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The main entrance to the EICC is on Morrison Street where there is a coach drop off point.

There are a number of car parks within walking distance of the EICC, they are marked on the map. For further details on car parking please visit our website.

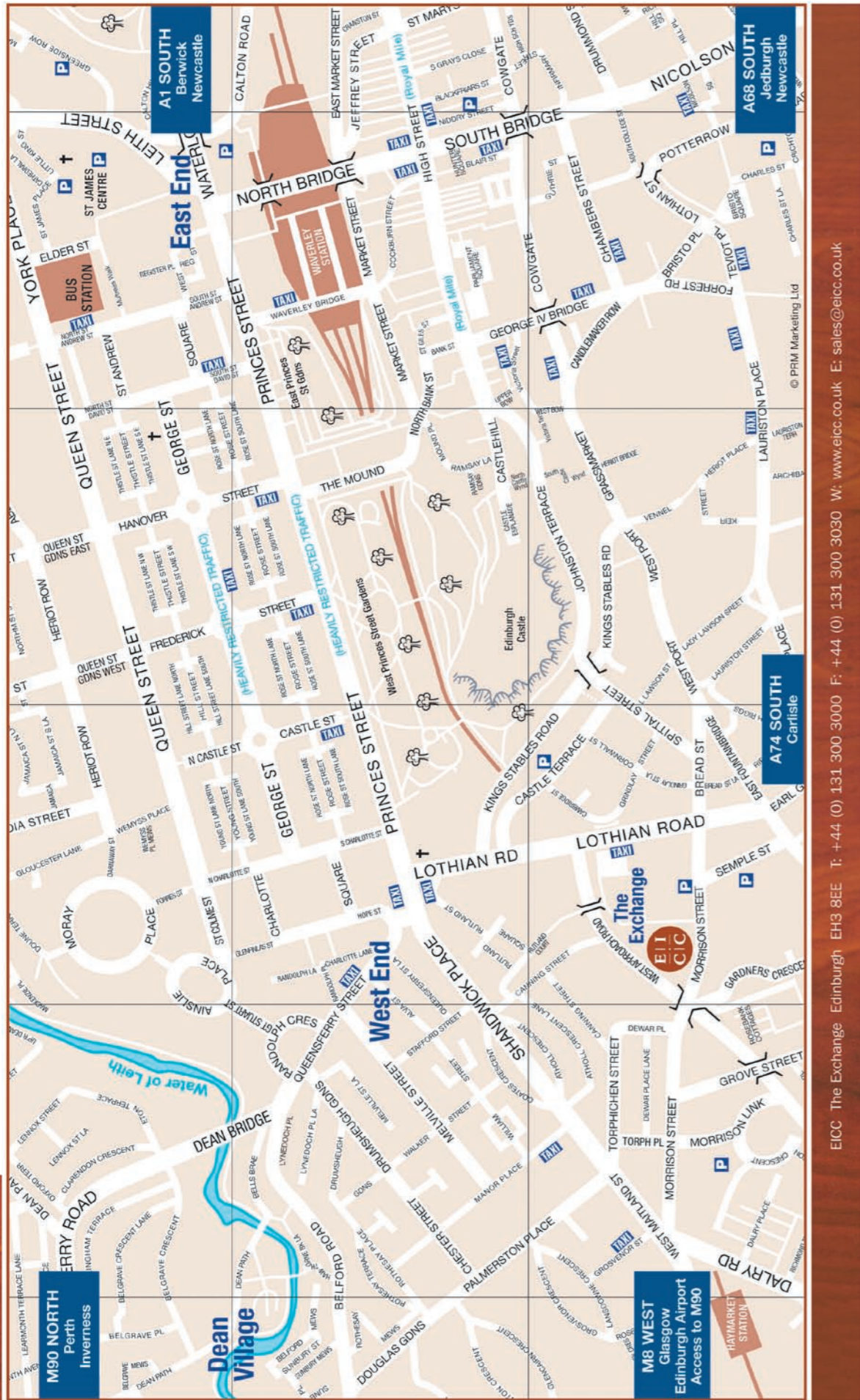
After 18.30 street parking is allowed in certain areas.

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BTS 9th Annual Congress 29 - 31 March 2006, Edinburgh

British Transplantation Society



9th Annual Congress
EICC, Edinburgh
29 - 31 March 2006



BRITISH TRANSPLANTATION SOCIETY OFFICERS

Executive

President: Mr John L R Forsythe (retires 2007)

Vice President: Mr Peter J Friend (presidency 2007)

General Secretary: Dr Wilson Wong (retires 2006)

Treasurer: Professor Stephen Powis (retires 2006)

Councillors

Mr Neil Parrott (2003 – 2006)

Dr Keshwar Baboolal (2003 – 2006)

Mr Christopher Watson (2004 – 2007)

Miss Lisa Burnapp (2004 – 2007)

Mr Keith Rigg (2005 – 2008)

Dr Christopher Dudley (2005 – 2008)

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Ethics: Mr Peter Rowe (retires 2006)

Standards: Dr Charles Newstead

Representatives

UKTCA: Mrs Rachel Stoddard-Murden

BSHI: Dr Robert Vaughan

Surgical Trainee: Mr Gabriel Oniscu

Archivist: Dr James Douglas

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BRITISH TRANSPLANTATION SOCIETY

9TH ANNUAL CONGRESS

29 – 31 March 2006

**The Edinburgh International Conference Centre
Edinburgh**

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BTS 9TH ANNUAL CONGRESS: 29-31 MARCH 2006
THE EICC, EDINBURGH

Welcome to Edinburgh

Welcome to the British Transplantation Society 9th Annual Congress in Edinburgh!

Edinburgh, capital of Scotland, is a cultured, cosmopolitan and thoroughly modern city. Edinburgh Castle, the striking centrepiece, sits astride a volcanic outcrop towering over the city. The gothic old town gives way to the open spaces of Princes Street, the modern city centre with beautiful gardens, galleries and shopping.



The Edinburgh International Conference Centre is located in the heart of the capital and within easy walking distance of hotels, pubs and shops. The raked seating auditorium is superbly equipped for scientific conferences and offers unparalleled flexibility for plenary and parallel sessions alike. It is set to enlarge even further with a £30m state-of-the-art multi-purpose expansion project to provide a further 2000 sq m of exhibition, meeting or function space.

Edinburgh also has a long history of transplantation with Sir Michael Woodruff performing the first successful kidney transplant in the UK in the old Royal Infirmary in 1960. Today, the transplantation unit is based in the new Royal Infirmary of Edinburgh, built on a greenfield site 3 miles south of the city centre. A large scientific facility developing on the same site promises to bring the interface of clinical medicine and basic science closer together, with exciting prospects for all.

We think that we have organised two varied and fun social events in the Caves and the Royal Museum of Scotland and we very much look forward to welcoming you there!

We hope that you have an enjoyable and successful meeting!

