditioning, antibody removal and improved donor genteics. When perioperative dysfunction is overcome, normal cardiac function and long-term survival is achievable. Further improvements in perioperative cardiac function may be achieved through more effective antibody removal and optimal donor organ preservation.

O28

The affects of human CD55 expression in GTKO heterotopic cardiac xenotransplantation.

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Cardiac xenotransplantation, if successful, can affect the shortage of donor organs. Gal-deficient pigs (GTKO) engineered with a mutation in the GGTA-1 galacosyltransferase do not express the α-gal antigen and have thereby minimized the role of anti-Gal antibody in xenograft rejection. GTKO graft rejection now occurs in response to the effects of non-Gal antibody-mediated injury to vascular endothelium. Previously transgenic expression of human complement regulatory proteins (hCRP) significantly reduced the impact of hyperacute rejection. In this study we examine the affect of human CD55 expression on a GTKO background using pig-to-primate heterotopic cardiac xenografts.

Methods: Heterotopic pig-to-primate cardiac xenotransplantation was performed with GTKO (n=6) and GTKO pigs expressing human CD55 (n=5). Immunosuppression using splenectomy, induction therapy with Rituximab and antithymocyte globulin, Tacrolimus, and Sirolimus maintenance without anticoagulation was identical for both groups. Biopsies were obtained 30 minutes after organ reperfusion. Explanted tissue was analyzed by standard histology staining, immunohistology for IgM, IgG, CD55 and C5b deposition. Molecular analysis of intragraft gene expression examined markers of endothelial cell activation. Non-Gal antibody responses were monitored by flow cytometry using GTKO endothelial cells.

Results: GTKO and GTKO;CD55 xenografts had a median survival of 21 and 28 days respectively. This was not a significant difference. One GTKO graft was hyperacutely rejected in 90 minutes. At explant this graft exhibited vascular antibody and complement deposition with a loss of vascular patency and widespread haemorrhage. All other grafts were rejected by delayed xenograft rejection (DXR) after a loss of contractility or showed some diminished contractility and evidence of an ongoing DXR at the time of recipient death. The histology of GTKO and GTKO:CD55 grafts showed chronic vascular antibody deposition apparent 30 minutes after organ reperfusion. There was a higher frequency of complement deposition and early organ injury in rejected GTKO organs compared to GTKO;CD55. Other assessments of graft rejection and induced antibody responses were similar between the groups.

Conclusion: Transgenic expression of human CD55 in the GTKO background limited histological evidence of complement-mediated injury to the graft. This suggests that enhanced complement regulation will be beneficial especially for preventing hyperacute rejection. Combined with more effective immunosuppression enhanced complement regulation may prolong graft survival or improve graft function. Further development and testing of GTKO pigs expressing CD55 or other human complement regulatory genes may aid the clinical application of xenotransplantation.

O29

Prolongation of Mouse Corneal Allograft Survival Following Systemic And Topical 3-hydroxykynurenine (3HK) Aministration.

Sarah Zaher[1], Frank Larkin[2], Andrew George[1]

[1]Imperial College London, London, UK, [2]Moorfields Eye Hospital, London, UK

Introduction:

Indoleamine 2,3-dioxygenase (IDO) has been shown to prolong corneal graft survival. IDO modulates the immune response by depletion of the essential amino acid tryptophan and by breakdown to kynurenines, which themselves act directly on T lymphocytes. The effect of kynurenines on corneal allograft survival is unknown.

Purpose:

IDO and kynurenines are potential targets for preventing allograft rejection. We investigated the role of kynurenine administration on corneal graft survival to determine whether this was the mechanism by which IDO delays rejection.

Methods:

In vitro analysis of the effect of kynurenines on T-cell proliferation; T-cell death; T-regulatory cell development; dendritic cell function, phenotype and viability was carried out. Two exogenous kynurenines were then administrered systemically and topically to inbred mice receiving fully MHC mismatched 2.5mm donor corneas.

Results:

T-lymphocyte proliferation was inhibited by two of the four different kynurenines: 3HK and 3-hydroxyanthranilic acid (3HAA). This was accompanied by significant T-cell death. Neither 3HK nor 3HAA altered dendritic cell function, nor did they affect apoptosis or pathogenicity to corneal endothelial cells. Administration of systemic and topical 3HK to mice receiving a fully mismatched corneal graft resulted in significant prolongation of graft survival (median survival of controls = 12 days, of treated = 19 days and 15 days respectively, $p<0.0003$).

Conclusions:

These data therefore indicate that one mechanism by which IDO prolongs corneal graft survival is by the production of kynurenines, in particular 3HK and 3HAA. In addition it highlights the potential of these molecules as agents for preventing allograft rejection in patients at high rejection risk.

Abstracts
Renal Transplant Outcomes

Great Hall

11:30 – 12:30

O30

Calcineurin Inhibitor Avoidance in De Novo Kidney Transplantation: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

Adnan Sharif[1], Jason Moore[2], Shazia Shabir[1], Andrew Bentall[1], Simon Ball[1], Richard Borrows[1]

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Introduction. Avoidance of *de novo* calcineurin inhibitor (CNI) administration has potential advantages by attenuating CNI-related metabolic and nephrotoxic side effects immediately post kidney transplantation. These strategies are limited by possible detrimental short-term graft outcomes related to insufficient concomitant calcineurin inhibition. To investigate this further, we conducted a systematic review and meta-analysis of all relevant randomised, controlled trials incorporating a *de novo* CNI avoidance strategy to ascertain the short-term graft outcomes of such approaches in kidney transplantation.

Methods. The search strategy used Ovid Medline, Embase and the Cochrane Library Database to identify all randomised, controlled trials that utilised a CNI avoidance strategy in the immediate period post-transplantation. This included all trials that incorporated *de novo* CNI avoidance by either delayed introduction, total avoidance or minimisation regimens. Two investigators independently examined each trial for eligibility and outcome measures. Missing information was requested from corresponding authors. Outcomes investigated were graft function (estimated glomerular filtration rate [eGFR]), graft survival, incidence of delayed graft function (DGF) and acute rejection (AR) between study groups and control groups (CNI avoidance and standard CNI based regimens respectively).

Results. A total of 35 randomised, controlled, clinical trials involving 7157 renal transplant recipients were identified by systematic review that were suitable for inclusion in the meta-analysis. These included all trials published up to November 2009 and all relevant abstracts presented in the last 3 years but not currently in published form. In view of significant heterogeneity, random-effects meta-analysis was performed for both DGF and AR outcomes (this model assumes each study has a different true effect and there is no single true treatment effect). There was no evidence of any difference in DGF between study and control groups (odds ratio 0.88 [95% CI 0.73-1.05], p = NS). CNI avoidance was associated with significantly greater risk of AR (odds ratio 1.47, 95% CI 1.14-1.88, p = 0.003) but there was no difference in eGFR (63.2ml/min vs. 59.5ml/min, p = NS) or graft survival (89.1% vs. 87.7%, p = NS) between study and control groups respectively.

Conclusions. There is no evidence that *de novo* CNI avoidance in kidney transplantation is of any benefit at reducing delayed graft function. CNI avoidance regimens are associated with odds of acute rejection almost 50% higher compared to CNI based immunosuppression but graft function and survival are equivalent. However, significant heterogeneity existed in our incorporated studies and this highlights the degree of variability in reported trials.

O31

Histology of 1-Year Surveillance Biopsies in a Trial of Daclizumab /Tacrolimus/MMF Versus Alemtuzumab/Tacrolimus Monotherapy

Andrew PT Smith[3], Terry Cook[2], Kakit Chan[1], Tom Cairns[1], David Taube[1], Adam Maclean[1], Candice Roufosse[2]

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Protocol biopsies contain histological features predictive of long-term graft outcome. As part of our randomized controlled trial of Alemtuzumab versus Daclizumab induction for conventional renal allografts, we found equivalence between the two arms for short-term rejection rates and graft survival. We describe our findings in 1-year protocol biopsies, in particular those that may predict long-term outcome and those associated with humoral damage.

Interstitial fibrosis (IF) was evaluated by conventional light microscopy (Banff ci score) and by computer-assisted image analysis of picrosirius red stained sections. Glomerular inflammation was assessed by conventional light microscopy (Banff g score) and by counting glomerular CD3- and CD68-positive glomerular cells. Banff coding was also used for inflammation (i), total inflammation (ti), chronic glomerulopathy (cg), peritubular capillary inflammation (ptc), and C4d status.

For statistical analysis, we used Fisher's exact test (i, ti, ci, g, cg, ptc, and C4d) or a two-tailed Mann-Whitney test (quantitative IF and CD3/CD68 data).

123 patients were enrolled in the trial (82 Campath, 41 Daclizumab). 101 had stable graft function with no indication biopsy between 6 and12 months post-transplant, and no contra-indication to protocol biopsy. 69 of these agreed to surveillance biopsy.

There were no significant differences between the 2 groups. All cases were cg0.

These 1-year protocol biopsy findings support our previously reported clinical experience that the two arms of the trial offer equivalent outcomes.

Interstitial fibrosis (image analysis) and glomerular inflammatory cells

	IF (mean %total cortex)	mean CD3 cells per glomerulus	mean CD68 cells per glomerulus
Daclizumab	7.84	1.60	2.70
Alemtuzumab	9.79	1.07	1.93
p (Mann-Whitney)	0.145	0.226	0.479

	i	ti	ci	g	ptc	C4d
Daclizumab (mean Banff score)	0.54	0.27	0.92	0.03	0.04	0.46
Alemtuzumab (mean Banff score)	0.70	0.23	0.86	0.18	0.02	0.44
Fisher's exact	1.00	0.44	.068	0.56	1.00	0.92

O32

Caveolin-1 gene polymorphism and kidney transplant survival

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

[1]University Hospital Birmingham, Birmingham, West Midlands, United Kingdom, [2]Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom, [3]University of Birmingham, Birmingham, West Midlands, United Kingdom, [4]National Blood Service, Birmingham, West Midlands, United Kingdom

Caveolin-1 (CAV1) is an inhibitor of tissue fibrosis and vascular smooth muscle proliferation. Using kidney transplantation as a model of accelerated fibrosis we studied the association of CAV1 variation with kidney transplant outcome.

We conducted a candidate gene association and replication study. Genomic DNA from 785 Caucasian kidney transplant donors and their respective recipients (Birmingham, UK; median follow-up 81 months) were analysed for common variation in CAV1 using a pairwise tagging approach. Validation of positive findings was sought in an independent kidney transplant donor-recipient cohort (Belfast, UK; n=697, median follow-up 69 months). Association between genotype and allograft failure was initially assessed by Kaplan-Meier analysis, and then in an adjusted Cox model. The primary outcome measure of interest was death-censored allograft failure, defined as a return to dialysis or retransplantation.

The presence of donor AA genotype for the CAV1 rs4730751 single nucleotide polymorphism (SNP) was associated with increased risk for allograft failure in the Birmingham group (donor AA vs. non-AA genotype, adjusted Cox model: HR=1.94; 95%CI: 1.14-2.27; p=0.005). No other tag SNPs showed a significant association. This finding was replicated in the Belfast cohort (adjusted Cox model: HR=1.65; 95%CI: 1.13-2.42; p=0.01), and in a stratified pooled analysis (HR=1.82; 95%CI: 1.36-2.43; $p=5x10^{-5}$).

This is the first replicated association between a candidate gene polymorphism and kidney allograft failure, and has implications not only in the field of renal transplantation, but also for other conditions characterised by tissue fibrosis.

O33

C4d positivity does not predict acute rejection in patients with anti-HLA donor specific antibodies

Michelle Willicombe, Candice Roufosse, Andy Palmer, Adam Maclean, Anthony Dorling, Terry Cook, David Taube, Tom Cairns

Imperial College Kidney and Transplant Institute, London, United Kingdom

Current Banff criteria for type I antibody mediated rejection [AMR] in renal allografts include the histological features of positive C4d staining and acute tubular necrosis [ATN] with serological confirmation of anti-HLA donor specific antibodies [DSA]. However strong C4d positivity can occur in grafts without being predictive of rejection or progressive dysfunction, typically but not exclusively in ABO incompatibility.

This retrospective study included patients who have had renal allograft biopsies for dysfunction. The aim was to analyse the predictive value of C4d status where the only other histological findings was ATN. Peritubular capillary staining of >11% was defined as positive.

140 patients were included [f:m=31:109, mean age: 46.70 ±12.06 yrs, mean HLA MM: 3.2 ±1.62, 1st grafts: regrafts =122:18, Deceased donor: living donor=85:55]. All patients had received monoclonal antibody induction together with a maintenance regime of tacrolimus ± mycophenolate mofetil. Corticosteroids were administered for 7 days post transplant. No patients received additional immunosuppression following these index biopsies. The mean follow up was 1.69 ±1.09 yrs.

95/140 [67.86%] were C4d negative and 45/140 [32.14%] were C4d positive on index biopsy. There was no difference in allograft survival between the C4d- group and C4d+ group from the time of index biopsy. Allograft survival being 91.6% and 93.3% respectively, p=0.70 (log rank). Antibody mediated rejection [AMR] on subsequent biopsies was not increased in the C4d+ group. The AMR free survival post index biopsy being 91.6% in the C4d- group and 97.8% in the C4d+ group, p=0.17 (log rank). There was also no difference in the risk of developing acute cellular rejection [ACR] in either group, the ACR free survival post index biopsy being 89.5% and 88.9% in the C4d- and C4d+ groups respectively, p=0.88.

The consequence of DSA in these biopsies was also analysed, 26/95 [27.34%] of the C4d- group had DSA and 14/45 [31.11%] of the C4d+ group had DSA [p=0.55, X^2]. When compared with the other groups, C4d-DSA+ patients [n=26] were at highest risk of graft loss [p=0.02 (log rank)] and also more likely on subsequent biopsy to have AMR and ACR [p=0.03 and p=0.01 (log rank) respectively]. None of the patients with C4d on biopsy and DSA [n=14] developed acute AMR or graft loss. Further follow up will be necessary to assess evidence of chronic AMR.

In our program, C4d positivity with no other light microscopy features of rejection on biopsy for graft dysfunction does not predict subsequent acute rejection even with evidence of circulating DSA.

O34

The Development of Abnormal Physiological Indices During the Withdrawal Phase Does Not Affect DCD Kidney Transplant Outcomes

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Department of Surgery, Cambridge University, Cambridge, United Kingdom

Introduction

Donation after Cardiac Death (DCD) is an increasingly important source of kidney transplants, but because of concerns of ischaemic injury during the agonal phase (from controlled withdrawal of lifesaving treatment (WLST) until cardiorespiratory arrest), many centres abandon donation if arrest has not occurred within one hour. We report our experience using a minimum 'cut-off' time of four hours.

Methods and Results

Between 2004 and 2009, 425 potential DCD donors were referred. The majority (56%) could not be pursued either because of medical unsuitability or relative refusal. Of the 173 (44%) who underwent WLST, 117 (68%) became donors. 234 kidneys were retrieved, but 31 were not implanted due to either poor perfusion or chronic disease on biopsy. 7 developed acute arterial or venous thrombosis and 6 never functioned. Median 3-month eGFR in the transplanted kidneys was 43.0ml/min/1.73m2, similar to that obtained by 111 contemporaneous DBD kidney transplants.

75% donors (88/117) arrested within one hour. Lengthening the cut-off time from one to four hours therefore increases donor numbers by 33%, but creates uncertainty as to the viability of kidneys from donors who deteriorate slowly and suffer lengthy instability prior to arrest. To address this, donors were scored according to the presence of five abnormal physiological indices during the agonal phase (acidaemia (frequency 36%), lactic acidosis (37%), and prolonged (>30mins) hypotension (32%) or hypoxia (28%) or oliguria (28%)).

DCD donors who arrested within 1hr of WLST scored less than those who arrested later (0.88 vs 1.93, p=0.0009). The impact of each of the agonal-phase indices on graft outcome (development of delayed graft function (DGF) and three-monthly eGFR) was then evaluated by multivariate regression analysis. Included in this analysis were donor characteristics previously associated with poor graft outcomes (age, sex, terminal creatinine, non-trauma death).

Surprisingly, there was no association between the agonal-phase variables and DGF or eGFR; either when the variables were considered individually or when the overall agonal-phase score was assessed. Although an association may possibly be revealed by larger study numbers, it is notable that the analysis demonstrated a strong impact of donor age upon eGFR, with a 10 year increase associated with a decline in recipient eGFR of 3.40 mL/min/1.73m2.

Conclusions

Relatively few (28%) of DCD referrals proceed to kidney retrieval. Our results indicate that this can be maximised, without compromising results, by extending the waiting time to four hours and pursuing donation despite development of unfavourable agonal phase characteristics.

O35

Effect of High Dose Erythropoietin on Early Graft Outcomes in NHBD and ECD Kidney Recipients: a Randomised, Placebo-Controlled Trial

Declan deFreitas[1], Beatrice Coupes[1], David Hoyle[2], Ian Read[1], Hany Riad[1], Paul Brenchley[1], Michael Picton[1]

[1]Manchester Royal Infirmary, Manchester, United Kingdom, [2]University of Manchester, Manchester, United Kingdom

Body: Non-heart beating donor (NHBD) and extended criteria donor (ECD) renal transplant recipients are at increased risk of delayed graft function (DGF) in the post-operative period. Evidence suggests that high dose EPO may confer protection from reperfusion injury. However, the efficacy and safety of high doses in renal transplant recipients have not been established. We investigated the effects of high dose EPO on biomarker production and renal endpoints in this population.

We performed a single centre, randomised, double-blind, placebo-controlled trial in 39 recipients of an ECD or a NHBD kidney. We randomly assigned patients to 100,000 units of EPO (Roche) over three days (n=19) or placebo (n=20) and followed them up for three months. The primary endpoint was the change in serum and urine biomarker profiles in the early post-operative period. Secondary endpoints were DGF, number of dialysis episodes, rejection rate, serum creatinine at 3 months, adverse events, patient and graft survival. Analysis was by intention to treat.

Demographics did not differ between the two groups. Changes in the levels of plasma and urine NGAL, IL-18, HGF and KIM-1 out to day 5 were not significantly different between the groups (mixed effects model), although urinary KIM-1 levels were closest to significance and lower in the EPO treated group. Delayed graft function occurred in 52% of EPO recipients and 55% of placebo recipients (p=0.88). The median number of dialysis episodes did not differ between groups (1 vs 1.5, EPO vs placebo, p=0.78). Rejection occurred in 26% of EPO treated patients and 15% of placebo patients (p=0.28). Serum creatinine at 3 months was not significantly different between EPO and placebo groups (152.4 ±60.9 vs 175.6 ± 83.68, p=0.33). No patients or grafts were lost at three months. There was no significant difference in haemoglobin, haematocrit or platelet levels over three months between the groups. No thrombotic complications occurred. There were no differences in mean arterial pressure at the end of the 3rd infusion (median 97mmHg for both groups).

High dose erythropoietin was safe in the early post-transplant period, but a protective effect has not been demonstrated by 3 months post-transplant in ECD or NHBD recipients..

Abstracts
Immunosuppression 1

Council Chamber

11:30 – 12:30

O36

Renal function in *de novo* kidney transplant patients receiving everolimus with reduced-dose ciclosporin or enteric-coated mycophenolic acid with standard-dose ciclosporin: Results from a large-scale, randomised, international trial

James Pattison[1], Hany Riad[2], Magdi Yaqoob[3], Helio Tedesco-Silva[4]

[1]Guy's Hospital, London, United Kingdom, [2]Manchester Royal Infirmary, Manchester, United Kingdom, [3]William Harvey Research Institute, London, United Kingdom, [4]Hospital do Rim e Hipertensao, Sao Paulo, Brazil

Long-term graft and patient survival correlate with renal function at one year post-transplant and with the occurrence and severity of chronic allograft nephropathy/interstitial fibrosis and tubular atrophy (CAN/IFTA). CAN/IFTA is exacerbated by calcineurin inhibitor-related nephrotoxicity. Everolimus, a proliferation signal/mTOR inhibitor, combines immunosuppressive and anti-proliferative actions, and can facilitate reduced CNI exposure with the potential to reduce CNI-related nephrotoxicity.

In the RAD 2309 trial, a 24-month, multicentre, open-label, non-inferiority study, 833 *de novo* kidney transplant patients were randomised to everolimus at an initial dose of 1.5mg/day targeting C_0 3–8ng/mL or 3.0mg/day targeting C_0 6–12ng/mL, both with reduced-dose ciclosporin (CsA), or to enteric-coated mycophenolate sodium (EC-MPS) (1.44g/day) with standard-dose CsA. All patients received basiliximab induction, with corticosteroids administered as per local practice. Demographics are summarised in the Table. The primary efficacy endpoint was the composite efficacy failure rate (treated biopsy-proven acute rejection, graft loss, death and loss to follow-up) at 12 months. The primary safety endpoint was renal function at 12 months, measured by calculated GFR (Modification of Diet in Renal Disease [MDRD] formula). Renal histology was assessed in patients with proteinuria and/or suboptimal renal function at 12 months. Renal data, including the change in calculated GFR over time and by treatment group, will be presented. These results will represent the largest data set available to date concerning optimal everolimus and CsA dosing in kidney transplant recipients to preserve long-term renal function.

	EVL 1.5mg+reduced-dose CsA (n=277)	**EVL 3.0mg.day+ reduced-dose CsA (n=279)**	**EC-MPS+standard-dose CsA (n=277)**
Mean age, years	45.7	45.3	47.2
Male, n (%)	176 (63.5)	191 (68.5)	189 (68.2)
Race, n (%)			
White	193 (69.7)	180 (64.5)	190 (68.6)
Black	34 (12.3)	40 (14.3)	39 (14.1)
Asian	32 (11.6)	38 (13.6)	36 (13.0)
Other	18 (6.5)	21 (7.5)	12 (4.3)
PRA ≥20%, n (%)	17 (6.3)	13 (4.8)	11 (4.1)
Living donor, n (%)	147 (53.1)	151 (54.1)	148 (53.4)

O37

Phase I clinical study of autologous infusion of expanded mobilized adult bone marrow-derived CD34 cells into patients with diabetes and functioning renal transplants

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Pancreas or islet transplantation as a cure for diabetes is limited by the shortage of organs, associated complications and variable success rates. An attractive option is the use of a stem cell population which can differentiate into insulin-secreting cells. This is the first reported study which assesses the safety and efficacy of the administration of autologous expanded mobilized adult progenitor CD34+ cells into the pancreas of diabetic patients.

We chose immunosuppressed diabetic renal transplant patients to reduce the risk of recurrence of the primary autoimmune disease.

5 diabetic patients with a stable functioning kidney transplant active on the pancreas after kidney transplant list were recruited into the study. [M:3, F:2; mean age 54.2 ± 5.9 yrs; mean weight 80.4 ±16.4 kg; mean creatinine 125 ± 15.8 µmol/L; DMI:4, DMII:1; mean insulin requirement pre treatment 66.3 ± 36.2 iu/day]. Mean follow up was 153.7 ± 5.1 days. Following granulocyte colony-stimulating factor (G-CSF) mobilization and leukapheresis, the autologous CD34+ cells were expanded and differentiated into insulin-secreting cells in vitro prior to being injected into the pancreas via selective arterial catheterization. All patients were monitored for side effects, toxicity, and changes in the clinical, haematological and biochemical parameters.

Patients had between 7.1 and 15.3 X 10^7 cells infused into the pancreas 3 weeks post CD34+ cells collection. One patient did not mobilize well in response to G-CSF administration, resulting in insufficient CD34+ cells to proceed with collection and in turn did not complete the study.

All patients tolerated the treatment protocol well without any complications or side effects related to the procedure. There were no side effects noted on long-term follow up. All patients had stable kidney graft function. There were no episodes of rejection and Donor specific antibodies remained negative pre and post treatment. 3 patients had no significant change in insulin requirement and glycaemic control. HbA1c was unaltered and C-peptide remained undetectable. In the only type 2 diabetic patient, there was significant reduction in mean daily insulin requirement post stem cell infusion [100iu vs 70iu; $p<0.05$] and good glycaemic control [HbA1c 5.5% vs 5.7%; $p=0.56$]. However, mean C-peptide did not significantly vary [2482 vs. 2055; $p=0.48$].

The study indicates that the stem cell product used was safe and well tolerated. The significant reduction in insulin requirement in the type 2 diabetic patient possibly suggests that there are better chances of engraftment and function when the cells are infused in a non-scarred pancreas. A further study is in progress.

O38

10 years of steroid sparing In renal transplantation

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Steroid sparing [SS] protocols are associated with more rejection in high risk groups, particularly Afro Americans, but a lower incidence of new onset diabetes after transplantation [NODAT], weight gain and hypertriglyceridaemia.

Whilst there are several medium term [$\geq$ 5 years post transplant] favourable reports of SS protocols, there are few long term studies which, in particular, address the issue of late allograft dysfunction due to rejection.

We have used a SS protocol since 2000 and in this study report the outcome of 803 patients [491m, 312f, 416 DD, 287 LD; mean age 46.5 $\pm$13.0 yrs; mean follow up 35.0 $\pm$ 27.2 mths]. 97/803 [12.1%] were Afro Caribbean.

All patients received 0.5 gms methyl prednisolone iv at the time of transplantation followed by prednisolone 1mg/kg/day for 3 days, reduced to 0.5mg/kg/day for 4 days and then stopped. Steroids were only reintroduced to treat rejection.

717/803 [89.3%] patients received CD25 or CD52 monoclonal antibody induction and all patients were treated with a Tacrolimus based immunosuppressive regime.

Allograft rejection was diagnosed by biopsy.

Patient survival at 1, 5 and 10 years was 98.9%, 95.5% and 92.4%. Allograft survival [censored for death with function] at 1, 5 and 10 years was 96.2%, 89.5% and 79.6%. Allograft function at 1, 5 and 10 years was stable [MDRD eGFR (ml/min/1.73m^2) 53.1+16.6+16.3, 49.3+16.7 and 71.7+5.6; eGFR changed at an average rate of 0.06 ml/min/1.73m2 per year (95% CI - 0.32, 0.44, p=0.760; Hierarchical Longitudinal Model)]

Rejection free survival at 1, 5 and 10 years was 84.1%, 87.0% and 86.0%. Cumulative risk of acute and chronic transplant glomerulopathy was 3.2%, 6.9% and 10.2% at 1, 5 and 10 years. Allograft survival and the incidence of rejection were not significantly different in our Afro Caribbean group. [HR for allograft failure: 0.7; 95CI: 0.3,1.6; p=0.412; HR for rejection 0.8; 95%CI: 0.46, 1.34; p=0.378]

The incidence of calcineurin inhibitor [CNI] toxicity [allograft dysfunction with arteriolar hyalinosis, stabilising or improving with reduction in Tac level] remains low with a 10 year CNI toxicity free survival of 86.1%.

NODAT free survival in the group of patients not receiving steroids was 92.4%, 89.0% and 87.8% at 1, 5 and 10 years. The risk of developing NODAT increased 3.7 fold after the start of steroids to treat rejection [p <0.001, 95% CI: 2.1,6.4; Cox time split model]. NODAT free survival was 86.4%, 80.4% and 76.1% at 1, 3 and 5 years after starting steroids.

This long term study shows that our SS regime is associated with excellent allograft survival, a low incidence of late rejection, transplant glomerulopathy, CNI toxicity, stable allograft function and a low rate of NODAT. Afro Caribbeans did not have an increased risk of rejection.

O39

Randomised prospective trial of Daclizumab induction followed by Sirolimus in association with Mycophenolate Mofetil and steroids versus standard Ciclosporin based triple therapy for rejection prophylaxis in renal transplantation: results at year 4.

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This group previously reported the 1 year results of an open label randomised trial comparing a CNI based and a CNI free regimen. We are now reporting on the outcome of four years follow up. The primary end point is renal function, as measured by Cockcroft-Gault GFR. The secondary end points are patient and graft survival, and rates of acute rejection and infection.

Eighty patients were randomised into the original study at 2 centres between 2003 and 2005 to either Daclizumab induction, followed by Sirolimus (SRL), Mycophenolate Mofetil (MMF) and steroids (N=41) or Neoral (CsA), MMF and steroids (N=39).

During the subsequent 36 months, two patients from the SRL arm were lost to follow up, leaving 39 patients on each arm. Of those, 25 (64.1%) were still on SRL and 25 on CsA at the end of the study.

The mean Cockcroft-Gault GFR for the per protocol (PP) patients at the end of year 1 was not different between the 2 arms being 62.92 ml/min (SRL) & 64.70 (CsA). At year 4, the SRL group increased to 74.32 ml/min (SRL); the CsA group was 63.48. The difference did not achieve statistical significance (p=0.119). The mean GFR for the intention to treat (ITT) groups were 68.06 (SRL) and 64.33 (CsA) respectively (n.s. p=0.571).

Of the 78 patients available for long term follow up there were five deaths throughout the whole course of the study. Two deaths (one in each study arm) occurred during the first year. In the subsequent three years there were three further deaths, 2 in the SRL arm and 1 in the CsA arm, giving a patient survival of 36/39 (92.3%) in the SRL group and 37/39 (94.87%) in the CsA group (n.s. p=0.634).

Graft survival rates were 35/39 (89.7%) and 37/39 (94.8%) respectively (n.s. p=0.391).

There were no rejection episodes after the first year.

There were no differences between the groups in terms of incidence of infections and drug side effects.

In conclusion, this is one of a few studies to provide a long term outcome of a CNI-free regimen. Although the renal function has improved in the SRL treated patients this did not reach statistical significance.

O40

Campath induction and Tacrolimus monotherapy: a novel and effective immunosuppressive regime for ABO incompatible live donor renal transplantation.

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This is the first reported study of Campath induction and Tacrolimus monotherapy in ABO incompatible live donor [ABOiLD] transplantation.

Results are compared with 23 ABOiLD transplants performed using Rituximab and Daclizumab, Tacrolimus and Mycophenolate Mofetil [RTX group]. Steroid sparing was used in all patients [Prednisolone 60mgs, day 0-4; 30mgs, days 5-7 then stopped].

23 patients [11m, 12f; age 53.6 ± 10.3 yrs] received Campath [30mg iv] and Tacrolimus [target level 8–11 ng/mL] 2 weeks before proposed transplantation. IVIg [100mg/kg] was administered after each plasma exchange. All patients had a pre-transplant blood group antibody titre ≤1:4. Post transplant, patients received a further dose of Campath [20mg iv].

Rejection [AR] was diagnosed by biopsy and classified using the Banff 2007 criteria.

Duration of follow up was shorter in the Campath group [13.2±6.8 vs 35.8±18.4 years; p=0.0001] and they were older than RTX group [53.5±10.3 vs. 45.2±12.0 years; p=0.01]. Otherwise groups were well matched for sex, donor age, number of previous transplants, and mismatches versus HLA A, B and DR.

Patient survival in both groups at 12 months was 100%. Allograft survival in the Campath group was better than in the RTX group at 1, 6 and 12 months [100% vs. 91.3%, 100% vs 91.3% and 93.3% 91.3%]. In the Campath group only 1 graft was lost after withdrawal of immunosuppression due to sepsis. In the RTX group 1 graft was lost from haemorrhage, 1 to recurrent FSGS/rejection and 1 graft was lost to resistant antibody mediated rejection.

Allograft function [plasma creatinine (μmol/L)] in the Campath group was similar to the RTX group at 1, 3, 6 and 12 months [121.5±7.3 vs. 135.1±14.4, 130.5±7.6 vs 151.9±26.8, 134.9±8.1 vs 127.6±5.3 and 139.9±6.7 vs 130.9±6.7 [p=ns] respectively].

The Campath group experienced less AR [9/23 (39.1%) vs. 12/23 (52.1%); p=0.61] and there was less AMR [3/9 (33.3%) vs. 8/12 (66.7%); p=0.059] when compared with the RTX group. All episodes of AR were reversed successfully in the Campath group but not in the RTX group.

This is the first study to show that ABOi transplantation can be safely, cheaply and successfully performed using a simple Campath induction and Tacrolimus monotherapy regime.

O41

A prospective randomised paired trial of Sirolimus versus Tacrolimus as primary immunosuppression following non heart beating donor kidney transplantation.

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Introduction: Non heart beating donor (NHBD) kidneys are subjected to significant ischaemia / reperfusion injury. An immunosuppresive regime with minimal nephrotoxicity is paramount to optimising long-term function. This study aimed to determine whether Sirolimus, used in combination with MMF and prednisolone is one such regime.

Methods: In this prospective, open, paired study, recipients of kidneys from each NHBD received daclizumab induction and were then commenced on MMF (2g/day) and prednisolone (20mg/day). Once renal function improved (creatinine <350 micromol/L) recipient pairs from each donor were randomised to start either sirolimus or tacrolimus (target trough 5-10 mcg/L for both drugs) and the MMF was reduced to 1g/day once a therapeutic drug level had been achieved.

The primary endpoint was eGFR at 1 year (Cockroft-Gault) and secondary endpoints were biopsy proven acute rejection (BPAR), patient and graft survival and safety.

Results: Of the 30 consecutive donors, recipient pairs from 19 donors were recruited (pairs were excluded for various reasons e.g. refusal, graft thrombosis etc).

Groups	N	Median eGFR	ml/min/ 1.73m^2		BPAR	1yr graft	1 yr patient
	(ITT)	3 mnths	6 mnths	1 year	N (%)	survival	survival
Sirol	19	56.7	67.1	51.1	5 (26)	100	
Tac	19	58.0	55.8	59.1	4 (21)*	100	

* All occurred prior to starting tacrolimus whereas in the sirolimus group, all BPAR occurred after starting sirolimus within 3 months of transplant

The intention to treat (ITT) analysis showed that patient and graft survival and eGFR's at all time points were similar. Ten of the sirolimus group had to be switched to tacrolimus for either BPAR or sirolimus complications. When these 10 were censored out the eGFRs were again similar at each time point (sirol vs tac, 65.4 vs 58, 67.1 vs 57.2, 57.3 vs 62.4 and 58.1 vs 60.7 at 3,6,9 and 12 months respectively).

Conclusion and Discussion - Sirolimus instead of tacrolimus as primary immunosuppression combined with MMF and prednisolone apparently does not improve long-term graft function. Better outcomes may be achieved if an alternative induction agent (e.g. ATG) is used or if tacrolimus is switched to sirolimus at 3 months post transplant.

Joint BTS/ISHLT Symposium on Cardiothoracic Transplantation

Committee Room 1

11:30 – 12:30

O42

De novo formed donor-specific HLA antibodies adversely affect long-term graft survival after cardiac transplantation.

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It is well established that the presence of pre-formed donor-specific HLA antibodies (DSA) are associated with poor allograft survival. Where possible, patients are transplanted in the absence of DSA. The purpose of this study was to investigate the effect of de-novo and persistent production of DSA after transplantation on allograft survival and cardiac allograft vasculopathy (CAV).

Two-hundred and 24 patients (transplanted from 1995-2004) who were DSA negative at the time of transplant and had survived at least one year were selected. Serum which had been taken at annual intervals for 1-13 years was tested by Luminex single antigen assays (One Lambda, USA) for HLA antibodies. Persistent DSA was defined as de-novo production of DSA which was found on all subsequent occasions when measured. Complement fixing DSA were also measured using a modification of the Luminex assay. CAV was assessed by angiography at 2 year intervals post-transplant.

The 5 and 10 year graft survival for patients with de novo and persistent DSA was 90.6% and 64.1% compared to 98.3% and 88.5% for those patients without persistent and de novo DSA, p=0.0002. Similarly DSA produced in the first year ($p<0.0001$), or within the first 2 years was significantly associated with worse survival at 5 and 10 years ($p<0.0001$). Patients who had produced persistent DSA in the first year developed CAV earlier than those without persistent DSA (p=0.0279, similarly the first 2 years (p=0.032). Complement fixing DSA were present in 26 of the 43 patients with de novo and persistent DSA, all exhibiting reactivity with class II antigens and only one with class I reactivity. Of the non-complement fixing antibodies 8 were reactive with class I antigens either alone (n=5) or in conjunction with class II (n=3). Both complement fixing and non-complement fixing de novo DSA were associated with poor graft survival if produced within the first 3 years after transplant (p=0.006 and $p<0.0001$ respectively). Complement fixing de novo DSA within 2 years developed CAV earlier than other patients (p=0.006). Multivariate analysis indicated de novo persistent DSA to be an independent predictor of poor graft survival (p=0.0004, Hazard ratio=3.928) as well as HLA-DR mismatch and donor age. Only increasing donor age was found to be an independent risk factor for earlier development of CAV.

In conclusion, production of persistent DSA at any time after transplantation is an independent predictor of poor cardiac allograft survival. The development of de novo and persistent DSA within the first 2 years of transplantation is associated with earlier development of CAV.

O43

Death following primary graft dysfunction in cardiac transplantation – are UK results improving?

Vamsidhar Dronavalli[1], Saravana Ganesh[1], Chris Rogers[3,4], Nicholas Banner[2,4], Jayan Parameshwar[4,5], David Collet[4], Helen Thomas[4], Robert Bonser[1,4]

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Introduction: Primary graft dysfunction (PGD) following heart transplantation (HTx) is a significant cause of mortality and reported risk factors include ischaemic time (IT), donor age (DA), donor UNOS risk score (derived from IT, DA, ethnicity mismatch and urea: creatinine ratio) , female donor and recipient age and diabetes. Using data from the UK Cardiothoracic Transplant Audit, we examined whether death following PGD (dPGD) in the HTx has improved over time.

Methods: HTx between 4/95 and 9/08 were studied. Case records of all in-hospital and <30-day deaths were reviewed and the cause of death adjudicated by an independent panel. The characteristics of the cohort and outcomes were compared across 4 time periods of approximate equal duration. The UNOS donor risk score was calculated for transplants in the last 2 time periods.

Results: In total 2080 HTx were studied; 270 patients died within 30-days (13.0%, 95%CI 11.6-14.5) and 214 deaths were d-PGD (10.2%, 95%CI 9.0-11.7). Results by era are shown in the table.

	1/95-7/98 N=719	8/98-11/01 N=528	12/01-03/05 N=441	04/05-9/08 N=343	P value
30-day mortality	90 (13%)	77 (15%)	54 (12%)	49 (13%)	0.65
d-PGD	72 (10%)	66 (13%)	33 (8%)	43 (11%)	0.08
Donor age (y)	34±12	36±12	37±12	38±12	<0.01
IT (min)	181±54	195±53	214±54	216±49	<0.01
Female donor - male recipient	185 (26%)	114 (22%)	82 (19%)	49 (13%)	<0.01
Recipient age (y)	49.±10	48±12	46±13	46±13	<0.01
Recipient creatinine (μmol/L) (median,IQR)	116 (36)	119 (46)	110 (43)	111 (43)	<0.01
Recipient diabetes	56 (8%)	39 (7%)	52 (12%)	27 (7%)	0.04

The median UNOS donor risk score was higher for deaths within 30 days compared with 30-day survivors (median 4 IQR 3-6 vs. 3 IQR 1-6, p<0.01) but was similar for d-PGD and non-PGD deaths within 30-days (p=0.75).

Conclusion: Thirty-day HTx mortality and the incidence of d-PGD have not changed in the last 12 years. Of recognised risk factors, the fraction of female donors transplanted into male recipients has reduced, the mean age of the donor and ischemia times have increased without affecting outcomes.

O44

US-derived quantitative donor risk score predicts mortality after orthotopic heart transplantation in the UK

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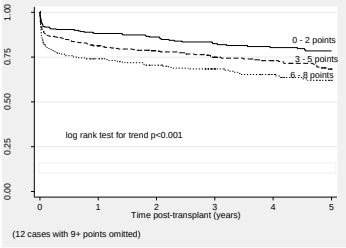
Background: A donor risk score for mortality after isolated first-time orthotopic heart transplantation was derived using data from the US United Network for Organ Sharing (Weiss, ES et al. J Heart Lung Transplant 28, S116). This risk score is applied to a UK cohort to assess whether it also predicts mortality after heart transplantation in the UK.



Methods: Data on transplants in adults (age ≥16 years) carried out between April 2000 and September 2008 were studied. The donor risk score is derived from four variables

(a) ischemia time (≤2 hours 0 points; >2-4 hours 1 point; >4-6 hours 3 points; >6 hours 5 points);
(b) donor age (<40 years 0 points; 40-50 years 3 points; >50 years 5 points);
(c) ethnicity mis-match (2 points);
(d) blood urea nitrogen to creatinine ratio (mg/dL) (ratio ≥ 30 3 points).

Scores are grouped into four pre-defined strata: 0-2 points; 3-5 points; 6-8 points and 9+ points. Post-transplant mortality to 5 years was compared across the strata.

Results: 1054 transplants were carried out and the data used to derive the donor risk score was complete for 872 transplants (82.7%). The median donor age and ischemia times were 38 years (IQR 27-47) and 3.5 hours (IQR 2.9-4.0) respectively. In 44 donors the blood urea nitrogen to creatinine ratio was ≥30 and there was an ethnicity mis-match in 102 transplants. Overall, 281 transplants (32.2%) scored between 0 and 2 points, 351 (40.3%) between 3 and 5 points, 228 (26.2%) between 6 and 8 points and 12 transplants (1.4%) had a score of 9 points or more.

Overall mortality at 30-days, 90-days and 5-years was 12.3% (95%CI 10.3-14.6), 14.2% (95%CI 12.1-16.7) and 30.2% (95%CI 27.0-33.8) respectively. Mortality to 5 years increased with donor risk strata (see figure p<0.001, 12 cases with 9+ points omitted). Each risk point corresponded to a 13% increase in mortality risk (Cox proportional hazard ratio 1.13 95%CI 1.07-1.20) and each risk strata was associated with a 42% increase in mortality risk (hazard ratio 1.42 95%CI 1.21-1.67) (c-statistic 0.59).

Conclusion: The US-derived donor risk index, which is simple to calculate and employable clinically, also predicts mortality after heart transplantation in the UK.

Abstracts
Ethics, Law and Public Policy

Great Hall

14:15 – 14:55

O45

Increase in Living Kidney Donors of Asian origin – the need for long-term follow-up

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Introduction: the number of living kidney donors has quadrupled in the last 10 years. Short-term outcome data for donors shows that it is a relatively safe procedure, and a small number of long-term studies in other countries show that donors are at low risk of long-term adverse consequences. There is little data which takes account of wider acceptance criteria currently employed, nor the increasing number of ethnic minority donors. In the UK the proportion of LKD of Asian origin has been at 4-7% for the last 5 yrs, with Asians constituting 15.7% of the national waiting list. In this centre the proportion of LKD of Asian origin has risen to 33% in 2009, reflecting the composition of the local waiting list with 32% of Asian origin.

Method: a literature review found unresolved issues around donors of Asian origin; there is a lack of data on long-term outcomes in non-Caucasian populations, yet there are ethnic differences in the patterns and progression of renal disease which may be important in living donors. The prevalence of type 2 diabetes and renal disease is increased four-fold among South Asians compared to indigenous populations (Fischbacher et al. 2003, Jenum et al. 2005). Age of presentation is also significantly earlier (UK Prospective Diabetes Study Group 1994). Conventional approaches to prevention and treatment may underestimate the risk in Asians as they are based on studies in Caucasian populations (Barnett et al. 2006). Renal disease is often linked to cardiovascular disease; the rate of ischaemic heart disease is 30–40% higher amongst Asian men than men in the general population of England (Department of Health 2001). In healthy UK South Asian men, CRP levels were found to be 17% higher than in Caucasian men; accounted for by greater central obesity and insulin resistance (Chambers et al. 2001). CRP levels in patients with the metabolic syndrome correlate directly with the number of metabolic abnormalities (Forouhi et al. 2001). Other markers have been proposed as predictors of diabetes or cardiovascular risk but have yet to be validated: lipoprotein(a), homocysteine, low levels of adiponectin, higher levels of fibrinogen and plasminogen activator inhibitor 1 (Barnett et al. 2006). Asians have a much greater tendency to deposit intra-abdominal fat, which is metabolically active and strongly related to insulin resistance (McKeigue et al. 1991). A BMI of 27.5 or more in an Asian person has been estimated to be associated with morbidities comparable to those in a Caucasian person with a BMI of 30. Follow-up of donors is poor in the UK: Hadjianastassiou et al. (2007) report that one year donor follow-up data returns were absent for 30.8% of donors.

Conclusion: The increased risk of diabetes mellitus and cardiovascular disease and their impact on renal function in the Asian population has implications for the long-term health of these donors. The questions we must ask are: can we identify potential donors at increased risk of kidney disease, and quantify that risk? Are recall or referral systems in place for long-term follow-up and is sufficient data collected? Can we modify the risk of kidney disease?

Evaluation of donors should be thorough with particular respect to any long-term risk of diabetes mellitus and other cardiovascular risk factors related to family or ethnic disposition and lifestyle. Long-term surveillance is essential to modify risk factors, allow early intervention and to further develop evaluation criteria for potential donors.

O46

Organ Donation In Black And Minority Ethnic Communities In The UK: Using Peer Educators To Access Hitherto "Hard-To-Reach" Populations.

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Purpose

The gap between the demand for and the supply of organs for transplantation is disproportionately wide in the UK's BME [black and minority ethnic] population, despite the fact that these communities have a disproportionately greater need. Our earlier research highlighted the need for more resources for BME communities to inform decision-making on this sensitive, and often taboo, subject. We found that the construction of an attitude may derive from multiple learning experiences in multiple contexts over time in an individual's life. This suggests that we should take an approach to public education that impacts on many different environments, if attitudes are to be informed more positively and organ donation become more acceptable. We have developed a novel approach, using Peer Educators, to gain access to those environments and disseminate knowledge about the need for organ donation.

Methodology

Peer Educators are active members of their community and represent diverse religious and cultural groups, with a natural empathy in terms of language, culture and health care experience. They raise public awareness through their networks and cascade information effectively and appropriately. By engaging Peer Educators in our work, it is possible to approach communities at grassroots level in a way that is not perceived as patronising, paternalistic and external. In collaboration with the local PCT, we trained and supported seven Peer Educators, who volunteered from within the local BME communities.

Results

During the first 3 months, the Peer Educators have attended over 60 events, which ranged from the small and local to the international. They made contact with more than 2000 people, actively engaging with almost 1000, thereby increasing knowledge of and enhancing dialogue on organ donation, to the extent that there were a significant number of participants, more than 150, who formally registered as donors on the Organ Donor Register (ODR). This does not include those reached through consequential media contacts (e.g. websites and community publications).