MURAT AKYOL
Local Organiser

LORNA MARSON
Local Organiser

Other Local Organisers: John Forsythe, John Casey, Ken Simpson, Steve Wigmore, Maureen Cunningham, Jen Lumsdaine, Donna Hill, Christine Jansen, Liz Waite, Karen Tuck, Rosanne Bate, Jackie Bradie, Gaby Oniscu, and Ewen Harrison

ACKNOWLEDGEMENTS

The British Transplantation Society would like to give special thanks to their Corporate Partners for their support throughout the year and during the Congress:

Gold Partners

Astellas
Novartis Pharmaceuticals

Silver Partners

Roche Products
Wyeth Laboratories

Bronze Partners

Dynal Biotech/Invitrogen
IVAX Pharmaceuticals
Genzyme

The abstracts for this meeting were kindly reviewed by:

Eleanor Bolton, Sue Martin, Wilson Wong, David Adams, Maggie Dallman, Nick Jones, Lisa Burnapp, Jen Lumsdaine, Paul Lear, Keith Rigg, Heather Tollerton, Chris Rudge, Steve Wigmore, Keshwar Baboolal, Gavin Pettigrew, Chris Watson, Giles Toogood and Ken Simpson

SPONSORSHIP

ASTELLAS

Delegate Wallets
Voting Devices – Ethics Session
Abstract Book (on CD)
Lanyards and Badges
Informal Social Event – The Caves
Travel Bursaries (x 7)
Pre-Meeting Liver Symposium

NOVARTIS

Internet Café
Informal Social Event – The Caves
Pre-Meeting Basic Science Symposium

ROCHE

Travel Bursaries (x 7)
Informal Social Event – The Caves

WYETH

Informal Social Event – The Caves

BRITISH TRANSPLANTATION SOCIETY
Company and Charity Annual General Meeting

Thursday 30 March 2006 (13.00 - 14.00)

EICC, Edinburgh

1. Welcome
2. Minutes of the last AGM held on 7 April 2005 (held as BTS Registered Charity No. 1098584
Company No. 4691176)
3. President's Report
4. Vice President's Report
5. General Secretary's Report
6. Treasurer's Report
 - a. Financial Report
 - b. Presentation of accounts (to be accepted by members)
 - c. Appointment of auditors –
To reappoint Mitchell Charlesworth as auditors to the Society from
1 November 2006 to 31 October 2007
7. 10th Annual Congress, Edinburgh
8. Any other business
9. Close of the meeting

By order of the Board of Directors

Date: 30 January 2006

Registered Charity Number 1098584
Registered Company Number 4691176

BRITISH TRANSPLANTATION SOCIETY

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

Thursday 7 April 2006 at 12.30, The Waterfront Hall Auditorium, Belfast

1 There had been no apologies received.

2 The minutes from the last AGM of the old charity held on 29 April 2004 were approved and accepted as a true record of the meeting.

It was noted that in the minutes from the last AGM of the new charity also held on 29 April 2004, that there were 5 lines missing from the printed version in the abstract book. This missing information related to the joint congress being held in Belfast. The minutes were then accepted as a true record of the meeting.

3 President's Report

3.1 ATC and ESOT bursary scheme

BTS Gold Corporate Partners, Astellas (previously Fujisawa) and Novartis had agreed to support a bursary scheme to be administered by the BTS for its members to attend both the ATC and ESOT meetings in 2005. As time was limited Council members were made aware of the plans and were given opportunity to comment on the proposed scheme. Phil Dyer had been leading on this initiative following Executive consultation.

The first round of the scheme to send members to attend the ATC meeting in Seattle was reported to have been successful. The bursary included registration to attend the meeting, accommodation and a cash travel grant. It was noted that a protocol for awarding the bursaries in the future would be drafted by Council before the ESOT application deadline.

The Gold Corporate Partners were thanked for their support in providing this scheme and for allowing the BTS to administer it.

3.2 Human Tissue Act

A document from the Department of Health website was distributed to members at the AGM and the key points were highlighted. Regulations for the Human Tissue Act would be drafted and sent out for consultation in the summer. Thereafter codes of practice would be drawn up as operative guidelines. A consensus protocol on how to move forward was being discussed at a UKT meeting in June. This would be an opportunity for the BTS to comment on the codes.

It was also noted that Keith Rigg had been appointed a member of the Human Tissue Authority.

3.3 UK Transplant

The new authority NHS BT had been formed with a merging of UK Transplant and the National Blood Authority. A Chair would be appointed at the end April, followed by its Board members in May and the Chief Executive would be appointed and announced. The BTS had been invited as a stakeholder group. It was stressed that transplantation must be recognised and well represented in the new group.

4 Vice President's Report

4.1 UK & Ireland Liver Transplantation meeting

The UK & Ireland liver transplantation meeting in Leeds had been very successful. It had formally become a part of the BTS as a Society Forum.

4.2 Pancreas transplantation

A first meeting of the pancreas transplantation group was also reported to have been a success. It was hoped that it would be run on a regular basis and may require some level of support from the

Society.

4.3 Review of constituent parts

The Society had undertaken a review of each of its constituent groups and this initiative was being led by a number of individuals in each sub-group. The review was looking at basic science; transplant surgery; liver transplantation; transplant coordinators/nurses; tissue typing; cardiothoracic; and nephrology.

5 **General Secretary's Report**

5.1 Election results

The elections had again been run by the Electoral Reform Services (ERS). There had been 38.4% ballots returned by the Society. The vote had been done by Single Transferable Voting.

The results were as follows:

Vice President (1 position)	<i>First pref</i>	<i>Exclusion of Lear</i>	<i>Exclusion of Koffman</i>
<u>Peter Friend</u>	98	102	132
Geoff Koffman	65	76	
Paul Lear	39		
Stephen Powis	73	86	115

Councillors (2 positions)	<i>First pref</i>	<i>Excl Muiesan</i>	<i>Excl Maxwell</i>
John Casey	38	39	42
<u>Christopher Dudley</u>	45	47	53
Nicholas Jones	27	28	34
Nizam Mamode	35	38	40
Heather Maxwell	24	25	
Paulo Muiesan	20		
Raj Prasad	29	36	38
<u>Keith Rigg</u>	55	60	64

Councillors (2 positions)	<i>Excl Jones</i>	<i>Excl Prasad</i>	<i>Excl Mamode</i>	<i>Excl Rigg</i>
John Casey	46	53	59	63
<u>Christopher Dudley</u>	58	63	72	74
Nicholas Jones				
Nizam Mamode	45	50		
Heather Maxwell				
Paulo Muiesan				
Raj Prasad	40			
<u>Keith Rigg</u>	71	81	94	75

Training (3 positions)	<i>First pref</i>	<i>Excl LAM</i>	<i>Surplus Augustine</i>	<i>Excl Soomro</i>
<u>Titus Augustine</u>	76	76	60.75	60.75
<u>Matthew Bowles</u>	51	53	57.16	70.16
<u>Simon Bramhall</u>	44	46	50.16	56.98
Nadey Hakim	36	39	41.08	46.86
FT Lam	10			
Naeem Soomro	26	29	33.68	

Ethics (3 positions)	<i>First pref</i>	<i>Surplus Baboolal</i>
<u>Keshwar Baboolal</u>	93	63.5
<u>Jen Lumsdaine</u>	53	64.6
Vassilios Papalois	19	28.2
<u>Peter Rowe</u>	69	69
Kenneth Simpson	20	28

5.2 Membership

The total current membership stood at 779 full members and 29 associate members. There had been

76 new applications made up to 31 January– a list of names could be found in the abstract book. 59 more new applications were made since then – a list of names were presented at the AGM.

5.3 Abstracts

There had been 400 abstracts submitted for the joint congress with the BTS and Renal Association. Of the 371 abstracts that were accepted, 112 were orals and 261 were poster presentations.

5.4 Awards

There had been 9 applications made for the two clinical Research Fellowships sponsored by Fujisawa and Novartis. Short-listed candidates for interview would be notified after the annual meeting. There would also be a non-clinical PhD Studentship award and there had been 4 applications made. There were two applications made for two available Travelling Fellowships.

5.5 Bids

A bid from Glasgow and one from Liverpool had been received to host the 2008 annual congress. The Executive and Council had selected Glasgow as the 2008 venue.

A call for bids to host the annual congress in 2009 was made. The deadline for proposals was 31 August.

6 Treasurer's Report

6.1 Financial report

It was noted that the costs for this joint meeting were substantial and posed an element of high risk to the Society. Expenses were estimated to be around £250 000. The main income was from the registration fees and these had been set on past patterns and in line with the Renal Association's previous meetings. Fees had been kept low for reduced and normal members who registered before the early registration deadline. Onsite fees were set high to encourage more members to register early. A bursary scheme had been put in place and nearly all applicants were awarded funds. This scheme will again be run in 2006 and members were encouraged to take these up.

6.2 Presentation of accounts

Summary accounts had been distributed at the AGM. Full accounts were available from the secretariat. It was noted that as this was the first financial year as the new charity there were no previous accounts to compare these with. The key figure was the unrestricted funds which were at £85 000. This had been further split into designated (committed for a future purpose) and general funds. The unrestricted undesignated funds were at £25 000 which was too low for the Society. The auditors had suggested that these should be at a level of £85 000.

These accounts were accepted and approved by the members.

6.3 Appointment of auditors

The Executive and Council had decided to reappoint Mitchell Charlesworth as the auditors for the Society for the period 1 November 2005 – 31 October 2006. There were no objections received by the members.

7 2006 Congress: Edinburgh

The meeting would be held from 29-31 March at the Edinburgh International Conference Centre (EICC) in Edinburgh. Murat Akyol and Lorna Marson were co-chairing the local organising committee. It was reported that the scientific programme was well under way and the social events had been completely organised.

There would be a basic science symposium held the day before the congress begins and would be

8 Any Other Business

Phil Dyer thanked the organisers of the 2005 joint congress; the Society for its support; the corporate partners; Triangle Three for their administrative support; and the Executive who had helped him through his presidency.

The two recently retired Councillors, Peter Andrews and Anthony Warrens, as well as the Training Committee chair, David Mayer, were all also thanked for their time given to the Society.

John Forsythe then made special thanks to Phil Dyer for this hard work and passion to transplantation and the Society over the years.

The BTS Applications for Membership

(to 23rd January 2006) 63 applications received

Candidates' sponsors are given in brackets

Agarwal, Kosh (D Talbot, D Manas): Freeman Hospital, Newcastle
Asthana, Sonal (N Ahmad, K Prasad): St James's University Hospital, Leeds
Barnard, James (K Poulton, S Sheldon): Wythenshawe Hospital, Manchester
Besarani, Dler (D Gray, S Fuggle): Oxford Radcliffe Hospitals, Oxford
Bhati, Chandra Shekhar (S Bramhall, D Mirza): Queen Elizabeth Hospital, Birmingham
Borchert, Dietmar (J A Bradley, R Praseedom): Addenbrooke's Hospital, Cambridge
Broderick, Andrew (R Stoddard-Murden, P Rowe): South West Transplant Co-ordinators, Plymouth
Brown, Roberta (J Routledge, J Muiesan): Kings College Hospital, London
Byrne, Catherine (R Ravanan, C Dudley): Southmead Hospital, Bristol
Cunningham, Maureen (J Lumsdsaine, K Tuck) Royal Infirmary of Edinburgh
Devlin, Robert (N Mamode, R Hilton): Guy's Hospital, London
Evans, Martha (N Hamilton, C Dudley): Southmead Hospital, Bristol
Fronek, Jiri (R W S Chang, I A M MacPhee): St George's Hospital, London
Gerstenkorn, Clemens (A K Hemandas, Z Zarka): Belfast City Hospital, Belfast
Glover, David Andrew (K Baboolal, R Moore): University Hospital, Wales
Guerreiro, Diamantino (M Zilvetti, D Roy): John Radcliffe Hospital, Oxford
Gunda, Smita (P Cockwell): Heathlands Hospital, Birmingham
Hamsho, Ahmed (A Asderakis, R Chavez): Harborne, Birmingham
Harper, Jennifer (A J T George, T Dorling): Imperial College, London
Heathcote, John (M Roberts, D Cook): Cardiff Royal Infirmary, Cardiff
Hubner, Louise Lesley (R Bowden, D Cunningham): Nottingham City Hospital, Nottingham
Jamieson, Russell William (M Zilvetti, P J Friend): John Radcliffe Hospital, Oxford
Jewitt-Harris, Jennie (S Ball, R Ready): Camberley
Jobson, Shirley (D Briggs, D Atkinson): National Blood Service, Birmingham
Jones, Stephanie (I Qureshi, A Stewart): Manchester Royal Infirmary, Manchester
Kanji, Hemali (S Kashi, P T Lam): University of Warwick, Coventry
Kelly, Lesley (L Buist, E McGregor): Western Infirmary, Glasgow
Khan, Adnan (A J T George, T Dorling): Imperial College, London
Kingsmore, David (L J Buist, R S C Rodger): Western Infirmary, Glasgow
Kubal, Chandrashekhar (R Bates, P Cockwell): University of Birmingham, Birmingham
Kumar, Avneesh (A Bakran, A K Sharma): Royal Liverpool University Hospital, Liverpool
Leegood, Emma (M Bowles, R Girlanda): Kings College Hospital, London
Lycett, Angela Elizabeth (M L Nicholson, M Brophy): Leicester General Hospital, Leicester
McCready, Gillian (A Ready, G Lipkin): Queen Elizabeth Hospital, Birmingham
McManus, Ciara (M Dunn, M Rose): University College Dublin, Ireland
Mistry, Natu (M L Nicholson, M Brophy): Leicester General Hospital, Leicester
O'Sullivan, Elaine (P Trzonkowski, M Carvalho Gaspar): University of Oxford, Oxford
O'Sullivan, Ros (D Walsh, K L Brown): Western Infirmary, Glasgow
Parker, Marie (J Pratt, J Peter Lodge): St James's University Hospital, Leeds
Peters, Christopher (K Prasad, S White): St James's University Hospital, Leeds
Railton, Dawn (C J Taylor, C Watson): Addenbrooke's Hospital, Cambridge
Roberts, Denise (N Webb, K Jessop): Royal Manchester Children's Hospital, Manchester
Roseke, Magnus (L Burnapp, N Mamode): King's College Hospital, London
Ruse, Sally (P Franklin, P Harden): Churchill Hospital, Oxford