Conclusion

Participation in this important debate has progressed. It is hoped that in the longer term, empowerment of BME communities will further reduce inequalities in availability of this scarce resource.

O47

Is the increase in DCD organ donors in the UK contributing to the decline in DBD donors?

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Introduction

Organ donation after cardiac death (DCD) is becoming more common in the UK but DCD donors provide fewer usable organs than donors with brain death (DBD) and recipients of DCD organs may experience more complications. There have been anecdotal reports of potential DBD donors becoming DCD donors but the extent of this practice is unknown.

Methods

A comprehensive analysis of all patients who became solid organ donors in the UK between April 1999 and March 2009 was performed to identify trends in donor characteristics. Data from a prospective audit of all patients under 76 years who died in non-cardiothoracic intensive care units in the UK between April 2003 and March 2009, were analysed to determine whether the increase in DCD donation may be due to a conversion of potential DBD donors to DCD donors.

Results.

Over the last decade, the annual number of deceased donors (DD) increased by 16% from 777 in 1999/2000 to 900 in 2008/9. The increase is due exclusively to an increase in DCD donation with an almost 8-fold increase in DCD donors from 33 in 1999/2000 to 288 in 2008/9. Over the same time period, DBD donation has fallen 13% from 714 to 622 donors per year. For both DBD and DCD donors the proportion of 'expanded criteria donors' (Port et al. 2002) has increased markedly from 18% to 27%. DD are now less likely to have died of trauma (22% in 1999/2000 and 11% in 2008/9) and more likely to be overweight (BMI>25) (39% versus 54%).

Over the five year period 2004/5 to 2008/9, the number of deaths in ITU fell by 5% from 16389 to 15516. Over the same period, potential DBD donors (i.e. those with confirmed brain death (BD) and no medical contraindication) declined from a total of 1333 to 1135 (15%). The number of potential DCD donors fluctuated over the period with 1425 identified in 2008/9 but the conversion rate of potential donors into actual donors increased for both DBD and DCD donors with a conversion rate increase of 6 percentage points to 51% and 11 percentage points to 16% for DBD and DCD donors, respectively.

The percentage of patients in whom BD was possible who were not formally assessed for BD fell from 31% to 22%, suggesting that there is unlikely to be a large number of DCD donors who could have become DBD donors.

Conclusion

The number of potential DBD donors has fallen over the past decade and, despite transplant centres' willingness to use more marginal organs, the number of actual DBD donors has also declined. DCD donor numbers have increased markedly but there appears little evidence from this analysis that significant numbers of potential DBD donors becoming DCD donors.

O48

Variation and uncertainty in approaches to the discovery of misattributed paternity during work up for living donor renal transplantation in the UK.

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BACKGROUND: Misattributed paternity (MP) is estimated to affect 0.5% of all living donor renal transplants. Genetic (HLA) testing done routinely before all transplants reveals whether donor and recipient are genetically related. There are no published guidelines for UK clinicians should MP be discovered.

AIMS: To explore attitudes towards, and management of MP amongst UK renal clinicians.

METHODS: An anonymous, online survey about a hypothetical case of MP in a donation from a daughter to her father was sent to all UK renal transplant centres. Respondents were asked both multiple choice and open-ended questions about their views on disclosure of MP.

RESULTS:

- 145 health professionals responded (49% physicians, 21% surgeons, 22% nurses and 8% others); 86% worked in hospitals with renal transplant units. 44% were aware of at least one case of MP on their unit. Only 14% knew of a relevant unit guideline or policy.
- There was a lack of consensus among clinicians about whether they would disclose MP. 20% stated they would always disclose whereas 13% would never disclose. 67% said their decision would depend on the circumstances. There was no significant difference in approach to disclosure between professions ($p=0.94$) or specialties ($p=0.71$).
- A considerable amount of clinical time is expended in multi-disciplinary team discussion of each case. Most respondents felt it was desirable to consult the ethics committee or legal department (87% and 80%).
- 56% of respondents said they would inform the donor's mother about MP. This was usually in order to gain further information and minimize harm to the family, despite the apparent breach of patient confidentiality.

CONCLUSION: Potential measures to reduce uncertainty, time and stress involved in managing the discovery of MP include:

- Discuss, with the aid of appropriate information sheets and consent forms, what information might be elicited by all pre-transplant tests with donor and recipient and establish their wishes regarding disclosure.
- Only perform tests that will contribute to clinical decision-making. The role of HLA testing in living donation should be carefully considered.
- Develop local or national policy so that there is consistency of approach.

Abstracts
Immunosuppression 2

Small Hall

14:15 – 14:55

O49

Primary Outcomes from a Randomised, Phase III Study of Belatacept vs Cyclosporine in ECD Kidney Transplants (BENEFIT-EXT Study)

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

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Introduction: Belatacept, a selective co-stimulation blocker, is being evaluated as an immunosuppressant in renal allograft recipients to avoid the renal and extra-renal toxicities of calcineurin inhibitors. As recipients of extended criteria donor (ECD) kidneys are at elevated risk of graft dysfunction and loss, they may particularly benefit from a non-nephrotoxic option such as belatacept.

Methods: BENEFIT-EXT is a 3-year, randomised, Phase III study in adults receiving an ECD kidney transplant. Patients were randomised 1:1:1 to receive a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids. The two co-primary endpoints were: composite patient/graft survival at 12 months and composite renal function (measured GFR <60 mL/min/1.73 m^2 at month 12 or a decrease in measured GFR ≥10 mL/min/1.73 m^2 from month 3 to month 12). Secondary endpoints included the incidence of acute rejection (AR).

Results: 543 patients were randomised and transplanted. Patient/graft survival with belatacept was non-inferior to CsA at month 12.

	Belatacept MI (n = 184)	Belatacept LI (n = 175)	CsA (n = 184)
Composite patient/graft survival, n (%)	158 (86%)	154 (88%)	156 (85%)
Composite renal function impairment endpoint, n (%)	124 (71%) (p = 0.002 vs CsA)	129 (76%) (p = 0.06 vs CsA)	151 (85%)
Mean measured GFR, mL/min (SD)	52.1 (21.9) (p = 0.008 vs CsA)	49.5 (25.4) (p = 0.10 vs CsA)	45.2 (21.1)
Acute rejection, n (%)	32 (17%)	31 (18%)	26 (14%)

The overall rates of infection and malignancy were comparable between groups. PTLD was observed in 1 (0.5%) and 2 (0.9%) patients in the MI and LI groups and in none in the CsA group in the first 12 months.

Conclusions: Belatacept regimens demonstrated better renal function, with comparable patient/graft survival and AR compared to a CsA-based regimen in ECD kidney transplant recipients. Belatacept represents a promising immunosuppressant therapy in ECD kidney transplant recipients.

O50

Primary Outcomes from a Randomised, Phase III Study of Belatacept vs Cyclosporine in Kidney Transplant Recipients (BENEFIT Study)

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

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Introduction: Belatacept, a co-stimulation blocker, is being developed as an immunosuppressant for kidney transplant recipients to avoid the renal and extra-renal toxicities of calcineurin inhibitors (CNIs) that impact long-term patient/graft survival. BENEFIT assessed belatacept-based regimens vs a cyclosporine-based regimen (CsA) in kidney transplant recipients.

Methods: BENEFIT is a 3-year, randomised, phase III study in adults receiving a kidney transplant from a living or deceased donor with an anticipated cold ischemia time <24 hours. 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. Co-primary endpoints were composite patient/graft survival, composite renal function (measured GFR [mGFR] <60 mL/min/1.73 m^2 at month 12 or a decrease in mGFR ≥10 mL/min/1.73 m^2 from month 3 to month 12), and incidence of acute rejection (AR).

Results: 666 patients were randomized and transplanted. 58% received living donor transplants; 42% from deceased donors. Patient/graft survival with belatacept regimens was non-inferior to CsA at month 12.

	Belatacept MI (n = 219)	Belatacept LI (n = 226)	CsA (n = 221)
Composite patient/ graft survival, n (%)	209 (95%)	218 (97)	205 (93%)
Composite renal function impairment endpoint, n (%)	115 (55%) (p <0.0001 vs CsA)	116 (54%) (p <0.0001 vs CsA)	166 (78%)
Mean measured GFR, mL/min (SD)	65.0 (30.0) (p <0.0001 vs CsA)	63.4 (27.7) (p <0.0001 vs CsA)	50.4 (18.7)
Acute rejection, n (%)	48 (22%)	39 (17%)	16 (7%)

The incidence of AR in the LI regimen was non-inferior to CsA. AR in belatacept patients had limited impact on graft survival and on the relative renal benefit of belatacept. Infection and overall malignancy rates were similar across arms; PTLD was observed in 1 (0.5%), 2 (0.9%), and 1 (0.5%) patients in the MI, LI, and CsA groups in the first 12 months.

Conclusions: At 12 months, belatacept regimens demonstrated superior renal function and similar patient/graft survival vs CsA, despite an increase in AR in the early post-transplant period. Belatacept represents a promising, non-nephrotoxic therapy option in kidney transplant patients.

O51

Belatacept is Associated with Preservation of Renal Function and Structure at 1 Year Compared to Cyclosporine in Kidney Transplant Patients (BENEFIT Study)

Josep Grinyó[1], Guillermo Mondragón-Ramirez[2], Prakesh Darji[3], Barbara Bresnahan[4], Thomas Pearson[5], Gregg Di Russo[6], Pushkal Garg[6], J Xing[6]

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Introduction: Post-transplant renal function at 1 year and chronic allograft nephropathy (CAN) correlate with long-term graft function and patient/graft survival. Belatacept is being investigated as part of a non-nephrotoxic immunosuppressant regimen in kidney transplant recipients to replace calcineurin inhibitors. This abstract focuses on renal endpoints.

Methods: BENEFIT is a 3-year, randomised, phase III study of belatacept in adults receiving a kidney transplant from a living or deceased donor with an anticipated cold ischemia time <24 hours. Patients were randomised 1:1:1 to receive a more intensive (MI) or a less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids. The primary renal endpoint was composite renal function (measured GFR [mGFR] <60 mL/min/1.73 m^2 at month 12 or a decrease in mGFR ≥10 mL/min/1.73 m^2 from month 3 to month 12). Secondary renal endpoints at month 12 included mGFR, calculated GFR (cGFR), and protocol biopsies to assess for CAN.

Results: 666 patients were randomised and transplanted. More CsA patients had reduced renal function vs belatacept regimens as shown by the composite renal endpoint.

	Belatacept MI (n = 219)	Belatacept LI (n = 226)	CsA (n = 221)
Composite renal function impairment endpoint, n (%)	115 (55%) (p <0.0001 vs CsA)	116 (54%) (p <0.0001 vs CsA)	166 (78%)
Mean mGFR, mL/min (SD)	65.0 (30.0) (p <0.0001 vs CsA)	63.4 (27.7) (p <0.0001 vs CsA)	50.4 (18.7)
Mean cGFR, mL/min (SD)	68.3 (19.2) (p <0.0001 vs CsA)	68.1 (19.0) (p <0.0001 vs CsA)	53.6 (16.9)
CAN prevalence, n (%)	40 (18.3%) (p = 0.001 vs CsA)	54 (23.9%) (p = 0.058 vs CsA)	71 (32.4%)

Differences in cGFR were apparent 1 month post-transplant and maintained through 1 year. There was concordance between overall mGFR and cGFR over the first 12 months.

Conclusions: Belatacept regimens demonstrated superior renal function and had a favourable impact on the development of CAN at 12 months compared to CsA. Differences in renal function were observed soon after transplant, were maintained through 1 year, and will be followed during the 3-year study.

O52

Belatacept is Associated with Improved Cardiovascular and Metabolic Risk Factors Compared to Cyclosporine in Kidney Transplant Patients (BENEFIT and BENEFIT-EXT)

Yves Vanrenterghem[1], Eduardo Mancilla-Urrea[2], Philippe Lang[3], M Agarwal[4], Alan Block[4], J Xing[4]

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Introduction: Hypertension, dyslipidaemia, and diabetes are common comorbidities in kidney transplant recipients that impact patient survival and can be exacerbated by certain immunosuppressive agents. Belatacept is a selective co-stimulation blocker that may avoid extra-renal toxicities associated with calcineurin inhibitors.

Methods: BENEFIT assessed belatacept in patients receiving a kidney transplant from a living or deceased donor; BENEFIT-EXT in extended criteria donor (ECD) recipients. Each assessed belatacept in more intensive (MI) and less intensive (LI) regimens vs cyclosporine (CsA). All patients received basiliximab, MMF, and corticosteroids. Secondary endpoints included changes in systolic (SBP) and diastolic (DBP) blood pressure, intensity of anti-hypertensive treatment; mean changes in non-HDL, total-, LDL-, and HDL-cholesterol and serum triglycerides (TGs); the intensity of lipid-lowering medication use, and the incidence of new onset diabetes mellitus (NODM). Endpoints through month 12 are presented.

Results: 1209 patients were randomised and transplanted across the two studies (n = 666 in BENEFIT; 543 in BENEFIT-EXT). Mean SBP was 6–8 mmHg lower and mean DBP was 3–4 mmHg lower in the MI and LI groups vs CsA ($p \leq 0.02$) in ECD or non-ECD recipients. More CsA patients used ≥3 anti-hypertensive medications compared to LI patients ($p < 0.02$ LI vs CsA in each study).

Non-HDL cholesterol was lower in the MI or LI groups (132–135 mg/dL) vs CsA (142–153 mg/dL; $p < 0.01$ MI or LI vs CsA in each study). Serum TGs were lower in the MI or LI groups (149–172 mg/dL) vs CsA (180–214 mg/dL; $p < 0.02$ MI or LI vs CsA in each study). Total cholesterol increased less in the belatacept LI group vs CsA in both studies ($p < 0.05$). Changes in LDL- and HDL-cholesterol were not significant between belatacept and CsA regimens. NODM occurred in 2.3%, 5.1% and 9.3% of the MI, LI, and CsA patients in BENEFIT-EXT ($p = 0.03$ MI vs CsA; p=NS LI vs CsA) and in 7.1%, 4.2%, and 9.9% of the patients in BENEFIT (p=NS MI or LI vs CsA).

Conclusions: Belatacept regimens had a better cardiovascular and metabolic profile than the CsA regimen, with less hypertension, dyslipidaemia, and NODM vs CsA. The differences in these cardiovascular and metabolic parameters will continue to be assessed over the 3-year trials.

O53

Belatacept Preserves Renal Function and Structure at 1 Year Compared with Cyclosporine in Extended Criteria Donor (ECD) Kidney Transplant Patients (BENEFIT-EXT)

José Medina Pestana[1], José M. Campistol[2], Maria del C Rial[3], Valter Duro Garcia[4], Thomas Becker[5], M Agarwal[6], Pushkal Garg[6], T Duan[6]

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Introduction: Calcineurin inhibitors (CNIs) contribute to diminished renal function and chronic allograft nephropathy that impact long-term graft survival in kidney transplant recipients. A belatacept-based immunosuppressive regimen that replaces CNIs may improve renal function and structure in extended criteria donor (ECD) kidney recipients. This abstract focuses on renal endpoints.

Methods: BENEFIT-EXT is a 3-year, randomised, phase III study in adults receiving an ECD kidney transplant. Patients were randomised 1:1:1 to receive a more intensive (MI) or less intensive (LI) regimen of belatacept or CsA; all patients received basiliximab induction, MMF, and corticosteroids. The primary renal endpoint was composite renal function (measured GFR [mGFR] of <60 mL/min/1.73 m^2 at month 12 or a decrease in mGFR ≥10 mL/min/1.73 m^2 from month 3 to month 12). Secondary renal endpoints at month 12 included mGFR, calculated (cGFR) GFR, and protocol biopsies to assess for chronic allograft nephropathy (CAN).

Results: 543 patients were randomised and transplanted. 71% of patients in the MI group, 76% in the LI group, and 85% in the CsA group met the composite renal function non-inferiority endpoint.

	Belatacept MI (n = 184)	Belatacept LI (n = 175)	CsA (n = 184)
Composite renal function impairment endpoint, n (%)	124 (71%) (p = 0.002 vs CsA)	129 (76%) (p = 0.06 vs CsA)	151 (85%)
Mean mGFR, mL/min (SD)	52.1 (21.9) (p = 0.008 vs CsA)	49.5 (25.4) (p = 0.10 vs CsA)	45.2 (21.1)
Mean cGFR, mL/min (SD)	50.1 (17.2) (p < 0.01 vs CsA)	49.5 (16.7) (p < 0.01 vs CsA)	42.7 (15.9)
CAN prevalence, n (%)	82 (44.8%) (p = NS vs CsA)	80 (46.0%) (p = NS vs CsA)	95 (51.6%)

Differences in cGFR occurred as early as the first month post-transplant and continued through 12 months.

Conclusions: Belatacept demonstrated better renal function in ECD kidney transplant recipients, with differences that occurred in the early post-transplant period and were maintained through the first year. Whether trends for lower CAN with belatacept will magnify differences in renal function over time will be assessed in this 3-year trial.

Abstracts
Histocompatibility

Council Chamber

14:15 – 14:55

O54

Optimising HLA matching for deceased donor kidney transplantation by determining alloantigen immunogenicity at the molecular level

Vasilis Kosmoliaptsis[1], Linda D Sharples[1], Afzal N Chaudhry[1], Rachel J Johnson[2], Susan V Fuggle[2], J Andrew Bradley[1], Craig J Taylor[1]

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Introduction: Conventional approaches to HLA matching for deceased donor (DD) kidney allocation regard all HLA mismatches within a given locus as having equal weighting. We hypothesised that HLA alloantigen immunogenicity for a given patient's HLA type can be predicted by differences in structural and physiochemical properties and examined whether this approach provides a better assessment of transplant compatibility.

Methods: A computer program was developed to compare each potential mismatched HLA class I (n=1,964) and class II (n=1,604) specificity with the HLA type of a cohort of highly sensitised patients (n=62) and calculate the number of amino acid mismatches (AAM, after inter-locus subtraction) and the overall hydrophobicity and electrostatic mismatch score (HMS and EMS). The ability of these immunogenicity indices to predict the likelihood and magnitude of an alloantibody response (determined using single antigen HLA class I and II antibody detection beads) against mismatched HLA was assessed. We next examined the influence of AAM, EMS and HMS on the outcome of adult DD kidney transplants, undertaken in the UK from 1990 to 2005. To enable direct comparison of the effect of each variable, independent of their confounding inter-relationships when there are multiple HLA mismatches present, we considered only zero HLA-A, -B, -DR mismatched transplants (n=1,737) and those with a single HLA-A or -B mismatch (n=2,327). Univariate and multivariate analyses were performed using log-rank tests and Cox-regression.

Results: There was a strong correlation between increasing number of AAM for both HLA class I and class II and the occurrence ($p<0.0001$, odds ratio for each AAM increase 3.85) and magnitude ($p<0.0001$) of alloantibody responses. Mismatched HLA class I and II specificities with 0-1 AAM led to weak alloantibody responses (median MFI 2,276 and 32 respectively) in contrast to those with ≥8 AAM (median MFI 11,822 and 5,128 respectively). Similarly, HMS and EMS correlated strongly with both alloantibody production and the strength of the alloantibody response ($p<0.0001$ for class I and II). Kidney transplants with a single HLA-A or -B mismatch had lower graft survival compared to fully HLA matched transplants (81.9% v 84.2% at 5 years, HR 1.2, $p=0.004$). Importantly, of the single HLA-A or -B mismatched transplants those with zero or 1 AAM had significantly higher survival compared to transplants with 2 or more AAM (89.3% v 81.8% at 5 years, HR 1.5, $p=0.03$), but similar to the survival of fully HLA matched transplants. This relationship was independent of any underlying serological HLA matching effect. However, the number of AAM and the overall physiochemical scores were highly correlated, such that no additional predictive value for transplant survival was observed in this dataset.

Conclusion: Information derived from the structural and physiochemical properties of HLA class I and class II allows prediction of HLA alloantigen immunogenicity for a given recipient HLA type and may be of greater clinical relevance than conventional HLA matching.

O55

Successful minimisation of perioperative antibody modulation in ABOi renal transplantation

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Blood group incompatible renal transplantation (ABOi) has become increasingly successful in recent years, with a strategy including B cell depletion, IvIg, and pre- and post-operative immunabsorption (IA). We have adopted an increasingly minimilast approach to ABOi transplantation, suggesting that not all of these therapies are required.

Methods: 36 patients (including 1 child) underwent ABOi. Initially patients were treated with pre-operative rituximab, 0.5g/kg IvIg, pre-operative IA and routine post-operative IA. Subsequently routine IvIg and post-operative IA were abandoned, as was rituximab in selected cases. Pre-operative IA was replaced by double filtration plasmapheresis (DDFPP) where pre-treatment titres were less than 1 in 128. Median baseline titres were 1 in 64 (0-512). Protocol biopsies were performed at 3 months.

Results: Mean age was 49 years, with 17 females. 15 patients had pre-operative IA, 14 had DFPP and 7 had no antibody removal. 26 patients had no pre-operative IvIG, and 31 had no routine post-operative IA or DFPP. 4 patients had no rituximab.

2 patients had 1 IA post-operatively after a rise in titres. 1 patient required 3 attempts at antibody removal for successful transplantation, and 1 patient had2 attempts. Only 1 patient has had an unsuccessful attempt at antibody removal.

Mean follow-up is 432 days (range 12-1605), with a mean serum creatinine of 130 umol/l (s.e.5.5). Graft survival is 100%. 1 (3%) patient had acute vascular rejection and 7 had acute cellular rejection (19%), with no acute antibody mediated rejection.

Conclusions: minimisation of antibody removal therapy in ABOi transplantation can be performed safely, with excellent results. Routine post-operative IA is not required, and B cell depletion can be omitted in selected patients.

O56

The significance of IgG subclasses in HLA antibody incompatible kidney transplantation

Dave Lowe[1,2], Rob Higgins[3], Nithya Krishnan[2,3], Daniel Zehnder[1], Rizwan Hamer[2,3], Mark Hathaway[1], Dan Mitchell[2], David Briggs[1]

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Introduction. Antibodies in prospective kidney recipients can be a barrier to transplantation, stopping about 250 living donor transplants in the UK annually. In response we implemented a programme of HLA antibody removal in 2003. Our observations in over 70 such procedures are that although pretransplant antibody reduction is required to avoid complement mediated hyperacute rejection or severe early graft damage, an early post-transplant antibody response occurs in most cases and in about half of these rejection is diagnosed. Our aims were to investigate whether the subclass of both pre and post-transplant donor-specific antibodies (DSA) and/or IgG subclass switching associates with subsequent early rejection. The purpose being to provide evidence for improved clinical management.

Method. 52 previous AiT cases were selected comprising two equal groups of rejectors and non-rejectors, with rejection diagnosed on the basis of clinical symptoms and/or histology. Daily serum samples were taken post-transplant with total level of HLA-specific IgG determined by single antigen bead assay. IgG1,2,3 and 4 HLA specific antibody levels were determined for all pretreatment, pretransplant and post-transplant peak samples.

Results. We have previously reported that in these cases the higher pretreatment total IgG levels predict rejection. Here we show IgG1 was the most common subclass, followed in order by IgG2, IgG3 and IgG4. IgG4 was restricted to the group of recipients who subsequently went on to have rejection episodes (6/26 vs 0/26, $p=0.001$). Examination of the difference in incidence of a response for each subclass (higher level at peak vs pre-treatment) showed that the IgG1 response provides the strongest correlation with rejection (HLA Class I DSA $p=0.026$, HLA Class II $p<0.001$) with an IgG2 response only significant for Class II DSA associated rejection ($p=0.041$). Finally we observed 8 rejector cases class switching to IgG2 compared with 2 non-rejectors ($p=0.03$).

Discussion. Our work demonstrates that IgG DSA subclass distribution is a predictor of early rejection and provides insights into the immunology of rejection in this setting. The association of Ig4 with rejection is strongly suggestive of the more chronically sensitised cases being the most likely to reject with implications in patient selection and treatment. IgG1 is the predominant subclass both pre and post-transplant. The appearance of IgG2 (relatively poor at complement fixation) with early rejection implies that complement mediated damage may not always be central to this rejection process. This is supported by the association of IgG4, the weakest complement fixing IgG with rejection and lack of association with IgG3, the strongest complement fixing subclass. The presence of specific IgG subclasses may reflect specific T cell dependent processes. Indeed we have shown that in these cases, rejection is most effectively treated with anti-T cell agents such as OKT3.

O57

HLA antibody incompatible live donor renal transplantation with and without T-cell depleting induction immunosuppression.

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Freeman Hospital, Newcastle upon Tyne, United Kingdom

INTRODUCTION Many protocols have been developed to allow renal transplantation despite the presence of donor-reactive HLA antibodies (donor specific antibodies, or DSA), with or without a positive cellular cross match (XM). The presence of DSA indicates a memory immune response, and HLA incompatible (HLAi) transplants are at increased risk of early acute rejection (AR). Here we describe protocols with or without Alemtuzumab induction, and a very low incidence of AR when Alemtuzumab is used.

PATIENTS AND PROTOCOLS Of 32 HLAi transplants performed in Newcastle between November 2006 and December 2009, 23 were consecutive live donor transplants. Between 2006 and 2008 immunosuppression comprised Rituximab 1 month prior to transplantation, antibody removal, IVIG, and a further dose of Rituximab on the day of transplantation. Those with low titre DSA who did not require antibody removal received Basiliximab induction and no Rituximab. From 2009, all patients with DSA received Alemtuzumab induction. Those requiring antibody removal received Rituximab 1 month prior to transplantation. All patients received Tacrolimus (TAC), Mycophenolate mofetil (MMF) and Prednisolone maintenance immunosuppression.

RESULTS 13 patients were transplanted between 2006 and 2008, with 1 graft removed on post-operative day 2 as a result of haemorrhage. Of the remaining 12, 9 were XM+ and 3 DSA+ but XM-. Biopsy proven AR was identified in 7 patients in the first 3 post-transplant months (Banff 1A in 2, 1B in 2, 2A in 1, 2B in 1 and AMR in 1). In addition, 1 patient with 1A AR was C4d+. 6 patients required treatment with Thymoglobulin. One graft was lost due to a combination of resistant 2A AR and BK nephropathy, and another due to refractory HUS without any evidence of AMR. The mean serum creatinine of the 10 functioning grafts is 129μmol/L (range 83-202) at a mean of 24 months follow-up. In contrast there have been no episodes of AR and no graft losses in the 10 Alemtuzumab-treated patients (6 XM+ including 2 HLA and ABOi patients, and 4 DSA+ but XM-). Mean serum creatinine is 121μmol/L (range 88-160), although follow-up in the Alemtuzumab-treated group is short (mean 5 months).

CONCLUSION Our experience suggests that Rituximab-based immunosuppression offers effective prophylaxis against AMR in HLAi transplantation, but that there is an unacceptable incidence of T-cell mediated rejection without the use of T-cell depleting induction therapy.

Basic Science

Council Chamber

19 March 2010

11:15 – 13:00

O58

Renal Allograft Fibrosis: T cells express Thrombospondin-1 activate latent TGF-ß

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Background: Transforming growth factor ß (TGF-ß) is a crucial profibrotic cytokine that can stimulate epithelial to mesenchymal transition and the accumulation of extracellular matrix (ECM) during renal allograft failure. The activity of TGF-β is regulated by the conversion of a matrix-bound latent complex into the active factor. This study was designed to determine whether thrombospondin-1 (TSP-1) contributes to the generation of active TGF-β by intragraft T cells.

Method: Purified T cells from healthy volunteers were activated by mixture with CD3/CD28-conjugated beads. After 72 hours these cells were co-cultured with human renal tubular epithelial cells (RTEC) or stimulated with latent TGF-β1 complex or bioactive TGF-β1 (both at 10ng/ml). Some cultures were also supplemented with either an LSKL peptide inhibitor of TSP-1, or a scrambled (SLLK) control sequence (both at 50µM). The expression of markers associated with TGF-β stimulation of activated T cells were examined by flow cytometry (CD103) and real-time quantitative PCR (αE integrin, Foxp3, LTBP-1, TGF-ß1 and TSP-1).

Results: Mixture of activated T cells with RTEC, latent TGF-β or active TGF-β all increased the expression of CD103 protein but the induction by RTEC or latent TGF-β was inhibited specifically in the presence of the TSP-1 inhibitor. Treatment with latent TGF-β1 for 6 hrs also increased the expression of mRNA encoding CD103 (3.8 fold; $p<0.01$) and Foxp3 (1.8 fold; $p<0.05$). Addition of the TSP-1 inhibitor reduced this induction of CD103 (24-fold reduction) and Foxp3 (4.9 fold reduction) in comparison with cultures containing the control peptide**.**

Conclusion: Activated T cells can respond to TGF-β which is generated from the latent complex by the action of T cell associated TSP-1. This may allow intragraft differentiation of CD103+ and FOXP3+ T cells which can modify the development of immune cell-mediated chronic allograft failure.

O59

Chronic Renal Allograft Rejection: Examination of the Sequestration and Activation of Latent TGF-β

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Chronic renal allograft failure is associated with increased activity of TGF-β leading to fibrosis. This growth factor is secreted in a latent form consisting of a mature cytokine dimer complexed with a dimeric latency-associated peptide (LAP). This in turn binds covalently to the latent TGF-β binding protein (LTBP), which binds to heparan sulphate (HS) glycosaminoglycans (GAGs), thereby regulating the concentration of TGF-β in tissue. This study will assess the potential to displace LTBP-anchored latent TGF-β from the renal matrix, reducing the potential for development of chronic fibrosis.

A cDNA sequence encoding an LTBP1 N-terminal fragment (N5) containing a putative heparin-binding sequence (HRRRPIHHHVGK) was cloned from human renal cell DNA. The protein was then synthesised as a his-tagged thioredoxin fusion protein using the *Origami* bacterial expression system, with transcription being induced using the lactose analogue, IPTG. After purification on a nickel column and subsequent thioredoxin cleavage with enterokinase, the 198 amino acid (21.5 kDa) protein was found to bind a heparin column (heparin is chemically analogous to HS) in fast phase liquid chromatography (FPLC) experiments. It was also found to bind solid-phase heparin bound to 96 well plates, and was competed away by incubation with soluble heparin (IC_{50} = 0.2μg/ml), heparan sulphate (IC_{50} = 33.2μg/ml), low molecular weight heparin (IC_{50} = 6.9μg/ml), and non-anticoagulant heparin (IC_{50} = 16.0μg/ml), suggesting a specific ionic interaction between LTBP1 and heparin-like GAGs. In a cell-based ELISA experiment, N5 was found to bind less efficiently to the GAG deficient cell line CHO 745 than to GAG expressing, wild-type CHO cells.

These data suggest that the N-terminus of LTBP1 is crucial for the sequestration of latent TGF-β to the ECM within the kidney. The potential of heparin-like GAGs to displace this latent TGF-β may have therapeutic potential for preventing fibrosis in chronic renal allograft failure.

O60

Corneal graft rejection in the inbred NIH minipig

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Purpose. To develop a pre-clinical model of corneal graft rejection in the semi-inbred NIH minipig and to validate the model clinically and by immunohistology. **Methods.** Swine leukocyte antigen(SLA)^{cc} and SLA^{dd} strain minipig and inbred Babraham pigs (SLA^{bb}) were obtained from the Institute for Animal Health, Compton. To facilitate post-operative handling, graft recipients were habituated to handlers by regular contact for at least 3 weeks before operation. SLA^{bb}, SLA^{cc} or SLA^{dd} strain corneas were transplanted to SLA^{cc} strain recipients aged 3-5 months. SLA^{cc} autografts served as controls. No immunosuppression was administered. Recipients were monitored for rejection by ophthalmological slit lamp. Grafts undergoing rejection, non-rejected grafts and contralateral corneas were excised post-mortem and processed for immunofluorescence histology. Infiltrating antigen presenting cells (CD14^{+}, CD16^{+}, CD163^{+}, MHC class II^{+}), T cells (CD3^{+}, CD4^{+}, CD8^{+}) and ingress of blood vessel were quantified by digital capture of 3-colour-channel images. Numbers of positive pixels for each fluorochrome were counted using *ImageJ* software, percentage areas of labelling were calculated and analyzed by factorial ANOVA. Some grafts were monitored for up to 30 days after rejection to determine whether opacity and oedema resolved, as an indicator of corneal endothelial repair. **Results.** Post-operative complications were minimal. Initial post-transplant oedema cleared within 7-10 days. Autografts (n=5) and SLA^{cc} to SLA^{cc} allografts (minor mismatches, n=5) remained clear thereafter. Rejection of SLA^{bb} (n=6) and SLA^{dd} (n=10) allografts in SLA^{cc} recipients was characterised by graft opacity and edema, an epithelial rejection line and neovascularisation to the centre of the graft. Median graft survival was 67 days (range 48->89 days) for SLA^{bb} grafts and 57 days (range 30->90 days) for SLA^{dd} grafts. There was a significant increase in leukocyte subsets in transplanted vs. contralateral eyes ($p<0.001$) and in clinically rejected compared with non-rejected grafts ($p<0.001$). Unlike rat and rabbit grafts, pig grafts did not recover clarity after rejection. **Conclusions.** Rejection in the NIH minipig resembles human rejection clinically and in proliferative capacity of corneal endothelium. It is therefore an excellent model both for testing potential rejection therapies and for study of the underlying immunobiology of allograft rejection.

O61

Blockade of OX40 costimulation reduces the alloreactive effector T cell pool and prevents CD8$^+$ T cell mediated skin allograft rejection.

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Background: OX40 (CD134) is a member of the tumour necrosis receptor superfamily and is a potent costimulatory molecule that facilitates effector T cell differentiation and survival. Blockade of the OX40-OX40L interaction has received much attention in models of autoimmune disease, but its role in transplantation is less well defined.

Methods: The alloimmune response of BM3 TCR transgenic T cells was measured *in vitro* by the incorporation of ^{3}H thymidine. *In vivo*, 1x10^5 naïve alloreactive TCR transgenic T cells (BM3) were adoptively transferred into syngeneic RAG$^{-/-}$ mice and the following day mice received an allogeneic H2^{b+} skin transplant with and without OX40 blockade. Skin allograft survival was monitored and the BM3 T cell number, phenotype and division profile was measured in the spleen and axillary lymph nodes using flow cytometry.

Results: *In vitro*, allogeneic stimulation of CD8$^+$ T cells isolated from BM3 mice and from wild-type mice resulted in upregulation of OX40 from day 3 of culture. OX40 blockade partially inhibited the proliferation of BM3 TCR transgenic T cells *in vitro* (54% ± 3.5). *In vivo*, OX40 blockade prevented skin allograft rejection mediated by naïve CD8$^+$BM3$^+$ T cells compared to controls until OX40 blockade was stopped (MST 59 vs. 19.5 days; $p<0.0014$). Surprisingly, analysis of the draining lymph nodes 10 days post transplant showed that OX40 blockade had no effect on the proliferation of BM3 CD8$^+$ T cells to the skin allograft but prevented the accumulation of BM3 effector T cells (control cell number - 43832 ± 14258; OX40 blockade cell number - 6610 ± 1956).

Discussion: Taken together, these data demonstrate that activated CD8$^+$ T cells express OX40 and that the blockade of OX40-OX40L interactions attenuates CD8$^+$ T cell responses to alloantigen *in vitro* and *in vivo* by reducing the survival of effector T cells. Therefore, we propose that blocking the OX40-OX40L interaction would be a worthwhile adjunct to pre-existing tolerance induction strategies and may result in the induction of a more reliable and robust form of operational tolerance to allografts.

Posters

Great Hall

17 March 2010

17:15 – 18:15

ABO Incompatible 1

Moderator: Dr Nick Torpey

P1

The Impact of HLA Donor Specific Antibodies in the Absence of desensitization in CDC Negative Recipients. Is their Presence always a veto?

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Introduction

In the last few years desensitisation protocols have found widespread application in the setting of live donation. We have shown previously, that re-transplanting patients who have developed donor specific antibodies (DSA), in the setting of cadaveric donation, is possible with good outcome in the presence of cytotoxic negative crossmatch.

Aim

Review the outcome of all cadaveric re-transplants that were performed with negative cross-match but possessed DSA according to traditional solid phase or flow cytometry methods, and associate the results with the Luminex measured levels of DSA.

Method and results

From 1998 to 2003 there were 55 retransplants from cadaver donors. As all these patients were transplanted with the knowledge of a negative Cytotoxic crossmatch (CDCXM), no specific changes were made in their immunosuppression management. On retrospective analysis using solid phase assay and then flow cytometry-based techniques we identified 10 patients with DSA. On flow cytometry (FC) cross matching (with donor samples) there were three patients who were T-cell positive and B-cell positive, three were T-cell positive and B-cell negative and four were T and B-cell negative.

We conducted retrospectively Luminex single bead assays, on the last available pre-transplant sample, to define the type and level of DSA's. DSA against either class II [DQ2 (MFI values 4235-9348), DQ6 (88-2224), DQ7 (3073-7014), DQ8 (772-4883)] or in 1 patient class I were identified [A11 (3700-3900), CW 3175].

Median follow up was 6 years. Two kidneys were lost early postoperatively, one due to renal vein thrombosis (on biopsy had no sign of rejection) and one due to recurrent FSGS respectively. No graft was lost due to an acute rejection and no humoral rejection occurred in the 1st year post transplant.

One patient died at 6 years with a functioning graft. Two grafts failed at 6 and 8 years, and 4 grafts are still functioning at 6 to 8 years post transplant giving 5-year graft survival of 80%. Functioning grafts have a mean creatinine of 175 and median of 155 μmol/l. There was no association of the kidney function and the graft survival with the MFI level of DSA on the last pre-transplant sample.

Conclusion

DSA detection in the presence of negative CDCXM does not always predict an adverse outcome or need for desensitisation even in the presence of positive FC crossmatch. Even relatively high levels of DQ DSA might be associated with long- term survival in the absence of pre-transplant desensitisation. Better ways are required to define which patients require intensive desensitisation protocols.

P2

Antibody mediated rejection after ABO incompatible living donor renal transplantation is mainly associated with HLA donor specific antibodies.

Jack Galliford, Ed Chan, Michelle Willicombe, Christopher Lawrence, Rawya Charif, Candice Roufosse, Terry Cook, Anthony Warrens, Janet Lee, Thomas Cairns, Adam McLean, Vassilios Papalois, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

There are few reports describing the nature and outcome of rejection in patients receiving ABO incompatible live donor [ABOiLD] renal transplants.

In this study, we report the incidence, nature and outcome of rejection in our ABOiLD patients compared with 355 ABO compatible living donor transplants [ABOcLD].

46 patients [25m, 21f; mean age 49.4 ±11.8 years; 23 Rituximab/Daclizumab induction, 23 Campath induction] underwent successful ABOiLD transplantation using plasma exchange [Px] and IVIg with Tacrolimus monotherapy and a 1 week steroid sparing protocol.

Pre-operative CDC and FXM cross-matches were negative and the titre of anti-blood group antibody was ≤1:4.

Allograft rejection [AR] was diagnosed by biopsy. Cellular AR was treated with steroids and MMF. Antibody mediated rejection [AMR] was treated with the above and IVIg and Px.

Patient survival at 60 months is 100% and censored allograft survival 90.2%. Four transplants have been lost: haemorrhage 1, recurrent FSGS/rejection 1, withdrawal of immunosuppression due to sepsis 1 and AMR 1.

The incidence of AMR was significantly greater in the ABOiLD group: 11/22 [50%] of the rejection episodes were antibody mediated in the ABOiLD group compared with 13/66 [19.7%] in the ABOcLD group [p=0.011].

In the ABOiLD group, 6/22 [27.3%] had pre-existing donor specific anti-HLA antibodies [DSAbs] and 5/22 [22.7%] developed de novo DSAbs. 3 /22 [13.6%] had a rise in anti-blood group IgG titre. AR was similar between induction protocols.

Pre transplant DSAbs were associated with a higher risk of AR [HR 4.1; 95% CI 1.5,11.4; p=0.007] whereas there was no effect of anti-blood group antibody titre.

Whilst AR is higher in ABOiLD transplant recipients, this is mainly due to HLA antibody, much of which is pre-formed.

These patients may benefit from augmented immunosuppression or pooled-paired transplantation.

P3

ABO incompatible transplantation is not associated with an increased risk of infection

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Recipients of ABO incompatible (ABOi) kidneys undergo antibody removal prior to transplantation and are more likely to receive treatment for rejection. There are concerns that this may result in a higher risk of infection. Despite this, there are few reports describing the incidence, nature and severity of infection following ABOi live donor (ABOiLD) renal transplantation.

We report the incidence and nature of infections in 35 ABOiLD recipients [M:21,F:14, mean age:51.8±11.0yrs] between November 2005 and May 2009. Mean follow up 22.0±11.7months. This was compared to 445 ABO compatible (ABOc) renal recipients [M:272,F:173, mean age 47.1±12.8yrs] transplanted in our centre during the same period.

All recipients received our steroid sparing regimen [steroids for 1 week]. ABOi patients were plasma exchanged, received induction with Daclizumab/Rituximab or Campath and maintenance with mycophenolate mofetil (MMF) and Tacrolimus (Tac) or Tac monotherapy respectively. ABOc patients received a similar immunosuppressive regime.

Positive urine, blood, bronchiolar lavage and drain fluid cultures constituted significant episodes of bacterial infection. CMV PCR positivity [> 1000 copies/ml] and BK viral nephropathy [diagnosed by allograft biopsy] were considered significant markers of viral infection. The results are expressed as episodes of infection per 100 patient years [pt yrs] as previously described by Snyder et al. [KI; Nov 2008].

ABOiLD patient survival was 100% and allograft survival at 1, 2 and 3 years was 95.6%, 84.0% and 84.0%.

The overall incidence rate of infection in ABOi and ABOc patients was 82.5/100pt yrs and 71.1/100pt yrs respectively [IRR 1.16, CI:0.88-1.5; p=0.03]. Urinary tract infection was the most common cause of infection [59.1/100 vs. 52.2/100pt yrs; IRR 0.89, CI:0.63-1.23; p=0.47] followed by blood stream infections [4.7/100 vs. 9.7/100 pt yrs; IRR 0.43, CI: 0.14-1.35; p=0.15]. CMV infection and BK viral nephropathy were uncommon and not significantly different between the two groups [p=0.83 and p=0.79 respectively].

There was no TB or PTLD.

This is the first reported study of infection after ABOiLD transplantation and shows that there is no increased risk of infection.

P4

HLA antibody incompatible transplantation across a positive complement dependent cytotoxic crossmatch

Rob Higgins[1], Daniel Zehnder[1,2], Simon Fletcher[1], FT Lam[1], Habib Kashi[1], Chris Imray[1], Lam Chin Tan[1], Rizwan Hamer[1], Nithya Krishnan[1], Dave Lowe[2,3], David Briggs[3]

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Risk assessment for HLA antibody incompatible (HLAi) transplantation is complex because combinations of donor specific antibodies (DSA) may be present at various levels. We report the outcomes of HLAi transplantation with +ve pre-treatment complement dependent cytotoxic (CDC) crossmatch (XM) (non-AHG enhanced).

19 patients received renal transplants with +ve pre-treatment CDC XM, compared to 61 who had HLA antibodies detectable by flow cytometry or Luminex assay. Graft number was first (6 cases), 2nd (12) and 4th (1). Only 4 patients had a single DSA, in other cases DSA were multiple. The main reactivity was HLA Class 1 in 2 cases, HLA DR in 2 cases, HLA DP, DQ and DRB3-4 in one case each, and multiple specifities including Class 1 or DR in 12 cases. The CDC crossmatch was positive at dilutions of 1:1 (8 cases), 1:2 or 1:4 (3); 1:8 or 1:16 (5), and 1:32 or greater (3). Three cases additionally had ABO incompatibility

Pre-transplant, 18 patients received plasmapheresis, and 4 patients were transplanted across a +ve CDC crossmatch in the operating room. These DSA in these cases were DP; DRB3-4; DR; a mixture with primarily DR and DQ.

Post-transplant, one patient died following caecal volvulus. One graft (CDC +ve at transplant due to HLA DR) failed immediately. One graft (CDC –ve at transplant, but primarily Class 1 antibodies, pregnancy induced DSA and husband to wife transplant combination) had early function but was lost to severe rejection despite ATG and eculizumab; one graft was lost at 3 months from glomerular microangiopathy; two grafts failed from transplant glomerulpathy, at 16 and 59 months.

Of the other 13 grafts, seven had early episodes of antibody-mediated rejection, but are still functioning, at follow up ranging from 15-61 months. Two have transplant glomerulopathy.

In summary, we have transplanted 19 patients with a pre-treatment positive CDC crossmatch due to HLA antibodies. The early rejection rate was 68%, death censored cohort graft survival was 83% at 1year and is currently 72% for the cohort. For some patients in whom exchange transplantation and other options have been exhausted, transplantation across a CDC +ve crossmatch may be a feasible, but better methods are still required to remove HLA antibodies and to prevent HLA antibody production.

P5

Facilitation of exchange transplantation by allowing low level HLA and ABO antibody incompatibility

Rob Higgins[1], Nithya Krishnan[1], Daniel Zehnder[1,2], Dave Lowe[2,3], Pat Hart[1], Simon Fletcher[1], Rizwan Hamer[1], David Briggs[3]

[1]University Hospital, Coventry, United Kingdom, [2]Warwick Medical School, Coventry, United Kingdom, [3]NHS Blood and Transplant, Birmingham, United Kingdom

Although antibody incompatible transplantation (AIT) is feasible, the results are not so good as antibody compatible transplantation. Exchange transplantation offers one potential solution to this, but only a small proportion of listed patients have been transplanted with antibody compatible exchange kidneys.

One potential option is to allow some antibody incompatibility in the exchange process, such that a patient might get offered an antibody incompatible exchange transplant, but at a far lower level of risk than from their 'own' donor.