Sagoo, Pervinder (M Hernandez-Fuentes, M Buckland): King's College, London
Sanchez, Tracy (T Horsburgh, I Underwood): Leicester General Hospital, Leicester
Sanni, Aliu Oladipupo (D Talbot, D Manas): Freeman Hospital NHS Trust, Newcastle
Sharif, Adnan (R Moore, R Ravanan): University Hospital of Wales, Cardiff
Shrestha, Pukar Chandra (D Talbot, I A M Ahmed): Freeman Hospital, Newcastle upon Tyne
Simmonds, Mary (P Franklin, P Harden): Churchill Hospital, Oxford
Singh, Rajinder, Pal (K Rigg, M El-Sheikh): Nottingham City Hospital, Nottingham
Spencer, Jacqueline Mary (R Stoddard-Murden, A Broderick): Derriford Hospital, Plymouth
Tamijmarane, Appou (D Sharma, G Morris-Stiff): Queen Elizabeth Hospital, Birmingham
Tan, Boon Kay (P Cockwell, A Ready): Russells Hall Hospital, Dudley
Toal, Isla Kathryn (M L Nicholson, M Brophy): Leicester General Hospital, Leicester
Tyler, Jennifer (J.A Kirby, H Robertson): University of Newcastle, Newcastle upon Tyne
Underwood, Ian (M L Nicholson, M Brophy): Leicester General Hospital, Leicester
Vallance, Caroline (B Shrestia, W McKane): Northern General Hospital, Sheffield
Wei, Bin (A Boyd, M M Carvalho Gaspar): John Radcliffe Hospital, Oxford
Weston, Stephen (T Horsburgh, M Nicholson): Leicester General Hospital, Leicester
Wilkinson, Miranda Jane (C Watson, A Taylor): Norfolk & Norwich University Hospital, Norwich
Wu, Douglas (K Wood, A Bushell): John Radcliffe Hospital, Oxford
Yii, Melinda Poh Chuo (H Vilca Melendez, P Muiesan): King's College Hospital, London

British Transplantation Society Membership Statistics

(As of 23rd January 2006)

Reduced Members	100
Normal Members	542
Consultant Members	132
Honorary Members	13
Retired Members	5

OVERALL CURRENT MEMBERSHIP	792
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ABSTRACTS

Plenary Session 2

Basic Science

Wednesday 29 March

11.30 – 13.00

O1

Pre-Transplant Induction Of HO-1 In Donor Aortae Inhibits Neointimal Hyperplasia Through Modulation Of Alloreactive CD8+ T Cell Responses In The Absence Of Immunosuppression

H M Clarke and A Dorling

Dept Immunology (rm 10N3), Imperial College, Hammersmith Campus, Commonwealth Building, Du Cane Road, London, W120NN, United Kingdom

Induction of heme oxygenase 1 (HO-1) in vascularised organ grafts protects against humoral rejection, through activation of cytoprotective mechanisms in endothelial cells (EC) and vascular smooth muscle cells. This effect is evident when HO-1 is induced in donor organs pre-transplantation. In contrast, the well described immunomodulatory effects of HO-1 on T cell function have only been defined in studies in which the recipient has undergone post-transplant manipulation.

In vitro the protoporphyrin hemin was used to induce HO-1 expression in murine EC. The proliferative response of allogenic T cells to these EC was significantly reduced compared to control EC, as was IFN γ production measured by ELISA. Altered responsiveness was seen within the alloreactive CD8+ T cell fraction. Chromium mesoporphyrin, which inhibits the enzymatic activity (but not expression) of HO-1 was used to demonstrate that altered responses to HO-1 expressing EC were dependant on HO-1 activity. To our knowledge, this is the first time that HO-1 induction in donor EC has been shown to modulate the response of unmanipulated alloreactive T cells. The molecular mechanisms involved are currently under investigation.

In vivo, the effect of donor HO-1 expression was tested in a murine aortic transplant model. Control fully MHC-mismatched allogenic aortas showed pronounced neointimal formation 42 days post transplantation. In contrast, aortas from donors pre-treated with two doses of hemin at 12 and 36 hours prior to transplantation showed significantly reduced neointimal thickening. To our knowledge, this is the first time that pharmacological induction of HO-1 in a donor organ has been shown to reduce T cell dependant pathology in completely unmanipulated recipients. It is also the first time that donor HO-1 expression has been shown to impact on chronic rejection in a murine model.

Work is currently underway to determine the extent and phenotype of graft infiltrating T-cells and the impact on HO-1-expressing donor tissue on the secondary responsiveness of murine T cells.

O2

Key Factors In Metanephros Transplant Development And Function

MJ Clancy¹, MP Dilworth², B Coupes¹, N Ashton², IS Roberts³ and PEC Brenchley¹

¹Manchester Institute of Nephrology and Transplantation, Oxford rd., Manchester, M13 9WL, United Kingdom, ²Department of Physiology, University of Manchester, Manchester, M13 9PL, United Kingdom and ³Oxford Radcliffe N.H.S. Trust, Oxford, OX3 9DU, United Kingdom

Introduction

Transplantation of the metanephros to the adult, with subsequent microsurgical connection to the recipient excretory tract, is a potential new treatment for end-stage renal failure. This process leads to growth and vascularisation of transplants under conditions different from normal development. Key factors affecting transplant growth and function achieved, including exposure to growth factors, site of transplantation, prior reduction in recipient renal mass and treatment with steroids are investigated.

Methods

We transplanted E15 metanephroi to the abdominal cavity of adult rats with subsequent microsurgical connection of the transplant ureter to the host ureter and transplant GFR measurement. Control groups received nephrectomy at the time of transplantation and incubation with previously described growth factor solution. Experimental groups included no growth factor exposure, alternative growth factor combinations, no nephrectomy, nephrectomy 1 month prior and recipient corticosteroid treatment . Different anatomical implantation sites were also compared using identical protocols. Growth success rates, formation of urine cysts, achieved GFR and expression of renal markers were compared.

Results

Transplants close to the abdominal aorta produced the largest metanephroi with highest mean GFR: 46.65 ± 22.42 ml/min per 100g body weight compared with the previously published 1.1 ± 0.2 for omentum.

Nephrectomy at transplantation led to higher GFR than nephrectomy at any earlier stage ($p=0.07$ v's next highest group)

Methyl prednisolone treatment led to lower mean GFR compared to controls. ($p=0.06$).

Published 12 growth factor solution led to higher mean GFR than other solutions used ($p=0.07$ v's next highest group)

Discussion

The anatomical site of implantation of metanephroi is crucial for transplant success. The higher GFR observed in aortic transplants is probably a function of local haemodynamics.

Though not necessary for growth, nephrectomy at transplantation increases transplant function. Similar mechanisms to compensatory renal growth may be involved. Steroid treatment and alternative growth factor incubation did not improve function. Patterns of exposure to exogenous growth factors may need to be highly complex if levels of function closer to normal are to be achieved. Strategies to reduce renal vascular resistance will be required for reliable, therapeutic function.

O3

Liver Macrophages Mediate Cholangiocyte Apoptosis And Proinflammatory Cytokine Release During Co-Culture

EB Alabraba¹, WK Lai¹, SR Bramhall², S Wigmore¹, DH Adams¹ and SC Afford¹

¹Liver Research Group, 5th Floor Institute of Biomedical Research, University of Birmingham, Birmingham, B15 2TT, United Kingdom and ²Liver Transplant Unit, Queen Elizabeth Hospital, Birmingham, B15 2TH, United Kingdom

Background Interaction between CD154 and its receptor CD40 plays a pivotal role in regulating TNF receptor mediated epithelial cell (hepatocytes and biliary epithelial cells) apoptosis in the liver. It is also proposed that they may modulate hepatic inflammation including regulation of inflammatory cell recruitment and activation. In animal models, CD40 blockade has been shown to prolong allograft survival and induce tolerance. In chronic liver allograft rejection, CD154 expression is increased and sustained on tissue macrophages and T cells in centrilobular regions of hepatocyte fallout and within the portal tract around bile ducts undergoing apoptosis. These CD154 +ve macrophages may play important role in the pathogenesis of the vanishing bile duct syndromes including chronic liver allograft rejection.

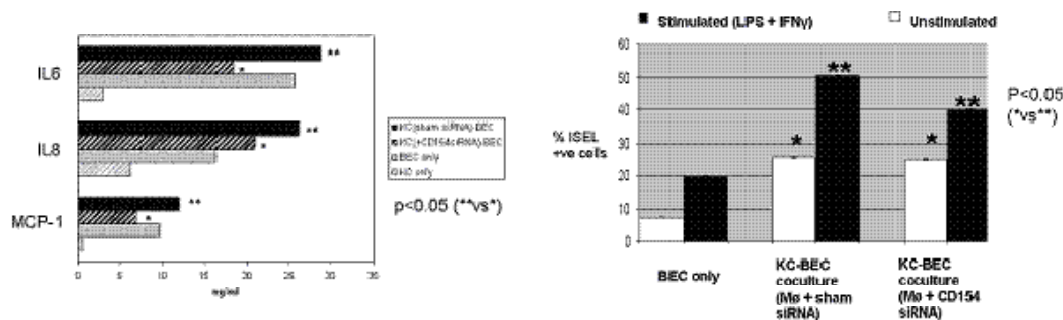
Hypothesis Liver derived macrophage (LDM) - biliary epithelial cell (BEC) interaction leads to CD154-dependent apoptosis and the generation of a proinflammatory environment.

Aims To develop a primary human macrophage-BEC co-culture system to determine whether CD154/CD40 interaction results in BEC apoptosis and proinflammatory cytokine release

Methods Tissue was obtained ethically from patients undergoing transplantation. Liver derived macrophages (LDM) were stimulated to upregulate CD154 expression and cultured for 3 days either as monocultures or co-cultures with primary human BEC. Stimulation with IFN γ and LPS was used to upregulate CD154 expression on LDMs. LDM CD154 expression was silenced using designed inhibitory siRNA and a commercially available transfection agent (Eurogentec, Belgium). Secretion of IL6, IL8 and MCP-1 was measured by ELISA and BEC apoptosis were determined using DNA end labelling assays.

Results Co-culture of LDM with BEC enhanced secretion of IL6, IL8 and MCP-1 compared with monoculture alone (Fig 1). Activated LDMs were able to induce apoptosis of BEC and inhibiting this pathway with siRNA confirmed the effects were dependent on CD40/CD154 interactions (Fig 2).

Conclusions Co-culture of LDM with BEC leads to the secretion of proinflammatory cytokines and the activation of CD40/CD154-dependent BEC apoptosis suggesting that CD40/CD154 interaction provides a molecular mechanism to amplify chronic inflammation and bile duct destruction in vanishing bile duct syndromes.



Parallel Session 3(b)
Stem Cell/Basic Science
Wednesday 29 March
14.00 – 15.30

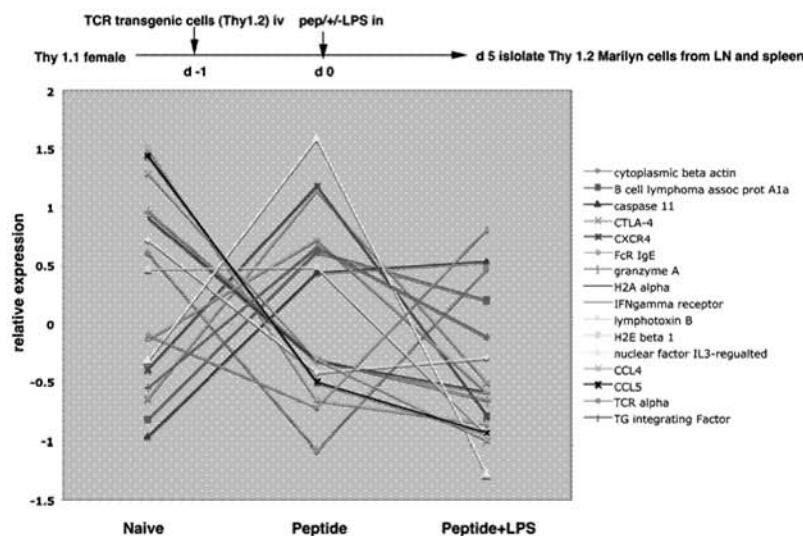
O4

Transplantation Tolerance Induced By Intranasal Administration Of HY Peptides

D M Scott¹, E James², H Dewchand¹, E Simpson¹ and J-G Chai¹

¹Transplantation Biology Group, Department of Immunology, Imperial College London, Hammersmith Campus, Du Cane Road, London, W12 0NN, United Kingdom and ²University of California, Berkeley, Department of Molecular and Cell Biology, Berkeley, CA 94720, USA

Having identified a set of minor histocompatibility (H) peptide epitopes that are responsible for expression of the murine male-specific minor H antigen, HY, we have used these to induce antigen-specific allograft tolerance. Intranasal (i.n.) administration of individual MHC class II restricted HY peptides induces indefinite survival of syngeneic male skin grafts and allows engraftment of male bone marrow and haematopoietic cells which can express 5 additional HY epitopes. Co-administration of peptide+LPS causes immunisation. Tolerance does not involve deletion. HY peptide specific CD4+ and CD8+ T cells expand on re-exposure to male antigen; these expansions are smaller in tolerant than control mice and fewer HY-specific cells from tolerant females secrete IFN γ and IL10. Adoptively transferred naïve TCR transgenic CD4+ T cells proliferate more transiently and to a lower extent in response to i.n. peptide alone compared with peptide+LPS and these cells express a characteristic gene profile compared to resting or immune cells. CD4+ cells from peptide pre-treated females fail to make IL2 responses to cognate peptide causing more limited expansion of the HY specific CD8+ populations that can cause graft rejection. Nevertheless both CD4+ and CD8+ T cells from these tolerant mice secrete IFN γ in response to peptide. IL10 does not appear to be critically involved, since tolerance is inducible in IL10 deficient mice. Adoptive transfer of tolerance into naïve neonatal recipients by splenocytes from long-term tolerant donors provides evidence for involvement of regulatory cells. Therefore, peptide induced tolerance appears to be due to a defect in the ability of HY-specific T cells to expand and produce pro-inflammatory cytokines rather than a deletional mechanism. In the presence of potentially cytotoxic HY specific CD8+ T cells that can be expanded both in vivo and in vitro by male antigen, maintenance of tolerance is associated with a population of CD4+ regulatory cells.