In the January, July and October 2009 matching runs, we attempted to facilitate transplantation for 5 patients (6 exchange runs). The most common strategy was to remove unacceptable antigens listed for HLA Class 1 and HLA DR if the current Luminex MFI was <2000u, and to remove unacceptable antigen listing for any selected HLA DQ, DP or DRB3-4. Attention was given to the likely haplotypes of potential donors to make sure that several low level 'acceptable' incompatibilities did not summate to an unacceptable total. Two patients have been offered exchange transplants, each of them having DSA against their own donor for Class 1, DR and either DP or DR53. In the exchanges offered, the DSA were only for DP or DR53. One exchange recipient dropped out for medical reasons, and the other transplant has a scheduled date.

There is an excess of donor-recipient pairs listed for exchange with blood group A donor and O recipient. However, the levels of antibody against blood group B are often lower than blood group A. In 34 blood group O normal subjects, the mean flow cytometric levels of A1 antibody were RMF 22.0 (IgG) and 16.0 (IgM), and for B antibody RMF 4.5 (IgG) and 16.0 (IgM). Of the nine patients with IgG A1 antibody > RMF 20, above the level at which ABO incompatible transplantation would be currently feasible, eight had IgG B RMF<10, five of whom had IgM B RMF<10. We changed the ABO status of one patient from O to B for the October 2009 matching run, she also had high level HLA antibodies and was not offered a transplant. Another candidate for this is a non-sensitised group O patient who has IgG antibody levels of 1:256 against A1 (his own donor), and 1:16 against group B.

In summary, for some patients who have not been offered an antibody compatible transplant through the exchange transplant system, one option is to modify the exchange process so that they may be offered a transplant which although antibody incompatible, is much lower risk than from their own donor. Choosing this option requires very detailed liaison between the clinical team, laboratory and the patient.

P6

The kinetics of donor HLA class I specific antibody absorption following a combined split liver and kidney transplant.

Tim Key[1], Menna Clatworthy[2], Reyna Goodman[1], Cheryl O'Rourke[1], Craig Taylor[1], Christopher Watson[2], Andrew Butler[2]

[1]Tissue Typing Laboratory Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, [2]Department of Surgery Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Introduction: Hyperacute rejection of a transplanted liver is rare even when the recipient has circulating donor-specific allo-antibodies (DSA). There is also evidence that a transplanted liver may provide immunological protection for other organs transplanted from the same donor. A transplanted liver seems able to absorb moderately high titres of donor specific antibody without immediate graft dysfunction. In split liver transplants the capacity to absorb antibody may be compromised by the smaller liver mass. Levels of circulating donor specific Human Leucocyte Antigen (HLA) antibody were measured sequentially beginning immediately after liver reperfusion in a combined split liver and kidney transplant recipient.
Method: Levels of HLA class I specific antibodies were measured in samples taken at 5, 10 and 30 minutes, 1, 2 and 6 hours and 1, 2, 5 and 91 days post liver lobe perfusion using Luminex based HLA specific antibody screening with single antigen beads (SAB).
Results: A 31 year old female patient with congenital hepatic fibrosis and polycystic kidney disease received a combined split liver and kidney transplant. The donor organs were a 1.1.1 (HLA-A,-B,-DR) mismatch to which she had circulating IgG HLA class I specific antibodies directed against HLA-A3 and HLA-B57. The pre-transplant complement dependant donor T lymphocyte IgG cytotoxic crossmatch was positive. There was a rapid decline in circulating donor specific antibodies within 5 minutes of liver lobe re-perfusion, such that levels of HLA-A3 were 38% and HLA-B57 25% of the immediate pre-transplant level. At 1 day post-transplant levels had declined to 16% (HLA-A3) and 6% (HLA-B57) of the immediate pre-transplant levels and at 3 months post-transplant were less than 5% of pre-transplant levels.
Conclusion: Depletion of HLA-specific antibodies post transplant has been indirectly measured previously by the conversion of a positive crossmatch to negative in some cases. This is the first report of the effects of a liver lobe transplant on the precise kinetics of HLA specific antibody depletion in the intra- and post-operative period. Our data indicate a rapid depletion of circulating donor-specific, HLA class I antibodies immediately following reperfusion of the transplanted liver lobe. This rapid fall in antibody titre suggests that antibody depletion does not require *de novo* synthesis of a donor specific neutralizing substance such as soluble HLA, but may reflect direct antibody binding to HLA glycoproteins on hepatic endothelial cells. The reduction in circulating DSA was not a temporary phenomenon, but was still present at 3 months, indicating an on-going protective role. Clinically, this resulted in excellent long-term function of both allografts without antibody mediated rejection.

ABO Incompatible 2

Moderator: Dr Phil Mason

P7

ABO incompatible living donor renal transplantation in West London

Jack Galliford, Ed Chan, Rawya Charif, Christopher Lawrence, Michelle Willicombe, Candice Roufosse, Terry Cook, Anthony Warrens, Neill Duncan, Janet Lee, Thomas Cairns, Adam McLean, Vassilios Papalois, Nadey Hakim, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

ABO incompatible living donor [ABOiLD] transplantation is a successful and accepted form of treatment for patients with renal failure, performed by an increasing number of transplant centres in the UK. The purpose of this study is to report our experience of ABOiLD transplantation, which is currently the largest programme in Europe.

Since 2004, 52 patients [30m, 22f; mean age 48.6±11.2 years] entered the programme. Patients have received plasma exchange after Rituximab [1g] or Campath [30mg] to achieve a pre-transplantation anti-blood group IgG antibody titre of ≤1/4. Oral immunosuppression has been Tacrolimus based and steroid sparing. Mycophenolate Mofetil was used pre-Campath era. Comparison is made with 355 ABO compatible living donor [ABOcLD] transplants performed over the same time period.

Six patients [11.5%] did not reach the required IgG titre for transplantation. 46/52 patients [25m, 21f; mean age 50.54±12.45 years] were transplanted and have been followed for a mean of 24.5±17.8 months [range 0.5-78 months]. This represents 11.8% of living donor transplantation during the same period. 16/46 [34.8%] were pre-emptive transplants, 8/46 [17.3%] regrafts, 36/46 [78.2%] unrelated donors and the mean mismatch was 3.6±1.6.

Patient survival is 100%. Allograft survival at 1, 2 and 4 years is 95.6%, 84.0% and 84.0%. Four allografts were lost; haemorrhage 1, antibody mediated rejection 1, recurrent FSGS and rejection1, withdrawal of immunosuppression due to severe sepsis 1.

Allograft function [eGFR; MDRD] at 1, 2 and 4 years is excellent and stable at 49.7±10.7, 51.1.1±13.5 and 51.0±14.5 mls/min/1.73m^2 and compare favourably to ABOcLD transplants at 54.6±16.2 [p=0.10], 51.7±14.9 [p=0.48] and 50.9±13.4 [p=0.98] mls/min/1.73m^2.

Acute rejection was significantly more frequent in ABOiLD patients [22/46 (45.6%)] than in ABOcLD patients [66/355 (18.6%); p<0.0001].

This study shows that ABOiLD transplantation is successful with similar excellent medium term outcomes compared with our ABOcLD programme and international competitors. Although we have observed a higher rate of rejection there has been no impact on allograft function as yet.

P8

Blood group antibody titres predict the feasibility of ABO incompatible kidney transplantation.

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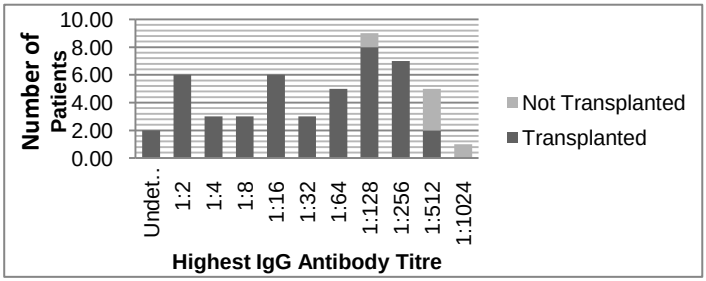
ABO incompatible live donor [ABOiLD] kidney transplantation requires antibody removal to low titres either by plasma exchange [PX] or immunoadsorption and augmented immunosuppression. This is not always successful and patients may receive unnecessary and costly treatment. This is the first reported study which defines a cut-off point for entry into an ABOiLD program.

We have removed anti blood group antibody from 53 patients [32m:21f, age 49.3 ± 10.3 years] by conventional PX [Cobe, Spectra] prior to ABOiLD transplantation. Induction immunosuppression included Rituximab and Daclizumab [25/53] and Campath [28/53] followed by Tacrolimus and MMF. Blood group antibody titre was determined by haemagglutination and/or modified gel card technology [DiaMed Card].

Patients were transplanted when anti blood group IgG titre was ≤1:4. 5/53 [9.4%] patients were not transplanted because they did not achieve anti blood group IgG ≤1:4 despite extensive PX [15.2± 6 v 8.0± 4 treatments, $p<0.05$]. Pre treatment IgG titres [All anti-A] were 1:1024 in 1 patient; 1:512 in 3 patients and 1:128 in 1 patient. Two of these have now been transplanted, 1 has undergone paired-pooled transplantation and 2 await deceased donor transplantation. 2/53 [3.8%] patients were transplanted with pre-treatment IgG titre 1:512, one of whom required 20 PX.

Highest IgG titre [Figure] and pre-PX titre were strongly associated with the number of PX delivered prior to transplantation [$r^2=0.565$, $p<0.0001$ and $r^2=0.569$, $p<0.0001$] and the number of PX required to actually achieve IgG ≤1:4 [$r^2=0.61$, $p<0.0001$ and $r^2=0.66$, $p<0.0001$]. Patients with IgG titre ≥1:512 were less likely to be transplanted [OR 92, $p<0.05$].



This study shows that patients with a pre-treatment titre of 1:512 are unlikely to achieve pre-transplant titres of ≤1:4 or may require extensive PX to do so. A cut off pre-treatment titre of ≤1:256 may be realistic. Patients should be counselled appropriately.

P9

Donor specific antibody titres predict antibody mediated rejection and response to treatment

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Although antibody mediated rejection [AMR] is associated with the presence of circulating donor specific antibodies [DSAbs], there are few studies linking the occurrence and outcome of AMR to DSAb titre, particularly in patients receiving Campath induction and Tacrolimus monotherapy.

Between 2005 and 2009, 480 patients [f:m=165:315; mean age 47.41 ±13.01 yrs; mean HLA MM 3.33 ±1.63; 1st graft: regrafts =426:54] were included in this study. All had negative CDC/FCXM cross matches at the time of transplantation.
All patients received Campath induction [30 mgs iv] and Tacrolimus monotherapy [target level 5 - 8 ng/ml] with 1 week of prednisolone. DSAbs were detected using single antigen luminex beads and DSAb titre was expressed as total mean fluorescence intensity [MFI]. AMR was treated with iv methylprednisolone [500mg x 3] followed by oral steroids, Mycophenolate Mofetil and ivIg [2gms/kg] with plasma exchange. Mean follow up was 1.7 ±1.16 yrs.

Patient survival at 3 years was similar in the group of patients with AMR compared with those patients without AMR [AMR+ 97.5% and AMR- 97.5% respectively, p=0.99 (log rank)].

41/480 [8.54%] patients experienced AMR. 10/41 [24.4%] AMR+ patients lost their grafts from rejection and graft survival was significantly reduced in this group at 3 years [AMR+ 77.5%, AMR- 99.5%, p<0.001 (log rank)]. Median time to AMR was 13.0 days post transplant.

32/41 [78.05%] of AMR+ patients were DSAb+ whilst 90/439 [20.50%] of AMR- patients were DSAb+ (p<0.001, χ^2). AMR+ patient DSAb titres were significantly greater than AMR- patients [AMR+ mean MFI 5276; AMR- mean MFI 2066, p <0.001].
AMR+ patients who subsequently lost their grafts had a significantly higher mean MFI pre treatment than AMR+ patients whose allografts survived [mean MFI in AMR+ patients and graft loss: 11,711; mean MFI in patients with AMR and graft survival: 5276, p=0.039 (log rank)].

This study shows that higher titres of DSAb are associated with AMR and subsequent graft loss and that DSAb MFI may be of prognostic and therapeutic value.

P10

Analysis and significance of pretransplant antibodies against endothelial precursor cells detected by XM-ONE assay

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There is significant interest in non-HLA antibodies and their potential influence on transplant outcome. We are performing a prospective study in living donor renal transplantation to explore the role of antibodies against endothelial precursor cells (EPC) detected using the XM-ONE assay (Absorber AB). This assay detects both IgG and IgM antibodies reactive with Tie-2+ EPC enriched from peripheral blood mononuclear cells (PBMC).

Forty donor/recipient pairs have been recruited to date. Patients were screened for HLA and MIC antibodies using Luminex technology. Pre-transplant crossmatches were performed by complement-dependant cytotoxicity (CDC) and flow cytometry (FC) and by FC on EPC using XM-ONE. In order to interpret the anti-EPC reactivity, simultaneous autologous XM-ONE testing was performed for 32/40 patients.

Donor-specific HLA antibodies were not detected by Luminex prior to transplant. CDC and FC crossmatches against donor PBMC were negative for all patients, but 14/40 (35%) recipients were positive in the XM-ONE assay (3 IgG only, 4 IgG +IgM and 7 IgM only). In 11 of these patients autologous XM-ONE crossmatches were performed, of which 4 were positive with the same class of antibody as detected in the allogeneic assay. Of the 7 XM-ONE allogeneic-only positives, 4/7 were IgG and 3/7 were IgM. The significance of the antibody class or autologous reactivity is not yet known and therefore we have not subdivided the XM-ONE+ patients at this stage.

XM-ONE+ patients were significantly more likely to be sensitised to HLA (57% XM-ONE+; 23% XM-ONE– ($p=0.04$)). There was no association between XM-ONE+ results and HLA-DR matching (0:1:2 DR mismatches; 57%:45%:0% vs 34%:58%:8% ($p=0.33$)) or biopsy proven rejection (2 patients in each group). Preliminary analysis of graft function has not revealed differences between XM-ONE+ and XM-ONE– patients (eGFR at 1 month: 6 month post transplant; XM-ONE+ 54±8: 59±12; XM-ONE– 51±13: 53±14 ($p=0.59$)).

We have demonstrated the presence of antibodies reactive with donor EPC in patients where CDC and FC PBMC crossmatches were negative. A subset of these patients also had reactivity with autologous EPC. Continued recruitment to this study will elucidate the significance of these antibodies, which may be a contributing factor to the poorer graft outcome in sensitised patients.

P11

Rapid and Specific Measurement of ABO Antibody Using Synthetic Blood Group Antigens: Application to ABO Incompatible Transplantation.

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Introduction

Clinical decisions in ABO incompatible kidney transplantation and its outcomes are directed by assessment of blood group antibody titre.

Despite attempts at standardisation, multiple studies have shown up to eight-fold variation in haemagglutination results.

Synthetic blood group trisaccharides (sBGT) have previously not been specific to the extent that this does not allow ABO typing according to Landsteiner's rule. We proposed to assess blood group antibody binding to sBGT by surface plasmon resonance (SPR).

Methods

Using SPR technology, sBGT (Dextra, UK) were coupled to a carboxyl chip. sBGT binding specificities were validated using commercial typing reagents.

The binding association of plasma from patients with known haemagglutination titre were analysed using SPR against A and B sBGT.

Results

Binding to synthetic antigens were 100% specific in terms of ABO groups. Binding to both A and B sBGT was 100% specific for typing reagent and all patient samples. Furthermore, there was a quantitative response observed representing binding association which is dependent on haemagglutination titre.

We are currently developing a mathematical model to describe this relationship.

Conclusion

Rapid assessment of both quantitative and qualitative blood group antibody will improve safety of clinical assessment in ABO incompatible transplantation. Our assay is precise and reproducible at physiological temperatures. We have shown a lack of non-specific binding to these synthetic antigens.

This is a very rapid and we believe reproducible assay that overcomes the shortcomings of haemagglutination, applicable to defining and monitoring antibody levels in ABO incompatible. The labelled chips are very stable and reusable hence consumable costs are minimal. Importantly, this multiplex assay will allow a detailed characterisation of the physical changes in antibody quantity, affinity and avidity associated with accommodation and antibody modulation in preparation for and during ABO incompatible graft transplantation.

P12

Successful Pancreas Transplant Against CDC Positive Crossmatch Due to DQ Antibody

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Transplants against positive crossmatch have become common in the setting of Live Donation but are infrequently practiced in Cadaveric Donation. The relative importance of cytotoxic DQ antibodies is a matter of debate and kidney transplants have been performed in the past against this barrier. Patients who possess such antibodies are routinely excluded from a large number of available cadaver donor offers. Pancreas transplant waiting time is much longer for patients with blood group O and those patients of this group who wait a graft due to life-threatening hypoglycemia remain at significant risk.

We present here the case of a PAK transplant performed against cytotoxic positive crossmatch in the setting of high level DQ6 DSA. The patient had a cadaver kidney Tx in 1999 and a PAK in August 2007 that failed for a mixture of reasons in April 2008.

The patient had acquired cytotoxic DQ6 Ab following his first panceas Tx. The patient had no other donor specific antibodies (DSA) identified with either cytotoxic or flow techniques but had other DSA identified with the Luminex technology. The patient had developed threatening hypoglycemia and also high HbA1c in spite of reasonable effort for good sugar control.

A good quality blood group compatible graft was identified that would have been appropriate for a second transplant (good vessels, absence of fat, good donor perfusion). Tissue typing had shown that the donor possessed DQ6. The results on transplantation date had shown, as expected, a very high Luminex MFI value of DQ 6 antibody (6083-10247) that would be the cause of a positive crossmatch. The patient also had shown A2 with MFI value (153-788), A3 of 977, DR15 474-734, DR51 800-1226. The cytotoxic B-cell crossmatch was positive and the Flow T-cell and B-cell crossmatch was also positive. Following extensive discussion with the patient about risk and benefit, a decision was made to proceed. The patient received Campath induction, Tacrolimus, Mucophenolate acid and steroids and 7 postoperative plasma exchanges from day 2 to day 16. He was discharged on day 8. Although his other Luminex Abs promptly disappeared, he remained positive for DQ6.

He had a scheduled biopsy at 4 weeks that did not reveal any rejection and confirmed the absence of C4d stainining. He had a further biopsy at 10 weeks that showed cellular rejection and again confirmed the absence of C4d. The patient was treated with 3 doses of ATG and, due to the high-perceived risk, 5 sessions of plasmapheresis (with 100mg/kg IVIG following each session). Nine months post-transplant his amylase is normal, HbA1c remains normal, his glucose tolerance test is normal and DSA luminex levels are all below 500 (negative) apart from DQ6 that remains around 4000.

This is the first case of successful medium term outcome of a Pancreas transplant in UK in the presence of cytotoxic positive crossmatch due to a DQ cytotoxic antibody. This has been achieved without high dose IVIG and did not result so far to an antibody mediated rejection. It averted potentially fatal hypoglycemias and ended in high patient satisfaction.

Intestinal Transplantation

Moderator: Mr Darius Mirza

P13

Cambridge- Miami (CaMi) pre-transplant risk score for intestinal and multivisceral transplantation in adults

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Introduction: Pre-transplant clinical and functional status of a transplant recipient influences their postoperative outcome following transplantation. Therefore a pre-transplant risk assessment score based on co-morbidity may offer semi-quantification of outcome and facilitate risk assessment, selection and management of the potential recipients. Significant improvements in the outcomes following intestinal and multivisceral transplantation have been achieved and some of this has been attributed to better selection and optimisation of the recipients. But pre-transplant risk assessment of these recipients still remains a challenge.

We have developed Cambridge-Miami (CaMi) preoperative risk assessment score based on the pre-transplant clinical status of the patients and here further validate it in a larger cohort, aimed to demonstrate its validity in the assessment of patients who have undergone intestinal and multivisceral transplantation.

Methods: The score combines putative preoperative risk factors for early, medium and long term survival. Factors included were loss of venous access, and impairment of organs or systems not corrected by transplantation. Each factor was scored 0 - 3. A score of 3 indicated co-morbidity approaching a contraindication for transplantation, that which might lead to but was not currently an adverse risk factor scored 1 and that presenting a definite but moderate increase in risk scored 2. The data was collected from two transplant centres, University of Cambridge, UK and University of Miami, USA between 1994-2009. The data collected were; patient and donor demographics, pre-transplant functional status and survival following transplantation.

Results: A total of 131 adults were included in this study with 52 patients in ≤ 2 and 59 in >2 CaMi score subgroups. No significant differences were observed in the patient or donor demographics between the CaMi subgroups except for longer time on the waiting list ($p = 0.030$) for ≤ 2 CaMi score subgroup. The median patient follow up time was 2.9 years The Kaplan-Meier (KM) curve analysis indicated that survival of the CaMi ≤ 2 was significantly greater ($p<0.0001$) than >2 subgroup. The Kaplan-Meier median survival hazard ration was 1.35 with 95% CI (1.27 -1.44) with a Harrell c-Index of 0.84 indicating excellent ROC characteristics.

Conclusion: The CaMi score is the first pre-transplant risk assessment model described for the patients referred for intestinal and multivisceral abdominal organ transplantation and our results demonstrate that it accurately predicts the post-transplant survival in adults. Its predictive value might allow better selection, focus pre-transplant preparation and facilitate informed consent for the procedure.

P14

Staged abdominal closure after small bowel or multivisceral transplantation

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After paediatric small bowel or multivisceral transplantation (SBMT), size discrepancy between the recipient's abdomen and the graft may lead to abdominal compartment syndrome (ACS), graft dysfunction and death. We report our experience with staged abdominal closure (SAC) in these patients.

Patients and methods: Between 04/1993 and 03/2009, 62 SBMTs were performed in 57 children. When abdominal wall tension seemed excessive for safe primary abdominal closure (PAC), SAC was performed: 1) Abdominal wall closed using a Silastic® sheet and skin left open with a vacuum occlusive dressing. 2) Iterative dressing changes and gradual patch narrowing. 3) Insertion of a permanent wound prosthesis and final skin closure. Transplantations with SAC [23 combined liver and small bowel (CLB)] were compared to transplantations with primary abdominal closure (PAC) [14 isolated small bowel (ISB) and 25 CLB].

Results: Indications for transplantation, pre-operative status (after stratification for ISB/CLB transplants), age at transplantation (median 2.1 years, range 0.6-16), donor to recipient weight ratio (median 1.6, range 0.6-6.7), reduction of bowel (13/62 grafts, 21%) and/or liver (27/48 grafts, 48%), and incidence of wound complications, were not different in both groups. Postoperative intubation, stay in intensive care unit, and hospital stay, were longer after SAC. Two deaths were related to ACS after PAC, none after SAC. Since 2000, 1-year patient survival is 75% after ISB transplantation, and 57% versus 75% after CLB transplantation with PAC versus SAC, respectively ($p=0.06$).

Conclusion: SAC was useful and safe after paediatric SBMT, and can be combined with graft reduction for transplantation of small recipients.

P15

Renal dysfunction is an early morbid event in Intestinal transplantation

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Introduction: Renal dysfunction (RD) following intestinal transplantation (SBTx) contributes to significant morbidity and is associated with reduced patient survival. Pre-transplant renal function and clinical state of the recipient, operative morbidity and Immunosuppressive therapy are associated with RD and the RD has been shown to occur within the first two postoperative years, but renal function in the early postoperative period is poorly described. We hypothesised that the onset of renal dysfunction occurs in the early post-operative period (within 3 months after transplant). So we aimed to investigate the deterioration of the renal function in patients following SBTx and also to ascertain the associations.

Methods: The study was performed in a single centre in United Kingdom and all the patients who had a minimum survival of 6 months following small bowel / multivisceral transplantation were included in this study. A total of 20 transplants were performed during the study period and 11 were found to be eligible for this study. The data collected were; recipient and donor demographics, immunosuppressive therapy. Renal function (measured by serum creatinine & e-GFR), serum Tacrolimus levels were at 7,14 & 21 days, 6, 12, 18 & 24 months and 3 years. In addition, number of admissions, acute rejection episodes, need for modulation of immunosuppressive therapy and function of the allografts. The data was retrieved from a prospectively collected database.

Results: 8/11 patients had deterioration in the renal function with mean serum creatinines at Day 14, 21 of 172.4 and 161.2 µmol and at 3 & 6 months 163.1 and 143.9 µmol respectively. The serum Tacrolimus levels were well controlled between 8.27 - 9.17µg/l throughout the study period. The RD was treated by 3/8 patients being converted to m-TOR inhibitors and in the other 5/8 patients reduced Tacrolimus levels were used. The renal function for patients converted to MTOR inhibitors improved. The mean number of admissions in the first year after the transplant was 3.66 and 4.13 during 3 years. There was an association between the number of readmissions and renal dysfunction suggesting that these patients had a poorer outcome as previously observed by others. However, we did not find an association between RD and Tacrolimus levels which other have reported.

Conclusions: In our cohort, the renal dysfunction was noted in 72% (8/11) of patients and it occurred within the first month of the SBTx. The association with readmission suggests it is related to impaired outcome, its cause remains speculative.

P16

Proposed Revascularisation Process For Modified Multivisceral Graft Implantation

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Introduction: Intestinal transplantation is a recognised and established treatment for intestinal failure with TPN intolerance. Where previous extensive intestinal resections have occurred, or in the case of complex motility disorders, combined transplantation of the stomach and pancreaticoduodenal complex may be necessary to form a modified multivisceral graft (MMV). Where MMV graft and liver are due for transplantation at different centres, the retrieval process requires careful consideration. The left gastric (LG) and splenic artery (SA) must be preserved in retrieval of the MMV graft, in conjunction with retrieving an adequate length and calibre of hepatic artery (HA) for liver transplantation in another recipient. Here we recount an already proposed method of MMV graft procurement (Vianna et al., Clin. Transplant. 2009: 23: 784 -787) and describe a new approach to revascularisation prior to transplantation.

Methods: The traditional approach to retrieval of MMV and liver graft is to divide the common hepatic artery (CHA) proximal to the gastroduodenal artery (GDA) but this may potentially shorten or reduce the calibre of the vessel for liver transplantation. Vianna et al. described a modified retrieval procedure which enables adequate vessel length and calibre for the liver team and reconstructable anatomy for the MMV team. They describe transection of the SA (at its origin) and coeliac axis (at origin of LG) with revascularisation by anastomosing the divided vessels end to end. We propose use of an interposition graft, ideally the common iliac artery and its bifurcation. The Y- graft is anastomosed to the divided SA and Coeliac axis distally and the GDA proximally. This reduces tension of the coeliac axis patch at implantation, in addition to enabling revascularisation of the GDA. The revascularised MMV graft can then be implanted and a liver with suitable vasculature provided for another recipient.

Results: This proposed revascularisation process has been used in 2 MMV transplants within the last 18 months. Long term follow up results are in progress but at the time of submission, no vascular complications had been noted.

Conclusions: With a recent increase in MMV transplants in the UK, the persisting need for retrieval of separate liver and MMV grafts is likely to arise more frequently. In such cases, knowledge of already described methods of retrieval is important to ensure transplantable grafts to both centres. Where MMV graft implantation occurs, use of an interposition Y- graft may provide a method of improved vascularisation together with reducing vessel tension due to increased length of coeliac axis patch.

Marginal Donors

Moderator: Mr Justin Morgan

P17

Donor biological age is a key predictor of renal function post transplant

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Donor age is considered to be the key predictor of post transplant organ function but lacks the predictive value required for targeted intervention. Recently, we have shown, that biological age, as determined by the level of CDKN2A expression, correlates with renal function at 6 months and 1 year post transplant. We measured renal CDKN2A expression pre-transplant and determined associations with organ function up to 2 years post transplant with a view to using it as a prognostic marker of post transplant organ function.

Pre-implantation deceased donor renal allograft biopsies (n=61) were assayed by Real Time-PCR for the expression of CDKN2A. Demographic and clinical data was collected prospectively in an electronic database (PROTON) and supplemented by clinical record review. Pre transplant, donor CDKN2A expression was analysed for associations with clinical outcome measures including urinary protein/creatinine ratio (UPCR) and white cell count.

Increased CDKN2A expression was associated with increased UPCR at 6 months ($p=0.022$), 1 year ($p=0.001$) and 2 years post transplant ($p=0.034$). This supports our previous findings that higher levels of CDKN2A are associated with elevated serum creatinine levels at 6 months and 1 year post transplant. Donor age was also shown to be associated with UPCR levels. At 1 year and 2 years post transplant the combination of CDKN2A and donor age contributed 23.8% ($p=0.004$) and 19.1% ($p=0.022$) respectively, to the variability in UPCR levels. Conversely, increases in CDKN2A levels were associated with decreased white cell count at 6 months ($p=0.0019$), 1 year ($p=0.0005$) and 2 years post transplant ($p=0.044$). There was no association between donor age and WCC. When patients were categorised by donor sex, the association between UPCR, WCC and CDKN2A was lost in patients receiving male organs. However, in patients receiving female organs, high CDKN2A expression remained significantly associated with increased UPCR ($p=0.061$, $p=0.021$, $p=0.069$) and decreased WCC ($p=0.031$, $p=0.001$, $p=0.065$) at 6 months, 1year and 2 years post transplant.

This study confirms that allograft biological age, as assayed by CDKN2A expression, is an important, novel prognostic determinant for renal function post transplant, as measured by UPCR. UPCR is routinely used as a sensitive marker of tubulo-glomerular damage and is a proven predictor of late graft failure. Interestingly we demonstrate a significant difference in the role that CDKN2A plays in influencing post transplant function in male and female donated organs. Elevated CDKN2A levels are associated with increasing biological age and in female organs this corresponded to poorer organ function post transplant. This was not observed for male organs and suggests there are gender specific mechanisms of biological aging. CDKN2A expression levels, in addition to donor age, may therefore provide valuable pre-transplant prognostic information on organ quality allowing improved patient counselling and providing the possibility for targeted intervention strategies.

P18

Outcome of kidney transplantation from elderlet donors (60ys and above) – Sheffield experience

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The waiting lists for kidney transplantation keep getting longer in most countries of the world. The objective of this study is to assess the outcome of kidney transplantation using kidneys from elderly donors. This is a retrospective study of all the cadaveric donor transplantation, donor age 60 years and above, at Sheffield kidney Institute between March 1969 and Feb. 2009. We determined the outcome of kidney transplantation from elderly donors by retrieving the donor, recipient and donor-recipient factors. We categorised donor ages into 60-64year, 65-69 year and ≥70 year.

Out of the total of 112 donors, 13.4 %(15 donors) were aged 70 years and above. 53(47.3%) were males. The cold ischemia time range from 1.5 hrs to 39.1 hrs and the number of HLA mismatches ranged from 0 to 6. The average rate of DGF was 41.1%. Seventy five percent of the recipients were on Calcineurin inhibitor based immunosuppressant posttransplantation.

The recipient mean age was 50.27 ± 13.72 years (Range 21-85 years). The overall patient survival at 1, 3, and 5 years were 92.0%, 69.6% and 63.4% while the graft survival at the same time were 79.5%, 56.3% and 48.2 percent. Taking the donor age into consideration there was no significant difference between the three old age classes in terms of death censored graft survival at 1year (p=0.21), 3(p=0.22) and 5 years (p=0.06). Similarly the CIT, recipient comorbidity and total number of HLA mismatches have no significant effect on graft survival at 1^{st}, 3^{rd} and 5^{th} year(p=0.81,0.30,0.90), (p=0.36,0.31,0.31) and (p=0.32,0.41,0.18) respectively

However, donor eGFR, AREs, age difference, DGF and mismatch on HLADR affect graft survival in variable ways

In conclusion, the patient and graft survival rates in the short and long term following transplantation of old cadaveric donor kidneys are impressive once the different confounding factors in the donor and the recipients are carefully considered. Interestingly, our results also demonstrate that donor eGFR and AREs are better predictive factors as against donor age that is currently being considered by most workers. The old age line can be shifted forward to accommodate some cadaveric donors above the age of 60 provided that other adverse factors are minimized or eliminated.

P19

Changes in the Plasma Metabolic Profile over Time and with High Dose Erythropoietin (EPO) in Recipients of Marginal Donor Kidneys.

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It is increasingly recognised that metabolomics could significantly improve the monitoring of renal transplants through the systems-wide study of metabolism (systems biology). We have conducted a randomised, double blind, placebo controlled study examining the effects of high dose EPO given at the time of reperfusion (T0) to recipients of marginal kidneys. The EPO group received 100,000iu of EPO over three days, starting at T0, and the placebo group received saline. The aim of the study was to compare the plasma metabolic profiles from 20 male recipients, 10 from the EPO and 10 from the placebo group.

Plasma collected at T0, 24hrs and 6 days post-transplant were analysed by Ultra Performance Liquid Chromatography coupled to a hybrid LTQ-Orbitrap mass spectrometer. Data were analysed using univariate Kruskal-Wallis and multivariate Canonical Variate Analysis (CVA).

The most significant changes in the metabolic profiles were pre- and post-transplant, irrespective of EPO treatment (shown in Fig 1 by the trajectory of the EPO or control group through multivariate space). A smaller change in the metabolic profile was observed when comparing EPO and placebo (shown in Fig. 1 by the separation of EPO and placebo, and supported by univariate analysis), of which the greatest changes were observed at 24 hours. Subgroup univariate analysis of ECD and DCD recipients revealed differences in each group dependent on the EPO intervention. Diverse areas of metabolism were influenced by both surgery and the administration of EPO.

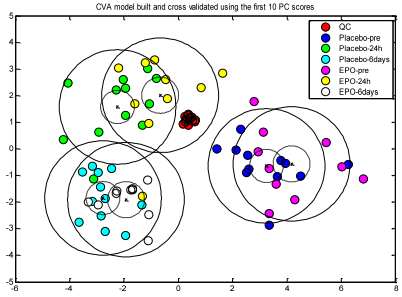

Fig 1: Changes in the metabolome in response to transplantation and to EPO treatment. Dashed circles represent 90% confidence intervals of the group mean.

These data support the hypothesis that metabolic profiling has a role in monitoring both renal tissue injury post-transplant, and the effect of drug intervention. Further work to validate these discoveries is underway.

P20

Trends in the quality of kidneys offered and transplanted in recent years. Are marginal donors the norm? And how marginal is a marginal donor?

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Background: Organ shortage has led to the increased use of so called marginal donors. Kidneys which were previously considered suboptimal are now being routinely accepted and used for transplantation in order to reduce the number of patients on the waiting lists. The only formalized definition of marginal kidneys is from Organ Procurement and Transplantation Network (OPTN) which was instituted in 2002 with the advent of the Expanded Criteria Donor (ECD). These deceased donor kidneys were demonstrated to convey a 70% or greater risk for graft loss for transplant recipients relative to an ideal donor kidneys and were characterized by a donor age older than 60 yr or older than 50 yr and accompanied by two additional risk factors, including a history of hypertension (HTN), elevated terminal donor serum creatinine (SCR), and cerebrovascular cause of death.

AIM and Methods: Retrospective analysis of cadaver renal transplants in a large unit between 2007-2009. We aimed to analyse the trend and the use of kidney organs offered our adults patients with particular focus on decease donor kidney organs in recent years.

Results: There were 239 cadaver renal transplants within this period with a distribution of: 2007 (HBD=48, NHBD=21), 2008 (HBD=76, NHBD=20) and 2009 (HBD=43, NHBD=31).

In table below the qualitative trends of donor organ renal transplants which are within formalised ECD is demonstrated (27%). HBD = 48 (29%), NHBD = 17(24%)

Donor Variables	**Donor Age Categories**					
	50-59 yrs			**≥ 60 yrs**		
	2007	**2008**	**2009**	**2007**	**2008**	**2009**
HBD = 48 (29%)						
CVA + HTN + SCR >130	1	4	1	1	1	
CVA + HTN	3	8	8	4	4	5
CVA + SCR >130		1	1		2	
HTN + SCR >130		1	2		1	
NHBD = 17 (24%)						
CVA + HTN + SCR >130						
CVA + HTN	1	4	4	1		5
CVA + SCR >130			1			
HTN + SCR >130			1			

Summery: Donor risk factors associated with poorer outcomes include age, previous diseases with a systematic influence on the vascular system (ie, arterial hypertension, diabetes mellitus), cause of death (cardiovascular or cerebrovascular disease), and brain death or NHBD. Combinations of risk factors significantly increase their impact on graft function. The number of HBD is declining and NHBD transplant is on the rise. The overall trends and results with such suboptimal donors should be monitored carefully throughout U.K.

Conclusion:

P21

Expanding the non-heart beating donor pool – is it working?

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The rate of renal transplantation is currently limited by the number of donor organs available. A valuable source of organs is currently supplied by non-heart beating donation (NHBD).

At the Richard Bright Renal Transplant Unit, in an effort to expand the number of deceased kidney donors, we have expanded our criteria for non-heart beating donation to include older donors. The upper age limit for NHB donors has been increased from 65 to 70. Donors aged >70 are discussed on a case-by-case basis. A number of centres have reported poorer recipient outcomes following the use of older NHBD kidneys as measured by glomerular filtration rate (eGFR), delayed graft function and graft survival.

Since 2003, 139 NHBD transplantations have been performed at our centre.

We undertook a retrospective analysis of prospectively collected data on all NHBD recipients between 2003 and 2009 to compare the clinical outcomes by assessing:

1) delayed graft function
2) eGFR at 1 month, 6 months, 1 year and 5 years

Our early data showed excellent results for non-heart beating donation. However, we found a trend in declining eGFR at all time points over the last seven years associated with an increase in the incidence of delayed graft function. This was associated with an increase in the average donor age from 43 in 2003 to 50 in 2009. Cold ischaemic time has remained constant.

Recipients of kidneys from older NHB donors (age >60) had significantly lower eGFRs at 1 month and 1 year and a higher incidence of delayed graft function compared to kidneys from donors aged <60. (eGFR at 1 month: 33.3 ml/min/1.73m vs 45.1 ml/min/1.73m, p=0.0125. At 1 year: 40.3 ml/min/1.73m vs 48.2 ml/min/1.73m (p0.05)). The incidence of delayed graft function in recipients of kidneys from donors aged >60 was 71% compared to 40% for <60 age group (p0.009).

Expanding the age limits of our NHB donor programme has led to an increased average donor age, reduced average eGFR and an increase in delayed graft function. It is too early to tell whether this will result in reduced graft survival.

P22

Current long term outcomes of both controlled and uncontrolled Non Heart Beating Donor (NHBD) kidneys – a five year follow up study.

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Introduction: The contribution of the Non Heart Beating Donor (NHBD) organs to the donor pool is ever increasing. Recent evidence suggests that the long term outcomes of NHBD kidneys are comparable to HBD kidneys. But those results are mainly from controlled donor organs, as very few tend to use organs from uncontrolled donors, which is due to the very limited evidence of their long term outcomes. In this study, we aim to analyse outcomes of both our controlled and uncontrolled NHBD kidney recipients, with follow up reaching up till five years. We specifically studied the patients who were transplanted post 2003, when we introduced improved techniques of preservation, such as usage of phentolamine and thrombolysis before retrieval, and dual transplantation.

Methods: A retrospective analysis form Jan 2004 till April 2009. A total of 170 kidneys were retrieved from 85 NHBD's (18 uncontrolled, 67controlled). 13 kidneys failed viability testing; 21 pairs were transplanted as duals. 136 recipients were finally followed up for post-transplant creatinine results at 3,12,24,36.48 and 60 months. Estimated Glomerular Filteration Rate (eGFR) were calculated using MDRD formula and analysed using Mann-Whitney U. Long term patient and graft survival were estimated using Kaplan-Meier survival curves.

Results: There was no significant difference in patient survival (87%v88.5%) and graft survival (78.3%v91.2%) rates of recipients from uncontrolled and controlled NHBD's, at 5 years (p=ns). Long term eGFR (ml/min/1.73m^2) results are as follows:

Long term Graft function Controlled v Uncontrolled

Controlled / Uncontrolled		eGFR3	eGFR12	eGFR24	eGFR36	eGFR48	eGFR60
Controlled	Mean	44.06	44.29	40.99	39.85	44.95	47.70
	N	108	85	65	38	23	13
Uncontrolled	Mean	47.76	47.87	47.06	50.27	42.09	78.41
	N	22	19	19	13	8	2
Mann-Whitney U		1089.00	758.00	511.00	212.00	83.00	5.00
Z		-.615	-.416	-1.139	-.756	-.406	-1.359
Asymp. Sig. (2-tailed)		.539	.677	.255	.449	.685	.174

Conclusion: In our study, contrary to the popular belief, the long term outcomes of uncontrolled donors are comparable to the controlled donors. And therefore, they are a precious means to help in improving the severe current organ shortage

Organ Preservation

Moderator: Prof Steve Wigmore

P23

Evaluation of the impact of preservation by machine perfusion and perfusion parameters on outcome of kidneys from donors after cardiac death

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BACKGROUND: Cumulative retrospective evidence suggests that preservation by machine perfusion (MP) is able to reduce the incidence of DGF in kidneys from donors after cardiac death (DCD). Interestingly, two contemporary randomised clinical trials designed to evaluate the effect of of machine perfusion in DCD kidney transplantation showed contradictory results.

OBJECTIVES: With the aim of addressing whether PP can reduce the incidence of DGF in kidneys from controlled donors after cardiac death (cDCD), a comparison of clinical outcome of 30 cDCD kidneys preserved by static cold storage (cDCD-SCS) and 50 cDCD kidneys preserved by PP (cDCD-PP) was performed. In addition, the impact of perfusion parameters (perfusion pressure, renal flow and resistance) and their ability to predict post-transplant outcome was investigated.

PATIENTS AND METHODS: All cDCD kidney transplants were performed between March 1st, 2002 and November 31st, 2009. Recipient data and clinical outcomes of the entire cohort were obtained retrospectively from our prospective transplant database and confirmed by review of the clinical files. Perfusion pressure, renal flow and intrarenal resistance were obtained directly from the Life-port kidney perfusion device. The primary end-points of the study were the incidence of primary non-function, delayed graft function and acute rejection (PNF, DGF and AR), the length of hospitalization and 1 and 5-years graft function and survival. Subsequently, univariate and multivariate analyses were performed to identify the relationship between perfusion parameters and clinical outcome in the cDCD-PP group.

RESULTS: Donor, recipient and pre-implantation data were well matched. DGF was significantly lower (30% (15/50) *vs* 83% (25/30) $p<0.000$) and the length of hospitalization shorter (10 vs 14 $p< 0.001$) in the cDCD-PP group. Similarly, 1 and 3-year graft function was statistically better in the cDCD-PP than in the cDCD-SCS (101±13 vs 178±24 mmol/L, $p<0.001$ and 121±18 vs 181±30 mmol/L, $p=0.002$. There was no difference in graft and patient survival at 5 years. There was no significant difference in perfusion pressure (Delta PP: ↓10% vs ↓20%, renal flow (Delta Flow: ↑101% vs ↑84%) and intrarenal resistance (Delta IR: ↓27% vs ↓39%) between kidneys with DGF (15/50) and those with immediate graft function (35/50). No significant correlation between these parameters and the incidence of DGF and levels of creatinine was found in the regression analyses.

CONCLUSIONS: In this cohort of kidneys from donors after cardiac death, clinical introduction of PP was associated with a significant reduction in the incidence of delayed graft function, shorter hospitalization and better graft function than SCS. None of the perfusion parameters investigated was able to predict neither the occurrence of delayed graft function nor the levels of serum creatinine after transplantation.

P24

Porcine model of extra-corporeal membrane oxygenation (ECMO) in the uncontrolled non-heart beating donor (NHBD); the effect on liver function and histology.

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Aims: ECMO has been introduced by certain groups with success, in NHBD's for liver transplantation. We sought to compare the effects of ECMO on liver functional and histological changes, with those from Cold Preservation (CP) method of intra-vascular and -peritoneal cooling in an animal 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, cold stored and then re-perfused on an ex-vivo oxygenation circuit using a mixture of autologous blood and RS-I solution. Throughout the period, multiple readings and samples were taken to assess liver viability and function and analysed using ANOVA (with Bonferroni) and Mann-Whitney U, as appropriate. Tissue samples were analysed using a semiquantitative score, by an expert liver histopathologist, blinded to the groups.

Results: During the preservation phase, the liver tissue lactate levels at 2hrs were significantly higher in the ECMO group (Z=2.121; p=0.034). Lactate pyruvate ratio was significantly lower in the ECMO group at 1hr (Z= -2.449; p=.014); at 2 hrs those trends continued to be better, but with no significant difference.

During re-perfusion, bile production increased in the ECMO group (Z=-2.25; p=0.0240). No differences were found in the oxygen consumption, weight gain and tissue lactate levels. The trends in reperfusate AST levels were higher in the CP group, but not statistically significant. No differences were noted in Albumin, ALT and Factor VII levels. On histological analysis, very obvious and drastic histological differences were noted in between the groups. The liver parenchyma was significantly better preserved in the ECMO group than the tissues in the CP group (p=0.016). Extensive damaged was consistently noted in the CP group (mean damage - 72%, median 90%), which is in contrast to the ECMO group (mean damage – 16.6%, median 2.5%). The damage noted had features such as hepatocytes with shrunken nuclei, discohesive plates, and microvacuolar appearance of the cytoplasm.

Conclusion: ECMO appears to cause much lesser damage to NHBD livers and therefore is probably better in preserving the tissue, in comparison to the CP method.