The Impact Of The MRP2 Gene Promoter Region Single Nucleotide Polymorphism C-24T On Mycophenolic Acid Exposure In De Novo Renal Allograft Recipients

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We demonstrated that UGT1A9 gene promoter region single-nucleotide polymorphisms (SNPs) T-275A and C-2152T are associated with significantly lower early mycophenolic acid exposure in renal recipients (Kuypers et al: Clin Pharmacol Ther 2005: 351-61).

The multidrug resistance-associated protein 2 (MRP2) is a key transporter involved in MPA metabolism, responsible for biliary excretion of the inactive glucuronide-metabolite of MPA (MPAG) and subsequent enterohepatic (re)circulation (EHC).

We examined the effects of the MRP2 gene promoter region C-24T SNP on MPA exposure in recipients during the first year posttransplantation in order to identify genetic determinants (e.g. UGT1A9 SNPs) that explain the large inter-individual variability in MPA kinetics. The MRP2 C-24T SNP was identified in 93 recipients by a PCR restriction fragment length polymorphism method and patients underwent MPA AUC plasma samplings at different time points (full 12-hour AUC sampling on day 7, abbreviated 2h AUC on day 42, abbreviated 4h AUC on day 90 and 360).

Dose-corrected trough MPA concentrations were significantly higher at 6 weeks, 3 and 12 months in recipients carrying the C-24T SNP (see table 1). On day 7, the presence of the C-24T SNP protected recipients from liver dysfunction-induced reduction in MPA exposure; probably by interruption of EHC (see table 2). These findings were not altered by the UGT1A9 SNPs carrier state (not shown). Carriers of the C-24T SNP had significantly more episodes of diarrhea than non-carriers (30% versus 13.2%; $p=0.04$) while no differences were observed in the incidence of leukopenia, anemia and acute rejection. The C-24T SNP of the MRP2 gene is associated with higher MPA pre-dose trough concentrations while carriers of the C-24T SNP are protected from liver dysfunction-induced MPA underexposure but suffer more gastrointestinal side-effects.

Table 1	MRP2 C-24T SNP		Table 2	No liver dysfunction	Mild liver dysfunction
	Non-carriers	Carriers			
Day 42	n=52	n=39	Day 7	n=77	n=16
AUC ₀₋₂ /dose (mg.hr/L.g)	89.0 ± 41.6	106.3 ± 37.5*	All patients		
C ₀ /dose (mg/L.g)	4.3 ± 3.7	5.4 ± 2.6*	AUC ₀₋₂ /dose (mg.hr/L.g)	81.2 ± 45.1	58.3 ± 44.7*
CL/F (L/hr)	14.3 ± 7.4	10.5 ± 3.3*	Partial AUC ₀₋₂ (mg.hr/L)	17.7 ± 12.7	9.6 ± 8.9*
Day 90	n=47	n=39	EHC (AUC ₀₋₆ /AUC ₀₋₁₂) (%)	32.5 ± 9.2	25.0 ± 10.6*
AUC ₀₋₂ /dose (mg.hr/L.g)	63.4 ± 32.7	74.9 ± 35.4	C ₀ /dose (mg/L.g)	3.9 ± 2.9	2.5 ± 2.0
C ₀ /dose (mg/L.g)	4.4 ± 2.6	5.9 ± 2.5*	Non-carriers of MRP2 C-24T	n=44	n=9
CL/F (L/hr)	20.7 ± 12.4	16.7 ± 9.2	AUC ₀₋₂ /dose (mg.hr/L.g)	82.6 ± 51.3	34.1 ± 16.8*
Day 360	n=43	n=34	Partial AUC ₀₋₂ (mg.hr/L)	19.4 ± 15.5	6.0 ± 4.7*
AUC ₀₋₂ /dose (mg.hr/L.g)	70.0 ± 39.0	84.6 ± 52.7	EHC (AUC ₀₋₆ /AUC ₀₋₁₂) (%)	33.1 ± 9.9	24.1 ± 10.4*
C ₀ /dose (mg/L.g)	5.0 ± 2.8	7.6 ± 7.4*	C ₀ /dose (mg/L.g)	3.8 ± 3.2	1.9 ± 1.6*
CL/F (L/hr)	18.9 ± 10.7	15.2 ± 7.3	Carriers of MRP2 C-24T	n=33	n=7
			AUC ₀₋₂ /dose (mg.hr/L.g)	79.2 ± 35.8	94.4 ± 50.4
			Partial AUC ₀₋₂ (mg.hr/L)	15.6 ± 2.0	15.1 ± 11.2
			EHC (AUC ₀₋₆ /AUC ₀₋₁₂) (%)	31.8 ± 8.2	26.5 ± 11.8
			C ₀ /dose (mg/L.g)	3.9 ± 2.5	3.4 ± 2.5

* $p<0.05$

O6

Chronic Allograft Nephropathy: Transforming Growth Factor- β and Bone Morphogenetic Protein-7 Regulate Epithelial to Mesenchymal Transition

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Chronic allograft nephropathy is the main cause of renal failure following transplantation, and results from a loss of nephrons with concurrent tubulointerstitial fibrosis. Epithelial to mesenchymal transition (EMT), the process by which epithelial cells develop into fibroblasts, has been implicated in chronic graft failure and can be driven by transforming growth factor- β (TGF β). Another member of the TGF β family, bone morphogenetic protein-7 (BMP7), is thought to antagonise EMT by stimulating a reverse phenotypic transition. Both TGF β and BMP7 exert their effects through the Smad signalling pathway, with TGF β 1 inducing phosphorylation (p) and nuclear translocation of Smad2/3 whilst BMP7 generates pSmad1/5/8. This study was designed to examine the expression levels of these two signalling molecules in tissue sections from normal and post-transplant kidneys and in cultured renal tubular epithelial cells exposed to TGF β 1, BMP7 or a mixture of both cytokines.

Analysis of kidney tissue sections showed that both pSmad2/3 and pSmad1/5/8 were present in the nuclei of tubular epithelial cells in normal and transplanted kidney with no rejection, suggesting maintenance of a homeostatic balance between these signalling molecules. However, the expression of pSmad2/3 increased in acute renal allograft rejection and chronic allograft nephropathy whilst anti-fibrogenic pSmad1/5/8 was markedly reduced in acute rejection and almost absent in chronic nephropathy. The expression of nuclear pSmad2/3 was increased compared to the control ($p < 0.001$) in tubular epithelial cells exposed to TGF β 1 for 72 hours, but exogenous BMP7 only transiently increased the expression of pSmad1/5/8. Importantly, a mixture of both TGF β 1 and BMP7 synergised to maintain high level expression of pSmad1/5/8 for up to 72 hours ($p < 0.001$).

These results suggest that intranuclear pSmad1/5/8 signals generated in renal tubular epithelial cells by BMP7 have the potential to 'balance fibrogenic signals produced by TGF β in normal kidney'. However, this balance is lost during rejection when the response to TGF β becomes dominant. We suggest that exogenous BMP7 could restore the balance of pSmad signalling during rejection, thereby preventing or even reversing chronic allograft nephropathy.

O7

Matrilysin (MMP7) Protects Grafts From Rejection Across a Minor MHC Mismatch in a Murine Skin Transplantation Model.

PE Herbert, R Kumar, LR Ambrose and AN Warrens

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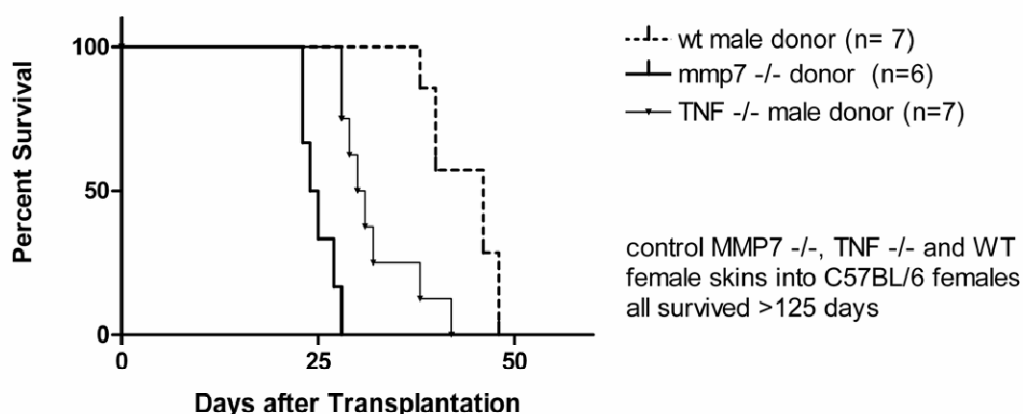
Background/Aim. Previous work by our group has shown that Fas Ligand (FasL) when expressed at physiological levels helps to prolong graft survival across a minor MHC mismatch. Fas L exists in both a membrane bound and soluble form, and is cleaved from membrane bound to soluble by the enzyme MMP7. In order to investigate which form of the FasL molecule could be responsible for its graft protecting effects we used MMP7 knockout mice in a series of in vivo and in vitro experiments. Since MMP7 also cleaves Tumour Necrosis Factor alpha (TNFa) from a membrane bound to soluble form TNF -/- mice were incorporated into our experiments.

Method. Male or female tail skin from either wild type (WT), MMP7 -/-, or TNF -/- C57/BL6 mice was transplanted into WT C57/BL6 female recipients according to the Medawar method. They were observed for signs of rejection, and deemed to have fully rejected when more than 50% of the graft surface had been destroyed. In T cell proliferation assays irradiated bone marrow derived dendritic cells were used as stimulators and CD4+ T cells (purity>90%) used as responders. They were pulsed with tritiated thymidine on day 6 and harvested after 16 hours.

Results. Male skin grafts from MMP7 -/- animals rejected an average of 20 days earlier than WT male controls ($p<0.0001$ (log rank test)) (see figure 1). TNF -/- skin rejected an average of 12 days sooner ($p<0.0002$ (log rank test)). In T cell proliferation assays with Balb/C DC stimulators both MMP7 -/- and TNF -/- CD4 cells proliferated significantly more than WT responders.

Conclusions. This data suggests that MMP7 acts to protect grafted tissue from rejection, possibly through reduced T cell apoptosis. This may be directly, or indirectly through its effects on FasL and TNF which we have also shown protects grafts from rejection. Our findings to date suggest the need for further investigation to elucidate the mechanisms involved which is currently ongoing.

Figure 1



O8

Proliferation and Maturation Signals in Developing Human Liver

I S Currie, J D Terrace, N M Masson, R W Parks and J A Ross

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Introduction

In the United Kingdom, the mortality rate of patients awaiting liver transplantation now stands at 20%. In order to reduce such mortality, new therapies for liver disease are required. Cell-based therapies represent a way forward. However, adult human liver cells in vitro fail to proliferate and survive only briefly. To provide a basis for cell therapy in liver disease, it was hypothesised that human fetal liver cells might undergo proliferation and functional maturation steps in vitro, in response to specific signalling molecules.

Methods

Liver tissue was obtained in an ethically approved study from 2nd trimester fetuses after therapeutic termination. Cell cultures were prepared by collagenase digestion, and cells were plated on type I collagen-coated polystyrene dishes. Cells were maintained in William's Medium containing 10% fetal calf serum, glutamine and antibiotics. Cells were incubated in the presence and absence of proliferation (Epidermal Growth Factor (EGF), Interleukin-6, Tumour Necrosis Factor, Keratinocyte Growth Factor or Hepatocyte Growth Factor) and maturation (glucocorticoid, tri-iodothyronine or glucagon) signals. Proliferation was assessed by a thiazylol blue technique and by cell counting. Proliferating cells were characterised by 2-colour flow cytometry (Fibrinogen and Cytokeratin 18). Maturation effects were estimated by measuring protein secretion using specific ELISAs, and urea synthesis.

Results

EGF alone caused a significant proliferative response, and flow cytometry demonstrated a specific expansion of primitive epithelial cells to 250% of control (Cytokeratin 18+ve/Fibrinogen-ve; $p < 0.05$). Glucocorticoid, but not tri-iodothyronine or glucagon, stimulated fibrinogen secretion. In fact, glucocorticoid led to an increase in Fibrinogen, α -Fetoprotein and α -1-antitrypsin secretion of at least 10 fold over control ($p < 0.05$), without any effect on proliferation. Urea synthesis was little changed by any agent.

Conclusions

These data show that human fetal liver can respond to proliferation and maturation signals in vitro. EGF caused proliferation, and glucocorticoids brought about a maturational response. EGF-induced proliferation of immature liver cells in vitro, followed by a maturational phase triggered by glucocorticoids, could provide the functional tissue mass required for cell-based therapies in human liver disease.

Plenary Session 1
Clinical Transplantation
Thursday 30 March
09.00 – 11.00

O9

Hepatitis C Virus and Liver Transplantation

HL Thomas¹, KM Barber¹, D Collett¹ and D Mutimer²

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On behalf of the UK Transplant Liver Advisory Group, UK Transplant, Bristol, BS34 8RR, United Kingdom

Background: The aim of this project was to assess the determinants of survival following liver transplantation of patients infected with hepatitis C virus (HCV-pos), and to examine whether these factors differed from those associated with survival of patients without HCV infection (HCV-neg).

Methods: Data on all first adult elective heartbeating liver only transplants in the UK, March 1994 to October 2005, were obtained from the National Transplant Database. Patients with unknown HCV status or with concurrent hepatitis B virus or liver cancer were excluded; 3,648 patients and transplants were available for analysis. Patient and graft survival times were calculated as time from first liver transplant to patient death or graft failure, respectively. The Kaplan-Meier method was used to estimate long-term survival. The effect of the following factors on post-transplant survival was assessed: (a) donor age, sex, diabetes and body mass index (BMI), (b) recipient age, sex and primary immunosuppression (cyclosporine or tacrolimus), and (c) year of transplant, cold ischaemia time (CIT) and warm ischaemia time (WIT).

Results: Eight-year patient survival for HCV-pos patients was significantly inferior to HCV-neg patients; 55% (95% CI 47-61) and 70% (95% CI 67-72), respectively. A similar effect was observed for graft survival.