P25

Preservation by normothermic perfusion: Molecular mechanisms associated with liver protection and survival

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BACKGROUND: Experimental and clinical evidence shows that extended organ preservation by cold storage (CS) induces cell death and allograft dysfunction. Previous work from our group demonstrated that pig livers retrieved after 40 minutes of warm ischaemia and preserved for 20 hours by CS developed primary non-function (PNF) after transplantation whereas livers preserved by normothermic machine perfusion (NMP) had immediate graft function (IGF). The aims of this study were to elucidate the molecular mechanisms by which preservation with NMP is more effective than CS and identify potential biomarkers of early post-transplant function in liver transplantation. **MATERIALS AND METHODS:** Cardiac arrest was induced in ten pigs, their livers were left *in situ* for 40min, flushed with cold University of Wisconsin (UW) solution and retrieved. Four livers were stored in UW for 20h (Group A), while six were perfused *ex vivo* for 20h with oxygenated blood at physiological temperature and pressures (Group B). All livers were transplanted into allogeneic recipients, immunosuppressed with cyclosporine and steroids and followed-up for 5 days. Global gene expression in liver biopsies taken before cardiac arrest (Baseline), at the end of preservation (Preservation) and 1h after transplantation (Reperfusion) from each group was investigated using microarrays and compared within and between groups. Gene and protein expression was confirmed by RT-qPCR and immunofluorescence. **RESULTS: Effect of CS:** All livers in group A developed PNF and their recipients died within 3h after transplantation. These allografts showed a significant over expression of genes associated with DNA damage (HSP70, HSP70.2, HSP40), kupffer cell activation and proliferation (KLF, IFRD1, IRF1), platelet-endothelial-leukocyte activation (SELE, CD140, CD142, CCL2, CCL3, CCL4) and blood coagulation homeostasis (PLAU, SERPINE1, THBS1) after reperfusion. **Effect of NMP**: All livers in group B showed IGF and over-expression of genes involved in the triggering (ADORA3, TLR2, TNFRSF1A, TNFa, NFKβIA and IL-6) and expansion of early (SOD2, BAG3, IL1βa) and delayed ischaemic preconditioning (STAT2, STAT5b, MAPK13, SPP1, ADM). **PNF vs IGF: T**here was a different regulation of key genes associated with DNA damage (HSP70, HSP90, HSP40, HSP6), cell protection (SOD2, BAG3, S100A, SSP1, and ADM) platelet-endothelial-leukocyte interactions, (TNFRSF1A, TNFa, CCL2, IL6, IL8) complement cascade (C1Q, C4B, C6A, C8A,C8B and C8G) and blood coagulation (SERPINE1, PLAU, F2, F5, F9 and F12) between livers with PNF and IGF. **CONCLUSIONS**: This molecular analysis shows that the benefit of normothermic preservation is associated with up-regulation of genes involved in the induction of ischaemic preconditioning (IP). In our model the induction of IP attenuated inflammatory and complement cascades resulting in hepatocyte protection and maintenance of the coagulation homeostasis. Expression of genes involved in inflammation, complement and coagulation cascades could represent attractive biomarkers of post-transplant function and potential therapeutic targets to counterbalance the effect of extended preservation injury in DCD liver transplantation.

P26

Machine perfusion of Non Heart Beating Donor (NHBD) kidneys: Continuous versus Pulsatile Perfusion

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Machine perfusion of Non Heart Beating Donor (NHBD) kidneys is one of the several measures that have been used to potentially improve recipient outcomes. Over the years it has shown to improve both viability as well as long term graft function. But there has been very little evidence to suggest the preferred type of machine perfusion.

In our study we aimed to compare long term effects outcomes between NHBD kidneys subjected to either continuous or pulsatile machine perfusion from matched donors.

Methods: A retrospective study from November 2004 to November 2007. Total no of donors 48, no of transplants 72 of which 18 were dual and were excluded. 24 kidneys failed viability testing and were not used. A total of 48 kidneys from 24 donors were included in the study and one kidney from each donor received either of the two methods of perfusion before transplantation. Recipients were followed up for a total of 2 years. Patient and graft survivals were the primary and secondary end points respectively and long term estimated Glomerular Filtration Rates (eGFRs) at 3 months, 1 and 2 years were used as indicators of graft function. Patient and graft survivals were calculated using Kaplan Meier survival curves and long term function was calculated by Sign test.

Results: There was no significant difference in patient survival (91.7% v 87.5%) and graft survival (95.8% v83.3%) rates in recipients from continuous and pulsatile groups. Two years eGFR(mL/min/1.73m^2) results are as follows:

Long term eGFR - Continuous v Pulsatile

	3 months	12 months	24 months	36 months	48 months	60 months
Pulsatile mean eGFR	38.5	38.5086	41.73	38.834	40.842	36.09
Continuous mean eGFR	42.1463	40.1757	35.3411	36.8809	45.72	68.515
Exact Sig. (2-tailed)	1.000[a]	.359[a]	.077[a]	.180[a]	1.000[a]	n/a

a. Binomial distribution used.

b. Sign Test

Conclusion: There appears a slightly improved patient and graft survival with continuous machine perfusion but this was not statistically significant.

P27

Hypothermic machine perfusion characteristics of porcine kidney and pancreas grafts

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Background:

The potential advantages of hypothermic machine perfusion (HMP) compared to cold storage for preservation of solid abdominal organs include facilitating a thorough vasculature washout; delivery of oxygen and nutrients and the removal of toxic metabolites; and the opportunity for real-time organ viability assessment and pharmacological intervention. The vast majority of research into HMP has been conducted in kidney preservation, while experimental studies into the use of HMP for pancreatic preservation are lacking, and may be related to the fundamental differences in their flow characteristics. The pancreas is physiologically a low flow organ, and thus an attempt to establish a pancreatic perfusion model is challenging. Here we compare a successful model of stable HMP of porcine pancreases to a high flow model of kidney HMP.

Methods and Results:

Four kidneys and six pancreases were retrieved, with a median warm ischaemia time of 10 & 30 minutes respectively from 8 landrace pigs after euthanasia via lethal injection. Each organ was benched and then underwent HMP using UW solution on a modified Waters Medical RM3 perfusion machine for 5 hours. Perfusion consisted of an initial priming phase (120 mins) followed by stable perfusion (180 mins). Perfusion dynamics were recorded throughout and a real-time perfusion flow index (PFI) calculated for each organ; graft weight gain at the end of stable perfusion phase was also recorded.

	Kidney (n=4)		Pancreas (n=6)	
	Start of Priming phase	Stable perfusion phase	Start of Priming phase	Stable perfusion phase
Flow rate (ml/min/100g)	47	43	12	26
Systolic pressure (mmHg)	51	40	20	30
Resistance (mmHg/ml/min)	0.68	0.48	0.63	0.47
PFI (ml/min/100g/mmHg)	0.83	1.06	0.64	0.91
% Weight change	48		53	

Conclusions:

This preliminary study demonstrated that optimum systolic perfusion requirements and flow rates for pancreatic HMP are lower than those used in renal HMP. Determination of viable flow using perfusion calculations shows that the use of lower perfusion pressures produces similar improvements in resistance and PFI, with an associated similar weight gain, in pancreases when compared to kidneys. It is important to consider these observations in the development of further protocols for effective HMP for preservation of pancreatic grafts.

P28

Is a Low K^+ organ preservation solution better for vascular endothelium?

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Aim:

To evaluate a novel organ preservation solution with low K^+ concentration using aortic ring baths in a rodent Non-Heart Beating Donor model.

Methods:

In Non-heart beating rats, after an hour of primary warm ischemia abdominal aorta was flushed with streptokinase(3500 IU). This was followed by intra-arterial cooling with a mixture of cold HTK(20 ml) and heparin(200U). Aorta was dissected out and 3-5mms thoracic aortic sections were cold stored(24hrs) in three different preservation solutions. Normal saline was used as a control. Of the three preservation solutions, one was the standard kidney preservation solution (KPS1, K^+25mmol/l). The other two contained low K^+ levels. One was a KPS1 variant (SK-5, K^+5mmol/l), and the other was a non-renal Organ Preservation Solution (nrOPS, K^+6mmol/l). After cold storage the aortic rings were stretched between two points, one containing a pressure transducer probe. The rings were then immersed in 10mls of Krebs-Henseleit solution and gassed with carbogen(95% Air / 5%CO_2) at 37^{o}C and 7.4+/-0.5 pH. Graduated doses of phenylepherine and acetylcholine were added to measure the contraction and endothelium dependant relaxation. Contraction/relaxation profiles of the solutions were compared using ANOVA(two factor within subjects) with Bonferroni.

Results:

10 male wistar rats provided aortic rings to allow simultaneous comparisons between solutions. The maximal mean contraction was higher for SK-5(71%) and KPS1 (73%) in comparison to nrOPS(25%)($p<0.05$) and control(5%)($p<0.001$). Overall relaxation (endothelial dependant) was significantly different within the groups; $F(3,27)=9.353$;$p<0.001$. SK5 produced a superior relaxation profile(end relaxation 20.2%) ($p<0.05$) as opposed to either nrOPS(end relaxation 1.5%) or control(end relaxation -6.9%). KPS1 had a relaxation profile in between SK5 and nrOPS, but it wasn't significantly different.

Conclusion:

Therefore endothelial function would appear to be slightly better with SK5 as opposed to more standard K^+ levels in normal KPS1.

Ethics Law and Public Policy

Moderator: Dr Antonia Cronin

P29

European legislation prohibiting organ commerce: quality and effectiveness

Michael Bos

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In Europe some 50.000 patients are currently on the waiting list for kidney transplantation. Each year only 1 out of 3 patients actually gets transplanted, waiting 2-5 years on average. Desperation drives an unknown number of patients to consider obtaining a commercial transplant abroad. However, a long list of international/European resolutions, treaties and guidelines state that 'transplantation from deceased & living donors is only permitted on condition that the organ does not give rise to financial gain or valuable consideration'. Also, national legislation in European countries without exception prohibits selling, buying or trading of human organs. We have analysed the legislation in 31 European countries to see to what extent these national laws follow international regulations, directives and guiding principles concerning prohibition of organ commerce. These rules include: prohibition of monetary payment or reward, of advertising the need or availability of organs (soliciting), and of brokering, and prohibition for health professionals to engage in or facilitate transplants with organs obtained by exploitation, coercion or payment (organ tourism or trafficking). We looked at quality and effectiveness of these laws, and also at penalties/sanctions imposed on persons who violate the law. Preliminary analysis showed that most countries (23 out of 31) have legislation dealing only in a very general and restricted way with prohibiting organ commerce (concerning only cadaveric donor kidneys, sanctions only directed at physicians making profit, small fines, no regulations against organ tourism). A group of only 8 countries could be identified as having strict and comprehensive prohibition of organ commerce (including living donation, brokering, solicitation, trafficking, heavy sanctions): this includes Germany, Switzerland, UK, Finland, Romania, Croatia, and to a lesser extent France and Portugal. Overall conclusion is that the majority of European laws is not specific enough, and nor effective against organ commerce. Examples of national legislation will be discussed and compared.

P30

Views and attitudes of patients excluded from the kidney transplant waiting list: A qualitative study.

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The prevalence of end stage renal failure [ESRF] continues to increase and the demand for organs for transplantation exceeds supply. Public and professional confidence in transplantation depends upon equitable and transparent access to the waiting list and the principle of 'distributive justice' in allocating organs. Policy makers should consider the views of all stakeholders, including patients excluded from the waiting list.

Wait listed patients may experience anxiety and patients who do not receive an anticipated transplant may experience feelings of loss. In studies of scenarios relating to the microallocation of scarce, lifesaving, resources the general public may prefer a 'natural justice' to a 'utilitarian' approach, emphasising the urgency of a clinical situation. There are few data on the views and attitudes of patients excluded from the transplant list.

The purpose of this study was to establish the views and attitudes of patients with ESRF who were not listed for kidney transplantation.

Research Ethics Committee approval was obtained. A focus group was undertaken to produce a semi-structured interview schedule. Ten patients [7M:3F], age 66.9 ± 6.7 years [mean ± 1SD], dialysis vintage 67 ±57 months were then interviewed by a clinical psychologist. Interviews were analysed using grounded theory, a systematic method which generates a reverse hypothesis from a minimum number of patients.

Five conceptual categories emerged: access to treatment; restricted lifestyles; the role of acceptance in coping; emotional experiences and patient to patient communication.

Six patients understood the reasons why they were not active on the waiting list but all ten expressed frustration that communication with the medical team was poor. The patients acknowledged their relatively advanced age and all were satisfied with the system for prioritization of younger patients. Whilst acknowledging the urgency of transplantation for older recipients the patients thought that younger patients should be prioritized as they were more likely to benefit from transplantation and less likely to develop post-operative complications. Adopting a positive mindset allowed patients to accept their situation and deal with restrictions imposed by dialysis.

In conclusion patients want clearer explanations for the decision not to activate them on the waiting list but believe that clinicians are best placed to decide who is fit for, and will benefit most from, transplantation.

P31

UK students of Indian and Pakistani descent: What are the factors that influence their attitudes towards organ donation?

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Background The shortage of organs donated for transplantation in the UK is well known and the situation is worse among ethnic minorities. The UK Organ Donation Taskforce has highlighted the need to better understand why ethnic minorities in particular have low donation rates. Current work has often studied ethnic minorities in broad groups as well as focusing on older populations. We set out to investigate the factors which influence attitudes towards organ donation of the younger generation ethnic minorities, focusing specifically on Indian and Pakistani students.

Methods Two qualitative approaches were employed: nine focus groups followed by eight semi-structured interviews. A total of fifty-eight participants were interviewed. Focus groups were divided by ethnicity and gender, and interviews were performed on each combination of ethnicity, gender and medical/non-medical background.

Results A thematic analysis of transcripts identified six factors that influence Indian and Pakistani students: religion, culture, awareness of the importance of donation, the treatment of donors and their organs, the impact of medical education and family attitudes. Islam was significantly the most important factor for Pakistanis while for Indians all six were relevant. Medical education specifically influenced attitudes to donation as opposed to general level of education as found in previous studies. Cultural changes gave an insight into how the younger generation may differ from the older generation because they are adopting British culture which is more positively disposed towards donation. Family views remained important. Awareness of the importance of donation was very low in both groups.

Conclusion Young Indian and Pakistanis are not against donation and in our study participants were generally open to the idea of donation after death. However the factors we identified suggested there is no single obstacle to organ donation therefore they all need to be addressed in a culturally relevant manner to improve donation rates.

P32

Adverse outcomes in recipients of commercial transplants

Michael Bos

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Insufficient numbers of organs retrieved and increasing waiting times for transplantation have resulted in growing numbers of kidney patients from the US, Canada, Europe, the Middle East and Australia travelling abroad to obtain a commercial transplant, involving a paid donor. Reports on these commercial transplants in the period 1980-1995 (although scarce) showed consistently that recipient outcomes were often considerably worse than for domestic transplants: graft and patient survival were less and peri- and postoperative complications higher than to be expected in experienced centres. Because of this information, commercial transplants were medically and ethically condemned by most transplant physicians in developed countries. However, this has not resulted in a marked decrease in commercial transplantation, and in fact, since the late 1990's there has been a further increase in the number of commercial transplants, and countries offering these services. We have analysed recent reports on outcomes of commercial transplants (published since 2003) to see if outcomes have lately improved in terms of patient mortality, graft survival and surgical complications. Although some reports (e.g. from Taiwan) show that outcomes of commercial transplants (in China) do not significantly differ from domestic transplants, the majority of reports still show inferior outcomes in patients transplanted abroad in commercial centres using paid donors (vendors). Furthermore, there is a disturbing lack of information on outcomes of commercial transplants within Europe (e.g. Moldova, Ukraine, Kosovo, Turkey). Another risk is the lack of proper screening procedures for paid donors, insufficient communication between commercial transplant centres and patients' home center, and underreporting of early peri- and postoperative complications. On the basis of recent information, patients considering the option of obtaining a transplant abroad should still be advised negatively and warned of running increased risk in terms of inferior graft and patient survival and surgical complications. In this presentation we will compare recipient outcomes from three periods (1980-1995, 1995-2005, and since 2005).

Histocompatibility

Moderator: Dr Sue Martin

P33

Epitope analysis of HLA-DP specific antibodies in patients awaiting cadaveric renal transplantation

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HLA-DPB1 encodes the β-chain of HLA-DP class II molecules which can be expressed by renal vascular endothelial cells. Several studies suggest that mismatching for HLA-DPB1 decreases kidney graft survival in re-transplant patients. We recently transplanted two patients possessing anti-DP alloantibodies across HLA-DPB1 mismatches. One recipient had severe acute antibody mediated rejection and subsequently lost the graft while the other recipient remains rejection free with a well functioning kidney. The mismatches observed for these two patients were located at different regions of HLA-DPB1. Therefore careful analysis of HLA-DP antibody profiles may allow us to identify permissible mismatches. Three hundred and four patients on our renal transplant waiting list were screened for HLA antibodies using LABScreen® kits. Those with HLA class II antibodies were further analysed using single antigen bead kits to identify antibodies specific to HLA-DR, DQ and DP antigens, Eighty eight patients (29%) were positive for a variety of HLA class II antibodies. Eighty two patients (27%) had antibodies to DR, 44 patients (14.5%) to DQ and 24 patients (7.9%) were producing DP-specific antibodies. Nineteen out of twenty four (69%) of the DP antibody positive patients had previous transplants. All patients producing DP-specific antibodies were HLA-DPB1 typed by sequencing. By comparing the individual DP-specific antibody profiles with the known DPB1 type of the patients, we were able to screen the amino acid motifs in the 6 hypervariable regions of HLA-DPB1 and determine if any epitopes dominated the DP-specific antibody responses. Comparison of the DP specificity of antibodies detected with the patients own HLA-DPB1 type indicated that polymorphisms located within the sixth hypervariable region of the DPB1 exon 2 are associated with the generation of DP alloantibodies in the majority of the patients studied. The patient who suffered acute rejection following a mismatched transplant was also mismatched for DPB1 hypervariable region 6.

P34

Is post-transplant crossmatching a more relevant test for donor specific antibodies than HLA antibody definition?

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Introduction: De novo donor specific antibodies (DSAs) have been shown to be associated with graft failure and their detection in post-transplant patients forms part of the criteria for Banff categorisation of antibody-mediated rejection.

Materials and methods: A total of 117 kidney (K), simultaneous kidney and pancreas (SPK) and pancreas alone (P) transplant recipients were investigated because they had a post-transplant DSA test requested between July 2006 and September 2009. All patients had a current *and* historic serum negative crossmatch prior to transplantation. Deceased donor (DD) organ recipients had complement-dependent crossmatches (CDC) pre-transplantation, living donor (LD) recipients had flow cytometery (FC) crossmatches, and sensitised (HLA RF > 50%) or re-graft (following previous graft failure) patients had both CDC and FC crossmatches. Upon request for post-transplant DSA testing, HLA specific antibody detection was performed by LabScreen Mixed (One Lambda Inc) and for HLA specific antibody positive patients, antibody specificity was defined using LabScreen Single Antigen or LabScreen PRA tests (One Lambda Inc). 29 out of 117 patients were DSA positive (25%) (23 K, 4 SPK and 2 P recipients). 20 of the 29 patients had stored lymphocytes available from their donor and were tested by CDC and FC crossmatching. Serum samples crossmatched included a DSA negative pre-transplant sample, and the post-transplant sample in which DSA had been defined. Graft outcome was investigated, and graft failure was defined as return to dialysis or removal of the transplanted organ. Follow up times ranged from 1 to 11 years.

Results: All crossmatches were negative for the pre-transplantation serum sample. DSA positive patients were divided into 3 groups according to crossmatch result:

1) FC + CDC Negative 2) FC Positive + CDC Negative 3) FC + CDC Positive

Group	functioning grafts	failed grafts	% failed grafts
1	9	0	0%
2	4	3	43%
3	2	2	50%

The P value obtained from a 2x3 way contingency table is 0.048.

Conclusion: Analysis of graft survival in relation to the crossmatch result gives a statistically significant P value, indicating that a positive crossmatch is associated with poorer graft survival in this cohort. We observed that the risk of graft failure stratified: “FC+CDC Pos” > “FC Pos+CDC Neg” > “FC+CDC Neg”. The lowest risk group having DSA defined only by LabScreen and not by crossmatching. The use of crossmatching in addition to HLA antibody definition by LabScreen aids assessment of the risk of graft failure associated with the production of DSAs post-transplantation.

P35

Low levels of donor-specific HLA antibody are associated with a memory response early after transplantation

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The advent of sensitive solid phase assays to measure HLA antibody levels has allowed the measurement of levels well below the threshold at which the flow cytometric crossmatch becomes positive. We have previously presented data indicating that patients transplanted across low levels of DSA (these are primarily antibodies HLA Class 1 specificities) had a risk of rejection of about 40% in the first year after transplantation, regardless of whether the flow cytometric crossmatch was positive or negative.

In order to investigate further the immunological response to HLA mismatching, 158 potential antibody responses were evaluated in 52 patients who underwent HLA antibody incompatible transplantation. The data set included all the recognised DSA, and also other HLA donor-recipient mismatches measured. The antibody level pre-treatment and the highest level in the first 30 days post transplant were recorded. The MFI level at which the flow cytometric crossmatch becomes positive in our laboratory averages about 2000u.

Initial antibody level, MFI units	n	N (%) with peak level double starting or >500u	N (%) with peak level 4x starting level or >1000u	N (%) with peak level >5000u
<250	30	3 (10%)	1 (3%)	1 (3%)
250-500	14	5(36%)	1 (7%)	0
500-1000	23	12 (52%)	8 (35%)	3 (13%)
1000-2000	16	10 (63%)	6 (38%)	7 (44%)
2000-5000	26	13 (50%)	3 (12%)[1]	14 54%)
>5000	43	2 (5%)[1]	0[1]	34 (79%)

1 – these data might be affected by saturation of the Luminex assay at MFI >10000u

These data show that DSA with low starting levels of MFI >250u showed a potential for at least a doubling of the level early after transplantation, though in many cases the peak level was less than 1000u. The risk of a peak DSA level of >5000u, likely to be associated with a higher risk of graft damage, rose when the starting MFI was >1000u. Increases in MFI levels in those with low starting levels was seen for all classes of HLA, Class 1, DR, DP, DQ and BRB3/4.

In summary, if a patient produced a detectable HLA antibody pre-transplant, there was a risk of resynthesis of this antibody in the early post-transplant period. The peak levels of antibody were associated with the pre-transplant level.

P36

Donor-specific HLA-DP antibodies in renal transplantation

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Background

Donor-specific HLA alloantibodies mediate both acute and chronic antibody-mediated rejection (AMR). However, not all HLA alloantibodies are considered pathogenic. Low expression of DP and DQ in renal endothelial cells[1], has led to the notion that DP alloantibodies are of minimal significance. In addition, some studies confirm that DP-antibody positive recipients do not have impaired allograft survival[2]. More recently, a number of reports suggest that donor-specific DP antibodies (dsDP) directly mediate allograft damage[3]. Having recently managed a patient with dsDP, who experienced recurrent AMR and graft loss, we wished to examine the prevalence and significance of dsDP in renal transplant recipients.

Methods

We retrospectively gathered data on all kidney transplants (from both deceased and living donors), performed at a single UK centre between January 2007 and September 2009 (n=332). Information on sensitisation, cross-match, alloantibody specificity, acute rejection, allograft function and patient/graft survival was noted.

Results

HLA-DP specific antibodies were detected in 30 of the 332 patients (9%). Of these, 12 had a transient DP antibody and in 3 the DP antibody emerged after graft loss, leaving 15 (5%) transplants for analysis. Five of these 15 (33%) had donor-specific DP antibodies, and no other donor-specific class I or class II antibodies. 2/5 (40%) of these patients experienced acute AMR compared with 1/10 (10%) patients with non-donor specific DP antibodies. There was also a non-significant trend towards poorer renal function in the dsDP group (indicated by higher mean serum creatinine at 3, 6 and 12 months).

Conclusion

This study confirms that HLA-DP specific antibodies are present in a minority of renal transplant recipients (in keeping with published data) but highlights that donor-specific DP antibodies may have a greater negative impact on transplant outcome than traditionally perceived. We suggest that routine risk stratification, through quantification of DP antibody (by single antigen beads) and donor HLA-DP genotyping, should be considered.

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P37

How many HLA typed donors are necessary to establish a cell therapy bank?

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Introduction: Cell therapy is an increasingly effective clinical procedure and establishment of a cell bank must recognise the need to provide HLA typed allogenic cells to facilitate minimal HLA mismatches (mm) with the majority of potential recipients. We are establishing a cell bank of cytotoxic T cells (CTL) from apheresis donors for treatment of EBV driven lymphomas. **Methods:** The HLA types of 200 apheresis donors (ADs) were assessed for HLA mismatches (NHSBT ODT "Minimum resolution" level) with 304 patients on the current East of Scotland kidney transplant list (PAT). ABO compatibility was a pre-requisite. A "*low grade mismatch*" (LGM) was defined as zero HLA-DR mm with a maximum of 2 mm at HLA-A and/or –B. 12.5% of the ADs were homozygous at –DR and 2% at -A, -B & -DR. Twenty ADs were a LGM for >90% of PATs. The AD phenotype -A1, -B8, -DR3 had a LGM with 33.3% of PATs and over half were '000' mm. Three-quarters of the ADs had LGM with <3% of PATs. In the 20 selected LGM ADs, 18 were –DR homozygous and 5 were -A, -B & -DR homozygous. We identified just 11 ADs who could be LGMs for 86.2% of PATs. 31 of the 42 PATs which failed to have a LGM with the 20 ADs had no LGM with any of the 200 ADs. **Conclusion:** We show that a bank of just 20 carefully selected HLA typed donors is sufficient to provide minimally HLA mismatched cells for therapeutic use.

P38

Frequent single antigen testing by Luminex is required to detect variations in donor specific antibody in sensitized patients awaiting transplantation.

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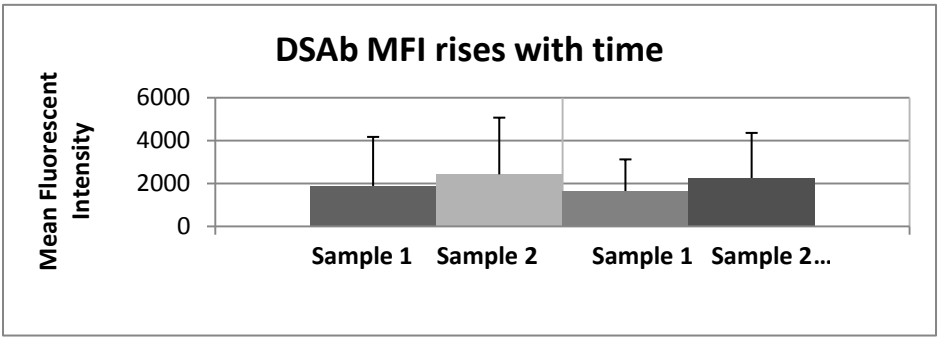
Donor specific anti-HLA antibodies [DSAbs] are detrimental to renal allograft function and survival. Luminex and LABScreen single antigen coated microbeads allow rapid and reproducible semi-quantitative assessment of DSAb. There are few data describing the natural history of DSAbs in patients on the waiting list and the purpose of this study was to define the variability of DSAb levels of sensitized patients awaiting transplantation.

Forty-Six sensitized patients with 2 or more pre-transplant Luminex single antigen screens [15.9± 15.5 months apart] were studied [35F:11M; mean age 50.2± 10.5 years; 28 1st graft: 18 subsequent graft]. One hundred DSAbs were identified in the 46 patients. Twenty-two patients had class I DSAb [CI]; 8 patients class II [CII] and 16 patients class I+II [CI+II].

31/46 patients were subsequently transplanted including 11/16 [68.75%] FCXM positive patients who were transplanted after plasma exchange, IvIg and augmented immunosuppression. Patients with positive CDC crossmatch were not transplanted.

Pre-transplant CI DSAb MFI rose from 1880± 2290 to 2424± 2644 [p=ns] and CII MFI from 1646± 1474 to 2253± 2104 [T test, p=0.05]. The average difference in MFI between the 2 samples was 1397± 1685. CI and CII MFI were equally likely to rise [37/62 v 26/38, p=ns]. Eleven patients [24%] developed a new DSAb between samples.



Patients with a positive FCXM were more likely to have a CI DSA [25/31 v 21/44, Fisher's exact test, $p<0.01$] and this was more likely to be at a higher MFI [2592± 2828 v 860± 1048, T Test, $p<0.05$] although in the 20 FCXM negative patients MFI was ≥1000 in 8/21 CI DSAb present.

This study shows that DSAb levels, as measured by Luminex single antigen beads, vary over time. Class II DSAb show a strong tendency to rise whilst Class I DSAb fluctuate with time.

Heart Transplantation

Moderator: Prof John Dark

P39

A Protective Role for Natural IgM Antibodies to Phosphorylcholine in Cardiac Transplant Recipients

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Objectives: Clinical and experimental evidence demonstrates that low levels of 'natural IgM antibodies' to oxidised - LDL (ox-LDL) and other modified forms of LDL such as malondialdehyde - LDL (MDA-LDL) and phosphorylcholine (PC) protect against atherosclerosis and stroke in non-transplant patients. Here we have investigated whether these antibodies are also associated with protection against cardiac allograft vasculopathy (CAV) in cardiac transplant recipients. **Methods**: Pre-transplant sera and post-transplant from 137 adult cardiac transplant patients were investigated by enzyme linked immunoassay for IgM and IgG antibodies to PC, ox-LDL and MDA-LDL. All patients were investigated by angiography for CAV at one, 3 and 5 years post-transplant. Patients were selected who had developed CAV at 3 years post-transplant (CAV +ve) and who were CAV free at 5 year post-transplant (CAV-ve). Sera were assayed pre-transplant and at 1, 2 and 5 years post-transplant. **Results**: The mean titres of IgM antibodies to PC and ox-LDL were significantly higher in pre-transplant sera from CAV –ve patients than CAV +ve patients (p=0.045 and p=0.034 respectively). There was a trend for higher levels of IgM anti-PC antibodies in CAV-ve patients at all times after transplantation, but these only reached significance at 2 years (P=0.021). Multivariate analysis of other risk factors for CAV revealed low level IgM anti-PC prior to transplantation to be an independent risk factor for CAV. Conclusions: These results demonstrate common mechanisms of pathogenesis between CAV and non-transplant atherosclerosis and suggest an important role for innate immunity in regulating disease progression in both types of atherosclerosis. The mechanisms where by natural IgM antibodies to PC protect against transplant atherosclerosis will be discussed.

P40

Is Heart type fatty acid binding protein a potential tool in cardiac donor assessment?

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Objectives

Donor cardiac troponin levels (cTnI and cTnT) are inversely related to the indices of cardiac function and may predict the occurrence of early graft dysfunction in the recipient. Heart type fatty acid binding protein (HT-FABP) is a further potential marker of myocardial injury with an earlier release profile than cTnT that could be of importance in donor heart assessment.

Methods

In 79 potential heart donors we assayed plasma HT-FABP and cTnT. UtilisingSwan-Ganz catheters and transthoracic echocardiography to cardiac functional parameters including wedge pressure (PCWP), cardiac index(CI), power index(CPI), LV ejection fraction(LVEF) and post-optimisation functional transplant suitability were recorded. Levels of HT-FABP were analysed by dichotomised cardiac functional parameters.

Results

Results are reported as median (IQR). HTFABP levels($\mu g.ml^{-1}$) were higher in donors with PCWP>14mmHg; 5.3(2.3-12.3) vs. 3.4(1.7-28), p=0.551; CI<2.4L.$min^{-1}m^{-2}$; 4.8(2.3-12.5) vs. 4.1(1.8-10.55), p=0.515; CPI <0.5Watts.m^{-2}; 4.65(1.7-12.9) vs. 4.5(2.3-11.85), p= 0.83 and LVEF<50%; 5.3(3.2-12.15) vs. 3.4(1.55-29.45), p=0.19 but did not achieve significance.

In contrast cTnT levels showed better discrimination; PCWP>14mmHg; 0.37 (0.31-1.19) vs. <0.03(<0.03-0.128-) p<0.01; CI<2.4L.$min^{-1}m^{-2}$;0.44 (0.107-0.807) vs.<0.03(<0.03-0.12), p<0.01; CPI <0.5Watts.m^{-2}; 0.36(<0.03-0.8) vs. <0.03(<0.03-0.15) p=0.013and LVEF<50%; 0.36(0.045-0.75) vs. <0.03(<0.03-0.11) p<0.01.

Conclusion

HTFABP, unlike cTnT does not adequately discriminate donor cardiac functional indices.

P41

Macrophages Mediate Chronic Cardiac Rejection through Monocyte-Induced by IFNγ (MIG)

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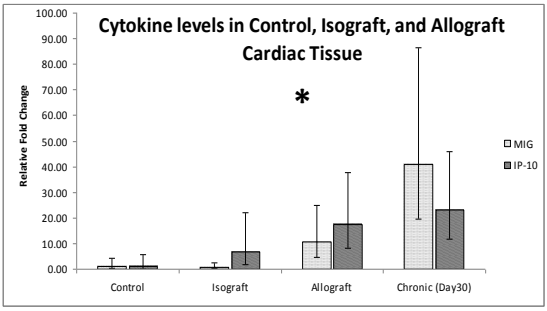
Introduction Chronic rejection (CR) in cardiac transplantation leads to allograft dysfunction and is the leading cause of transplant related heart failure. Attempts to prevent acute rejection (AR), so to prevent CR, are directed at T cell processes which obviously are insufficient. We investigated the role of the macrophages and in particular monocyte-induced by IFNγ (MIG) and IFN-inducible protein 10 (IP-10), known T cell chemoattractants, in chronic cardiac allograft rejection.

Methods BALB/c (H-2^d) hearts were transplanted into C57BL6 (H-2^b) recipients (n=6). Group AR had no treatment given. In group CR, 1mg i.p. of GK1.5 (anti CD4) was given Day -1, 0, 7. The hearts were analysed using qRTPCR and immunohistochemistry. The spleens underwent FACS analysis.

Results In group AR, all hearts rejected at day 7. In group CR, the functioning hearts were harvested at day 30 and trichrome analysis of the hearts confirmed the presence of CR. The allografts underwent qRTPCR analysis and whilst there was a significant increase in allograft MIG and IP-10 in group AR, relative to isografts (*$p<0.05$), only MIG was significantly upregulated in group CR relative to both group AR and isografts. ($p<0.05$)) This corresponded with a significant increase in the ICH staining for macrophages in the group CR allografts compared to both the group AR allografts and the isografts. FACS analysis of the splenocytes in group CR detected macrophages to be twice as abdundant compared to the group AR (40% vs 22%, respectively, $p<0.05$).



Conclusions Chronic cardiac allograft rejection, which is a significant clinical problem, may be a macrophage dependent process, potentially mediated through the chemokine MIG, both at the graft and systemic level.

P42

Primary graft dysfunction following lung transplantation and short term outcomes.

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Introduction:

Primary graft dysfunction(PGD) following lung transplantation may increase early and late mortality, rejection and development of bronchiolitis obliterans.

Methods:

We studied 3 month outcomes in UK lung transplant recipients categorised according to the presence of ≥ ISHLT grade 2 PGD at 6, 24, 48 and 72 hours following transplantation.

Results:

Of 139 lung transplants(mean age 47±13 years; 107 bilateral) 34(27%), 31(24%), 9(8%) and 12(11%) exhibited PGD at 6, 24, 48 and 72 hours respectively(42(30%) overall). Donor age 43±13 vs. 42±14; p0.7, recipient age 48±13 vs, 48±13; p=0.9, cold ischaemic time(IT) 173±53 vs. 176±58; p=0.5, and bypass times 262±122 vs, 243±90; p=0.3, were not different PGD versus non-PGD with a total IT of 324±116 vs, 272±67; p=<0.01. 11(30%), 18(58%) and 1(11%) of recipients with PGD at 6, 12 and 48hrs hrs improved to no-PGD before the next assessment time, while 8(9%) and 4(4%) of non-PGD recipients progressed to PGD at 24 and 48 hours.

The occurrence of PGD at any time point was associated with a non-significantly higher 3 month mortality (11 vs. 6%;p=0.6) and rejection incidence (0.3±0.8 vs. 0.5±0.7 ; p=0.4). Median ITU length of stay was increased 11(IQR 7-38) versus 4(2-8); p=<0.01).

Conclusion:

PGD at 6 and 24 hours is common and affects 25% of recipients. 57% of 6-24h PGD has recovered by 72 hours. In this series the impact of PGD on recipient survival and rejection incidence was small.

Immunosuppression 1

Moderator: Dr Richard Baker

P43

Everolimus with reduced-dose ciclosporin as a strategy to optimise long-term renal function: Results from a randomised study in 833 *de novo* kidney transplant recipients

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Everolimus, a proliferation signal/mTOR inhibitor, combines immunosuppressive and anti-proliferative actions, targeting the main causes of short- and long-term graft failure.

Study A2309, is a 24-month, multicentre, randomised, open-label, non-inferiority study that compares three immunosuppressive regimens in *de novo* kidney transplant recipients: everolimus at an initial dose of 1.5mg/day targeting C_0 3–8ng/mL or 3.0mg/day targeting C_0 6–12ng/mL, both with reduced-dose ciclosporin (CsA), or enteric-coated mycophenolate sodium (EC-MPS) (1.44g/day) with standard-dose CsA (controls). CsA C_0 target ranges in the two everolimus cohorts were 100-200ng/mL at day 5, 75-150ng/mL at month 2, 50-100ng/mL at month 4 and 25-50ng/mL at month 6. In the EC-MPS group, CsA C_0 target was 200-300ng/mL at day 5 and 100-250ng/mL from month 1 onwards. All patients received basiliximab induction, with corticosteroids administered according to local practice. The primary objective was to compare the composite efficacy failure rate (treated biopsy-proven acute rejection, graft loss, death and loss to follow-up) between the three treatment arms at 12 months. Secondary endpoints include graft loss, death, renal function and renal histology (in patients with proteinuria and/or suboptimal renal function) at 12 months. In total, 833 renal-transplant recipients were enrolled at 79 centres, with similar demographics in each group. The majority of patients were male (everolimus 1.5mg/day 63.5%, everolimus 3.0mg/day 68.5%, EC-MPS 68.2%) and white (69.7%, 64.5% and 68.6%, respectively). Mean age was 45.7, 45.3 and 47.2 years, respectively. Panel reactive antibodies ≥20% were present in 6.3%, 4.8% and 4.1% of the everolimus 1.5mg/day, everolimus 3.0mg/day and EC-MPS groups. The proportion of living donors was also similar (53.1%, 54.1% and 53.4%, respectively). Key findings at month 12 will be presented, informing decision-making about optimising everolimus and CsA dosing in kidney transplant recipients.

P44

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

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Background: Renal transplants from DCD are increasing; 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 6 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: In both groups demographics, HLA mismatch, CIT and donor characteristics were comparable. At 6 months, patient survival was 90.5% vs. 95% (NS) and graft survival was 95.2% (secondary to primary non function) vs. 100% (p 0.0001) respectively for ATG vs IL2Mab. Analysis was performed on the remaining patients:

Outcome parameter(%)	**ATG**	**IL2Mab**	**P**
DGF	52	65	0.08
HD sessions	38	62	**0.0001**
BPAR	0	13	**0.003**
Infections requiring admission	17	57	**<0.0001**
Patients readmitted	17	39	**0.0009**
Average serum Cr	137	168	NS
Average bed stay days post transplant	14	18	NS

Cost analysis included all patients with a functioning transplant at 6 months and results showed statistically significant savings in the ATG arm:

Parameter	**ATG (£)**	**IL2Mab (£)**	**P**
Immunosuppression	47255	41508	NS
Bed stay days post transplant	95600	167200	**0.0004**
Bed stay days for readmission	19200	40400	**<0.0001**
HD sessions	10384	20064	**<0.0001**
Clinic visits	93760	167200	**0.007**
Total Cost	266199	407412	**0.002**
Average cost/patient	15659	19401	**0.002**

Conclusion At 6 months, patients in the ATG arm had better outcomes and incurred 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.

P45

Steroid sparing protocols following non-renal transplantation: a systematic review and meta-analysis

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Background: We have recently reported that steroid avoidance or withdrawal (SAW) following renal transplantation results in an increase in acute rejection (AR) rates but does not affect graft or patient survival. Cardiovascular risk factors (hypertension, hypercholesterolaemia and new-onset diabetes) are all significantly reduced with SAW in renal recipients. Very little data has been reported to date regarding SAW protocols in recipients of other solid organ transplants.

Methods: This study is a systematic review and meta-analysis of SAW protocols in non-renal solid organ transplantation. A detailed literature search was performed using Ovid Medline and Embase, the Cochrane Library and the Transplant Library from the Centre for Evidence in Transplantation. All trials comparing a maintenance steroid group with either complete avoidance or withdrawal of steroids were included in the review. All studies were assessed for methodological quality. Meta-analysis of extracted data was performed where appropriate using the statistical software R. Where data is sparse, narrative review was performed. Discrete data are reported relative risk (RR) with 95% confidence intervals (CI).

Results: 7 relevant studies were identified (23 publications): 5 in liver, 1 in cardiac and 1 in pancreatic transplant recipients. No relevant studies were identified in small bowel or lung recipients. In liver recipients SAW regimens significantly increased the risk of acute rejection over maintenance steroids (5 studies, RR 1.49, CI 1.10 – 2.02, P=0.01), with no difference in hazard for graft loss or death. No difference in Hepatitis C recurrence was seen (4 studies, RR 1.02, CI 0.76 – 1.36, P=0.91). Data regarding cardiovascular risk factors were sparse, with just one study reporting an increase in antihypertensive use and need for diabetic therapy and higher serum cholesterol levels with maintenance steroids. Risk of infections did not differ between groups. The study in cardiac recipients demonstrated an increased risk of early (<3 month) AR along with an increase in steroid resistant AR. SAW was also associated with reduced antihypertensive use and lower serum cholesterol levels. In the study in pancreatic recipients, no differences in AR or survival were seen with SAW. Lower serum cholesterol and triglyceride levels were associated with SAW in simultaneous kidney pancreas, but not pancreas-after-kidney recipients.

Conclusions: Studies in non-renal transplant recipients are sparse and so firm conclusions are difficult to draw. The general trend appears to be similar to that in SAW protocols in renal recipients: an increase in risk of acute rejection with little impact on graft or patient survival, associated with improvements in cardiovascular risk factors. Further randomised controlled trials are required before the true risk/benefit ratio of SAW protocols in non-renal transplant recipients can be ascertained.

P46

De novo donor specific antibodies are associated with antibody mediated rejection in patients receiving Campath induction

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The detection of de novo donor specific antibodies [DSAbs] post renal transplant is associated with rejection, allograft dysfunction and loss. These studies have been conducted in patients receiving a variety of induction and maintenance immunosuppressive agents with no reports referring to the use of Campath.

In this study we describe the significance of de novo DSAbs in patients receiving Campath induction and Tacrolimus monotherapy.

435 patients[f:m=141:294, mean age: 47.44±13.14 yrs, mean HLA MM: 3.26±1.66, 1st graft: regrafts = 400:35] who were CDC/FCXM negative and had no DSAb detectable by luminex technology at the time of transplantation were included. All patients were screened for the development of DSAb post transplant using single antigen beads. All patients received Campath induction [30 mgs iv] and Tacrolimus monotherapy [target level 5 - 8 ng/ml] with 1 week of prednisolone. Mean follow up was 1.69±1.16 yrs.

131/435 [30.11%] patients developed de novo anti-HLA [DSAb and non donor specific anti-HLA (NDSAb)] post transplant. 78/435 [17.93%] developed anti-HLA DSAb. Actuarial patient survival at 3 years was similar in the DSAb+ and DSAb- groups [98.0% vs 96.2%, p=0.42 (log rank)]. Patients with de novo DSAb were at increased risk of graft loss [RR DSA+ 3.5, p=0.0045]. 27/78 [34.62%] of DSAb+ patients experienced an episode of AMR. The relative risk of AMR following the development of DSAb was 17.13, p<0.0001. There was no significant increased risk of ACR in DSAb+ patients. Allograft function was inferior in the DSAb+ group with a mean MDRD GFR at 12 months of 52.86 ±19.83mls/min and 58.49 ±17.51mls/min in the DSAb+ and DSAb- respectively [p=0.037].

Patients who developed both de novo anti-HLA Class I and Class II DSAb were at highest risk of developing AMR [RR 3.34, p=0.01] when compared with DSAb negative patients. Recipients who developed a DSAb with a mean fluorescence index [MFI] >1000 were also at higher risk of developing rejection [RR 1.74, p=0.01] when compared to patients with a DSAb with a MFI of <1000.

This is the first reported study of the incidence and relevance of de novo DSA in patients receiving Campath induction. It shows that the development of de novo DSAb is not uncommon and is associated with increased risk of AMR and inferior allograft survival. Patients should be screened post transplant for the presence of de novo DSA and may benefit from augmented immunosuppression.

P47

Alemtuzumab and steroid-free immunosuppression coupled with continuity of clinical follow-up reduces the risk of acute rejection and allograft loss in patients at high risk of non-adherence

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Non-adherence with immunosuppression is an important cause of allograft loss accounting for > 80% of graft loss in young adults aged 16-24 loosing their transplant. Graft loss is seven-fold more common in non-adherent compared to adherent transplant recipients. Multiple strategies are required to minimise the risk of graft loss in potentially non-adherent recipients. Few specific immunosuppressive strategies have been tried to minimise the risk of graft loss secondary to non-adherence.

We identified 9 young adults (median age 23 (21-36) years; 7 male; 2 female) who had demonstrated very poor adherence to maintenance dialysis regimens including poor biochemical and blood pressure control (hypertension-related seizures n=2). An elective immunosuppression protocol including Alemtuzumab 30mg intravenously (single dose at transplantation{n=6} or two consecutive doses at transplantation[n=3]) followed by Tacrolimus (target trough levels 8-12ng/dl) and Mycophenolate Mofetil 750mg bd with no concurrent steroid was specifically used in these individuals at transplantation. 7 received an elective live donor kidney transplant and 2 received a heart-beating cadaveric renal transplant. Medical follow-up included consistent clinical supervision from a single senior transplant nephrologist and repeated education from a transplant pharmacist.

Median(range) serum creatinine post-transplantation : 3 months was 113(95-138) umol/L;

6 months was 111 (96-125) umol/L; 12 months was 119 (95-149) umol/L and 113(97-113) umol/L at median latest follow up of 13.5 months. There have been no episodes of acute rejection and tacrolimus levels were consistently in the target therapeutic range.

Targeted immunosuppression with a regimen including alemtuzumab is a useful strategy in transplant recipients at high risk of non-adherence to immunosuppression and potential graft loss. A specific high risk of non-adherence immunosuppression protocol coupled with consistent continuity of medical care and regular transplant pharmacy input may dramatically reduce the risk of allograft loss.

Immunosuppression 2

Moderator: Dr Matthew Howse

P48

Preformed donor specific antibodies are associated with high incidence of antibody mediated rejection despite Campath induction

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The presence of preformed donor specific antibodies [DSAbs] detected by luminex technology at the time of transplantation despite a negative CDC/FCXM has been shown to be associated with adverse renal allograft outcomes. There are no published data on the relevance of preformed DSAbs in patients receiving Campath induction with tacrolimus monotherapy.

480 patients [f:m=165:315; mean age 47.41±13.01 yrs; mean HLA MM 3.33±1.63; 1st graft:regrafts =426:54] who were CDC/FCXM negative at the time of transplantation were screened for DSAb using luminex single antigen beads. All patients received Campath induction [30 mgs iv] and Tacrolimus monotherapy [target level 5 - 8 ng/ml] with 1 week of prednisolone. Rejection was diagnosed by allograft biopsy and classified using modified Banff 2005 criteria. Mean follow up was 1.7±1.16 yrs.

45/480 [9.38%] patients were DSAb+ at the time of transplantation [anti-HLA Class I (CI): 23 patients, anti-HLA Class II (CII): 14 patients, class I + II: 8 patients]. 30/45 [66.67%] patients had a mean fluorescence index [MFI] greater than 1000. Actuarial patient survival at 3 years was similar in the DSAb+ and DSAb- groups [97.8% vs 97.5%, p=0.90 (log rank)]. There was no significant difference in allograft survival at 3 years between the two groups [DSAb+ 88.9%, DSAb- 94.7%, p=0.11 (log rank)].
However DSAb+ patients were at significant risk of developing antibody mediated rejection [AMR]. At 3 years, AMR free survival was 73.3% and 92.9% in the DSAb+ and DSAb- groups, respectively, $p<0.0001$ (log rank). There was no significant difference in the incidence of acute cellular rejection between the 2 groups, ACR free survival being 88.0% and 88.9% in the DSAb- and DSAb+ groups respectively, p=0.89 (log rank).
Allograft function was inferior in the DSAb+ group; mean MDRD eGFR at 12 months was 48.47 ±47mls/min compared with 55.99 ±18.10mls/min in the DSAb- group [p=0.044].

Patients with anti-HLA CI DSAbs [alone or in combination with CII DSAbs] were significantly more likely to develop rejection than patients with no DSAbs [p=0.04, p=0.0006 respectively, Fisher ‘s exact test]. The detection of CII DSAbs alone was not associated with a higher risk of rejection. Patients with a CI DSAb with an MFI>1000 were more likely to develop rejection than patients with a MFI<1000 [p=0.02].

This study shows that despite Campath induction, patients with low level preformed DSAbs have an increased risk of AMR and impaired allograft function and may benefit from augmented immunosuppression.

P49

Diltiazem increases tacrolimus exposure in Black patients

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Background:

Oral bioavailability of tacrolimus is lower in patients of sub-Saharan African genetic origin (Black) than in patients from other ethnic groups, probably due to the high prevalence of expression of the metabolic enzyme cytochrome P450 3A5 (CYP3A5) and genetically determined high levels of expression of the drug efflux pump P-glycoprotein (P-gp). Finding the optimal initial dose of tacrolimus for Black patients has proved difficult and a possible strategy would be the use of the CYP3A5 and P-gp inhibitor diltiazem to block the active barrier to drug absorption. CYP3A5 expressers are known to be less susceptible to the drug interactions of the imidazole antifungals with tacrolimus and there are no published data on the interaction between diltiazem and tacrolimus in Black patients.

Methods:

Search of our transplant follow-up database identified nine Black renal transplant recipients in whom diltiazem had been commenced when on treatment with tacrolimus (Prograf). The mean of 3 determinations of dose-normalised tacrolimus blood concentration (ng/mL/mg/kg) was recorded before and after commencing treatment with diltiazem.

Results:

The median daily diltiazem dose was 120 mg (range 60-300 mg). Dose-normalised tacrolimus blood concentration increased from (mean±SD) 37.5 ± 14.9 to 60.7 ± 16.7 (paired sample T-test $p<0.0001$). *CYP3A5* genotype was known for 7 patients: 5 *1/*3 and 2 *1/*1 (all predicted to be CYP3A5 expressers). When data for these patients alone were analysed, dose-normalised tacrolimus concentration was 33.5 ± 10.3 before commencing diltiazem and 53.0 ± 12.3 after ($p<0.002$).

Conclusion:

Diltiazem increased dose-normalised tacrolimus blood concentrations in Black patients, including those known to be genetic *CYP3A5* expressers. Use of diltiazem to block the active barrier to drug absorption would be a feasible strategy for increasing the oral bioavailability of tacrolimus in Black patients.

P50

A Liquid Chromatography Mass-Spectrophotometric Method for the Simultaneous Measurement of the Calcineurin Inhibitors Cyclosporine A and Tacrolimus

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We describe a validated liquid-chromatography tandem mass-spectrophotometric (LCTMS) method for the simultaneous measurement of the calcineurin inhibitors (CNI), cyclosporine A (CyA) and Tacrolimus (Trl) in whole blood.

The technique of LCTMS is increasingly used in clinical laboratories for the measurement of small molecules such as immunosuppressants. Building on the experience of monitoring Trl by LCTMS we have developed a combined method for both Trl and CyA (CNI method). CyA had previously been monitored using an Enzyme Mediated Immuno Technique method (EMIT, Siemens Healthcare Diagnostics).

The LCTMS system was a Waters Acquity LC system with sample manager coupled to a Waters TQD mass spectrophotometer. The technique requires a sample volume of 25μL whole blood, and is highly selective for CyA and Trl. Specificity is achieved by monitoring the specific *m/z* transitions of the ammoniated ions of Trl (821>768), CyA (1220>1202) and the corresponding internal standards, ascomycin (809>758) and deuterated CyA (1232 >1214). Throughput was 30 samples per hour. Assays' were calibrated with commercial whole blood calibrators (Chromsystems, Germany) and internal quality control was achieved using commercial whole blood quality control material (More Diagnostics, USA). The LCTMS assay was linear up to a concentration of 50μg/L for Trl and 1700μg/L for CyA. The total assay variability for CyA by the LCTMS (n=40), using controls was 5.4% @ 87μg/L, 3.4% @ 171μg/L and 3.4% @ 362μg/L compared to 6.4%, 7.1% & 13.3% for EMIT. Variability for Trl was 11.9% @ 1.9μg/L, 4.4% @ 7.6μg/L and 6.7% @ 11.7μg/L.

The accuracy of LCTMS was assessed by the recovery of Trl from samples provided by the International Proficiency Testing schemes for Cyclosporine and Tacrolimus (Analytical Unit, St.George's Hospital Medical School, UK) median recovery was 93.2% (n=26, range 82.5 to 102.7%) and 95.7% (n=27), range 85.5 to 108.8%).

The methods were compared using Passing-Bablock regression and Bland-Altman difference plots. Trl concentrations as measured by the CNI method were compared to the original LCTMS method in 460 samples from adult renal transplant patients; analysis gave an intercept (mean (±95% CI)) of –0.10 (-0.23 to 0.05) and slope of 1.00 (0.98 to 1.02) with no significant bias. CyA concentrations as measured by the CNI method were compared to the EMIT in 428 samples from adult renal transplant patients, analysis gave an intercept (mean (±95% CI)) of -3.36 (-5.35 to -0.36) and slope of 0.90 (0.87 to 0.92) and indicated proportional bias of -14.9%.The EMIT assay over-estimated CyA by 14.9% compared to LCTMS using the Bland-Altman plot.

The LCTMS method is specific, precise, and cost effective for routine therapeutic monitoring of CNI's. In addition to the increased analytical range for CyA, which would provide for routine C2 monitoring, the new assay for CNI's has resulted in an improved laboratory workflow.

P51

Steroid sparing regimes are not associated with a high incidence of recurrent disease after renal transplantation

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Recurrent disease after renal transplantation is an important cause of allograft dysfunction and loss. Whilst steroid sparing [SS] immunosuppressive regimes are associated with more reversible rejection in high risk groups but a lower incidence of steroid related adverse events, there have been no systematic studies of recurrent disease [RD] after transplantation using SS regimes.

617 patients [254f, 363m; 288 DD, LD; mean age: 46.4 12.7 yrs; mean follow up: 29.4+21.3 months] transplanted using our steroid sparing protocol since 2002 were included in this study. All patients received either CD25 or CD52 monoclonal antibody induction with a Tacrolimus based immunosuppressive regime. Patients received a week of steroids after transplantation. Rejection and recurrent disease were diagnosed by biopsy. All biopsies were examined by light and electron microscopy.

169/617 [27.3%] patients had a specific pre transplant diagnosis of a primary glomerulonephritis. 12/169 [7.1%] of these patients were subsequently found to have RD diagnosed by renal biopsy for indicative reasons [allograft dysfunction, abnormal urinary sediment]. Patient survival at 7 years was similar in the patients with RD [RD+] and without RD [RD-], 100% and 93.9%, respectively, logrank p=0.5301. Allograft survival, censored for death with function was similar in the RD+, 100% and 84.7% in the RD- group at 7 years, logrank p=0.3584. Allograft function [MDRD eGFR, ml/min] at 1, 5 and 7 years was impaired in the RD+ group, 52.1+14.7, 37.7+13.8, 40.0+3.1 compared with the RD- group, 51.4+16.3, 48.0+17.1 and 47.9+14.6; statistical significance was achieved at 7 years, p=0.004.

45 recipients had IgA nephropathy [IgAN] and 4 of these patients [7.3%] developed recurrent IgAN. 33/169 [19.5%] recipients had FSGS and 2/33 [6.1%] developed recurrent FSGS. No allografts were lost from recurrent disease.

This study shows that in the medium term, our SS is not associated with a high incidence of significant RD. However allograft function is impaired in the group of patients with RD and longer term data are awaited.

P52

Routine reduction in mycophenolate mofetil from 1g twice daily to 500 mg twice daily after the first month does not compromise short-term outcome

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Background

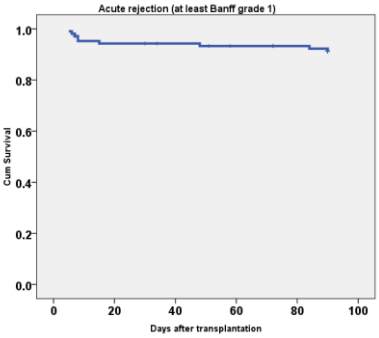
The FDCC study (van Gelder, *et al*. 2008;86:1043) suggesting that higher doses of mycophenolate mofetil (MMF) are required during the first month after renal transplantation (2g daily) to achieve optimal exposure but subsequent to this lower doses are required (1-1.5g).

Methods

In May 2007 we changed our protocol to use 1g MMF twice daily for the first 30 days after renal transplantation with subsequent dose reduction to 500 mg twice daily. All patients were treated with basiliximab and tacrolimus with target trough blood concentrations of 8-15 ng/mL for the first 30 days and 8-12 ng/mL from day31-day 90. All patients were treated with prednisolone, discontinued after 7 days in 26 patients (at high risk of NODAT) and continued throughout the first 3 months for the remainder. Data are shown for 107 consecutive patients treated with MMF using this protocol.

Results

There were nine episodes of acute rejection of at least Banff grade 1 in severity diagnosed on indication biopsies during the first 90 days after transplantation with no clear pattern of increased acute rejection during the period of reduced dosing (Figure).



Conclusion

Planning MMF dosing based on predicted exposure from the FDCC study rather than the 'standard' dose of 1g daily delivered excellent efficacy and was well tolerated.

Infection

Moderator:Dr Rachel Hilton

P53

What is the Long-term Effect of CMV Infection after Renal Transplantation?

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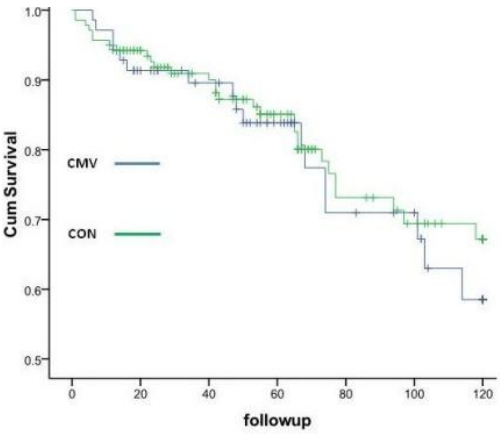
Introduction: Cytomegalovirus infection is a major cause of morbidity after renal transplantation. Consequently most centres use some form of prophylaxis, particularly in high risk (D+/R-) kidney recipients. Though successful this strategy is associated with a significant incidence of CMV infection after standard 100 day prophylaxis. Recent study evidence has shown that the incidence of late CMV disease can be halved by extending prophylaxis to 200 days but this has financial implications. Here we have analysed all detected CMV infections over a 20 year period in a single transplant centre.

Methods: We have compared the graft function and both graft and patient survival after an episode of CMV infection. Blood tests to detect CMV infection were only sent when there was clinical suspicion of CMV infection. All patients who were CMV D+R- received prophylaxis for 100 days. 70 patients with CMV viremia (CMV) were identified from our transplant database between 1988-08. Two age, baseline GFR and graft vintage matched controls (CON) were selected for each patient with CMV viremia. Actuarial survival analysis is performed by Kaplan Meier method to study patient and graft survival.

Results: A total of 210 patients were followed up for a maximum period of 10 years. Patients had similar mean age (CMV 49 ±15yrs, CON-48 ±15yrs), baseline GFR (CMV-58.6 ±2, CON-57.1 ±1.7), gender distribution, DR mismatches and graft numbers in both the groups. Other baseline demographics were similar. Kaplan Meier analysis does not show any significant differences in graft survival (figure-1) or patient survival between the CMV and CON groups (Median patient survival CMV-173 months, CON-157 months, log rank p=0.5; Median Graft survival CMV-97 months, CON-99 months, log rank p=0.6). Renal function (eGFR) did not differ between the two groups at 5 years after transplantation (CMV 34.3 ml/min/1.73m^2 vs. CON 38.1 ml/min/1.73m^2 p=0.4).

Conclusions: In this study, patients with similar baseline renal function achieved comparable long-term outcomes irrespective of their CMV viremia status. Given the lack of significant longer term impact of CMV infection on graft and patient outcomes in our study population, extended antiviral prophylaxis should be contemplated with caution.



P54

Swine 'flu in a renal transplant population

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Background:
H1N1 pandemic influenza has proved to be a mild self-limiting illness for the majority of sufferers in the general population. However, there is limited information available on the natural history of H1N1 in immunocompromised patients.

Methods:
We conducted a survey of five renal transplant units in London and South East England to ascertain rates of admission for complications of H1N1 influenza. All cases were laboratory confirmed.

Results:
Five renal transplant centres were surveyed. The total number of renal transplant recipients under follow-up at these centres was approximately 3,300. Of the five units surveyed, a total of 21 laboratory-confirmed cases were diagnosed since the outbreak began (representing 0.6% of the population at risk). This is likely to be a significant underestimate of the overall incidence since milder cases are likely to have been managed in primary care. These laboratory-confirmed cases presenting to secondary care are likely to represent the more severe end of the illness spectrum.

All 21 patients (100%) received treatment with oseltamivir. 13/21 (62%) patients were hospitalised but the majority had a mild illness with only 3 patients (14%) developing complications. 2 patients (9.5%) required admission to ITU with respiratory failure. 20/21 patients (95%) made a full recovery. One patient with other co-morbid conditions continues to recover in intensive care. One patient died from a CVA after recovering from swine 'flu but there were no deaths directly attributable to swine 'flu.

Conclusions:
Our experience suggests that H1N1 influenza follows a benign course for the majority of renal transplant recipients.

P55

Cytomegalovirus Viral Load Kinetics in Predicting the Risk of CMV Disease in Solid Organ Transplantation

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INTRODUCTION: Cytomegalovirus (CMV) is a major viral pathogen complicating solid organ transplantation. The real-time quantitative polymerase chain reaction (PCR) assay is the primary method used for diagnosis and management of CMV infection. The lack of international standardization of CMV testing has made it difficult to interpret the results and define a common threshold for initiating treatment. It was our aim to evaluate the CMV viral load that would identify the patients most at risk for developing CMV disease after liver, kidney and kidney-pancreas transplantation (KPT).

METHODS: Between January 2006 and July 2009, 461 solid organ transplantations were performed at the Royal Infirmary of Edinburgh (RIE): 205 liver transplants, 215 renal transplants & 41 KPTs. Data were retrospectively collected from hospital databases (RIE, Aberdeen Royal Infirmary, Ninewells Hospital, Dundee & Raigmore Hospital, Inverness) and patient notes as sources of information. 52 patients developed CMV viraemia within 18 months post-transplantation. CMV viraemia was defined as the detection of CMV DNA in blood samples. CMV disease was defined as an episode of ill health with fever and organ involvement together with typical histological findings, PCR measurement of viral DNA in blood or specific tissue, or a diagnostic rise in antibody level. Statistical analysis of data included Chi-Square contingency and Mann Whitney tests, $p<0.05$ considered statistically significant.

RESULTS: Viral loads were significantly higher in liver transplant patients who developed CMV disease than in asymptomatic individuals (median value 894 copies/ml versus 375,744 copies/ml, $p= 0.0004$). The number of asymptomatic patients in kidney-pancreas or renal transplant groups was too small for similar comparison. CMV DNA levels were significantly higher in the D+R- patients than in D+R+ recipients due to much higher viraemia in primary infection (liver transplant patient 518.608 copies/ml versus 11.726 copies/ml, kidney-pancreas recipients 306.000 copies/ml versus 29.282 copies/ml and renal transplant patients 1.673.897 copies/ml versus 100.385 copies/ml). Using a threshold of 5000 copies/ml of CMV DNA, all the patients who developed clinical CMV disease were identified in D+R- group. All the patients whose infection did not progress (and who were not treated) were below this threshold. The 5000- copies/ml threshold could also identify 70% of D+R+ patients but in this patient group, the generally lower viral loads were less predictive of disease development.

CONCLUSION: CMV viral loads over 5000 copies/ml predict clinical CMV disease in D+R- category and could be used as a threshold to start treatment. New local guidelines for the management of CMV infections in solid organ transplant patients will be issued.

P56

Immunity to varicella-zoster virus and vaccination in potential renal transplant recipients

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Aim

Primary varicella infection is associated with significant morbidity and mortality in the immunocompromised host. There is considerable evidence in the paediatric population to support the safety and efficacy of varicella vaccination in potential renal transplant recipients; the European best practice guidelines recommend vaccination in this population and VZV vaccination has been shown to be clinically effective at boosting protection in seropositive patients reducing shingles by 50%. We sought to determine current practice in UK transplant centers, together with the efficacy and safety of VZV vaccination in our population of seronegative patients with end stage kidney disease.

Methods

23 UK transplant centers were surveyed by phone or E-mail regarding their policy for screening and vaccination. In our centre all patients on the adult renal transplant waiting list or in the work-up process for listing are tested for VZV antibody (IgG) to assess their immune status; those who are VZV seronegative, and without any contraindication, were offereed two doses of live attenuated VZV vaccine, administered 6-8 weeks apart, with a follow-up serum sample test 4-8 weeks after the second dose in line with unit policy. Side-effects were specifically sought and recorded.

Results

17 of 23 transplant units responded to the survey. Of these the majority (88.2%) of units screen for VZV as part of work up, however only 23.5% of units have a vaccination policy for VZV negative patients. In our unit 21 of 600 (3.5%) potential renal transplant recipients were non-immune to VZV, 17 of who complied with the recommended vaccination schedule. There were 8 males; the median age was 51.2 years (range 29-72 years). The vaccine doses were well tolerated and no patients developed a fever or vaccine-related rash. Seroconversion occurred in 15 (88.2%), 2 (11.2%) remained seronegative.

Conclusion

Susceptibility to primary VZV infection following kidney transplantation is predictable but risk is not universally ascertained in UK transplant centers and only a minority of units vaccinate in line with European best practice guidelines. Vaccination in these individuals is safe with seroconversion in the vast majority. Given the potentially fatal course of primary VZV infection consideration should be given to vaccination of non-immune patients likely to have a renal transplant.

P57

Cost effectiveness of 100 versus 200 days prophylaxis with valganciclovir (Valcyte®) for CMV disease in at risk renal transplant recipients

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INTRODUCTION: Cytomegalovirus (CMV) disease is a major problem in high-risk (D+ / R-) transplant recipients. Such patients usually receive standard CMV disease prophylaxis consisting of 100 days of valganciclovir (VALGAN). A recent presented double-blind, randomised, trial (IMPACT) reported that the extension of VALGAN prophylaxis from 100 to 200 days significantly reduced the incidence of CMV disease up to 1 year post transplant (36.8% v 16.1% , $p<0.0001$). The objective of this analysis was to assess the cost effectiveness of extending CMV disease prophylaxis from 100 days to 200 days in a UK setting.

METHODS: An economic model was developed to evaluate the health outcomes and direct costs of 200-days versus 100-days VALGAN prophylaxis. The analysis captures costs from an NHS perspective. Patient disease progression to graft failure and dialysis is modelled through a Markov model. Patients enter the model post transplantation. The incidence of CMV disease and acute rejection from the IMPACT study is used to populate the model in the first year. The risk of graft failure is derived from the published literature. Health outcomes are estimated as quality adjusted life years. All cost and benefits are discounted at 3.5%.

RESULTS: Patients in the 200 day VALGAN arm experienced less CMV disease and acute rejection episodes which translates within the model into a reduced incidence of graft failure and return to dialysis in the long term. Therefore, despite the higher prophylaxis cost of 200 days VALGAN the extended prophylaxis arm is estimated to be cost-saving when capturing all relevant cost and benefits. The model estimates over £1,000 cost savings and an incremental benefit of 0.02 QALYs in the 200 days arm.

CONCLUSION: This analysis demonstrates that extended CMV prophylaxis using valganciclovir can be regarded as a cost effective option in the UK.

P58

BK viremia following renal transplantation: management and outcomes

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The presence of BK virus is detrimental following renal transplantation. BK viremia is the result of over immunosuppression but efforts to reduce immunosuppression usually start a vicious cycle between BK nephropathy and rejection. Many transplant units have now established screening programs to detect BK viremia but with only limited success to date.

We present the data of all patients identified with BK viremia who have received a kidney or simultaneous kidney-pancreas (SPK) transplant in a single transplant unit, their treatment adjustment and outcomes.

The majority of the patients are maintained on Tacrolimus and mycophenolate mofetil (MMF), and induction with antithymocyte globulin (ATG) is used for all SPK recipients and kidney transplant recipients from donors post cardiac death (DCD). It is the policy of this unit to test any patient who has graft dysfunction without a clear cause for BK virus in the blood by polymerase chain reaction (PCR) and also to stain their allograft biopsies for the virus.

During the 3-year time period between June 2005 and May 2008 294 transplants were performed, 205 kidney transplants from brain stem dead donors, 42 from donors post cardiac death and 47 SPKs.

Twelve patients (4%) were identified as having BK viremia with titres ranging from $\log_{10}$ 2.14 copies/ml to $\log_{10}$ 5.91 copies/ml. The median time from transplant to diagnosis was 8 months (range 2-22 months). During the study period a total of 90 patients received ATG and of these 2 (2%) were subsequently identified to have BK viremia.

In 2 patients Tacrolimus was changed to Rapamycin. One of them became BK negative and the other has low viremia levels but improved kidney function. In 8 patients MMF was withdrawn, and in 2 no real change was made to the immuosuppression regime. One patient died from intracerebral bleeding and no patient has lost their graft so far.

The median eGFR at diagnosis was 30.5 ml/min/1.73m^2 and at a median follow up of 24 months post-diagnosis (following reduction of immunosuppression) the median eGFR had improved to 38 ml/min/1.73m^2. Nine out of the 12 patients are negative for BK on their most recent serum sample.

In conclusion BK viremia affects at least 4% of this transplant cohort. It is associated with poor kidney function that improves following reduction of the immunosuppressive load. Interestingly BK does not seem to be associated with the use of ATG induction in this series and has not caused any graft loss in the short to medium term.

P59

Is H1N1 really a contraindication to organ donation?

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There are now over 8000 people registered on the UK transplant list with the vast majority awaiting a kidney transplant. The number of highly sensitised recipients continues to rise and finding organs for these patients is becoming an increasingly challenging problem.

With the increased incidence of swine flu in the population there is a risk that potential organ donors may be infected, or have infection suspected. The current recommendations from the Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO), advises that any potential donor dying from proven swine flu should not be an organ donor. In addition the guidelines suggest that a potential donor with a confirmed or suspected concomitant diagnosis of swine flu should not be a donor unless 10 days has elapsed after diagnosis and adequate treatment with Oseltamivir (tamiflu) has occurred.

Such guidelines have the potential to significantly reduce the donor pool at a time when not only is the number of potential recipients increasing but also the number of good quality young donors is falling.

We present the case of a 50 year old patient who had been on the transplant waiting list for 11 years due to being highly sensitised with a PRA of 96% after previous transplantation. We were offered a kidney from an aged and sex matched Deceased after Brain Death (DBD) donor who was suspected of having died from H1N1 having had a positive nose and throat swab. The mismatch was 0-0-0. Given the excellent match, the degree of sensitisation and the length of time that our recipient had been on the waiting list, we believed that the organ had to be used as this was in the best interests of the patient. The patient was fully counselled and we liaised closely with our virologists in order to provide an appropriate screening and prophylaxis programme which consisted of regular nose and throat swabs and a five day course of Oseltamivir (tamiflu). Six weeks post transplant the patient has a creatinine of 73 mmol/l and is completely well with no complications. To date all nose and throat swabs have been negative for H1N1.

We believe that the current guidelines could potentially result in the loss of good quality organs at a time when demand is high. It is highly likely that transplanting organs from donors infected with H1N1 will result in no adverse outcomes. All potential recipients should be fully counselled and in our experience involvement of the virologist team is also essential. Our experience, all be it with one case, suggests that it was completely appropriate to transplant our recipient but that this may not be the case in all similar situations and therefore should be on a pragmatic case by case basis.

P60

Viral Surveillance in Paediatric Renal Transplants

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Introduction

Primary viral infection and reactivation are significant problems in immunosuppressed children who receive solid organ transplants. Routine blood surveillance and transplant biopsy are the mainstay of diagnosis. We reviewed the notes of 18 children transplanted between December 2007 and July 2009 to look at our management of this problem in the first year post transplantation.

Methods

18 children aged between 2years 10 months and 17yrs 8 month with a wide range of underlying diagnoses. 14 (78%) of the transplanted kidneys were from live donors. Prior to transplantation, 4 children had negative serology for both EBV and CMV. A total of 27 biopsies were performed in 18 children, In our post transplant protocol, surveillance for both CMV and EBV are routinely performed.

Results

Only 4 children showed no evidence of viral infection in the first year post-transplant. Of the 14 with viral infections, 13 were asymptomatic and detected on routine surveillance, and one had evidence of infection on transplant biopsy.

EBV - 10 children developed a EBV viraemia, in whom 4 acquired primary infection, treated by reduction of immunosuppression. One child developed Post Transplantation Lymphoproliferative Disorder which resolved with reduction of immunosuppression alone.

CMV – 6 of the cohort acquired CMV (one primary infection) of which 4 children were treated with IV and oral valgancyclovir until the viral load was undetectable. The remaining two cleared the virus within 1 month without treatment. One child had CMV detected on renal biopsy.

BK -1 child developed BK viraemia with graft dysfunction which resolved within a month with reduction of immunosuppression.

Adenovirus - adenovirus detected in the blood in 1 patient, who also had concomitant EBV, also responded to immunosuppression reduction.

Conclusions

The recent use of more potent immunosuppressive agents appears to be associated with a significant rate of viral infections, although not with greater graft loss. This may be due to increased awareness as a result of routine surveillance, and early effective treatment with current antiviral agents, together with careful reduction of immunosuppression.

In this cohort, the outcome at one year was good with 100% patient and graft survival.

Kidney 1

Moderator: Dr Paul Cockwell

P61

Predicting kidney transplant outcome using donor genetic markers

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Donor genetic variation has demonstrated association with allograft outcomes, the study aim was to attempt replication of previously identified donor genetic polymorphisms in a large transplant cohort and most importantly assess predictive utility for long-term allograft survival.

A sophisticated literature search was performed to identify any donor genetic polymorphism associated with adverse kidney transplant outcomes. Genomic DNA from 785 Caucasian kidney transplant donors (Birmingham, UK; median follow-up 81 months) were analysed for identified genetic variants. Association with acute rejection, delayed graft function, 1 year serum creatinine and long-term death-censored allograft failure was assessed using logistic, linear and Cox regression with further assessment where appropriate with KM-analysis. All polymorphisms were genotyped successfully, SNPs and I/D polymorphism on ABI7900HT using Taqman® and microsatellite analysis on ABI3730 DNA analyser following restriction length polymorphism.

The literature search revealed: 10 single nucleotide polymorphisms (SNPs) [TNF-α rs3093662, TNF-α rs1800629, TGF-β codon 10 rs1800470, INF-γ rs2430561, CCR5 rs1799987, IL-6 rs1800795, C3 rs2230199, TLR4 rs4986790, TLR4 rs4986791, EET rs1042032]; 1 insertion deletion (I/D) polymorphism [SERPINE/PAI-1 rs1799889]; and 1 microsatellite polymorphism [HO-1 GT(n)]. One polymorphism was associated with acute rejection (C3 CC genotype OR: 3.13; 95% CI 1.29, 7.59; p=0.01), one with delayed graft function (HO-1 SS genotype: OR: 2.09; 95% CI 1.11, 8.93; p=0.02), and one with death-censored allograft loss (EET AG genotype: HR: 0.71; 95% CI 0.53, 0.933; p=0.01). No polymorphism was associated with 1 year creatinine.

Despite identifying associations between donor genetic polymorphisms and allograft outcomes, no replication of the original studies was achieved. This suggests limited predictive utility of donor genetic markers.

P62

Elevated pre-transplant BAFF is associated with subsequent acute antibody- mediated rejection

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Introduction : B cell-activating factor belonging to the tumour necrosis factor family (BAFF) (also known as BLyS) is a cytokine which enhances B cell and plasma cell survival[1]. BAFF-transgenic mice have elevated B cell and antibody levels. There is also data linking BAFF with acute renal transplant rejection and C4d staining on biopsy[2]. A number of therapeutic agents have been developed to target this pathway including an anti-BAFF antibody.

Purpose of the study : We wished to determine whether pre-transplant BAFF levels predicted subsequent susceptibility to acute antibody-mediated rejection (AMR) in highly-sensitised transplant recipients.

Methods : Serum samples were obtained from 32 patients sensitised to HLA antigens undergoing antibody incompatible (AI) transplantation prior to desensitisation and from 319 patients undergoing routine renal transplantation. BAFF levels were measured by ELISA using reagents from Biosupply UK. Subsequent statistical analysis was performed using GraphPad Prism.

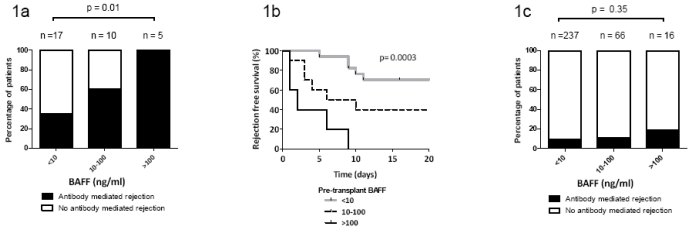
Results : In those transplant recipients undergoing desensitisation, pre-transplant (pre-desensitisation) BAFF levels of >100ng/mL were associated with an increased risk of AMR (Figure 1a, b; $p<0.05$). In a cohort of patients undergoing routine transplantation (without desensitisation),18.8% of patients with pre-transplant BAFF levels of >100ng/mL had

an episode of humoral rejection post-transplant compared with 9.9% of those with BAFF levels of <100ng/mL, p=ns (Figure 1c). There was no association of high pre-transplant serum BAFF levels with acute cellular rejection.

Conclusions : High pre-transplant BAFF levels were associated with an increased risk of developing AMR in patients undergoing AI transplantation. Our data suggest that agents targeting BAFF neutralisation may be useful in individuals with high BAFF levels undergoing de-sensitisation who are at increased risk of AMR.

References : 1. Mackay F et al. Ann Rev Immunol 2003;21:231-64. **2.** Xu H et al. Transplant Proc 2009;41:112-6.

Figure 1



P63

Regression of Proteinuria during the first three years after Renal Transplantation is associated with improved Graft Outcomes

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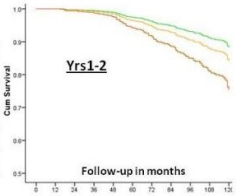
Introduction: The significance of early low grade post transplant proteinuria is well established. However proteinuria is dynamic and the impact of its changes on graft outcomes is less clear. We analyse the changes in low grade proteinuria within the first three post-transplant years and its impact on graft survival.

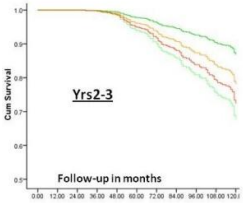
Methods: Protein creatinine index (PCI) is used to measure proteinuria. 32000 PCI readings are analysed and median PCI calculated annually for the first three years for 826 patients (1988-2007). Patients with proteinuria >1g and those with graft survival< 1 year are excluded. Patients are divided into two groups based on the PCI. (Low<150mg & high>150mg). Patients are further divided into 4 groups based on changes from years 1- 2, 2-3 and 1-3 (Low/low, high/low, low/high, and high/high). Survival analysis was performed (multivariate Cox proportional hazards model) with a follow-up of 10 years. Potential confounders are adjusted for in the analysis.

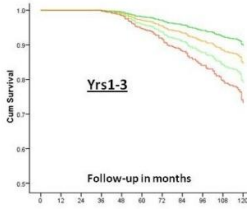
Results: Figure-1 shows that patients in the low/low group at any time point have the best graft survival Patients with proteinuria in regression (high/low) have better outcomes than those with deteriorating proteinuria (low/high, high/high). In 502 patients where data for medications was available, a sub-analysis has been performed which shows that patients on ACE-inhibitors or ARBs have more reduction in proteinuria when compared to the rest of our population (mean change ACE/ARB=-143, no ACE/ARB=-100, p=0.03). A 100mg change in proteinuria from year1-3 was shown to affect the graft survival with HR-1.1 (95%CI-1.0-1.2, p=0.04) in multivariate analysis.

Conclusion: In conclusion this study shows that regression of proteinuria is associated with better graft outcomes. The impact of ACE-i/ARB on the regression of proteinuria is interesting. A multicentre prospective randomized trial to look at the impact of ACE-i/ARB usage after transplantation on proteinuria and long term outcomes would address this issue.

Proteinuria groups	Years1-2 (HR)	Years2-3 (HR)	Years1-3 (HR)
Low/low	1	1	1
High/low	1.4	1.7	1.5
Low/high	2.3	2.8	2.2
High/high	2.3	2.3	2.9







P64

THE TROUBLED TRANSPLANT: Can Early Surveillance Biopsy Predict the "At Risk" Renal Allograft?

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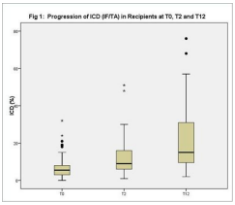
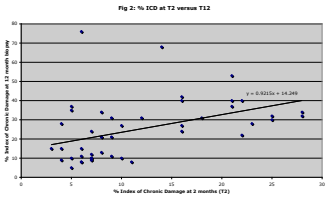
INTRODUCTION: Graft damage occurs early post-transplantation and is progressive in the first year. Preliminary data suggests histological changes on early protocol transplant biopsy (interstitial fibrosis, tubular atrophy IF/TA) may predict long-term graft outcome. More precise quantification of these changes might improve the predictive value of this surrogate marker. We developed a standardized method for quantification of IF/TA on biopsy, expressing the result as an index of chronic damage (ICD). Our aim was to determine whether the ICD at the 2 month biopsy was predictive of later changes.

METHODS: We studied a cohort of consecutive transplant recipients maintained on a calcineurin inhibitor and mycophenolate mofetil with early steroid weaning. Surveillance biopsies were conducted at 3 time intervals: implantation (T0, n=189), 2 months (T2, n=180) and 12 months (T12, n=84). Samples were anonymised and assigned an ICD. ICD is a morphometric assessment of the degree of IF/TA expressed as a percentage of the cortical cross-sectional area. Primary endpoint of the study was ICD at T12. Initial exploratory analysis of data was conducted to identify if IF/TA at T2 was predictive of IF/TA at T12. This was followed by multivariate regression analyses of ΔICD (the difference in ICD between T0 and T2) and other clinical risk factors (cold ischaemic time, delayed graft function, donor age) to evaluate their potential effects on T12.

RESULTS: To date, we have analysed 210 specimens from 70 patients transplanted between Sept 06 and Aug 09, with ICD values at all 3 time intervals. The cohort comprised, live donor (n=17), non-heart beating (n=20) and heart beating (n=33) recipients. Sub-clinical rejection was treated with IV methylprednisolone (n=7). Fig.1 charts incremental rise in ICD over 1 year ($p<0.05$). Fig. 2 demonstrates ICD at T2 is predictive of changes at T12 ($y=0.92$, $r^2=0.86$). Using multivariate analysis, IF/TA at T12 was predicted by ΔICD (incremental rise in ICD between T0 and T2), ($r^2=0.79$, $p=0.009$).





CONCLUSION: Early surveillance biopsy is a robust predictor of severity of IF/TA at one year and therefore may assist in the timely identification of the "at risk" graft. If this finding is reproduced with greater numbers of patients, it may render the 12 month biopsy obsolete, with favourable implications for patient acceptance and a concomitant reduction in costs. Further work is needed to establish whether changes on T2 biopsy are also predictive of long term graft outcome.

P65

A cause for concern - total symptom burden in renal transplant patients

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Background. Renal transplantation is seen as the gold standard of care for patients with end-stage renal disease and it is often believed that patients with functioning renal transplants have few symptoms. Evidence on symptom prevalence is generally limited to the dialysis population and little is known about symptoms in transplanted patients. This cross sectional study was undertaken to assess symptom prevalence in patients transplanted more than one year previously.

Design. Symptom data was collected from patients attending the transplant clinic in one UK renal unit in December 2009, and transplanted at least one year before study entry. Data was collected using the renal version of the Palliative care Outcome Scale symptom score-renal (POSs-renal). This patient-completed instrument identifies the presence and severity of 17 symptoms. Nine further transplant-specific symptoms were added: seven physical (headache, increased appetite, weight gain, weight loss, bloating, tremor, and poor libido) and two psychological (guilt and dissatisfaction with body image) symptoms. Demographic and clinical data was also collected, including estimated glomerular filtration rate (eGFR) using the MDRD formula, primary renal diagnosis and co-morbidity.

Results. Symptoms were evaluated in 110 patients, with a mean age of 47 [SD 13.6] years [range 20-78]. Mean eGFR was 46 [SD 16.8] mL/min [range 14-101]. In patients with a renal transplant, on average, symptom burden is high, with patients reporting a mean of seven symptoms. However, there is considerable variation, with some individual patients reporting markedly greater or lesser symptom burden [SD 5.2, range 0-22]. The most prevalent symptoms were weakness (56%, with 95% confidence interval (CI) 47-65%), difficulty sleeping (46%, with 95% CI 37-56%), dyspnoea (42%, with 95% CI 33-51%), feeling anxious (36%, with 95% CI 28-46%) and drowsiness (36%, with 95% CI 28-46%). Not only were symptoms highly prevalent but certain symptoms were frequently reported as moderate to severe; 30% of all patients reporting moderate to severe weakness, 24% moderate to severe difficulty sleeping, 22% moderate to severe dissatisfaction with body image, 17% moderate to severe dyspnoea, and 16% moderate to severe drowsiness.

Conclusions. This cross sectional study demonstrates that symptom burden in renal transplant recipients is high, approaching that of dialysis patients. However, transplant patients typically report a different pattern of symptoms, with predominance of transplant-specific symptoms and less pain, anorexia, and immobility. Routine symptom assessment should be undertaken in transplant patients to identify these often undisclosed symptoms. Further research is required to determine both the underlying pathophysiology and best interventions to manage and improve symptoms.

P66

A matched comparison of chronic kidney disease (CKD) complications in non-transplant and transplant patients

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It has been suggested that patients with advanced Chronic Kidney Disease (CKD stage 5) following renal transplantation fall below targets established for non-transplant CKD patients. The purpose of the study was to directly compare CKD parameters and targets, across the entire spectrum of CKD, in transplant recipients with a matched group of non-transplant patients.

Adult (≥18 years) renal transplant recipients (n=216), all performed between 2003-2006 were studied. Prevelant detailed demographic, clinical and laboratory data were recorded over a fixed 2 month study period (March 2008 – May 2008). The variables of interest were those complications with targets set by either the UKRA or the US K-DOQI guidelines. In addition, the same variables were collected from an age, sex, ethnicity and CKD stage matched cohort of non-transplant CKD patients. Significant differences in CKD parameters between the groups and target attainments were identified.

Of all CKD stages, transplanted patients within CKD stage 3 (n=82) demonstrated the most striking difference with the non-transplanted population. Transplanted patients had significantly higher systolic and diastolic blood pressures (146 vs 134 and 81 vs 74 mmHg respectively, $p<0.001$ for both), lower serum albumin (41 vs 43 g/L, $p<0.001$), lower serum bicarbonate (25 vs 27 mmol/L, $p\leq0.001$) and higher serum corrected calcium (2.4 vs 2.2 mmol/L, $p<0.001$). Conversely, transplant recipients had lower serum phosphate levels (0.97 vs 1.09 mmol/L, $p<0.001$) and markedly lower urinary albumin creatinine ratios (9.8 vs 66.9 mg/mmol, $p<0.001$), despite higher blood pressures. Significantly fewer transplant recipients achieved target systolic and diastolic blood pressures (SBP 22% vs. 42%, $p = 0.02$ and DBP 45% vs. 71%, $p = 0.03$). No other significant differences in achievement of parameter targets were seen.

This report demonstrates a disparity between CKD parameters post transplantation with the non-transplant population. It highlights the need for attention to be given to the complications of CKD, at earlier stages than previously reported (CKD3T), when there is a propensity to focus solely on transplant specific management, if guideline targets are to be achieved.

P67

Vitamin D Deficiency is widespread amongst Renal Transplant Recipients and is associated with Proteinuria

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Vitamin D (25-Hydoroxy Vitamin D) deficiency (VDD) is common in renal transplant recipients. Vitamin D affects the function of many cell types in the kidney including podocytes and mesangial cells and has both immunomodulatory and anti-fibrotic properties. Proteinuria is a known marker of graft fibrosis and is associated with poor outcomes. In this cross sectional study we analyse the relationship between Vitamin D levels and the degree of proteinuria in renal transplant recipients.

484 unselected adult patients were screened for VDD (Normal>72nmol/L, Insufficiency 52-72 nmol/L Deficiency <52nmol/L). Proteinuria was assessed by protein creatinine index (PCI) on the same day and compared across the three groups. Other parameters that affect proteinuria were also compared across these groups.

VDD was widely prevalent in our transplant population (66.3%). Other demographic features are shown in table-1.

	normal vitamin-d	insufficiency	deficiency	
frequency	14.3%	19.4%	66.3%	
Age	52yrs	46yrs	50yrs	p=0.04
% non-Caucasian	2.9%	5.3%	18.7%	P<0.001
% female	33.3%	33%	43%	
systolic BP	139 mm Hg	137 mm Hg	135 mm Hg	
Diastolic BP	78 mm Hg	77 mm Hg	77 mm Hg	
e-GFR	45.6	51.3	47.3	
graft vintage	11yrs	11yrs	8.5yrs	p=0.001
% cadaveric grafts	85%	83%	81%	

VDD patients had significantly worse proteinuria when compared to the other groups (Mean PCI Normal Vit-D group-237, 95% CI 176-297, Vit D insufficiency group- 287, 955 CI 215-358, VDD group-601, 95% CI 425-777, p=0.03) . There was no difference in systolic, diastolic blood pressures or e-GFR across the groups. To exclude the impact of deteriorating grafts on proteinuria a sub-analysis was performed on patients with e-GFR of >30. A similar trend in PCIs (normal Vitamin D - 202, Insufficiency- 287, Deficiency -400) is apparent in the sub-analysis as well although significant statistical difference exists only between the normal and deficient groups.

In conclusion our study confirms a high prevalence of VDD in our patients and demonstrates an inverse relationship between Proteinuria and VDD. Even though no causal relationship can be established this phenomenon is interesting and requires further study. The need for vitamin D supplementation after renal transplantation needs to be urgently addressed.

Kidney 2

Moderator: Dr Alan Jardine

P68

Development of a Computer based Transplant Waiting List to Ensure Compliance with Data Protection Legislation

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In 1997 the Chief Medical Officer of England commissioned a review to address concerns about the ways in which patient information was being used in the NHS and the need to ensure that confidentiality was not being undermined. This led to the Caldicott report and subsequently the Data Protection Act 1998

This states that individuals who handle information about patients are legally obliged to protect that information. This must be achieved by ensuring that only as much information as is needed is collected, that the information is relevant and up-to-date, and ensuring that the information is kept securely.

The Liver Unit in Birmingham, UK has one of the largest liver transplant programmes in Europe; we have now performed over 3300 transplants. As donor organs can become available at any time, transplant surgeons and the Liver Recipient Transplant Coordinators (LRTC) have in the past carried with them a copy of the transplant waiting list. This list is required to contain personal information about the patients. Traditionally the list has been in the form of a paper document. The LRTC would update the list as required and print off copies for distribution to the consultant surgeons and themselves.

Following a series of revelations in the national news about 'leaks' of sensitive personal data, and bearing in mind the recommendations of the data Protection Act, in February 2007 the LRTC approached the Caldicott Guardian of University Hospital Birmingham (UHB) to discuss the issue of patient confidentiality in relation to the liver transplant waiting list. It was agreed that it was no longer acceptable in its paper format and UHB protocols in relation to carrying patient information on paper outside of Trust premises were drawn up.

Working with the Trust's IT department the LRTC developed a format for the waiting list which is generated on computer and can be accessed outside UHB premises on the users Blackberry Smartphone. As these phones are password protected the list remains secure and can still be accessed day or night by the t surgeons and LRTC. The challenge was to produce the list in a format which allows it to be viewed on the small screen of the Smartphones but still contains all of the information which the surgeon requires in order to select a suitable recipient for each liver offer and changes to how the transplant team work.

There are advantages and disadvantages to this system, and challenges that all users have faced, alongside changes in how we work. However a system has been produced which ensures that our waiting list patients' data is safely stored and meets the requirements of the Data Protection Act.

P69

Assessment of biomarkers of endothelial injury and blood oxygen level dependent magnetic resonance imaging in paediatric renal transplantation

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Introduction:

Interest is growing on the advantages of non-invasive monitoring of renal allografts. Our aim was to examine the feasibility of undergoing non-invasive testing of stable renal allografts with markers of endothelial injury and blood oxygen level dependent (BOLD) magnetic resonance imaging (MRI), which obviates the need for using gadolinium.

Methods:

Renal transplant recipients (RTR) with stable renal allograft function underwent biomarker assessment of MRI BOLD imaging and endothelial markers (with circulating endothelial cells (CEC) and endothelial microparticles (EMP)) compared to controls.

Results:

Six paediatric RTR (83% male) aged 9.9-18.4 (median 14.5) years at 1.1-12.7 (median 5.2) years post-renal transplantation (50% living related) with plasma creatinine levels of 74-285 (median 136)umol/l and estimated glomerular filtration rates (eGFR) of 20-59 (median 39)mls/min/1.73m^2 were assessed. There was no statistical difference between MRI BOLD values of intra-renal oxygen bioavailability between RTR and 7 healthy controls imaged twice on different days, although low cortical R2* values were seen in two RTR with the lowest eGFR. RTR had significantly higher CEC counts than compared to 8 healthy adults ($p < 0.02$), although the number of CEC and EMP values in RTR were similar to those in 23 children with inactive vasculitis and 25 healthy children (who had lower EMPs compared with other controls). However, CEC were higher in 32 children with active vasculitis ($p = 0.08$). There was a strong positive correlation between eGFR and CEC counts in RTR ($r = -1.00$, $p = 0.01$).

Conclusions:

These results show that MRI BOLD and endothelial markers are non-invasive biomarkers that are feasible and reproducible in young RTR. This pilot data provides a basis for future studies to investigate the correlation between eGFR and CEC counts in RTR.

P70

NGAL, IL-18 and KIM-1 in Native Urine Confound the Prediction of AKI and DGF in the Early Post-Transplant Period

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NGAL, IL-18 and KIM-1 have been identified as biomarkers of acute kidney injury. It has also been suggested that they may be predictive of delayed graft function (DGF) following kidney transplantation. We have conducted a randomised, double blind, placebo controlled study examining the effects of high dose erythropoietin, given at the time of reperfusion, to recipients of NHBD and extended criteria kidney grafts.

In total, 39 patients were recruited into the study. Urine samples were collected longitudinally from before surgery until day 5 post-transplantation. 21 out of the 39 recruited patients provided a native urine sample. NGAL, IL-18 and KIM-1 levels were measured by immunoassay and corrected for urine creatinine levels. Urine production pre-operatively was assessed by a questionnaire at the time of enrolment.

Urine NGAL (uNGAL) levels ranged from 0 - 10367ng/mgCr and were inversely correlated with native urine output (Spearman r = -0.66, p=0.001). Urine KIM-1 (uKIM-1) levels ranged from 0 - 9980pg/mgCr and were also inversely correlated with native urine output (Spearman r = -0.46, p=0.048). Urine IL-18 (uIL-18) levels were not correlated with urine output and ranged from 0 - 2630pg/mgCr. Haemodialysis patients had higher uNGAL compared to peritoneal dialysis or pre-dialysis patients (ANOVA, p=0.004). uIL-18 and uKIM-1 levels did not correlate with dialysis modality. DGF, defined as the need for haemodialysis in the first week post transplantation, occurred in 9/21 patients and did not correlate with native uIL-18 or uKIM-1 levels. High uNGAL levels were present in native urine from patients who subsequently developed DGF (Mann Whitney p=0.02). Finally, native biomarker levels of uNGAL and uKIM-1 were the strongest predictors of post-transplant levels out to day 5, in a mixed effects model containing NGAL, IL-18, KIM-1 and donor type ($p<0.004$).

High levels of the biomarkers NGAL and KIM-1 were found in native urine in the pre-operative period and were the strongest predictors of post-transplant levels, in the early post-transplant period, irrespective of donor type. Thus native urine biomarker levels may confound early post operative measurements, which need to be viewed with caution when used in the prediction of AKI and DGF.

P71

The Economic Burden of Post-Transplant Events in Renal Transplant patients (PORTRAIT Study) in a single UK centre

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Introduction

Little information is available regarding the prevalence of post-transplant events and resource utilization associated with such events in renal transplant patients in real-life treatment settings. The PORTRAIT study aims to describe the healthcare resources used and estimate the cost of managing post-transplant patients using observational data in a selection of transplant centres across Europe. This abstract presents the first results from a single UK centre.

Methods

This is a retrospective observational study of consecutive renal transplants from a single centre over a ten year period. A pilot study was undertaken in which resource usage over a 3 year period calculated from Healthcare Resource Groups (HRGs) was employed to derive costs with results stratified by glomerular filtration rate (GFR) status at 1 year post transplant. Comparison of costs was undertaken using the non-parametric Mann-Whitney test.

Results

Data were available from 879 patients who had a GFR measurement at one year post transplant. Overall 14.8% (n=130) had a GFR of < 30mL/ min/1.73 m^2; 60.1% (n=535) had a GFR between >30 and ≤ 60mL/min/1.73 m^2 and 24.3% (n=214) had a GFR > 60mL/min/1.73 m^2. Overall three-year HRG derived costs were significantly lower in the > 60mL/min/1.73 m^2 group at £497 (SD=£111) compared to the 30-60 and <30 mL

/min/1.73 m^2, at £1,323 (SD=£1,245) and £1,448 (SD=1,726), (p=0.025) and (p=0.01) respectively.

Discussion

This study provides evidence that post transplant resource usage in a real-life treatment setting (assessed using HRG tariffs) is approximately three times higher in those patients with lower post transplant GFR. Therefore management strategies that promote renal function post transplant are likely to provide important resource savings. An ongoing database study has been implemented to confirm these observations using a bottom-up costing approach.

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The Economic Impact of Renal Graft Failure: A Cost Analysis Based on Literature Review in a UK Setting

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INTRODUCTION: The costs of end-stage renal disease (ESRD) have become an increasing component of health care expenditure in the UK. Compared to dialysis, kidney transplantation is a highly cost-effective choice for most patients with ESRD. A key objective post transplantation is to maintain a functioning graft. When graft failure occurs, the majority of patients return to dialysis, which not only associated with significant financial burden compared to maintaining a functioning graft, but also means that the previous investment on transplantation and management of the graft post-transplant are lost. This study is performed to assess the cost of renal graft failure in a UK setting.

METHODS: A systematic literature review was performed in PubMed and the UK NICE (National Institute for Clinical Excellence) literature database to find articles related to the cost of renal graft failure in UK setting. This study adopted an investment perspective - all the medical resource used on patients from organ procurement to the treatments on graft failure were taken into consideration to gain a better view of the economic impact of renal graft failure. A model was built using data from the UK renal registry to estimate the number of graft failures occurring in the first year after transplantation. Costs for procurement, transplantation, and for the treatment of graft failure, were derived from the result of the systematic review.

RESULTS: The cost of renal graft failure reaches approximately £60,000 when taking account of the all medical resource used from the investment point of view (including transplantation cost, immunosuppressive medication cost and resource to treat post transplantation adverse events for graft failure patients).The post graft failure cost is calculated to be close to £30,000 in the UK in 2007-2008. The most important cost contributors are dialysis cost, transplantation cost and post transplantation immunosuppressive medication cost.

DISCUSSION: Estimating the economic impact of graft loss post-transplantation should take into account the cost of management of patients post graft failure, as well as previous medical investment that is lost with the graft (including costs associated with procurement of the organ and transplantation). Improvements in the management of renal transplant patients are needed to reduce the risk of graft loss and the economic burden of graft failure to the healthcare system.

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Standing on the shoulders of giants

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Context: Like all branches of science and medicine, transplantation has evolved by *"standing on the shoulders of giants*", as Newton famously remarked in a letter to his intellectual adversary, Hooke, in 1676. This philosophy was modernised by Popper in "*Conjectures and Refutations: The Growth of Scientific Knowledge"* in 1963. Which giant shoulders should we encourage newcomers to transplantation to stand on? **Methods:** Recent BTS Presidents were asked to identify a single publication which they require trainees to read and digest. Two publications were excluded in the belief that all new to transplantation must surely read them (1) Billingham, Brent & Medawar *"Actively acquired tolerance of foreign cells*" Nature 1953 172 October 3rd (2) Hume, Merrill, Miller and Thorn *"Experiences with renal homotransplantation in the human: report of nine cases"* J Clin Invest 1955 34:327-382. Fortunately, many seminal publications are easily and freely accessible electronically. **Results:** All Presidents approached enthusiastically replied:

J Fabre (1993-96) :-

Zinkernagel & Doherty "Restriction of in-vitro T cell-mediated cytotoxicity in lymphocytic chorio-meningitis with a syngeneic or semiallogeneic system." Nature 1974 248:702-702.

JA Bradley (1999-02) :–

Terasaki, Cecka, Gjertson et al "High survival rates of kidney transplants from spousal and unrelated living donors" NEJM 1995 333:333-336.

PA Dyer (2002-05)

Klein, "The major histocompatibility Complex of the mouse" Science 1979 203:516-521.

JLR Forsythe (2005-07) :-

Murray, Merrill, Hartwell et al "Prolonged survival of human-kidney homografts by immunosuppressive drug therapy" NEJM 1963 268:1315-1323

PJ Friend (2007-09) :-

Calne, White, Thiru et al "Cyclosporin A in patients receiving renal allografts from cadaver donors" Lancet 1978 Dec 23 & 30 1323-1327.

K Rigg (2009-11) :-

Morris, Bradley, Doyal et al "Face transplantation: A review of the technical, immunological, psychological and clinical issues with recommendations for good practice" Transplantation 2007 83:109-128.

Comment: The contributor's justification of these choices will be presented. With more than 50 years of clinical and experimental transplantation we should not forget the foundations of the discipline; gems of information are hidden in these publications. At least, the modernisation of the presentation of scientific and medical data will be evident. Even though scientific and medical knowledge in transplantation has advanced tremendously in the last half-century, there are key questions remaining unanswered and these are often evident in these seminal publications and are indicators of the need for effective and incisive research.

P74

Completed pregnancy is well tolerated after renal transplantation and has no significant effect on renal function

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Introduction: About 2% of women of fertile women age become pregnant after transplantation. There are concerns regarding the effects of hemodynamic changes of pregnancy on the graft.

Methods: In this study we have analysed various parameters including serum creatinine, e-GFR, proteinuria measured by Protein Creatinine Index (PCI), systolic and diastolic blood pressures, haemoglobin and serum albumin during and after 53 successful pregnancies in 34 patients. Immunosuppression used for these patients is also recorded.

Results: The table below shows the changes in various parameters through the course of these pregnancy episodes.

	3/12 pre-conception	conception	3/12 post-conception	6/12 post-conception	term	6/12 post-partum
serum creatinine	123micmol/L	117micmol/L	105micmol/L	105micmol/L	119micmol/L	120micmol/L
proteinuria	245mg	296mg	253	351	1343	333
systolic BP	136mm Hg	137mm Hg	132mm Hg	131mm Hg	137mm Hg	136mm Hg
diastolic BP	85mm Hg	86mm Hg	78mm Hg	75mm Hg	81mm Hg	83mm Hg
haemoglobin	12.4g/dl	12.7g/dl	11.9g/dl	10.5g/dl	10.9g/dl	12.5g/dl
albumin	44.3g/dl	44.1g/dl	42g/dl	37.1g/dl	36.5g/dl	42g/dl

Serum creatinine decreases at term but gradually returns to pre-conception baseline levels by 6 months. Patients who had a pre-conception creatinine of more than 132umol/L did not show any variation from this pattern. Even though mean proteinuria increases reaching its peak at term the levels come back to baseline by 6 months post-partum. Systolic and diastolic blood pressures along with haemoglobin and serum albumin fall during pregnancy reaching the trough level at term. However all the parameters reach pre-conception baseline levels by 6 months.

Conclusions: In conclusion short-term follow up of our patients do not reveal any permanent changes in various parameters analysed. Interestingly patients with high pre-conception creatinine demonstrated similar patterns to those with no evidence of progressive graft dysfunction.

Kidney – Compliance / assessment

Moderator: Dr Paul Harden

P75

Obesity in Renal Patients – Problem or Prejudice?

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Background: Obesity is an evolving problem from which potential kidney transplant recipients are not exempt. There is currently no consensus or guidelines in the transplant community as to how to manage these patients. Increasingly, patients with raised body mass index (BMI) are being accepted for transplantation with units altering cut-off points for consideration for surgery. The outcomes for these patients are historically known to be suboptimal but recent reports have suggested that morbid obesity may not be as detrimental as first thought. In addition patients who received kidneys with anatomical aberrations (multiple vascular structures or ureters) are known to be at increased risk of adverse outcome. We aimed to establish the degree of increased risk with raised BMI and the cumulative increased risk that obesity and anatomical aberration together posed to establishing a functioning graft.

Methods: Patients undergoing renal transplantation over a 67 month period (Jan 2004 to July 2009) were analysed using graft survival, 3 month and 1 year Creatinine as primary endpoints. Secondary endpoints included rates of wound infection, lymphocoele and urological complication. Further sub-group analysis was carried out on patients with anatomical aberrations (multiple vascular or ureteric structures).

Results: 576 patients (M = 328; F = 248; Live = 228; Cadaveric = 289; NHBD = 59; aberrant anatomy =1 66; mean age = 44.3±0.6) underwent renal transplantation over the period. Mean BMI was 26.5±0.2 (<20 : 37 patients; 20-25 : 208 patients; 25-30 : 200 patients; 30-35 : 105 patients; >35 : 26 patients) Overall graft survival was 91% with survival best in the BMI 25-30 groups (92.5%) Graft survival was worst in the highest BMI group (80%). Aberrant anatomy led to an overall graft survival of 83% but was worst in the the BMI>30 group (71%; $p<0.0001$) In surviving grafts, there was no difference in Creatinine at either 3 months or 1 year. Increased BMI also resulted in a greater incidence of wound infections compared to the total group (15% and 8% respectively; $p<0.01$) In addition, patients with aberrant anatomy had a 19% rate of wound infection ($p=0.03$)

Conclusion: In an era in which the pool of potential organs becomes more precious, utilitarian decision may have to be made to optimise the use of appropriate organs. In addition we are faced with increasing difficult decisions as to whether to transplant patients with increasing BMI. We have shown that increased BMI and anatomic aberrations cumulatively result in worse graft survival. It may be appropriate that if we are going to utilise organs like this in patients, that the patient with the increased BMI could be given the anatomically 'normal' kidney from the donor pair if at all possible. NHSBT guidelines for allocation of organs may need to include considerations for patients with raised BMI's receiving anatomically aberrant kidneys.

P76

The incidence of peri-operative myocardial infarction and the reliability of T*roponin T* in its detection in patients undergoing kidney or kidney and pancreas transplant

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Introduction: chronic renal failure (CRF) is one of the major risk factors for cardiovascular disease. Myocardial infarction (MI) is one of the leading causes of death in patients with CRF. There are few studies concerning the perioperative cardiovascular risk in patients undergoing renal or simultaneous kidney and pancreas (SPK) transplant.

Aim of the work: to determine the risk of perioperative myocardial events after kidney or spk transplantation and to evaluate suitability of ***troponin T*** (Tn.T) in detection of cardiovascular events.

Methods: Patients undergoing either kidney transplant or SPK were prospectively enrolled in the study for one year. All patients underwent resting electrocardiogram (ECG). Patients with diabetes mellitus, 50 years or older or those with a history of cardiac problems underwent further functional assessment including echocardiogram, and stress ECG, stress echo or myocardial perfusion scan. Coronary angiogram was performed where inducible ischaemia was demonstrated. Tn.T was measured on day 0 and day 5 postoperatively in all patients and clinical events were recorded. MI was defined as a rise in Tn.T above 0.1 on day 5, irrespective of ECG or clinical symptoms.

Results: 106 patients (60 males) were included in the study. Median age 48years (range 17-69 years).11 patients underwent SPK and 95 underwent kidney transplants, with 59 live donor kidneys. Risk factors included; diabetes mellitus (19 patients), hypertension (92), history of MI (8), history of angina (4), positive family history of cardiac diseases (11), and history of smoking (62). 7 patients had a preoperative coronary angiogram and a coronary abnormality was detected in 4 cases, 2 needed coronary stenting preoperatively.

3 patients had a postoperative MI; one of them had a preoperative coronary angiogram with a 30% stenosis in the left anterior descending artery. This patient developed MI on day 8 postoperatively after having a re-exploration for urinary leak and wound infection. The other 2 had postoperative coronary angiograms followed by stenting. 3 patients developed chest pain but no ECG changes or change in their base line Tn.T. One patient developed rapid atrial fibrillation but no chest pain or change in Tn.T.

Day 0 Tn.T was higher than normal (mean 0.082, SD 0.173) in 38 patients (23/60 Haemo Dialysis (HD) patients, 11/20 Peritoneal Dialysis (PD) patients and 4/26 Pre-emptive patients). In 20/23 HD patient, 9/11 PD patients, and 4/4 preemptive patients, postoperative day 5 Tn.T returned to normal levels (mean value 0.016, SD 0.008). All these patients had a successful transplant with early graft function. 2/ 5 patients in whom the Tn.T did not return to normal level had MI and the other 3 had delayed graft function and never had chest pain or ECG changes.

Conclusions: Incidence of postoperative MI in patients undergoing SPK or renal transplant in this study is 2.8%. Baseline Tn.T level was high in 35.8% of patients. The level of Tn.T returns back to normal level in all patients with early graft function. Tn.T might not be an ideal marker for detection of cardiac events in this group of patients.

P77

Native nephrectomy for autosomal dominant polycystic kidney disease: before or after kidney transplantation?

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the commonest genetic cause of chronic kidney disease, and approximately half of affected individuals progress to end stage renal failure (ESRF). The indications and optimal timing of native nephrectomy in ADPKD patients remains ill-defined, especially in those listed for renal transplantation. Nephrectomy is a major surgical undertaking in such individuals, associated with significant morbidity and even mortality.

Aim: To analyze indications, timing and outcomes of nephrectomy in ADPKD patients listed for kidney transplantation.

Methods: We evaluated all ADPKD patients who had a native nephrectomy prior to or following transplantation in 2003-2009 at our center, and those undergoing the sandwich technique (removal of the most severely affected native kidney prior to transplantation, and the other afterwards).

Results: There were 35 individuals in our cohort (M:F = 16:19), with a mean age of 52.4 years (range 43-65). There were 20 patients in the pre-transplant nephrectomy group (unilateral = 10, bilateral = 10), 12 in the post-transplant group (unilateral = 10, bilateral = 2), and three underwent the sandwich technique. The commonest indications for nephrectomy were pain/discomfort, space for transplantation, ongoing hematuria, recurrent infections, and early satiety. Six individuals in the pre-transplant group and three in the post-transplant group required critical care admission after nephrectomy. Transient renal graft dysfunction occurred in two post-transplant bilateral nephrectomy patients. Two patients (20%) in the bilateral nephrectomy pre-transplant group and one (10%) in the bilateral nephrectomy post-transplant group died in the immediate post-operative period. None of the patients undergoing unilateral nephrectomy, pre- or post-transplant, died in the immediate post-operative period. No complications or mortality arose in the sandwich technique group. Histopathological analysis revealed four incidental small tumours, three malignant and one benign adenoma measuring 2mm. The malignant tumours were two clear cell carcinomas 8mm and 12mm in diameter, and one papillary carcinoma measuring 15mm in diameter.

Conclusions: Native nephrectomy in ADPKD is a major undertaking associated with significant morbidity especially in the pre-transplant group. Pre-transplant bilateral native nephrectomy is associated with the highest post-operative complications and mortality rate, whereas post-transplant unilateral native nephrectomy appears to be a safer approach with fewer complications.

P78

Does ethnicity and gender influence severity of coronary artery disease and cardiac survival in potential renal transplant recipients undergoing coronary angiography?

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It is well established that chronic kidney disease [CKD] is associated with premature atherosclerosis and results in an increased risk of cardiovascular morbidity and mortality. However there are limited data available in the literature on the prevalence of coronary artery disease [CAD] and cardiac survival, other than for predominately white male patients. We are interested in the influence of gender and ethnicity on the severity of CAD, specifically within the end stage renal disease [ESRD] population.

In a prospective cohort of 470 patients [m=307 f=163 age=56.75±10.15 years] referred for angiographic evaluation prior to transplantation, we examined the impact of gender and ethnicity on all-cause mortality and cardiac event free survival. The population of patients in West London is ethnically diverse; only 202/470 [42.9%] patients were of Caucasian ethnicity in this study. 184/470 [39.1%] patient were South Asian, 48/470 [10.2%] were Afro-Caribbean and 36/470 [7.8%] were classified as "Other" ethnicity.

Caucasian and South Asian patients had the highest incidence of significant CAD; 68/202 [33.7%] Caucasian patients and 58/184 [31.5%] South Asian patients were offered coronary revascularisation for flow limiting CAD on coronary angiography. In the Afro-Caribbean patients and "other" ethnicity patients flow limiting CAD was found in only 11/48 [22.9%] and 9/36 [25.0%] respectively.

For the entire cohort, 36 deaths were reported with an overall survival of 97.0% and 91.2% at 1 year and 3 years respectively. 12/36 [33.3%] deaths were due to cardiovascular causes; 4/36 [11.1%] patients died from cerebrovascular events, 8/36 [22.2%] patients died from cardiac events. Neither gender nor ethnicity influenced in-hospital mortality.

44 cardiac events occurred during the follow up period of 31.21± 8.25 months. Multi-variant analysis suggested that after adjusting for well known risk factors including older age, smoking, diabetes and hyperlipidaemia, South Asian ethnicity has a 2 fold increase risk of cardiac events [HR 2.0 CI 0.96-4.2; p=0.065] compared to Caucasians. Gender was not influential.

This study has shown that there is a trend towards a higher risk for cardiac events in South Asian patients with ESRD. Female gender is not protective against cardiac events in the ESRD population; highlighting another reason why the Framingham risk stratification for cardiac disease needs to be used with caution in the ESRD population.

P79

Is pre-emptive coronary artery revascularisation responsible for a low number of cardiac events following transplantation in the short and medium term?

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Renal transplantation improves quality of life and prolongs survival in patients with end stage renal disease [ESRD]. It is also acknowledged that patients are at highest risk for cardiac events in the initial 3 months following transplantation.

Our practice is to aggressively manage coronary artery disease [CAD] prior to transplantation irrespective of cardiac symptoms, in order to protect patients from post operative cardiac events and prolong long term survival.

Between Jan 2006 and Feb 2008, 470 patients [m=307, f=163, age=56.75±10.15 years] underwent coronary angiography as part of their pre-transplant assessment. 416/470 [88.5%] patients were wait listed and 179/416 [43.0%] patients were transplanted during the follow up period of 31.21± 8.25 months. All patients transplanted had their coronary angiogram performed within 3 years of the date of their transplant [average 12.6±9.83 months].

146/470 [31.1%] of patients were offered coronary intervention. 38/146 [26.0%] underwent coronary artery by pass surgery, 101/146 [69.2%] underwent percutaneous revascularisation, 7/146[4.8%] declined intervention and as a result were not wait listed. 38/146 [26.1%] patients who had coronary revascularisation went on to receive a renal transplant.

For the entire cohort overall survival was 97.0% and 91.2% at 1 year and 3 years respectively, with 36 deaths reported. 12/36 [33.3%] deaths were due to cardiovascular causes; 4/36 [11.1%] patients died from cerebro-vascular events, 8/36 [22.2%] patients died from cardiac events. 4/8 [50%] cardiac deaths may have been avoided, as these patients were advised revascularisation but had declined.

Patients who underwent transplantation, had a 98.0% and 95.6% cardiac event free survival at 1 yr and 3 yrs respectively, comparable to those patients in whom intervention was not indicated. Only two cardiac events occurred during the first year after transplantation, at days 23 and 154.

Our data suggest that pre emptive coronary angiography and intervention within 3 years of transplantation optimises the cardiac status of transplant patients, with low short term and medium term cardiac event rates.

P80

Low blood pressure syndrome in haemodialysis patients – rapid resolution after successful renal transplantation.

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It is well recognised that some patients on long term haemodialysis develop intractable low blood pressure, despite receiving no antihypertensive medication and optimisation of fluid balance. The cause of this syndrome is poorly understood. A series of cases receiving renal transplantation are described.

Between June 2003 and December 2009, 85 patients received AIT transplants. Eight of these were identified pre-transplant as having dialysis associated hypotension. In four (100% women, mean duration on dialysis 10.5 years (range 7-15), no previous renal transplant) the pre-dialysis systolic blood pressure (SBP) was normally less than 100mmHg (90-100 in 1 case; 70-80 in one case, 50-70 in 2 cases). Before pre-transplant therapy started, one patient lost vision in both eyes from retinal venous thrombosis, and another had transient visual disturbance, both associated with SBP in the range 50-60 mmHg. In the other 4 cases, the SBP was normally over 100mmHg predialysis, but usually fell to less than 100mmHg during dialysis. Of the 77 normotensive patients, 43 (56%) were female, 84% had previously been transplanted, and the mean duration of the recent dialysis stint was 4.6 (range 0-16) years. Pre-transplant, the blood pressure did not respond to fluid loading or steroids. Of the 8 hypotensive patients, 6 received double filtration plasmapheresis (DFPP). Two tolerated this, but in the other four DFPP was reduced. Two experienced fistula thrombosis. One patient with recent visual loss and dependent on noradrenaline was transplanted across a significant HLA antibody barrier with no antibody removal, and required early treatment for presumed antibody mediated rejection. The most recent case was treated with cryofiltration pre-transplant, since this procedure has been well tolerated in patients with cryogloubulinaemia. Starting with an SBP of 70-80mmHg, there was only one transient fall in SBP to below 60mmHg, and the treatment resulted in a satisfactory fall in donor specific antibody levels.

Post-transplant, our first case experienced hypotension on DFPP (SBP 50 mmHg), and developed inoperable bowel ischaemia. Subsequent patients have been treated with noradrenaline or metaraminol infusions to maintain a SBP >100 mmHg. Notably, the blood pressure has improved in every case within 48 hours of establishment of transplant function. Of the seven surviving patients, all are currently alive, with one graft failure from transplant glomerulopathy at 32 months.

In summary, severe dialysis associated hypotension was successfully treated with renal transplantation and interestingly the BP normalised rapidly after establishment of graft function. Cryofiltration has not previously been described in HLA antibody AIT.

P81

Long term follow up of young adult transplant recipients following transfer from a single paediatric renal unit.

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Introduction: Young adult transplant recipients are a vulnerable group of patients as they transfer from paediatric to adult services. High levels of preventable graft loss have been reported in the literature raising awareness of this issue and resulting in much discussion; however resources now need to be directed to service developments

Aim/Objective: A group of young adults who transferred from a paediatric unit to a single adult transplant unit during 2000-2001 were reviewed in December 2009. The original audit compared rejection rates, adherence with follow up and number of inpatient days in their final year in paediatric care vs. their first year in adult care.

This follow up audit revisited the same group with regard to long term outcomes, such as graft function, general health and functionality as adults in society.

Results: 16 young adults (F:M ratio 8:8) were reviewed more than 9 years post transfer.
At the time of transfer 62% (10/16) patients still had their 1st graft, 19% (3/16) 2nd graft, 13% (2/16) 3rd graft and 6% (1/16) 4th graft.
Mean age at 1st transplant = 11.8 years (range 1-18 years)
Deceased donor (DD): Living Donor (LRT) 87.5% (14/16) :12.5 % (2/16)
At time of review (December 2009)
Patient survival 94% (1 patient died - PTLD)
66% (10/15) remain transplanted with the same graft
7% (1/15) have been re-transplanted (LRT after 1 year on dialysis)
27% (4/15) are currently receiving dialysis therapy

Quality of life (QOL) issues
25% (4/16) attended university with 2 continuing study for a post graduate degree
88% (14/16) are in paid employment
QOL questionnaires in first audit revealed in many cases that patients felt unsupported and would have liked more formal attention to psychosocial needs

Medical & nursing staff were often not able to predict patients who were at higher risk for complications and non-adherence.

Conclusion: Long term follow up of young adults demonstrated a 94% patient survival and a 66% graft survival. No patient was lost to long term follow up. 88% of patients were in paid employment, making a positive contribution to society. These results demonstrate a positive picture of the long term follow up of young adults who have originated from a single paediatric unit.

Resources are now being directed to developing a robust service with emphasis on seamless transfer from paediatrics to adult services with ongoing peer support.

P82

Poorer adherence to medications and lifestyle advice in adults with paediatric presentation of end-stage renal failure

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Introduction:

Adherence to medications is important to improve renal allograft survival, but is difficult among the adolescent age group. Our aim was to evaluate adherence in young adults with end-stage renal failure.

Methods:

Initial questionnaire and further face-to-face interviews of adults with ESRF identified from paediatric and adult databases of nephrology programmes.

Results:

296 adults (52% male, 73% currently with functioning renal allograft) of mean current and ESRF onset ages of 25 and 17 years respectively, were questioned on the importance of control over health versus complying with advice over different aspects of health. There was a significant perception that diet (including frequency of eating 5 fruits and vegetables) and exercise ($p = 0.01$ and 0.02) was a matter for following health professional advice. 66% of respondents reported that personal control of their own health was important, and this extended to their alcohol consumption and smoking habits. 86% and 43% of respondents thought it was very important to take medications and check their own blood tests results respectively, while 65% thought it very important to follow health or treatment advice. Only 10% missed taking medication weekly or more often. Higher frequency of missing medication was related to dialysis (as opposed to transplant) patients ($p = 0.05$), and assigning lower importance to taking medication ($p < 0.001$) as well as feeling lonely, depressed and pain ($p < 0.001$, 0.003 and 0.04 respectively). However, age < 23 years was associated with attaching lesser importance to complying with advice about treatment and health ($p = 0.02$), especially if age of onset of ESRF was < 16 years ($p = 0.01$).

Conclusions:

Adherence to medications, fluids, diet, lifestyle, clinic appointments and investigations is of importance to renal transplant recipients, who wish to have personal control over their own life and health. The importance of clinicians providing health care advice has been emphasised in this questionnaire.

Kidney – Live Donation

Moderator: Mr Nizam Mamode

P83

The impact of age on peri-operative complications, subsequent renal function and blood pressure in laparoscopic living kidney donors in a single UK centre: a comparative study.

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AIMS: Transplantation with a living donor kidney is the treatment of choice for patients in renal failure. Protection of the donor from peri-operative complications as well as from medium term reno-vascular disease has resulted in selection criteria designed to limit cardiovascular risk, therefore avoiding elderly donors. The aim of the study was to compare immediate and medium term complications in elderly versus younger patients undergoing laparoscopic donor nephrectomy.

METHODS: Data for all patients aged 60 years and over undergoing Hand Assisted Living Donor Nephrectomy (HALD>60) at a single UK centre between 2004 and August 2009 was compared with a group of randomly selected patients below the age of 60 years (HALD<60). Complications were classified using the Clavien classification. The effect of nephrectomy on short and medium term renal function and blood pressure was also compared between the two groups.

RESULTS: Forty nine patients aged >60 years underwent HALD and were compared with 49 patients from the HALD< 60 group. Mean HALD>60 age was 64 years (60-84) with a median follow up of 21.4 months. The HALD<60 group had a mean age of 42 years (21-59) with a median follow up of 21 months. HALD>60 systolic blood pressure (SBP) was significantly higher than in the HALD<60 group (132.7 mmHg versus 125.2 mmHg, $p<0.03$) as was the proportion taking antihypertensive medication (14 versus 2, $p<0.0006$). Creatinine clearance measured using the EDTA technique (EDTA-GFR) was significantly higher in the HALD<60 group (99.3 ml/min versus 85.2 ml/min, $p<0.0001$). Mean length of stay was higher in the HALD>60 cohort (5.93 days versus 4.6 days) but was not statistically significant. There were no significant differences in gender, BMI or nicotine use between the two groups. The proportion undergoing right donor nephrectomy versus left was similar between groups, as were the number of cases involving multiple vessels. Complications classified according to the Clavien system were very similar, with seven Class 1 and twelve Class 2 complications in each group. There was a single Class 3a complication in the HALD>60 group (seroma needing aspiration). Two further general anaesthetic interventions (Class 3b) were needed in the HALD>60 group (one return to theatre for bleeding and one incisional hernia repair) and 3 in the HALD<60 group (3 incisional hernia repairs). The most serious complication was the return to theatre for bleeding described above requiring splenectomy and ITU admission (Class 4a). There were no significant changes in either diastolic or systolic blood pressure in either group at 1, 3, 12 or 24 months. Neither group developed proteinuria on dipstick testing. One, 3, 12 and 24 month serum creatinine rises were no different between the two groups.

CONCLUSIONS: When carefully selected, elderly donors do not experience any more peri-operative complications when compared with an otherwise matched significantly younger cohort. Neither does there appear to be a significant difference in the effect on medium term blood pressure or serum creatinine between the two groups. These data support the practice of offering HALD nephrectomy to elderly donors.

P84

Cancer screening in potential living kidney donors: Need for guidelines.

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Introduction

The accidental transmission of malignant disease from donor to recipient by kidney transplantation is well described. Since 2002, 3 living donors in our unit (aged 63, 57 and 64) have been diagnosed with colorectal cancer shortly after donating a kidney. Current British Transplant Society guidelines do not normally recommend specific screening to exclude occult malignancies.

We aim to assess current cancer screening practice in living kidney donor assessment in UK transplant centres.

Method

A questionnaire was sent to the 25 living donor centres in the UK. Questions asked related to 6 common malignancies: lung and colorectal (men and women), breast and cervix; prostate and testis. Units were asked whether they screened for these cancers; and if so how and in which age ranges. Questionnaires were sent and returned electronically.

Results

We have responses from 14 centres so far (56%). 13 centres screen for lung cancer with a chest radiograph in patients of all ages. 13 centres screen for cervical cancer by asking to see the last smear result but the ages varied. 10 centres screen women over the age of 50 for breast cancer with mammography. 9 centres screen men for prostate cancer with PSA and 6 screen for testicular cancer with examination. Only one centre screens for colorectal cancer using faecal occult blood (FOB) when indicated by a strong family history. Overall there was a wide variation in screening practice and virtually no screening for colorectal cancer.

Conclusion

There is no agreed consensus on cancer screening in the kidney donor population. Current UK national screening programmes exist for breast, cervix and colorectal cancers and these are limited by age. The National Bowel Cancer Screening (NBCS) programme offers biennial FOB screening to all men and women aged 60-69. We suggest expansion of the NBCS criteria to include all potential donors over the age of 50.

We recommend that guidelines need to be developed and implemented to allow a national consensus in cancer screening practice for potential kidney donors.

P85

Laparoscopic donor nephrectomy from donors with short arteries is feasible

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Introduction

The United Kingdom Guidelines for Living Donor Kidney Transplantation recommend that donor nephrectomy should not be performed where the donor renal artery has a length of less than 14mm from the aorta to its first branch ("At least 14mm of main stem renal artery is needed to provide a single vessel for anastomosis and safe haemostatic ligation/clipping in the donor.").

The Newcastle unit has previously performed donor nephrectomy in donors with shorter arteries and decided to review outcomes in this group to determine whether this practice should continue.

Methods

We reviewed our series of laparoscopic donor nephrectomies from 2002 to 2009, dividing the transplants into two groups depending on whether the unbranched length of the donor renal artery is greater or less than 1.4cm. Donor complications were the primary endpoint, with recipient function forming a secondary endpoint, as the BTS guideline is primarily for donor safety.

Results

138 laparoscopic donor nephrectomies were performed in this series, by two surgeons experienced in laparoscopic nephrectomy. 17 were performed in donors with a renal artery length of less than 1.4cm before the first branch. The mean length in the short artery group was 0.9cm, with a minimum length of 0.5cm in two cases, and a further case which branched at the origin and was treated as two separate arteries.

The only surgical complication in the series was a splenic laceration in one of the donors with longer renal artery; this was managed conservatively. No donor complications occurred in the shorter renal artery group.

Calculated GFR in recipients at one week in the short and long renal artery groups was 64.0±55.3 and 56.8±37.0 ml/min/1.73m^2 respectively (mean ± standard deviation based on 4-variable MDRD formula, p=0.493, t test).

Conclusion

Performing laparoscopic donor nephrectomy in donors with short renal arteries is feasible and safe when performed by surgeons experienced in the procedure.

P86

Ethnicity does not determine outcome 5 years after donor nephrectomy

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Because the incidence of end stage renal failure is up to 10 times greater in our South Asian (SA) and Afro Caribbean (AC) populations, we have been concerned that this might impact on outcomes after live donor nephrectomy in these ethnic groups.

In this study, 332 consecutive live donors 2000-2008 were examined at their annual follow-up visits. We analysed 5-yr follow-up data for MDRD-GFR, Creatinine Clearance (CrCl), 24-hour protein excretion and blood pressure control as well as the need for anti-hypertensive agents.

Of 332 donors 214 (64%) were Caucasian (C), 63(19%) were SA and 42(13%) were AC. The mean age at donation was 45.8±12.4 years (C=48.1, SA=42.8, AC=39.4) and the M:F ratio 1:1.2 (C=1:1.2, SA=1:1.15, AC=1:1.15) with a body mass index (BMI) of 26.9 (C=27.5, SA=25.5, AC=26.6). The mean follow-up was 42.7 ± 23.3 months. Some donors were lost to follow up. At 5 years, complete data on 65% (53/81) of the donors was available.

The mean MDRD-GFR [mls/min] was 80.5±15.9 (C=78.1±15.0, SA=82.7±17.2, AC=86.2±17.0) pre-donation and 61.6±10.5 (C=58.9±9.0, SA=61.7±7.8, AC=70.4±14.3) at 5 years (p=NS). The mean CrCl in mls/min was 107.7±29.4 (C=110.5±30.2, SA=93.8±23.3, AC=115.1±28.7) at time 0 and 94.4±19.3 (C=98.0±16.7, SA=81.5±18.6, AC=103.0±26.2) at 5 years. Although there was a significant difference in the absolute CrCl values between the SA and AC groups with the AC group starting with higher CrCl than the SA group, the rate of change in CrCl was not significant (5-yr p=0.24). Protein excretion in grams/24 hours at 5 years was minimal in all 3 ethnic groups at 0.08±0.13 (C=0.08±0.15, SA=0.08±0.08, AC=0.09±0.06).

There were 28 hypertensive donors and 35 donors developed hypertension during the 5-yr period (risk of hypertension at 5 years was 34.6%). At 5 years, the AC group had a significantly higher risk of hypertension compared to the Caucasian group [50% (4/8) vs 40% (12/30); $p<0.05$]. The risk for the SA group was only 8% (1/12). The number of donors at 5 years is small but the trend may be explained by the already described higher incidence of hypertension in the AC population compared to normal population. In addition, there was significant difference in mean age between hypertensive and non-hypertensive donors (54 v 46, p=0.0004). Blood pressure control was satisfactory at 136/80 at 5-years and most hypertensive donors were on a single antihypertensive agent.

This study shows that donor nephrectomy in high risk ethnic groups is not associated with poorer outcomes as demonstrated by renal function, degree of proteinuria or blood pressure control

P87

Hand assisted extraperitoneal living donor nephrectomy, single centre experience with 188 cases.

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BACKGROUND: This is a report of 188 consecutive hand assisted retroperitoneoscopic live donor nephrectomies (HARS). The main benefit of this approach is increased safety. Risk of bleeding and intraabdominal injury is low thanks to hand assistance and extraperitoneal approach, less dissection is required, when comparer to the transperitoneal technique. We have therefore adopted this method for all living-donor nephrectomies in our unit since 2005.

METHODS: This study reviews all our cases of living-donor nephrectomies performed since the introduction of HARS. Data were collected prospectively. The operation is performed in the manner described by Wadström *et al* 2002, with minor modifications. Statistics were performed using SPSS v16.

RESULTS: In 23 cases the right kidney was retrieved. Some 89 donors had complex anatomy (multiple vessels or ureters, retroaortic vein, horseshoe kidney). One of the early operations was converted to open. The median age was 48 years (IQR 15). There were 97 males. The median warm ischaemic time (WIT) and cold iscaemic time (CIT) were 90 seconds and 49 minutes respectively. The median blood loss and operative time were 20ml and 126.5 min respectively. The median post-operative hospital stay was 2 days. Significance of outcomes, according to BMI (high ≥30), complex anatomy and nephrectomy side, are shown in the table.

Minor complications include one wound infection and four urinary tract infections. Major complications included bleeding from a lumbar artery requiring retroperitoneoscopic exploration and two incisional hernias. All donors have long term follow up. All transplanted kidneys had immediate function except two (none of which were related to the donor nephrectomy).

CONCLUSIONS: Unlike complex anatomy, high BMI, and right sided nephrectomy make no difference to the outcome measures shown. HARS is a safe way of performing living-donor nephrectomy with minimal morbodity and fast recovery. It is safe and quick alternative to the intraperitoneal approach. Since the introduction of this technique, the number of potential living donors has increased in our unit.

P88

Oesophageal Doppler monitoring of haemodynamic changes during live donor kidney transplant: pilot study.

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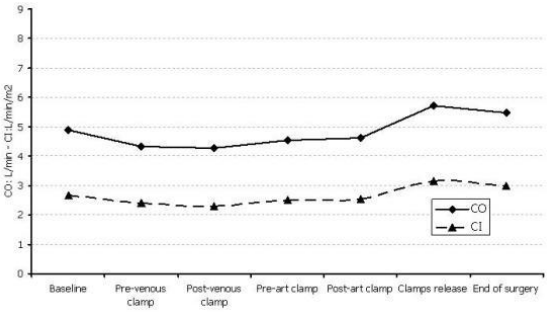
Background: Haemodynamic changes may occur during renal transplantation (1), one of the potential causes being intraoperative filling in order to boost the new organ's perfusion. Moreover, new, less invasive haemodynamic monitoring devices are becoming increasingly popular in anaesthetic practice as substitutes for traditional intravascular monitoring. In this prospective pilot study we monitored live donor kidney transplant (LDKT) recipients intraoperatively using oesophageal Doppler (OD), to test its feasibility and safety profile and to monitor any acute haemodynamic changes.

Materials and methods: We consecutively monitored 32 patients undergoing LDKT with OD under general anaesthesia as per standardised protocol. Data and trends derived from OD were used to guide fluid management during the procedure.

Results: There were no perioperative complications linked to the use of the OD probe. No significant changes in monitored haemodynamic parameters occurred post venous- or prior to arterial clamping. After clamps release we observed a significant increase in both cardiac output (CO) and cardiac index (CI) compared to baseline (2-tailed T-test, p=0.004 for CO and p=0.007 for CI, see graph). These changes were still significant at the end of surgery (2-tailed T-test, p=0.017 for CO and p=0.039 for CI). Similar changes were observed in stroke volume (SV) and peak velocity (PV) (2-tailed T-test, p=0.034 for SV and p=0.006 for PV at clamps release; p=0.018 for SV and p=0.002 for PV at the end of surgery, both compared to baseline).

Conclusion: In this pilot study, OD was a safe and feasible technique for haemodynamic monitoring during LDKT. Further studies are needed to determine whether the observed haemodynamic changes are at least partly due to the presence of the transplanted organ and, if so, whether they are permanent in nature.

Reference: 1. Freilich JD, Waterman PM, Rosenthal JT: Acute hemodynamic changes during renal transplantation. Anesth Analg. 1984 Feb;63(2):158-60.



P89

Ex-vivo reconstruction techniques of multiple renal arteries in living donor kidney transplantation

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Introduction and Aim

The shortage of allografts in living kidney transplantation has forced the use of grafts with multiple renal arteries (MRA) that were previously considered to be unsuitable for transplantation. Several surgical techniques have been described for the reconstruction of MRA. We compared different reconstruction techniques of living donor kidney grafts with MRA.

Methods

We retrospectively analysed 144 living donor kidney transplants during the period from May 2005 to November 2009. There were 34(23.6%) allografts with MRA. We used reconstruction techniques such as ex-vivo reconstruction on recipient internal iliac artery (11), ex-vivo pantaloon (12), ex-vivo anastomosis of polar artery to main renal artery (2) and insitu anastomosis of MRA to recipient arteries/ligation of polar artery (9).

Results

Variable Total number (n)	Ex-vivo internal iliac artery (11)	Ex-vivo Pantaloon (12)	MRA with ligation of polar artery (5)	MRA in situ reconstruction (4)	RA end to side reconstruction (2)
Donor Age	49.8 (32 -69)	48.5(28 -64)	49 (37-65)	46.5(42-53)	62.5(57- 68)
Recipient age	41(17-62)	41.2(20-69)	49.8(39 -64)	31.9 (20 -46)	49.8(44 -56)
No. of renal arteries (Avg)	2.18	2.07	2.2	2.25	3.5
Cold Ischaemic Time (min)	207.6	140.6	104.7	141.2	69
Vascular anastomosis time (min)	58.8	59.6	53.6	64.5	60.5
Avg. Graft Survival (months)	11	18	26	23	41
Thrombosis of polar artery	0	0	0	1	0
Urological complications	0	0	0	0	0

Conclusion

The ex-vivo reconstruction of multiple renal arteries minimizes the risk of stenosis or thrombosis. Ex-vivo reconstruction decreases the secondary warm ischaemic time. There was no difference in urological complications.

P90

Cancellation of Planned Living Donor Renal Transplants: Can they be avoided?

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Aim

Living donor kidney transplantation (LDTx) requires months of planning. It needs close coordination between services and factors for the transplant to go ahead. Not to proceed with the transplant on the chosen date has major repercussions for both donor and recipient. It also results in loss of theatre time, further cross matching by the Transplantation Laboratory and potential further medical investigations for either the donor or recipient. Therefore it is imperative that all potential factors that could cause delays are identified and avoided.

Method

Details of all potential living donor/recipient pairs are maintained on a database. This was interrogated to identify all patients who had been given a transplant date between 2002 and 2009. All LDTx (adult and paediatric) that had been given a transplant date which did not go ahead were reviewed and the reasons for the delay identified. The final outcome for the donor-recipient pair was also studied.

Results

Out of a total of 291 scheduled LDTx, 247 (85%) were successfully completed on the first surgical date given. There were 44 recipients and 45 donors where surgery did not proceed on the initial date. Four recipients were postponed or cancelled more than once. There were a total of 49 cancellation episodes. The most common reason for cancellation was recipient related (26), followed by logistical issues (10), donor issues (7), unexpected positive cross matches (5) and a failed paired-pooled exchange when the other recipient received a deceased donor transplant shortly before the planned LDTx.

27 of the 44 patients eventually received a kidney from the planned donor. Two patients received a kidney from another donor; for one of these the cancellation had been due to a positive cross match and the second recipient had been medically unfit on the initially planned day of surgery. In that case the altruistic donor kidney had already been removed and had to be re-allocated through the national kidney allocation scheme. Ten transplants were cancelled completely and the recipients have not undergone transplantation, 7 due to recipient related factors and 3 due to donor issues. One patient in this sub-group was found to have a large caecal mass at the time of vessel exposure. Four additional patients are pending further investigations and one patient received a deceased donor kidney which is functioning well.

Conclusion

In over 65% of the cancelled cases, recipients did eventually receive a LDTx. The majority of cancellations were due to the recipient being unwell just prior to the planned date. In most cases this was unavoidable. Worryingly, logistical issues caused 20% of the cancellations and this is an area that should be addressed to prevent last minute delays in a procedure that affects more than just the recipient.

P91

Quality Of Life Following Live Donor Renal Transplantation

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Purpose: The aim of this study was to examine the quality of life (QoL) of the live donor renal transplant (LDRTx) recipients pre- and post-transplantation and correlate with their pre-transplant (pre-Tx) dialysis status and immunosuppressive regimens post-transplantation (post-Tx).

Methods: 57 LDRTx recipients and 38 healthy individuals as controls participated in the study. The Kidney Transplant Questionnaire (KTQ) and the Medical Outcome Survey Short Form 36 (SF-36) questionnaires were used to assess QoL. **Results**: The post-Tx scores SF-36 scores were significantly higher than the pre-Tx scores in all dimensions but were significantly lower than the control group's scores in the dimensions physical functioning, role physical, general health, physical component score and total. There was a significant improvement in KTQ scores post-Tx in all dimensions except appearance (A) where there was a significant drop in scores ($p=0.035$).

The pre-emptively Tx patients had the highest post-Tx SF-36 scores which were similar to the control, whereas the patients who received haemodialysis (HD) and peritoneal dialysis (PD) had significantly lower scores. An increase in the dimension A was seen in the PD group, whereas a reduction was seen in the HD and pre-emptively transplanted group. There was significant difference in the score of this dimension between the PD and pre-emptive group ($p=0.0042$).

The patients on tacrolimus had the highest SF-36 scores in all dimensions except mental health which was highest in the patients on cyclosporine. The bodily pain, vitality and social functioning dimension scores were higher in the tacrolimus group than the control's, although this was not significant. The best score in the dimension A was observed in the tacrolimus group.

Discussion: There was significant improvement in QoL following LDRTx as evidenced by an increase in all SF-36 and KTQ dimensions, except in the Appearance dimension, with pre-emptively transplantation and a tacrolimus based regimen having the best outcomes.

Kidney - NODAT

Moderator: Dr Mark Harber

P92

Campath induction and Tacrolimus monotherapy is associated with a low incidence of NODAT

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The DIRECT study reported a 33.6% incidence of glucose intolerance and a 16.8% of new onset diabetes after transplantation [NODAT] at 6 months in patients receiving Tacrolimus [Tac] and steroids. We observed a 20% incidence of NODAT at 12 months in our own patient group receiving Tac and steroids and developed a steroid sparing regime with Campath induction and low dose Tac monotherapy.

NODAT was defined as the de novo use of hypoglycaemic medications.

492 patients [185f, 307m; 241 DD, 251LD; 253 Caucasian, 51 Afro Caribbean, 155 South Asian, and 33 other ethnicity patients, mean age 47.5 ±13.2 years; follow up 22.7 ±17.3 months] were transplanted in our centre using Azm induction, medium dose Tac [0.1mg/kg daily; target trough level: 5-8 ng/ml (LCMS)] monotherapy and a steroid sparing regime, [prednisolone 60 mgs/day for 4 days, 30 mgs per day for 3 days and then stopped]. Steroids and MMF were only used to treat rejection.

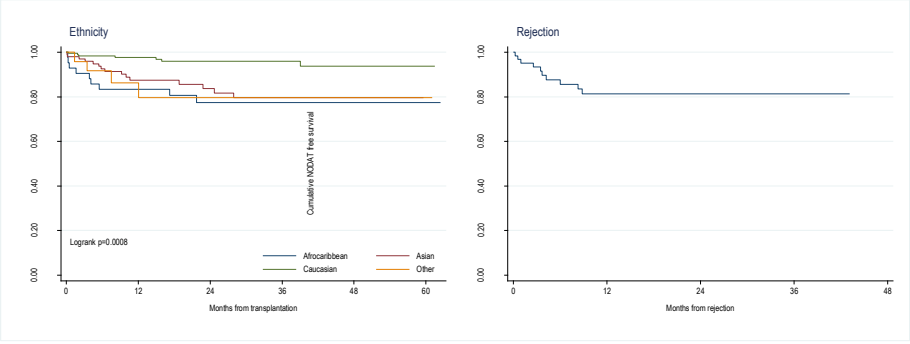
1 and 5 year patient survival was 99.5 and 95.9%. Allograft survival [censored for death with function] was 96.6% and 86.7% at 1 and 5 years.

1, 2, 3, 4 and 5 year NODAT free survival was 94.4%, 92.2%, 88.8%, 86.4% and 86.4%.

Multilevel modeling shows the use of steroids for rejection [OR:3.5 95% CI(2.7,4.4) p<0.001], ethnicity [Afro Caribbean OR:9.1 95% CI(6.5, 12.8) p<0.001, South Asian OR: 10.6 95% CI(7.5,15.0) p<0.001] and obesity [Weight above 90kg OR:1.5, 95% CI(1.2, 2.0) p=0.001] are associated with a high risk of NODAT.

This study shows that our Campath induction and Tac monotherapy regime without steroids and MMF delivers excellent clinical outcomes with a low incidence of NODAT.

We also show that NODAT is associated with the use of prednisolone for rejection, ethnicity and obesity.



P93

The use of metformin in diabetic post-transplant patients leads to an improvement in cardiovascular risk factors.

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Diabetes is a common co-morbidity in renal transplantation recipients, either as a complication of transplantation or as a pre-existing diagnosis. Poor glycaemic control and weight gain can be difficult to manage after transplantation and are both strong cardiovascular risk factors. In the non-transplant diabetic population, metformin has a comparatively favourable cardiovascular risk profile with a weight neutral or reducing effect.

Aim: To examine the effect of metformin on weight, blood pressure (BP), diabetic control and lipid profile in a population of transplant recipients with pre-existing (DM) or new onset diabetes post-transplantation (PTDM).

Methods: A single centre, retrospective chart review of renal transplant recipients with PTDM or DM. Data collected included: weight, BP, HbA1c, total cholesterol and triglycerides at the start of metformin treatment (T0) and at 6 months (T6) and 12 months (T12) post treatment. Patients on reducing steroid regimes were excluded. All values are expressed as mean and analysed by repeated measures ANOVA.

Results: A total of 22 patients were identified (PTDM=15, pre-existing DM=7). 5 patients were on low dose (2-7.5mg) prednisolone which remained unchanged during the study period. Insulin and oral hypoglycaemic agent utilisation did not change significantly. Weight reduced significantly ($p<0.02$) from 90.5 kg at T0 to 88.3kg at T6 and 86.2Kg at T12, with an average 4.3% reduction in body weight. There was a trend to reduction in HbA1c from 8.18% at T0 to 8.06% at T6 and 7.53% at T12 ($p=0.08$).

There was a significant improvement in the lipid profile with a reduction in total cholesterol from 4.76mg at T0 to 4.47mg at T6 and 4.06mg at T12 ($p=0.001$). Triglycerides fell from 2.90mg at T0 to 2.18mg at T6 and 2.15mg at T12 ($p=0.008$). There was a non-significant reduction in BP; systolic (138.2mmHg at T0 to 136.5mmHg at T12) and diastolic (81.9mmHg at T0 to 79.4mmHg at T12).

Conclusion: The addition of metformin for the control of diabetes post-transplant can significantly reduce body weight and improve lipid profiles. Further studies are required to delineate whether this intervention leads to an improved cardiovascular risk.

P94

De novo Rapamycin and NODAT

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Background

The development of new-onset diabetes mellitus after transplantation (NODAT) is a common and serious complication after kidney transplantation and is associated with an increased risk of cardiac events, peripheral vascular disease, graft failure, and death. The immunosuppressive drug classes of calcineurin inhibitors and steroids represent the most important pharmacological risk factors for NODAT but rapamycin has been also implicated.

Methods

All patients from a single transplant centre who received rapamycin de novo following renal transplantation during a 3 year time period between November 2004 and October 2007 were studied. These patients were compared with the next chronological kidney recipient who did not receive rapamycin (control group). The primary outcome measure was incidence of NODAT.

Results

Fourteen patients received de novo rapamycin, 7 in combination with tacrolimus (with withdrawal of tacrolimus at 3 months) the other 7 in combination with MMF. All 14 patients also received oral steroids. Of the fourteen control patients 12 received tacrolimus in combination with steroids and an antimetabolite and the remaining 2 tacrolimus and an antimetabolite only. There was no significant difference in primary cause of renal failure (including APKD), BMI, or ethnic origin between the two groups. The rest of the characteristics of the recipients were also evenly distributed. After a median follow-up of 48 months (range 25-61), none of the rapamycin group had developed NODAT compared with 3 (21%) of the control group.

Conclusion

In this study de novo rapamycin was associated with a lower incidence of NODAT than primary tacrolimus based immunosuppressive regimes.

Paediatric Kidney Transplantation

Moderator: Mr Marc Clancy

P95

Renal transplant outcomes in children under 6 years of age

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Introduction Renal transplantation remains the preferred treatment for end stage renal failure. However, the management of very young children in particular has been challenging. We report our experience of renal transplantation at Great Ormond Street and Evelina Childrens Hospitals in children less than 6 years of age over a 5 year period.

Method The data of all children under the age of 6 who had a renal transplant between Jan 2004-Oct 2009 was analysed retrospectively. Demographic details of age, gender, height, weight, form of dialysis prior to transplant, donor type and age and surgical details were recorded. The outcome variables included the duration of admission, PICU admission, complications and the survival of the graft and patient. Creatinine was noted at discharge and sequentially to 60 months.

Results Forty five children (78%) male, aged 15-71 (median 37) months received a renal transplant with a median weight and height of 15 (9-25) kg and 87 (74.5-112) cm respectively. 22% of the renal transplants were pre-emptive.

53% (24) of the children received a kidney from a deceased donor whilst the remaining received a live related transplant. 92% of the donors were from adults with a median age of 34 years (7-39) and 91% of the transplants were performed using an intra-peritoneal approach.

The median hospital stay was 14.5 days (7-60) and 58% of the children (26) were admitted to PICU during this time. 28% (13) of the children had a post operative complication.

38% (17) of the children had a histologically proven episode of acute rejection and 2 of the 3 children with focal segmental glomerulosclerosis had recurrent disease.

There was primary function in 91% (41) of the children. Delayed graft function in 7% (3) and primary non-function in 2% (1) patient due to thrombosis.

The median creatinine at discharge and 5 years was 33µmol/L (12-126) and 94µmol/L (62-137) respectively.

The 2 year graft and patient survival was 98% and 100% respectively and the 5 year graft and patient survival were both 98%. The child whose transplant failed died 30 months later from sepsis.

Conclusion We report a large series of children receiving renal transplants under the age of 6, predominantly from adult donors, using an intraperitoneal approach. The use of live related donors in our unit has trebled from 10 years ago[(1)]. Paediatric intensive care input is frequently required in young transplant recipients. Excellent 5 year graft and patient survival has been achieved in young recipients with appropriate medical support and experienced surgeons.

(1) J Kari Paediatr Nephrol, 1999, 13:730-736

P96

Increasing living donation for paediatric recipients: the importance of blood group incompatible donors

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Living donation is preferable for paediatric recipients, despite shorter waiting times for deceased donors when compared with the adult population. Living donor kidneys offer better long term outcomes, and elective surgery is preferable for often complex and high risk recipients, due to congenital bladder (or other) abnormalities and haemodynamic instability after transplantation in small children. In our centre, living donor transplantation increased in the 1990s, but remained static in the last 6 years, with 76 living donor transplants performed in the period 2003-2009. We wished to determine whether there were potentially resolvable barriers to living donor transplantation, which allow a further rise. We therefore studied the reasons for failure to progress with living donation over the period 2003-2009.

A total of 464 living donors presented during this time period and in 249 (54%) transplantation was not performed. The reasons for failure to progress are listed in Table 1 below. The most significant cause is blood group incompatibility, accounting for 29% of cases. The lower number of medically unsuitable donors when compared with donors for adults reflects the younger, fitter donor population, most of whom are parents.

It is concluded that performing blood group incompatible transplantation in children could significantly increase the number of living donor transplants, and we have therefore instituted such a programme, with one successful transplant so far. We recommend that blood group titres are always measured in cases of blood group incompatibility, since these may be neat or very low, obviating the need for additional therapy prior to transplantation.

Cause	**Total**
Blood group incompatibility	71
Medically unsuitable donors	50
Social	41
Positive cross-match	22
Other (misc)	65
Total	**249**

Table 1: Causes of failure to progress with living donor transplantation

P97

Chronic respiratory symptoms and bronchiectasis in paediatric renal transplant recipients on mycophenolate mofetil

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Objective:

The use of more potent immunosuppressive regimens in paediatric renal transplant patients has improved renal allograft survival but increases susceptibility to infection. We evaluate the incidence of respiratory system complications, in particular bronchiectasis, in paediatric renal transplant recipients receiving mycophenolate mofetil (MMF) as a part of their immunosuppressive therapy.

Methods:

A search of the renal transplant database was performed and all children who presented to the renal transplant clinic with a chronic history of cough and chest signs on clinical examination were identified. A retrospective chart review was performed and the immunosuppressive therapeutic regimen used and the interval from transplantation to symptom onset documented for all transplant recipients irrespective of immunosuppressive regimen used. We assessed data for associations between therapy used and onset of symptoms.

Results:

Chest radiographs (CXR) were obtained and pulmonary function tests performed in all symptomatic children. Patients with radiographic abnormalities on CXR were referred for a thoracic CT scan. Of 143 transplant recipients, 93 (65%) received MMF as part of their immunosuppressive regimen. Eleven (12 %) of these patients developed chronic respiratory symptoms requiring referral to our respiratory team, compared to none of the patients (0/50) on other immunosuppressive regimens ($p<0.05$)**.** Five of ten (50%) symptomatic patients who underwent CT scanning had radiographic evidence of bronchiectasis. Two of these patients required bronchoscopy and bronchoalveolar lavage due to the severity of symptoms. The time to onset of symptoms in patients who received MMF ranged from 9 - 96 (mean 31; median 24) months and, in asymptomatic patients, the duration of therapy ranged from 1 - 98 (mean 32; median 29) months ($p>0.05$). The duration of immunosuppressive therapy among patients who received non-MMF immunosuppressive regimens ranged from 10 - 170 (mean 55; median 49.5) months ($p<0.001$). Mean 12-hour trough MMF levels in symptomatic and asymptomatic patients were 6.85 and 3.78 mcg/ml respectively ($p<0.001$).

Conclusion:

We report a high incidence (12%) of significant chronic respiratory symptoms related to the use of MMF. A significant association is demonstrated between high trough MMF levels and the development of symptoms. No association was found between duration of MMF-based, or other immunotherapy and the onset of respiratory symptoms. Bronchiectasis should be considered in all patients who develop chronic respiratory symptoms post-renal transplantation.

P98

Use of Sirolimus in Paediatric Renal Transplant Recipients

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Introduction:

Sirolimus (SRL) has been described as an alternative immunosuppressant agent to calcineurin inhibitors with particular benefit due to reduced nephrotoxicity. Paediatric experience in renal transplant patients is limited to only a few cases per centre.

Methods: Retrospective folder review of paediatric renal transplant patients on SRL based immunosuppression at a single centre from 2002 -2009 auditing demographics, reason for switch to SRL, dosing and levels, length of time on SRL and complications, reasons for subsequent discontinuation of SRL and renal outcome.

Results:

Twenty-one paediatric renal transplant recipients. Gender: M: F 14:7.

Age at time of SRL commencement 3.5-16.2 years (mean 8.9 years, median 7.8 years)

Deceased donor: Live related donor: 13:8. De novo use of SRL: 5%(1/21) only.

Reasons for switch: rejection (both cellular and vascular), calcineurin toxicity including seizures, chronic allograft nephropathy, glucose intolerance and gingival hypertrophy.

Patients were loaded with Sirolimus for 3 days at $3mg/m^2$ bd and then $3mg/m^2$ daily with dose adjustment according to levels. In patients under 7 years, a twice-daily dosing regime was continued.

Side effects included less bone marrow suppression (only Hb lowered but no effect on white cells or platelets) than described in adults. Lipid studies showed raised cholesterol requiring statins in 48%(10/21) patients. Infections were a frequent complication especially when SRL levels > 8ug/l – bacterial specifically skin 29%(6/21), recurrent UTI's 19%(4/21), mouth ulcers 10%(2/21) and chest infections 19%(4/21). Viral infections also a problem – EBV, CMV, Shingles, Herpes all seen. Surgical complications - only 1 lymphocoele.

Renal complications were significant, including haematuria 43%(9/21), proteinuria 38%(8/21) and thrombotic microangiopathy 5%(1/21). Period of time on SRL 0.2-6.5 years(mean 2.8 years) with levels of 3.6-14.2 ug/l (mean 8.9) before this drug was stopped as a result of renal problems in 10/21. The remaining group 52%(11/21) remain on SRL for a mean of 3.5 years with levels between 2.5-10ug/l (mean 4.8), stable renal function and non-active urine findings.

Conclusion:

In the biggest series in paediatric renal transplants using SRL in UK, we found SRL useful in rejection (both vascular and steroid resistant), provided the GFR was still well maintained and haematuria or proteinuria did not develop. Infections are a significant problem and aiming for lower drug levels in range of 4-7ug/l is recommended. Sirolimus is useful provided there is careful monitoring of urine, adequate GFR and low dosaging.

P99

Adult Surgeons performing Paediatric operations: Can Renal Transplantation be the exception?

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Background: Paediatric procedures in General Surgery have historically been performed by Surgeons who operated on adult and paediatric patients unselectively. With the advent of sub-specialisation, many transplant units have opted out of paediatric practice. However, the international paucity of dedicated Renal Transplant Surgeons has largely resulted in paediatric transplants being performed by General Surgeons who operate on both adult and paediatric patients. In recent years, paediatric renal transplantation has also become increasingly offered in fewer centres, sometimes geographically distant from the patient's base nephrological unit.

Methods: A retrospective review of regional paediatric renal transplant numbers and outcomes over 18 years at a single paediatric institution by 'adult' Renal Transplant Surgeons was performed. Demographic data, type of transplant, graft and patient survival at 1, 5 and 10 years was assessed and compared with established national guidelines of the British Transplantation Society (BTS). In addition, serum Creatinine at 1 year and last recorded follow up was collated.

Results: 181 renal transplants were carried out on 169 paediatric patients (101 male; 68 female) between 1991 and 2008. 11 patients had multiple renal transplants whilst 22 patients received organs from live related donors and 159 from cadaveric heart beating donors. 11 patients had simultaneous liver and renal transplantation. There was a 12% (23/181) graft loss in the first year, equivalent to published transplant loss in adult practice in the first year. Creatinine values at 1 year and at discharge to adult care or last recorded follow up were115±15.7 μmol/l (range 40-327) and 191±21.2 μmol/l (range 32 to 1434) respectively (Mean follow up to discharge 62.6±4.0 months; range 4-170 months.) 5-year and 10-year graft survival was 83% and 73% and compares favourably with BTS data for adult and paediatric transplantation (81% and 64% respectively.)

Conclusion: 'Adult' Transplant Surgeons performing paediatric transplants demonstrate results that compare favourably with established standards for both adult and paediatric programmes worldwide. This occurred despite documented confounding paediatric factors such as non-compliance and the greater technical requirements of paediatric recipients. Specialised paediatric expertise is therefore not a necessity for adequate provision of a successful paediatric transplantation programme. This could prove to have profound effects on service provision planning for paediatric transplantation in the future.

P100

Surgical burden in children with established renal failure

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Introduction - Established renal failure (ERF) in children differs significantly from that in adults in many respects: underlying aetiology, dialysis access needs and requirement for interventions to aid growth and nutrition. There is a greater incidence of underlying urological pathologies, which themselves may require surgical interventions. These factors lead to a greater need for multiple surgical procedures. Our aim was to ascertain the surgical workload posed to paediatric surgical services by children with ERF.

Materials - We reviewed casenotes of all children cared for in our tertiary paediatric renal unit between 1990 and 2009, retrieved from our prospectively maintained database. We calculated how many dialysis access and transplant- related procedures were performed under general anaesthesia, only over the time during which the children were dialysis-dependant or until stable renal function was achieved following renal transplant. We also looked at how many ERF – related procedures were performed (both urological, and procedures such as gastrostomies to aid growth), as well as those unrelated. Underlying aetiology of ERF, age at initiation of dialysis, number of years in ERF (ERF years), types of operation were noted. Procedures performed under sedation were excluded, as well as all renal biopsies, changes of gastrostomy buttons and those performed elsewhere or by adult services. Children undergoing pre-emptive renal transplantation were excluded from the study.

Results - 72 children with ERF were studied (37 boys). The commonest aetiology of ERF was glomerulonephritis (18), followed by dysplastic kidneys (14), reflux nephropathy (7), MCDK with dysplastic kidney (5), posterior urethral valves (5), nephronophthisis (4) and other causes.

Median age at initiation of dialysis was 5.0 years. Mean number of "ERF years" was 3.8 years.

76.2% of surgery was related to dialysis access and transplantation.

Other surgery directly related to ERF totalled 19.6 % and other incidental procedures 4.2%.

Overall, 51.4% required 5-10 operations, 25 % required greater than 10 procedures: only 23.6% underwent less than 5 procedures.

For every ERF year, a mean of 4 operations were performed.

Discussion - Our data suggests that a very large proportion of children with ERF require numerous surgical procedures, more than half of children between 5 and 10 operations. 76.2% of operations involved management of the ERF. This very significant burden posed on surgical services is important to grasp when administering a paediatric ERF service, and justifies the allocation of additional surgical resources adapted to this activity.

P101

Paediatric presentation of end-stage renal failure is associated with poorer social and educational achievements

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Introduction:

Recent studies have suggested poor attainment of social relationships and educational achievements in adults who have end-stage renal failure (ESRF) in childhood. Our aim was to evaluate the outcomes of adults with end-stage renal failure within two groups (paediatric [under 16 years] versus adult presentation of ESRF).

Methods:

Initial questionnaire and further face-to-face interviews of adults with ESRF identified from paediatric and adult databases of nephrology programmes.

Results:

296 adults (mean age of 25 years, 52% male and 79% Caucasian) were questioned of whom the mean age of onset of ESRF was 17 years with 73% currently with functioning renal allograft. 39% had a complex ESRF history (with more than one modality of dialysis and/or failed renal transplant) and 5% were still attending paediatric renal services. Outcomes of patients aged > 23 years who currently were stable were compared between paediatric presentation (57 patients with median age at ESRF of 10 years) and adult presentation (89 patients with median age at ESRF of 21 years). 30% and 20% patients with paediatric and adult presentation respectively were registered disabled ($p = 0.02$). Although 49% paediatric and 62% adult presentation patients respectively were living independently of parents (with friends, partner or alone; $p = 0.14$), more paediatric presentation patients that were living with their parents were more likely to be living in rented accommodation ($p = 0.05$). Educational attainment was lower in the paediatric presentation group (below GCSE level in 18% vs 7%, $p = 0.04$). Paediatric presentation patients were less likely to be in full or part time paid work (57% vs 76%, $p = 0.02$).

Conclusions:

Adults who presented with ESRF during childhood have poorer social and educational achievements, compared to their counterparts who present in adulthood. Increased resources are required to ensure that these patients are able to achieve their goals with respect to relationships, education and occupations.

P102

Mycophenolate Mofetil (MMF) in Paediatric Renal Transplantation: Challenging Chests

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Introduction: Within our current cohort of paediatric renal transplant patients mycophenolate mofetil (MMF) has been used as an immunosuppressant in 50% (43) of cases. A group of patients have developed chronic respiratory complications whilst receiving MMF therapy and this audit further examines these cases.

Objectives: To review all paediatric renal transplant cases in the current cohort in our unit who developed problematic respiratory symptoms following the introduction of MMF looking for any common factors.

Method: Retrospective audit of all case notes of renal transplant patients in current cohort who developed respiratory complications during treatment with MMF.

Results:

	Case 1	Case 2	Case 3	Case 4	Case 5
Age, sex	12y 9m, F	12y 4m, M	11y 7m, M	11y 4m, M	8y, M
Diagnosis	Dysplasia	Congenital Nephrotic	Congenital Nephrotic	Dysplasia	FSGS (Asthma)
Age at Tx	2y 6m	3y 11m	2y 9m	2y 4m	4y 4m
Age MMF started	9y 2m	4y 5m	6y 6m	7y 8m	4y 4m
Reason for MMF	↑ Cr, Sirolimus intolerance	Rejection	CNI toxicity	CNI toxicity	Rejection
Clinical picture	Chronic sinusitis	Recurrent pneumonia	Recurrent pneumonia	Recurrent pneumonia	Recurrent pneumonia
Radiology findings	Maxillary sinusitis	Bronchiectasis	Pulmonary PTLD	Bronchiectasis	Bronchiectasis
Time from start of MMF to symptoms	2 months	4 months	1 month	2y 1month	9 months
Total MMF	1y 9m	5y 5m	10m	2y 3m	2y 11m
Current Status	Well, eGFR 50	Ongoing infections, rejection eGFR 20	Lost graft, eGFR 35 at MMF cessation	Chest improved, eGFR 46	Recurrent infections, respiratory f/u eGFR 52

Discussion: The advent of better immunosuppressive therapy to prevent organ rejection results in an increase of infective complications in paediatric renal transplant patients. In the cases above, it appears that the patients are well (one with predisposing asthma), until they get a respiratory infection they can't clear, and this in turn results in chronic lung damage (bronchiectasis in 3 of the cases).Other factors were involved in the PTLD patient.

Kidney – Surgical Aspects

Moderator: Mr Andrew Butler

P103

Encapsulating Peritoneal Sclerosis following Renal Transplantation: A single centre review

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Introduction

Encapsulating Peritoneal Sclerosis (EPS) is a rare, but potentially life threatening complication of peritoneal dialysis. The bowel is cocooned with a thick membranous shell that causes gut failure with mal-absorption and subsequent malnutrition. Transplant patients rely on a functioning gut to absorb immunosuppressants agents so development of EPS can potentially results in loss of a functioning graft. The aim of the review was to determine the outcomes of patients with EPS after transplantation

Method

A review of a prospectively maintained database at a large EPS centre dating from 2000. Factors such as length of time of PD dialysis and the timing of EPS with relation to the transplant and consequences EPS were studied.

Results

Between 2000 and October 2009 there were 19 patients (8 female) underwent enterolysis and peritonectomy for EPS which came on after transplantation. 2 patients had undergone simultaneous pancreas and kidney transplantation. Ten patients presented to the unit in an emergency situation with bowel obstruction. The remaining nine were semi-elective planned admission with pre-operative nutritional maximisation. Their symptoms were intermittent vomiting, abdominal distension and weight loss. All but one patient received tacrolimus based immunosuppression. The one exception received cyclosporine based regime.

The average length of time on PD dialysis was 48 months. The timing of EPS presentation following renal transplant ranged from 3 to 28 months with a mean of 7 months.

There was a postoperative mortality of 16% which is lower than patients who are on haemodialysis.

Conclusion:

Post transplant EPS is a rare condition which can be successfully treated with surgical enterolysis. There is a not insignificant mortality rate, however successful treatment appears to preserve graft function.

P104

Encapsulating sclerosing peritonitis is an important cause of death after renal transplantation.

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Encapsulating sclerosing peritonitis [ESP] is a rare complication of peritoneal dialysis [PD] causing partial or complete bowel obstruction, intestinal failure, sepsis and death.

There are few reports detailing the incidence, course and outcome of ESP after renal transplantation.

521 patients were transplanted in our centre between October 2005 and November 2009 with Campath induction, Tacrolimus monotherapy and a steroid sparing regime [steroids for 1 week post transplant]

48/521 [9.2%, 25m, 23f; mean age 48.8± 13.0 years] patients were on PD, 365 [70.1%, 230m, 135f; mean age 47.3 ±12.9 years] were on haemodialysis [HD] and 108 [20.7%, 63m, 45f; mean age 47.1 ±12.2 years] were pre-emptively transplanted [PreD].

Cumulative patient survival for PD patients at 1, 12, 24 and 36 months was 100%, 97.7%, 92.3% and 92.3% respectively and significantly poorer than the HD patients [99.7%, 99.1%, 98.6% and 98.6%] or PreD patients [100%, 99.0%, 97.7% and 97.7%] at equivalent time points [p=0.0092].

During this period, there have been 11/521 [2.1%] deaths in our programme. 4/48 [8.3%] of PD group have died with intestinal failure from complications of sepsis.

Only 5/365 [1.4%] of HD patients and 2/108 [1.9%] of the PreD patients have died. The risk of death in the PD group is 6 times that of the other groups [Hazard Ratio Model HR 6.0; 95% CI 1.6, 22.5,17.6; p=0.008].
13/48 [27.1%] PD patients had ESP and 6 [12.5%] of these had ESP at the time of transplantation and one has died. 7/42 [16.7%] patients developed ESP after transplantation and 3 [48.2%] have died.

4/13 of those with ESP who have not died have experienced intestinal failure requiring parenteral or enteral feeding which is indefinite in 2 patients.

ESP after transplantation is associated with a 25% mortality, significant morbidity and is the commonest cause of death in our transplant programme.

P105

Risk Factors of Delayed Graft Function in Kidney Transplantation

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Introduction

Delayed graft function remains a significant complication in kidney transplantation. It is associated with inferior outcomes by a variety of measures including rejection rates and graft failure. Some associated factors such as recipient age and PRA cannot be favourably modified but ischaemic time, perfusion method and peri/post-operative graft perfusion may be modified in order to ameliorate DGF. We assess the effect of peri-operative and post-operative perfusion (as assayed by CVP and peripheral BP) on DGF

Methods

Demographic, clinical and biochemical data for patients who received either deceased or live kidney transplant from January 2007 to March 2009, were collected prospectively in an electronic database supplemented by clinical record review. DGF was defined as either the need for dialysis post-transplant, or failure of reduction in serum creatinine by 50% by day 7 of transplant. Peri/Post-operative CVP and BP were recorded from review of patient charts. CVP <8cm H_20 or MAP<85mmHg was regarded as being below target. The occurrence of below target CVP and MAP in the 24 hours after was analysed for associations with DGF using univariate and multivariate linear regression analysis alongside other potential confounding factors (SPSS).

Results

DGF rate was significantly higher in deceased donor grafts ($p<0.01$) and in patients who had peri-operative hypotension ($p=0.04$) and post-op hypotension ($p=0.017$). A fall in CVP below target range was not associated with development of DGF. DGF was also more commonly observed among the following groups although the results did not reach statistical significance: cold ischaemic time (p 0.105), re-transplants ($p=0.080$), HLA mismatch ≥ 1 ($p=0.488$), donor age, donor's serum creatinine level, donor hypotension, anastomotic time, and tacrolimus level in the immediate post-operative period.

Discussion

With the increased risk of rejection/graft failure following DGF, and the increase in hospital stay with its associated complications as well as the increase in overall cost, measures should be taken to prevent or manage the risk factors that predispose to DGF. Current UK management frequently entails intermittent CVP and ABP measurement post operatively. This predisposes to perfusion "dips" between measurements with a time-lag before fluid/inotrope therapy can improve the perfusion. Continuous, invasive ABP monitoring might allow a goal-directed approach and facilitate the maintenance of graft perfusion at levels which avoid further injury to it. Such an approach should complement measures like machine preservation and virtual cross-matching in ameliorating DGF.

P106

Urinary Tract Infections in the first year Post Renal Transplant

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Introduction: Urinary Tract Infection (UTI) is an important complication post renal transplantation, with associated patient morbidity, potential worsening of graft function and effect on long term graft survival.

Aims: To investigate the incidence, timing, microbiology and antibiotic resistance patterns of UTI in the first year post renal transplantation.

Methods: A retrospective study of microbiology and renal databases at our institute between January and December 2008. All renal transplant patients with 1st year follow-up at our institute were included in the study. UTI was defined on the basis of positive MSU. Antibiotic sensitivity / resistance patterns were analysed. Patients received a single prophylactic dose of Amikacin at the time of transplant and at the time of stent removal and a single daily dose of co-trimoxazole 480mg for the first 3 months after transplant as urinary tract and pneumocystis prophylaxis.

Results: 68 transplant patients were included in this study: 27 deceased donor (DD) kidney transplants, 34 living donor (LD) kidney transplant and 7 SPK. 5 of 7 (71%) SPK patients had at least one UTI compared to 22 (36%) kidney-only transplant patients. UTI in DD recipients was 48% compared to LD 26%. Recurrent (>3) UTIs occurred in 15% (2 SPK, 5 DD and 3 LD patients) with 3 kidney transplant patients having pre-disposing urological causes.

There were 72 positive urine cultures in the 22 kidney-only transplant patients with UTI. E coli and enterococcus faecalis were the commonest bacteria cultured. However a wider spectrum of bacteria was cultured during the first 6 weeks post transplant. The majority of UTI (69%) occurred in the first 3 months post-transplant (83% in DD; 51% LD (P=0.003)); with many occurring in the first 6 weeks (52% in DD; 31% in LD). 3 patients (2 DD; 1 SPK) had UTI on the day of transplant; none of these patients had recurrent UTI. No isolated bacteria were resistant to Amikacin but 64/72 (88%) were resistant to Trimethoprim.

Conclusion: The majority of UTI occurred in the first 3 months after transplant, a time frame during which the urinary tract is instrumented to remove the urinary catheter and ureteric stent; and during which immune-suppression is often at its greatest. The higher incidence of UTI in DD compared to LD recipients may be a consequence of longer cold ischaemia and delayed graft function of DD organs that may predispose this group to UTI. Interestingly recipients with UTI on the day of transplant did not have recurrent UTI. Attention to the timing of transplant stent removal and prophylactic antibiotic regime may permit a decrease in the incidence of UTI in kidney transplant patients, which may in turn benefit long-term graft outcome.

P107

Parathyroidectomy post-renal transplantation: does it affect graft function?

A single centre's experience

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Background:

The management of refractory hyperparathyroidism post-renal transplantation is controversial. Previous literature (mostly single-centre, retrospective studies) suggests parathyroidectomy has a detrimental affect on graft function. We aimed to examine the use of parathyroidectomy in our transplant centre and the impact on subsequent graft function.

Patients and methods:

Using Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes, all renal transplant recipients undergoing any operation of the parathyroid gland between 01/01/2003 and 01/10/2008 were identified. Thirteen patients undergoing parathyroidectomy had functioning transplants; for each, notes were reviewed and demographical, clinical and laboratory data collected. eGFR was calculated using the 4-variable MDRD equation. Each eGFR measurement recorded in the 12 months before and after (if available) parathyroidectomy was plotted. A line of best fit was applied to each set of values (minimum of 7 eGFR measurements per 12-month period) and the rate of change in eGFR was calculated pre- and post-parathyroidectomy, and a Wilcoxon rank sum test performed.

Results:

On 31/12/2008, 706 patients were registered at our transplant centre with a functioning renal transplant. Of these, 13 had undergone parathyroidectomy during the study period. One patient was excluded from the eGFR analysis due to a lack of eGFR measurements following transfer to another unit post-operatively. 8/13 were female. Mean age at time of operation was 49.8. All had been on dialysis prior to transplantation (mean 72 months, range 20-180). The mean time from transplant to parathyroidectomy was 77 months. eGFR in the year following parathyroidectomy was 9.1ml/min/1.73m^2 lower than in the year preceding parathyroidectomy (IQR 4.9 to 14.21 ml/min/1.73m^2), but no difference was observed in the rate of change of eGFR post-parathyroidectomy (p=0.1). Three patients had renal biopsies performed within 90 days of their parathyroid surgery for a perceived reduction in function - one showed acute rejection, one chronic allograft nephropathy and one was normal.

Discussion:

Our results, although derived from a small, single-centre cohort, suggest that parathyroidectomy in cases of refractory hyperparathyroidism post-renal transplantation does not negatively affect graft function. The small study cohort, lack of control group and older transplant vintage than in many previously published studies, limits interpretation.

Large, multi-centre studies are required to examine the long-term consequences of post-transplant parathyroidectomy.

P108

Pilot study- To assess the effectiveness of Transverse Abdominus Plane (TAP) block for postoperative analgesia in Renal transplant patients.

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Background: The side effects of strong opiods like morphine and fentanyl in renal transplant patients for the first 2-3 postoperative days because of inadequate renal functions in the transplanted kidney is well recognised. This prospective study was carried out to look into alternative analgesic technique which can produce an opioid sparing effect.

Aim: To assess the effectiveness of TAP block for postoperative analgesia in renal transplant recipients.

Objective: 1. To assess the effectiveness of TAP block by recording pain scores using numeric pain rating scale.

2. To assess the opioid sparing effect of TAP block by calculating the post-operative opioid consumption.

Methodology: A prospective study involving 18 renal transplant recipients. The study population comprised of three different groups **Group A** (TAP block with continuous TAP catheter infusion and Patient controlled analgesia, N-5), **Group B** (Continuous TAP catheter infusion and Patient Controlled Analgesia, N-7) and **Group C** (Patient Controlled Analgesia only, N-5) and one patient out of the 18 with only TAP Block.

Primary outcome - Post-operative pain scores at various times in the first 24 hours post-operatively

Secondary outcome – Total amount of fentanyl used by patients from the Patient Controlled Analgesia syringe pump.

Results:

	Group A	Group B	Group C
Median Pain Score @ recovery	2	5	7
Median Pain Score @4 hours	3	4	5
Median Pain Score @12 hours	1	3	4
Median Pain Score @24 hours	0	2	2
Median Opioid Usage Fentanyl (mcg)	1200	1760	1880

Conclusion: The above results prove the effectiveness of TAP block as the pain scores in patients with the block is better. Also the amount of opioid used is less in patients with TAP block proving the opioid sparing effects of the block. Hence TAP block is a good adjunct in the post-operative analgesia management strategy.

P109

Assessing two rival definitions of delayed renal allograft function for their association with graft failure: which provides superior prognostication?

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Delayed graft function (DGF) following renal transplantation is associated with a deleterious effect on long term graft survival. Multiple definitions of DGF have been proposed, most commonly the requirement for dialysis in the first week post transplantation. A more "functional" definition of DGF has been proposed by Boom as failure of the serum creatinine to fall by greater than 10% on three successive days in the first week post transplantation, irrespective of dialysis requirement, and in that single study its presence was associated with inferior allograft survival. Whether this functional definition of DGF (fDGF) or the traditional dialysis-requirement based definition (dDGF) serves as a better marker of subsequent outcomes is unknown.

We investigated this by studying adult patients who underwent transplantation between 1996 and 2006 in a large UK single centre. After exclusion of early technical failures, 775 patients were available for analysis (Caucasian: 627; South Asian:114; African-Caribbean: 34; male: 480; age: 44.8±13.4 years). All patients received ciclosporin-based immunosuppression from the day of transplantation. Data was retrieved from a prospectively collected clinical database and electronic laboratory records.

197 patients fulfilled criteria for both fDGF and DGF; 58 displayed dDGF but not fDGF; 89 displayed fDGF but not dDGF. Over a median of 8.1 years (range 4-14 years), there were 77 deaths and a further 155 graft failures. Cox regression was used to identify the association between DGF and the 2 endpoints of death-censored and overall graft failure.

Univariate associations were seen between both fDGF (HR: 1.72; 95% CI: 1.26, 2.36; p=0.001) and also dDGF (HR: 1.59; 95% CI: 1.16, 2.18; p=0.004) and death-censored graft failure. When compared simultaneously in a bivariate model, fDGF showed a closer association than dDGF (HR: 1.52; 95% CI: 1.13, 2.25; p=0.01 and HR: 1.23; 95% CI: 0.84, 1.83; p=0.28 respectively). The final model adjusted for the following covariates: recipient ethnicity, donor and recipient age and sex, acute rejection, regraft, total HLA and DR mismatch, adjunctive immunosuppression (MMF vs AZA), donor source (live versus deceased), CMV serostatus and preservation time. Here also, fDGF showed a clear association with death-censored graft survival (HR: 1.41; 95% CI: 1.05, 2.10; p=0.03), which was lacking for dDGF (HR: 1.14; 95% CI: 0.76, 1.69; p=0.53). Similar results were seen for fDGF and dDGF in the final adjusted model for *overall* graft failure (HR: 1.35; 95% CI: 1.06, 1.87; p=0.04 and HR: 1.02; 95% CI: 0.73, 1.43; p=0.90 respectively).

This is the first confirmatory study of the utility of fDGF as an early marker of subsequent inferior allograft outcomes, and furthermore suggests its superiority over the more traditional dialysis-based definition. This has implications for clinical management and short term outcomes in clinical trials.

P110

The Implantable Cook-Swartz Doppler Flow Probe in Kidney Transplantation.

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Introduction After kidney transplantation, surveillance of graft blood supply is critical. A delay in detecting compromised graft perfusion can impact on organ survival. Current practice involves using doppler ultrasound as the main tool to monitor vessel patency and graft perfusion and is performed repeatedly following kidney and pancreas transplantation. The implantable probe allows for easy attachment and safe, continuous monitoring of vascular anastomoses. It has been used in observing microvascular tissue transplants, free flaps and paediatric liver transplants but not yet in kidney transplantation.

Methods The Implantable Doppler Cook-Swartz flow probe 20 MHz crystal is attached to a cuff and was placed in 5 live donor related kidney transplant patients.

Our post-op monitoring protocol was as follows**:**

Day 1: Monitor continuously, noting any noticeable change in signal.

Day 2: Monitor once per hour.

Day 3: Monitor every 2 hours.

Day 4: Monitor every 3 hours.

Day 5: Monitor every 4 hours.

Discontinue after day 5.

Remove probe on day 5-7.

Probe removal requires a gentle traction on the wire; 1/10th lb (50g) pressure disengages the crystal from the cuff, which remains permanently in place around the vessel. There are no documented cases of removal damaging the anastomosis.

Results All 5 transplants were followed as per protocol. Only a single Doppler ultrasound was ordered during the entire 5 admissions compared to frequent scans routinely ordered. There were no complications and all probes were straightforwardly removed.

Conclusion The probe potentially saves precious organs. It can monitor continuously or periodically as required and can instantly identify flagging or loss of blood flow allowing earliest possible intervention. In a pre-emptive kidney transplant, urine output is misleading thus continuous doppler surveillance can be vital. It also confers other advantages including obviating the need for bulky doppler machines at the bedside, decreasing costly usage of radiological facilities (often out-of-hours) and removing wound infection risk from repeated duplex probe contact over the surgical wound.

Liver Transplantation

Moderator: Mr Simon Bramhall

P111

Liver transplantation for familial amyloid polyneuropathy; the King's College Hospital selection criteria

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Introduction: Familial amyloid polyneuropathy (FAP) due to mutations in the transthyretin gene is the commonest form of hereditary amyloidosis. Liver transplantation (LT) is the only available treatment. Patients and methods: 94 FAP patients associated with 19 different transthyretin (TTR) variants, of whom 68 received LT. Evaluation included neurologic and cardiac assessment. Patients were categorized as TTR Met30 (58 cases) or non-Met30 variants (36), and in Met30 as early- or late-onset through cut-off age 50yrs at presentation. Results: All Met30 cases presented with either peripheral neuropathy or autonomic neuropathy most commonly involving the gastrointestinal tract with constipation or diarrhoea and the cardiac sympathetic or parasympathetic system; cardiac amyloidosis was a rare and late feature. In contrast, 93% of non-Met30 patients had evidence of cardiac amyloid at presentation and neuropathy was late manifestation. At median follow-up 71 months after liver transplantation, neurology improved in 88% of Met30, but deteriorated in 71% of non-Met30. Cardiac amyloid progressed in all non-Met30 cases, whilst echocardiograms stabilized in early-onset Met30. Serial amyloid scintigraphy demonstrated regression or stabilization of extra-cardiac visceral amyloid in 82% of Met30 cases and all of non-Met30 cases, despite concomitant progression of cardiac amyloidosis in the latter. Cumulative survival was 93% in early-onset Met30, 33% in late- onset Met30, and 33% in non-Met30. On univariate Cox regression analysis, age at transplantation, TTR variant, cardiac amyloid preoperatively ($p<0.01$), polyneuropathy disability (PND) score, ($p<0.05$), were statistically significant risk factors. On multivariate analysis, patient's age was independent pretransplant risk factor , and early progressive amyloid cardiomyopathy independent posttransplant risk factor ($p<0.001$). Conclusions: LT is rational and effective treatment for FAP. In order to improve outcomes we propose transplant selection criteria which accommodate the phenotypic heterogeneity amongst different variants and take into account relevant risk factors

P112

Organ 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 online measurements of the metabolic markers of ischaemia. This abstract reports the first preliminary results from our 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. The kidneys were monitored at room temperature for 4 hours post-retrieval. A microdialysis probe (CMA12, PAES, 2mm) was tunneled superficially into the parenchyma of the renal cortex using a 21 gauge angiocath. Probes were perfused with perfusion fluid containing (Na^+ 147mM, K^+ 4.0 mM, Ca^{2+} 2.3 mM, Cl^- 156 mM). 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.

We have successfully monitored 7 porcine kidneys. On commencement of microdialysis monitoring stable levels were achieved within 10 minutes, with quantifiable lactate concentrations. 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.

This fall 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. 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.

P113

Renal dysfunction in liver transplant recipients in the United Kingdom

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Chronic kidney disease (CKD) is a well recognised independent predictor of outcome in liver transplant (OLT) recipients. In addition chronic renal insufficiency is a known complication of organ transplantation. 18% of OLT recipients developed renal insufficiency (GFR <30) by 5 years[1]. Calcineurin inhibitor (CNI) therapy is principally implicated in this. Currently we have little UK information on the impact of CKD post OLT.

Aims: 1.What proportion of patients in UK have evidence of CKD at OLT.
2.What proportion of existing OLT recipients have CKD and is there evidence that units are tailoring immunospression in response to this.

Methods: All 7 UK liver transplant units participated in this retrospective review on patients who underwent elective OLT April to June 2008 and those patients who underwent OLT between April 2005 and March 2007 that were reviewed in April 2008. The severity of renal dysfunction was defined as per NICE CKD guidelines ie Normal/Mild GFR > 60, moderate GFR 30–59, Severe GFR < 30.

Results: Of 121 patients undergoing OLT, 98 (81%) had normal/mild, 22 (18%) moderate and 1 (1%) severe CKD. No patients with moderate CKD required renal replacement therapy (RRT), the patient with severe CKD required 6 days RRT. Only 5 (23%) patients with moderate dysfunction received IL2R monoclonals . No patient was on a CNI free regime but 10 (45%) of patients with moderate renal dysfunction received mycophenolate and trough Tacrolimus levels were lower at discharge in those patients.

At a mean of 25 months post OLT, 225 patients were reviewed. Of these 105 (47%) had mild/normal, 111 (49%) moderate and 9 (4%) severe CKD. Only 9% of patients with moderate CKD were on a CNI free regime as compared to 56% of patients with severe CKD. Comparing these groups 34% and 56% were receiving mycophenolate respectively. Mean tacrolimus levels (ng/mL) were lower in those with severe (1.86) and moderate (5.9) as compared to mild (6.4) CKD. The blood pressure was comparable between all groups. At 2 years 44% of those with severe CKD required insulin. Only 7% of patients with moderate and 11% with severe CKD were on a statin

Conclusions: At 2 years post OLT 53% of patients had evidence of moderate to severe CKD. Only 9% of patients with moderate CKD were on a CNI free regime and 34% on mycophenolate. This suggests that there may be the opportunity to further protect renal function in this group of patients. Blood pressure was acceptably controlled and only a few patients are on a statin. This study was sponsored by Roche Products Ltd.

1.Ojo et al NEJM 2003;349.931

P114

Liver ischaemic preconditioning and endothelial nitric oxide synthase: the effects on liver ischaemia reperfusion injury and microcirculation

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Background. Liver ischaemia reperfusion (IR) injury is a major cause of morbidity and mortality in liver resection surgery and liver transplantation. Understanding the mechanisms of liver ischaemia reperfusion injury will aid the development of strategies to counteract this injury. Ischaemic preconditioning is where a short cycle of ischaemia and reperfusion protects against IR injury. Endothelial nitric oxide synthase (eNOS) has been implicated as one of the mediators of ischaemic preconditioning in various models, but its role in the liver is unclear. We sought to clarify the preconditioning protocols which are protective, their effects on liver microcirculation and the role of endothelial nitric oxide synthase (eNOS) in liver warm IR injury.

Methods. C57BL6 and eNOS knockout mice were used. Both groups of animals underwent inhalational anaesthesia and midline laparotomy. Ischaemia was induced by occluding the portal triad supplying the left lateral and medial lobes (70% ischaemia) using an atraumatic microvascular clip. Ischaemia was confirmed by change of colour of the cephalad lobes. Minimal blood loss and trauma to liver lobes was ensured. During reperfusion periods the laparotomy was closed with clips. Core temperature was maintained with a heat pad.

There were three groups (n=5 for all interventions) 1. Sham laparotomy. 2. Liver ischaemia reperfusion (IR) only of 45 min ischaemia and 2 hours reperfusion. 3. Liver ischaemic preconditioning (IPC) (3, 5 or 10 min ischaemia and 10 or 15 min reperfusion) immediately followed by IR (45 min ischaemia and 2 hours reperfusion). Laser Doppler blood flow was monitored at four time points from preischaemia to the end of reperfusion. Tissue H&E fixed sections were scored by a histolpathologist using the Suzuki classification. Serum was analysed for alanine transaminase (ALT).

Results. In C57BL6 mice, IPC of 5 min ischaemia/10 min reperfusion reduced liver IR injury (ALT 560+/-260 IU/L vs 1805+/-454 IU/L), with no protection with the other IPC protocols ($P<0.01$). The microcirculatory dysfunction found during reperfusion in the liver IR only group was significantly reduced in the IPC 5/10 group, but not with the other IPC protocols (ANOVA, $P<0.01$). IPC 5/10 reduced histological injury compared to the IR only group ($P<0.01$). Only IPC 5/10 was used in eNOS knockout mice. There was no significant difference ($P<0.05$) in liver injury between the group with IPC and with IR only in terms of serum ALT (1904+/-1059 IU/L vs 3655+/-2607), histological scores and laser Doppler flow.

Conclusions. One cycle IPC of 5 min ischaemia and 10 minutes reperfusion only protects against liver IR injury following 45 minutes ischaemia and reduces microcirulatory dysfunction. The serum, histological and microcirculatory improvements of IPC are partly mediated by eNOS, as IPC 5/10 made no difference to liver IR injury in knockout mice.

P115

Is graft steatosis relevant when transplanting NHBD livers?

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Introduction: Liver Transplantation (LT) using Non Heart Beating Donors (NHBD) came back into practice due to the organ shortage, and contributes approximately to 10% extra-grafts. NHBD graft selection is the key to obtain outcomes similar to LT with donors after brain death (DBD).
Aim: to evaluate the outcomes of LT using steatotic liver grafts from NHBD.
Methods: from November 2004 to September 2009, 52 adults were transplanted with NHBD livers. Visual appearance at retrieval was recorded in all cases. Fine needle post-reperfusion biopsy was available in 38 cases. Steatosis of the graft at liver biopsy was defined as mild (<30%), moderate (30 to 60%) or severe (>60%). Patient and graft survival at 1 year was analyzed by Kaplan-Meier method and compared with the log-rank test. A value of $P<0.05$ was considered significant. Means were compared with Student *t* test and proportions were compared with Fisher's or chi-square tests.

Results: Out of the 38 NHBD LT recipients with available post-reperfusion biopsies, 4 (10.5%) patients received a non steatotic, 23 (60.5%) a mildly steatotic and 11 (28.9%) a moderately steatotic graft. No severely steatotic grafts were transplanted. Two groups were analysed: A: mild or absent steatosis (71%); B: moderate steatosis (28.9%). Median follow-up post-transplantation was 290 days (range 1-1739). Donor and recipient population were homogeneous, particularly in terms of age, cold ischaemia time (CIT) and follow up. Overall survival was 94.7% and 89.5% for recipients and grafts. There were six deaths, 3 for sepsis, three for haemorrhagic, cerebrovascular and cardiovascular complications respectively. Two patients were retransplanted, one for primary non function and the other for early hepatic artery thrombosis. There was no significant difference in patient or graft survival between the two groups. One-year patient survival was 92.3% vs. 100% ($p=0.33$) and graft survival was 88.5% vs. 91.7% ($p=0.75$) in groups A and B respectively.
Two recipients, in group A, developed biliary complications (3.8%): the first a mild anastomotic stricture, not requiring intervention and the second an anastomotic stricture dilated and stented at endoscopic retrograde cholangiopancreatography. There was no statistically significant difference between the two groups in terms of biliary complications.
Conclusion: In selected cases, steatotic NHBD grafts are suitable for transplantation, provided the total ischemia time is kept as short as possible. Technologies like the National Organ Retrieval Imaging System (NORIS) may provide a timely visual evaluation of the NHBD graft, thus allowing the transplant team an early start of the transplant and potentially contributing to keeping CIT short.

P116

Hereditary systemic fibrinogen A a-chain amyloidosis and the role of liver transplantation; the King's College Hospital 15-year experience

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Introduction: Variants of fibrinogen A α-chain (AFib) cause the commonest type of hereditary amyloid nephropathy in Europe and the United States. Variant fibrinogen is produced in the liver, and isolated renal allografts fail within 1-7 years with recurrent amyloidosis. Patients and methods: We report the phenotypic and clinical features and outcome of 22 patients with AFib and stage 3-5 chronic kidney disease (CKD), who were assessed for combined liver and kidney transplantation (LKT). Twenty-one had E526V, and one the R554L variant. Results: Coronary atherosclerosis was identified in 68% of cases, andcarotid or aortic atheromatosis in 55%. Vascular atheroma excised at endarterectomy contained abundant amyloid solely derived from variant fibrinogen. Endomyocardial biopsies revealed deposition of fibrinogen amyloid. Half of cases had autonomic neuropathy. Nine patients received LKT between 1996-2009. In 2 cases LKT was performed at stage 4 CKD before initiation of haemodialysis (HD), one patient had LKT at 2 months of HD and 6 had been on long-term dialysis. At median follow-up of 67 months (33-155), all three patients who received LKT preemptively are alive and well with good allograft function; LKT however was successful in only 50% of cases who had been on long-term renal replacement therapy. Cumulative survival was 67%. Fatal outcomes in 3 cases occurred in the short term postoperative period, and were due to complications of biliary dyskinesia and resultant acute necrotising pancreatitis and biliary leaks (2), poor quality tissues, bradyarrhythmia and ischemic coronary events, and hepatic artery thrombosis in one case. All surviving patients have good allograft function with no evidence of progressive amyloidosis. In contrast to inexorable progression to complete ESRF in the disease natural course, serial ^{99m}Tc-DMSA renal scintigraphy in the 2 cases of pre-emptive LKT, demonstrates preserved native kidney residual function up to 5 yrs follow-up. Four explanted livers were used successfully for domino liver transplantation. Conclusions: Fibrinogen A α-chain amyloidosis is a systemic disease with visceral, vascular, cardiac and neurological amyloid involvement. Combined liver and kidney transplantation can be curative. Our data further encourage evaluation of preemptive solitary liver transplantation early in the course of amyloid nephropathy to prevent requirements for renal replacement therapy and kidney transplantation.

P117

Mycophenolate moeftil (MMF) and low dose Tacrolimus based immunosuppressive regimen following Orthotopic liver transplantation (OLT): Is it cost-effective?

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Background: Tacrolimus-induced nephrotoxicity is the major cause of renal failure following OLT. An MMF (Cellcept®) and low dose Tacrolimus (Prograf®) based regimen (MMFT) has been shown to be less nephrotoxic compared to an Azathioprine (AZT) and Tacrolimus based regimen (AZTT). However, MMF is expensive and cost is the major limiting factor for its widespread use following OLT. The aim of this study was to compare the inpatient healthcare expenditure associated with MMFT regimen in contrast to AZTT regimen. **Material and Methods:** Between 2003 and 2008, 683 (Males, n=386) patients (mean age=50.2; range: 16.4 -76.4 years) underwent OLT. 411 patients, 78 on MMFT (cases) and 333 patients on AZTT regimen (controls) were selected for further analysis. We compared the major inpatient healthcare costs incurred by immunosuppressive medication, intensive care unit stay (ITU), hospital stay, renal replacement therapy (RRT), and the overall hospital costs between both groups. The data was collected prospectively and the unit costs were applied retrospectively. We then calculated the mean health care costs per patient in each group and looked at the differences in the cost (between groups) for each type of cost and overall costs. Bootstrapped 95% confidence intervals were calculated for each cost difference. **Results:** There were no significant differences in the mean age, gender, Model For End-Stage Liver Disease (MELD) scores, number of patients on pre-operative RRT, acute rejection and re-graft rate, and the overall hospital mortality between both groups. The mean pre-operative creatinine clearance levels were significantly lower in the MMFT group (76+/-33 vs. 89+/-34ml/min, p=0.004) and more patients in the MMFT group had combined liver and kidney transplants (6.4% vs. 0.9%; p=0.002). More patients in the MMFT group required RRT compared to the AZTT group (33% vs. 19%; p=0.007). However, there was no significant difference in the RRT duration between both groups (23 vs. 17 days; p=0.29). The median hospital (13 vs. 11 days; p=0.0001) and ITU stay were (4 vs. 3 days; p=0.002) longer in the MMFT group. Patients in the MMFT group were on significantly lower median dose of Tacrolimus per day (6 mg vs. 8 mg; p<0.0001). Per patient immunosuppressive drug cost was similar between the MMFT and AZTT groups (UK £13+/-3.5 per day vs. £12.6+/-4.5; p=0.2). However, there was a significant difference in the mean per patient ITU (£2694.09, 95% CI: -184.64 to 6210.60, p=0.03), RRT (UK £373.09; 95% CI 70.73 to 756.01; p=0.0001), and the total inpatient cost (UK £ 2997.93; 95% CI -42.29 to 7668.85; p=0.006) between MMFT and AZTT groups. **Conclusions:** There was no difference in the cost of the immunosuppressive drugs between patients on the MMF and low dose Tacrolimus compared to AZT and Tacrolimus. However, the overall in-patient cost is much higher for the patients on the MMF and low dose Tacrolimus, most likely due to poor pre-operative renal function.

Pancreas Transplantation

Moderator: Mr Argiris Asderakis

P118

Utilizing Older Donors In Pancreas Transplantation

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Introduction: An increased demand for donor organs has led to the transplantation of organs previously considered to be 'marginal'. Donor age is the most common reason for classifying the grafts as 'marginal' and here we analyse the effect of donor age >45 on outcomes in pancreas transplantation.

Methods: 267 pancreas grafts were retrieved from donors after brainstem death between Apr 2004 and Oct 2009. 197 of these donors were aged <45 (YD), the remaining 70 being older donors (OD). All pancreatic grafts were implanted intraperitoneally with enteric exocrine and systemic venous drainage. Retrospective analysis with particular focus on graft, patient outcomes and complication rates was performed.

Results: The OD group consisted of 60SPK, 6PAK and 4 PTA transplants. The YD group consisted of 156 SPK, 25 PAK and 16 PTA transplants. Median follow up was 23 months in the OD group and 29 months for YD. Donor age in YD was 30 $\pm$10 and 53 $\pm$5 in OD. Recipients in YD were significantly younger (43±7) compared to OD (47±8) (P=0.0001) to allow for donor age matched transplantation. There was little difference in donor BMI; 24±8 (OD) vs. 25±3. There was no significant difference in the incidence of DGF of either kidney (11.6% in OD vs. 10.2% in YD) or pancreas (2.8% in OD vs. 1.5% in YD). Primary non-function was significantly more common in the OD group for pancreas (5.7% vs. 0.5% in YD P=0.01) and kidney (5% vs. 1.6% p=NS) despite similar cold ischemia time (684±180min vs. 690±136min). Median hospital stay for YD recipients was similar to OD recipients (14 (7-88 days) vs. 14(7-91 days)), as was the re-admissions (18% vs. 24%), rejection (16% vs. 7% p=0.06) and re-operations (24% vs. 20%). Overall pancreas (83% vs. 89% p=ns), kidney (91% vs. 90%) and patient survival (95% vs. 96%) of YD vs. OD were similar. Where SPK transplants were performed, pancreatic graft survival was 93.8% in OD compared with 99.4% in YD.

Conclusions: The use of older donors in pancreas transplantation may be associated with an increased incidence of primary non-function of pancreas or kidney (when transplanted simultaneously). Despite this, use of older donors is not associated increased risk of other complications and they may provide a valuable source to combat the current donor shortage.

P119

The Effect of Increased Recipient Age on Outcomes in Pancreas Transplantation

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Introduction: With surgical advances and improved outcomes in pancreas transplantation (PTx), the criterion for listing patients for transplantation has been liberalised. One such example of this is the listing of older patients for PTx. Here we analyse the results of PTx in elderly recipients (ER, age >50 years) to assess if this is associated with adverse outcomes.

Methods: 267 Pancreas transplants were performed between March 2004 and October 2009 from donors after brainstem death. All pancreatic grafts were implanted intraperitoneally with enteric and systemic venous drainage. Retrospective analysis of these cases was performed focusing on graft and patient outcomes, in addition to morbidity in comparison with younger recipients aged 50 or less (YR).

Results: 216 SPK, 31 PAK and 20 PTA were performed in this period. The ER group consisted of 49 recipients (39 SPK, 6 PAK and 4 PTA) with the remaining 218 in YR (177 SPK, 25 PAK and 16 PTA). YR had longer median follow-up (29 months) in comparison to ER (23 months). Average recipient age was 55 +4 years in ER compared with 41 +6 years in YR. Mean donor age in ER was 41 +14 compared with 35 +13 in YR in an attempt to age-match organs to recipients. Minimal difference was noted in complication rates between the ER and YR groups; with venous graft thrombosis occurring in 4.1% and 4.6% respectively and re- operation in 32.7% and 20.6% (p=NS) respectively. Crucially, there was little difference in hospital stay (median 16 days in ER and 14 in YR). Rejection was numerically more common in YR (10.2% in ER vs. 14.2% in YR, P =0.6). CMV PCR positivity was more common in the ER group (6.1% vs. 2.8% in YR). No grafts or patients were lost due to infectious complications in ER. Delayed graft function of pancreas and kidney in the ER group occurred in 2% and 10.2 % cases compared with 1.8% and 8.3% in YR group (P= NS). Survival rates of patient pancreas and kidney were 85.7% and 93.9% in ER vs. 84.9 % and 95.4% in YR (P=NS).

Conclusions: Pancreas transplantation in older recipients is associated with good graft and patient outcome when compared to younger recipients. Elderly recipients appear to be at greater risk of CMV in the early post- operative period and an awareness of this in monitoring and prophylaxis is essential to optimize graft and patient survival.

P120

Renal function after pancreas transplant in Type 1 diabetics: a 1-year follow-up study

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BACKGROUND: The post-transplant changes in the renal function are an important parameter in the selection process of patients listed for a pancreas transplant. All recipients, irrespectively of the type of transplant, pancreas alone (PTA) or pancreas after kidney (PAK), almost always suffer from a degree of subclinical diabetic nephropathy. Additionally, the renal function is affected by the use of nephrotoxic drugs, such as the calcineurin inhibitors. Published data has suggested that renal function may deteriorate after PAK or PTA and pre-transplant eGFR of 60-70 ml/min/1.73 m^2 has been proposed as an estimated level below which the renal function may be significantly affected.

AIM: The purpose of our study was to investigate any deterioration in the renal function after pancreas transplant and especially in patients with borderline initial eGFR.

METHODS: Our sample consisted of 59 patients, with a mean age of 43.2±8.66 years at the time of the operation, who received a pancreas transplant, PAK or PTA, in our unit between 01/2005 and 01/2009. Creatinine and eGFR levels pre-transplant and at 3, 6 and 12 months post-transplant have been analysed retrospectively.

RESULTS: Three months after transplant, a statistically significant increase in the eGFR ($p=0.030$) of the patients was identified, while a trend was revealed in the decreasing creatinine levels ($p=0.056$). Both levels at 6 and 12 months post-transplant were not significantly different. In the PTA sub-group (n=24), no significant differences were found in either creatinine or eGFR levels at any point of follow-up. In the PAK sub-group (n=35), an overall decrease in the creatinine levels after transplant was noticed, which reached statistical significance only 3 months after the operation ($p=0.023$), while the concomitant increase in the eGFR reached statistical significance at 3 ($p=0.016$) and 12 months ($p=0.036$) after transplant. Furthermore, the patients were divided into two sub-groups, based on eGFR levels of greater or less than 45 ml/min/1.73 m^2 before the time of the operation. Analysis of the results of the high eGFR sub-group showed no significant differences in the levels of creatinine and eGFR. Even more interestingly, in the low eGFR sub-group, creatinine was found to significantly reduce and the eGFR to significantly increase at 3 ($p=0.030$ and $p=0.014$ respectively) and 6 months ($p=0.017$ and $p=0.010$ respectively) post transplant. No significant difference was found in the two parameters at 12 months after the operation.

CONCLUSIONS: Our results suggest that renal function does not deteriorate after pancreas transplant. On the contrary, it was found significantly improved in the PAK patients 12 months after their operation. Improved renal function initially was also noticed in post-transplant patients with a pre-transplant eGFR level below 45 ml/min/1.73 m^2, which returned to non-significant levels 12 months after the operation, while no difference was found in patients with a pre-transplant eGFR level above 45 ml/min/1.73 m^2

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Perioperative Management and Morbidity & Mortality associated with Pancreas Transplants.

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Background:

Pancreas transplant offers a potential cure for patients with Type1 diabetes with freedom from insulin. Our unit is one of the largest in the U.K. performing 30-40 pancreas transplants per year. The aim of this retrospective observational study was to look at the perioperative management, 30 day morbidity and mortality and critical care and in-patient length of stay.

Methods:

Data was collected retrospectively from April 2008 to March 2009.

Results:

31 patients (18 male, 13 female) had a pancreas transplant out of which 20 (65%) had a simultaneous pancreas/kidney transplant, 8(25%) a pancreas after kidney transplant and 3(10%) a pancreas transplant alone. The median age was 47 years (range: 28-63 years), median BMI 26 (range 19-31) and all patients were ASA 3. 25 patients (80%) had a pre-operative myocardial perfusion scan of which 10 were abnormal but did not require further investigation or coronary angiography. The cold ischaemia times were 10-12hrs in 7%, 12-14hrs in 23% and >14hrs in 70% of patients.

Intraoperative haemodynamic monitoring included continuous IABP and CVP monitoring in all patients with the Oesophageal Doppler monitor used in 4 patients to guide fluid therapy.

An epidural was used in 24 (78%) patients and Fentanyl PCA in 7(22%) patients for post-operative pain relief. 24 (78%) patients were extubated immediately post-op and nursed in a Critical Care Unit. Immediate post-op extubation was not possible in 7 (22%) patients due to prolonged surgery, bleeding or a late surgical finish.

30 day cardiovascular, respiratory and bleeding morbidity rates were 8(25%), 10(32%) and 14(45%) respectively. Transplanted pancreas or kidney dysfunction occurred in 14(45%) and 7(22%) respectively. The relaporotomy rate was 30% (9 patients) with 19% (6 patients) undergoing pancreatectomy. Median length of stay in critical care was 5 days (range 2 -98) and in hospital was 19 days (range 10-98). There was 1 death at 28 days.

Conclusion:

Pancreatic transplantion is associated with significant morbidity as highlighted by this study. Rigorous patient selection and a multidisciplinary approach to perioperative management is the key to a successful outcome. We have introduced perioperative management guidelines to improve outcome in this group of patients. Regular audit and appraisal of current practise will be crucial to ensure delivery of a high standard of care for a specialised service.

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Surgical challenges post pancreas transplantation. A single centre experience.

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Introduction: Complications after pancreas transplantation still remain high. Several recipients may require repeat surgery for various indications.

Objective: To review major surgical complications and their management after pancreas transplantation in our centre.

Methods: 193 pancreas transplants were performed in our centre between June 2001 and November 2009. Clinical data were collected prospectively into an electronic database (Microsoft Excel). All surgical complications, their management and outcomes were analysed.

Results: Two recipients had intra-operative ischemia of the head of pancreas. One underwent resection of the head with direct ductal implantation to the bladder. The other had percutaneous pancreatic ductal drainage. Duodenal necrosis developed intraoperatively in two patients. The duodenum was excised in both cases and the ducts directly anastomosed to the bladder. Both patients underwent staged enteric conversion. Two patients developed severe haematuria following transplantation requiring urgent enteric conversion, one led to a further severe native pancreatitis. In the longer term complication one patient developed a chronic transplant pancreas pseudo-cyst which was drained into the bladder. A second patient had stenosis of a duodeno-cystostomy with duodenal perforation. A bladder drained kidney pancreas recipient whose kidney failed developed a vesico-cutaneous pancreatic fistula leading to severe skin maceration managed by duodeno-cystic disconnection and enteric drainage.

Conclusion and discussion: Complications after pancreas transplantation may cause significant morbidity. Their management requires innovative decision making based on standard surgical principles.

P123

Incidence, Management and Outcome of Surgical Complications Following Simultaneous Pancreas-Kidney Transplantation in a UK Centre

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AIMS Simultaneous pancreas-kidney transplant (SPK) is the most common transplant involving the pancreas, and remains the gold standard treatment for uraemic patients with type 1 diabetes who are fit enough to undergo major surgery. However, implantation of the pancreas carries a significantly higher risk of surgical complications (reported as high as 38%) than kidney transplantation alone, including intra-abdominal haemorrhage and collections, vascular thrombosis and donor duodenal segment (DS) leak or necrosis. Our aims were to establish the incidence of surgical complications after SPK transplantation and determine the effect of these complications on graft and patient survival.

METHODS Details of all SPK transplants performed at our centre were recorded onto a computerised database. Outcomes (immediate post-operative, 1-year and 5-year) were compared between patients who experienced no surgical complication (NSC) and those who did experience a surgical complication (SC).

RESULTS Since 1996, there have been 190 SPK transplants performed in our centre. Median recipient age was 39, and 25% of patients were pre-dialysis (no significant difference between the NSC and SC groups). Mean daily insulin requirement was higher in the SC group (48 vs 40 units, $p=0.02$). Median donor age was 32, and median cold ischaemic time was 12 hours (pancreas) and 14 hours (kidney) (no significant difference between the NSC and SC groups). 51% of patients had bladder and 49% had enteric exocrine drainage (excluding subsequent bladder to enteric conversions, no significant difference between the NSC and SC groups). There was no significant difference in the incidence of pancreatic or kidney delayed graft function between the 2 groups. 40 patients (21%) experienced a surgical complication. 35/40 patients required a median of 2 repeat laparotomies (11 patients of which required a laparostomy) and 5/40 patients required radiologically-guided percutaneous drains. 24 patients had intra-abdominal collections; a DS leak was identified in 7 patients. 4 patients underwent graft pancreatectomy (3 for venous thrombosis, 1 for DS necrosis), 1 of whom simultaneously underwent transplant nephrectomy. 3 patients required a repeat laparotomy for haemorrhage. 4 patients developed a pancreatic or entero-cutaneous fistula. Median hospital stay was higher in the SC group (47 vs 16 days, $p<0.001$). Overall 1-year pancreatic graft survival was 90%, and this was lower in the SC group compared to the NSC group (74 vs 94%, $p=0.004$). Overall 5-year pancreatic graft survival was 74% (no significant differences between the NSC and SC groups). Overall 1- and 5-year kidney graft survival was 96% and 82% and overall 1- and 5-year patient survival was 96% and 87% (no significant differences between the NSC and SC groups).

CONCLUSIONS Surgical complications following SPK transplantation have a significant morbidity and adversely affect early pancreatic graft survival. However, with appropriate surgical, radiological and critical care management, complications such as DS leak and intra-abdominal sepsis do not affect long-term graft or patient survival.

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Managing upper gastrointestinal bleeding in the enterically drained pancreas transplant

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Introduction

There are increasing reports of upper gastrointestinal (UGI) bleeding after enterically drained pancreas transplantation. In most cases this occurs in the early post-operative period and is usually from the duodeno-jejunal anastomotic line. There is little literature describing how best to manage such bleeds, particularly in the early post-operative period when bleeding rates appear highest. We propose a strategy for the management of all UGI bleeds in the enterically drained pancreas transplant and report the outcomes before and after the development of our protocol in all the pancreas transplants performed in our unit.

Methods

We performed a retrospective analysis of all pancreas transplants performed during the first five years of our programme and identified all cases with significant post-operative bleeding that returned to the operating room. We identified which of these cases had bled from the duodeno-jejunal anastomotic line. We then developed a protocol for any post operative UGI bleeding after pancreas transplantation and reviewed all subsequent pancreas transplants that had an UGI bleed to identify which of these patients had to return to the operating room for revision surgery.

Results

266 pancreas transplants were performed during the first 5 years of our programme. 26/266 (9.7%) patients had a major post-operative bleed that required a return to the operating room. 3/26 had an UGI bleed with evidence of bleeding from the duodeno-jejunal anastomotic line requiring revision of the anastomosis. Following the development of our management strategy we have seen 2 post-operative UGI bleeds in 51 pancreas transplants. Both patients settled conservatively and did not need to return to theatre for revision of the anastomosis.

Conclusions

UGI bleeding is a recognised complication after pancreas transplantation with enteric drainage. Our management strategy involves withdrawing anticoagulation, starting intravenous omeprazole, blood transfusion and UGI endoscopy to exclude a gastric source. In the absence of a true native UGI source, patients return to theatre at 48 hours for revision of the duodeno-jenual anastomosis if there is ongoing bleeding. Since its development we have seen only 2 UGI bleeds which settled conservatively within 48 hours. We believe this approach ensures safe management of potentially life threatening bleeding without compromising the pancreatic graft.

P125

Cardiopulmonary Exercise Testing (CPET) as a pre-operative assessment tool in Simultaneous Pancreas and Kidney transplantation (SPK)

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Introduction - SPK offers patients with Type 1 Diabetes Mellitus complicated by renal failure improved survival and quality of life. Patients undergoing SPK surgery are at high risk of cardiac morbidity and mortality (approximately 6% at one year[1]). All patients score at least 3 on Lee's Revised Cardiac Risk Index[2] (surgery, insulin treated Diabetes and renal failure). Cardiopulmonary Exercise Testing (CPET) is an established clinical test used worldwide to assess functional capacity and to evaluate cardiac and pulmonary disease. Pre-operative CPET is able to identify patients at increased risk of post-operative mortality following major vascular and abdominal surgery. There is currently no published data examining the role of pre-operative CPET in the SPK patient population.

Method - Since July 2008, CPET has become a routine investigation at Manchester Royal Infirmary, alongside stress cardiac imaging for the routine work-up of patients prior to being activated on the SPK transplant list. During this period we have performed CPET on 42 consecutive patients being assessed for SPK transplantation. A maximal incremental CPET test on a cycle ergometer was used for all patients, with anaerobic threshold determined using the V-slope and/or ventilatory equivalent method.

Results - Patients showed reduced functional capacity (both Peak VO_2 and Anaerobic Threshold)as compared to predicted values (Table 1). 22 (52.4%) patients had an anaerobic threshold of < 11ml/kg/min of whom 6 (14.3%) also had known reversible ischaemia on myoview. Only 14 (33.3%) patients achieved > 80% of predicted peak heart rate.

Table 1

Age (years)	42 (8.6)
Sex	26M:16F
Anaerobic Threshold (ml/kg/min)	11.1 (2.2)
Peak VO_2 (% predicted)	55 (14.1)
Anaerobic Threshold (% peak predicted VO_2)	35.1 (10.2)
Eq CO_2 at Anaerobic Threshold	29 (3.5)
Maximum Heart Rate (% predicted)	83.4 (8.4)

Values are mean (SD)

Conclusions

Patients undergoing SPK transplantation are at high risk of perioperative cardiac morbidity and mortality . As demonstrated in other forms of major surgery preoperative CPET can identify patients at increased risk of peri-operative mortality. Preoperative CPET therefore has the potential to identify those patients being considered for SPK who are at highest risk of post-operative cardiac morbidity and mortality. This will provide further information to improve patient selection, improve patient risk stratification and allow for a more informed consent process for patients.

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2. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major non cardiac surgery. *Circulation.* 1999;100:1043-49.

P126

Imaging of complications following pancreatic transplants: a pictorial review

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Background: Pancreatic transplantations are increasingly being performed for the treatment of type 1 diabetes mellitus. To date, more than 23000 pancreatic transplantations have been performed worldwide.[1] Pancreatic transplantation is a major operation with significant associated mortality and morbidity. Long-term advantages of transplantation have to be balanced against the potential morbidity and mortality associated with the surgical procedure itself and long-term immunosuppression requirement.

Imaging is often employed by the clinical team to assist in the assessment of the post-operative pancreatic transplant patient. Radiology has both a diagnostic and interventional role in the management of complications following pancreatic transplantation.

Aim: In this pictorial essay, we will aim to discuss imaging modalities that may be used to assess for complications following pancreatic transplantation. We will also describe imaging findings of various pancreatic transplant complications and review the role of image guided intervention in these patients.

Content: We will present multimodality (computed tomography, magnetic resonance, ultrasound, fluoroscopy and catheter angiography) images of complications including :

- Parenchymal
  - Rejection
  - Pancreatitis
- Enteric leaks and fistulation
- Peripancreatic
  - Lymphocoele
  - Abscess
  - Haematoma
  - Pseudocyst
- Vascular
  - Thrombosis
  - Haemorrhage
  - Pseudoaneurysm

Summary: Imaging has a role in the assessment of complications following pancreatic transplantations. However, correlation with clinical findings is necessary as early complications such as graft pancreatitis or rejection may be associated with normal or non-specific imaging findings.

1. International Pancreas Transplant Registry.*www.med.umn.edu/ipt Accessed October 2009.*

Science

Moderator: Mr Luke Devey

P127

Monocytosis is associated with transplant ischaemia reperfusion injury

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Introduction. Recent evidence suggests a role for monocytes in the pathogenesis of ischaemia reperfusion injury in myocardial infarction- being mobilised *en masse* from a resting pool in the spleen 24 hours after injury[1]. We hypothesised a similar systemic response might be elicited after renal transplantation using kidneys donated after cardiac death (DCD).

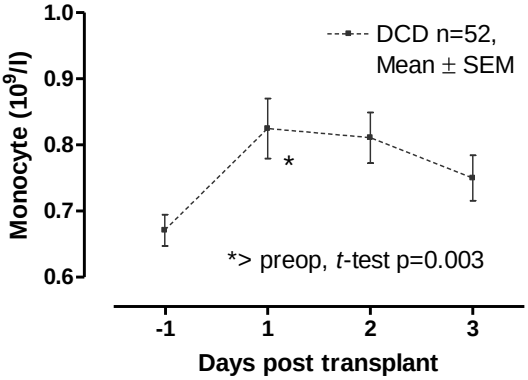
Methods. We reviewed the records of 128 consecutive kidney transplants (Oct 07 to Oct 09) from DCD (n=52) and live donors (LD, n=76) and correlated peripheral blood monocyte (PBM) counts with renal function.

Results. PBM counts were significantly elevated day 1 after DCD transplantation (mean 0.81 vs. 0.67 pre-op, *t*-test p=0.003), but not after LD transplantation. Renal function on day 1 post transplant was significantly worse from DCD donors (serum creatinine DCD 611 vs. LD 295 mmol/l, p<0.0001). A significant correlation was evident between graft function and PBM counts on day 1 (p<0.0001), which diminished over the next 2 days.

Conclusions. PBM counts are elevated early after renal ischaemia reperfusion injury and associated with graft dysfunction.

Reference 1 Swirski FK et al. Science 2009; 325: 612-616

Figure 1.



P128

A novel role for TonEBP in inflammatory renal lymphangiogenesis

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Introduction:

We have previously demonstrated *de novo* lymphangiogenesis in failing human renal allografts (Transplantation 2007) and in a rat allograft model of interstitial fibrosis and tubular atrophy (BTS 2009). Recent work has indicated that macrophage expression of the lymphangiogenic growth factor VEGF-C is regulated by the transcription factor TonEBP that responds to changes in tissue tonicity (Machnik et al *Nat Med* 2009). The aim of this study was to examine both the kinetics and pathogenesis of *de novo* lymphangiogenesis in the rat model of unilateral ureteric obstruction (UUO). The UUO model develops interstitial fibrosis much more rapidly than experimental transplantation and may provide insights relevant to the chronic changes that are seen in renal allografts.

Materials and Methods:

Male Sprague-Dawley rats (300g) underwent UUO and were sacrificed at one, two and three weeks (5 rats per group). Tissue was immunostained with podoplanin and prox-1 (lymphatic markers) and ED-1 (rat macrophage marker). Expression of VEGF-C and the transcription factor TonEBP (tonicity enhanced binding protein) was determined by real time quantitative PCR.

Results:

A significant increase in the number of lymphatic vessels was evident in obstructed kidneys at all time points compared to normal control tissue with a 12-fold increase in lymphatic vessel number evident at the 3 week time point. Vessels were confirmed as lymphatics by staining with both podoplanin and Prox-1. The *de novo* lymphangiogenesis associated with UUO was present in the interstitium; an area normally devoid of lymphatic vessels. Significant lymphatic proliferation was demonstrated by dual immunofluorescence with podoplanin and PCNA. Expression of VEGF-C and TonEBP was markedly elevated in obstructed kidneys. Infiltrating macrophages expressed with VEGF-C. Immunofluorescent staining indicated expression of VEGF-C by ED1 positive macrophages.

Conclusions:

These studies indicate involvement of TonEBP in the lymphangiogenesis associated with renal inflammation and suggest that increased interstitial tonicity may be an important inducer of lymphangiogenesis via macrophage VEGF-C. The role of TonEBP in allograft-associated lymphangiogenesis merits study.

P129

Allograft Tertiary Lymphoid Organ Development Requires Humoral Immunity

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Introduction

Tertiary lymphoid organs (TLOs) are found at sites of chronic inflammation including solid organ transplants. The aim of the present study was to determine the role of B cells in their formation within cardiac allografts undergoing chronic rejection.

Methods

TLO formation was studied in bm12 hearts transplanted into B6 recipients; a model of allograft vasculopathy characterised by development of donor-T-cell-dependent effector autoantibody responses (Win TS et al 2009). Hearts grafts were excised after 40-50 days, sectioned and the presence of intra-graft TLOs confirmed by discrete aggregates of B220+ B cells and CD4+ T cells, associated with MECA-79+ high endothelial venules (HEV). The contribution of B cells to TLO formation was assessed by using, as recipients, either B6.□MT mice or rituximab-treated B6hCD20 (that express human CD20 on B cells).

Results

TLOs were detected in 9/10 allografts (mean 1.6 TLOs /graft). Although T cells were detectable, the TLOs were composed predominantly of B cells, typically with features of germinal centre-activity (follicular dendritic cell accumulation and staining for peanut agglutinin). $CD138^{+}$ plasma cells were also present and IgG secretion confirmed by ELISPOT of graft homogenate. Although a cellular infiltrate was evident, no TLOs developed in B cell deficient recipients (□MT or rituximab-treated B6hCD20 mice). To further examine the role of B cells in TLO development, bm12 donors were treated with depleting anti-CD4 antibody prior to heart graft retrieval. This abrogated autoantibody responses while maintaining the recipient B cell population; TLO formation was nevertheless reduced significantly (0.3/graft, p=0.008).

Conclusions

Intra-graft TLO development requires active humoral autoimmunity; neither naive B cells nor host T cell alloimmune responses are sufficient. The presence of germinal centres and IgG secreting plasma cells suggest that once formed, TLOs contribute to autoantibody-mediated allograft vasculopathy.

P130

The Effects of Hypoxia and Reoxygenation on Hepatocyte Reactive Oxygen Species Generation and Sensitivity to CD40 Mediated Cell Death.

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Background: During transplantation surgery the liver is exposed to periods of hypoxia and reoxygenation which result in inflammation and hepatocyte death as a consequence of ischemia-reperfusion injury (IRI). Hepatocyte injury can be driven by distinct mechanisms involving the production of reactive oxygen species (ROS) and activation of TNF receptors including CD40 which induces hepatocyte apoptosis when activated by its ligand, CD154. Studies in renal and cardiac transplantation suggest that CD40 activation influences graft survival but little is known about the relationship between CD40 activation and ROS generation in mediating hepatocyte apoptosis during IRI.

Hypothesis/Aims: Hypoxia and reoxygenation drive hepatocyte ROS production and sensitise cells to CD40 mediated apoptosis.

Methods: Human hepatocytes isolated from liver tissue using a two-stage collagenase perfusion technique were cultured for up to 48 hours under conditions of hypoxia and reoxygenation in the presence or absence of CD154 and/or mitochondrial inhibitors and antioxidants. Hepatocyte ROS production, apoptosis, autophagy and necrosis were determined by labelling cells with 2',7'-dichlorofluorescene, annexin, monodansylcadverine and 7-ADD respectively in a four-colour reporter flow cytometry assay.

Results: Hepatocytes increased ROS accumulation during hypoxia and reoxygenation resulting in increased apoptosis, autophagy and necrosis. Inhibition of ROS using rotenone, NADPH oxidase inhibitor, diphenyleneiodonium (DPI) or anti-oxidant *N*-acetyl cysteine (NAC) attenuated cell death. Co-incubation of hepatocytes with CD154 augmented ROS accumulation during normoxia and reoxygenation via a NADPH oxidase-dependent mechanism, further enhancing apoptosis. Pre-treatment with DPI abrogated CD154 mediated cell death demonstrating a link between ROS generation and CD40 mediated apoptosis.

Conclusions: CD40 activation increases ROS production via a NADPH-dependent mechanism leading to enhanced hepatocyte death. This novel finding suggests that inhibition of oxidative stress induced by CD154 may provide a potential avenue to limit ROS mediated allograft damage following liver transplantation.

P131

Endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS) and haem oxygenase-1 (HO-1) in liver ischaemic preconditioning

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Background. Liver ischaemia reperfusion (IR) injury is a major cause of morbidity and mortality in liver resection surgery and liver transplantation. Ischaemic preconditioning is where a short cycle of ischaemia and reperfusion protects against IR injury. Endothelial nitric oxide synthase (eNOS), iNOS and HO-1 has been implicated as mediators of ischaemic preconditioning in various models, but their roles and interactions are not well understood. This study sought to clarify the interactions and roles of eNOS, iNOS and HO-1 in early and late IPC protection against warm liver IR injury.

Methods. C57BL6 and eNOS knockout mice were used. Both groups of animals underwent inhalational anaesthesia and midline laparotomy. Ischaemia was induced by occluding the portal triad supplying the left lateral and medial lobes (70% ischaemia) using an atraumatic microvascular clip. Ischaemia was confirmed by change of colour of the cephalad lobes.

To study the early phase of IR injury, there were three groups for C57BL6 and eNOS knockouts.1. Sham laparotomy. 2. Liver ischaemia reperfusion (IR) only of 45 min ischaemia and 2 hours (hr) reperfusion. 3. Liver ischaemic preconditioning (IPC) (5 min ischaemia and 10 min reperfusion) immediately followed by IR (45 min ischaemia and 2 hr reperfusion). Another three groups of C57BL6 only were recovered at the beginning of reperfusion and killed 24 hr later to study the late phase of IR injury. Western blots (eNOS, iNOS, HO-1, phosphorylated-eNOS and caspase-3) and RT-PCR (HO-1) were done. H&E fixed sections were scored using the Suzuki classification. Serum ALT was measured.

Results. In C57BL6 (Wild type) mice, IPC of 5 min ischaemia/10 min reperfusion reduced early and late liver IR injury ($P<0.01$) and reduced histological injury compared to the IR only group ($P<0.01$). There was no significant difference ($P<0.05$) in serum ALT or histological scores with IPC compared to IR only in the eNOS knockout mice, although histological injury was worse in all groups compared to the wild type equivalent groups. In the wild types, eNOS and phosphorylated eNOS was upregulated most in the IR only, then the IPC group in early and late phases of injury. iNOS was significantly increased in the IR only group over the other groups in the wild types in late, but not early, IR injury and in the eNOS knockout mice. HO-1 was not detected on Western blots in wild types or knockouts in early IR injury, but HO-1 mRNA was detected in wild type and knockout groups in early IR injury. HO-1 protein was detected in late IR injury with highest levels in the IPC group.

Conclusions. eNOS is utilised by injurous and IPC pathways in liver IR injury. Different downstream pathways are activated by eNOS depending on the upstream signal. iNOS is injurous in late IR injury only. Activation of iNOS is inhibited by eNOS. HO-1 is expressed later than and independent of eNOS. HO-1 partly mediates IPC protection in late IR injury.

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Proteomic analysis in kidney transplantation – optimising protein extraction methods in urine samples.

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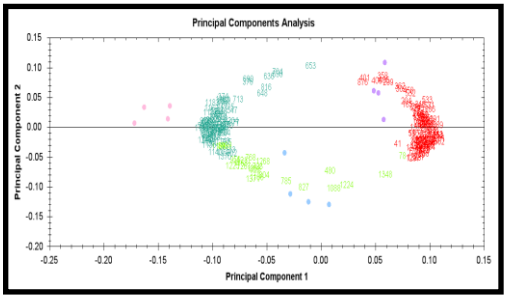
Early identification of problems following kidney transplants is critical in improving care for transplant patients. Analysis of the urinary proteome may help to detect problems earlier but the methods used are poorly standardized. Optimization of methods to ensure accurate quantification of protein abundance differences and allow focus on the molecular sub-populations of interest is essential since extraction procedures influence which sub-population of peptides / proteins will be analysed. Analysis of urine protein extraction methods has been performed in order to apply them to complications that occur in the early phase following kidney transplantation. Comparison of solid-phase extraction (SPE), spin concentration (SC) and solvent precipitation with 90% acetonitrile (ACN) has been performed by 2-dimensional difference in gel electrophoresis (2D-DIGE) using an internal standard design. Urine samples, after the addition of protease inhibitors, were filtered (70µm) and centrifuged at 2000g for 10minutes, before being split into three and processed by each method. Mean protein recoveries were: SPE 14.3%, SC 72.3%, ACN 65.2%. Of the 1049 gel features seen, 193 were significantly different between the methods (using $p<0.05$ and power >0.8). Principal Components Analysis (*Figure 1*) shows good separation of differing features which, when mapped to the gel profile, indicate that SPE tends to reveal more of the low molecular weight proteome, whilst 90% ACN precipitation reveals more of the high molecular weight proteome. This has implications for studies seeking to elucidate low molecular weight changes in the urinary proteome for biomarker discovery such as in renal transplant rejection. Furthermore, analysis of the supernatant in the ACN group by surface-enhanced laser desorption / ionisation mass spectrometry (SELDI-MS) revealed peptide profiles (<15kDa) suggesting this may itself represent an enrichment method for the low molecular weight proteome. These data emphasise the importance of clear methodological evaluation before techniques are applied to clinical samples, since extraction techniques influence the sub-proteome being analysed. These methods are now being applied to renal transplant patients.

Figure 1: Principal Components Analysis (red – ACN, turquoise – SPE, green – SC)



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