In univariate analysis, WIT had a significant effect on patient survival in both HCV-pos and HCV-neg patients. Donor diabetes and BMI, recipient age and sex, and CIT also affected patient survival among HCV-neg patients. Graft survival in both HCV-pos and HCV-neg patients was significantly influenced by donor BMI, recipient age and WIT. In addition, there was an association with CIT in HCV-neg patients. There was no statistically significant effect of donor age or sex, year of transplantation or choice of immunosuppression in either group for patient or graft survival.

Conclusion: HCV infection is associated with inferior long-term patient and graft survival. In univariate analysis, there were no adverse determinants of survival that were specific for HCV-pos patients. It seems likely that there is interaction between some variables, so multivariate analysis will establish the true impact of HCV on survival, following adjustment for relevant risk factors.

O10

A Local Allocation System for Non Heart Beating Kidneys- Transplanting Long Waiting Patients without Prejudicing Outcome.

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²Department of Surgery, Southmead Hospital, Bristol, BS10 5NB, United Kingdom, ³Department of Renal Medicine, Southmead Hospital, Bristol, BS10 5NB, United Kingdom and ⁴Department of Immunology, Southmead Hospital, Bristol, BS10 5NB, United Kingdom

The median waiting time for patients on the UK renal transplant waiting list is 729 days with approximately 33% of patients waiting for more than 3 years (1096 days). Currently matching is prioritised on the UK allocation scheme, but this can disadvantage recipients who are blood group B, homozygous for DR antigens or who have uncommon tissue types. In 2002, our unit had 90 patients waiting >1096 days for transplant with a longest waiting time of 6,330 days. The introduction of a non heart beating kidney donor (NHBD) programme provided an opportunity to prioritise local organ allocation according to waiting time. A scoring system was devised based on waiting time, with further adjustment favouring younger patients, low matchability scores, and first transplants. A series of simulated ‘match runs’ was carried out to check that the allocation algorithm was effective in prioritising waiting time.

For each pair of kidneys from a NHBD, one was allocated locally according to the national algorithm based on “best match” and the other according to the new scoring system. This approach was adopted to avoid allocating both kidneys to higher risk recipients. The same immunosuppression protocol was used for both groups.

Since July 2002, we have transplanted 54 patients with NHBD kidneys. 26 recipients were long waiting patients (median wait 2002 days) & 28 were best matched recipients (median wait 434 days). Median HLA matching for both groups was 121 & 111 respectively, illustrating that HLA matching has not been compromised for the long waiters. Median 3 month plasma creatinine for the long waiting group is 148 (range 72-315), compared to 125 for the best matched group (range 72-315). At 1 year, median plasma creatinines were 137 (range 77-396), & 130 (range 63-156) respectively. Out of the 54 NHBD transplants, 52 patients have a functioning graft. 1 graft in the long waiting group failed due to rejection, & 1 recipient from the best matched group died with a functioning graft.

The adoption of a local allocation system that prioritises patients according to waiting time has resulted in 23% of our long waiters being transplanted. Despite these being higher risk recipients, we have demonstrated excellent results in both patient groups & addressed the problem of long waiting recipients through a NHBD scheme.

O11

Marginal Organ Allocation In Liver Transplant Recipients– Does The Meld Score Matter?

S Asthana, T Khan, AI Aldouri, SG Pollard, GJ Toogood, MH Davies, C Millson, JPA Lodge and KR Prasad

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Introduction:

The shortage of suitable donors is a major problem in liver transplantation. Marginal donors which were previously considered unfit for transplant have been used to increase the donor pool. Objective data on recipient selection and outcomes for such organs from the United Kingdom is limited. This study was conducted to analyse the impact of marginal donor criteria and MELD score on graft and patient outcome.

Patients and methods:

531 consecutive adult liver transplants performed in a single unit between 2000 -2005 were included in this study. Donor criteria studied included- donor age>65, cold ischemic time >12hours, steatosis, inotropic support, ICU stay >4 days, or a non heart-beating organ recovery. Donors with more than 3 criteria were considered marginal. Recipient data studied included age>65 years, MELD score and the warm ischemic time. Outcome measures studied included graft outcome - primary non-function (PNF), initial poor function (IPF), failure, 90-day mortality and overall mortality. Categorical and continuous data were analysed using the chi-square and 't' test respectively, and significant variables were further studied using regression analysis. The impact of MELD scores on two patient groups- marginal and non-marginal donors- were analysed using the log-rank test.

Results:

Marginal donors were significantly associated with IPF (p=0.003) and 90-day mortality (p=0.012), while recipient age and MELD scores were associated with graft failure and overall mortality (p=0.02 and 0.003 respectively). A higher MELD score significantly increased the risk of IPF and 90-day mortality in recipients with marginal livers as compared to those with non-marginal livers (p<0.001 and p=0.004) However, long-term graft and patient outcomes were comparable in patients receiving marginal and non-marginal organs, irrespective of the MELD score at the time of transplant.

Conclusion:

Marginal livers can be safely used without increasing the long-term graft failure and survival rates. The higher incidence of graft dysfunction may prolong hospital stay in such recipients. Patient selection is important, and organ allocation should be determined keeping MELD score and donor organ status in consideration.

Parallel Session 2(a)

Renal

Thursday 30 March

11.30 – 12.30

O12

Does Transplantation Improve Survival For End Stage Renal Disease Patients In The UK?

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Background: The survival benefit of receiving a kidney transplant over remaining on the waiting list is often quoted from an American study. Fewer patients in the UK are diabetic and data from the UK Renal Registry show that survival on dialysis is better in the UK. We therefore analyse UK data to investigate the benefit of receiving a kidney transplant. Exclusion of patients never listed means that bias associated with the selection of (lower-risk) patients for transplant can be avoided.

Methods: Data from the National Transplant Database held by UK Transplant were combined with data from the UK Renal Registry to produce a cohort of 10503 adult patients listed for a first kidney only transplant between 1995 and 2000. Patients were followed from date of listing to September 2005 or death if earlier. Of the patients analysed, 6793 (65%) received a deceased donor transplant while 797 (8%) received a living donor transplant. Risk-adjusted standardised mortality ratios (SMRs) were calculated to compare death rates of patients who remained on the transplant list with those of patients receiving a transplant. Time-dependent Cox regression analysis was also used to evaluate the survival benefit of transplantation.

Results: The SMR for patients receiving a transplant was 35% lower than that for all patients listed for transplant (SMR=0.65, 95% confidence interval (CI) 0.61-0.69). Cox regression analysis showed differing risks of death after listing according to year of listing, primary renal disease, ethnicity, age, time on dialysis and receipt of transplant. Compared with remaining on dialysis, the relative risk of death up to 10 years after transplantation was 0.32 (95% CI 0.23-0.43) for a living donor transplant and 0.56 (95% CI 0.51–0.61) for a deceased donor transplant. Compared with remaining on the transplant list, and depending on the individual patient, the increased risk of death in the immediate post-transplant period resolves approximately 4 months after transplant, after which point there is an increasing survival benefit of transplantation.

Summary: In UK patients listed for kidney transplantation between 1995 and 2000, the risk of death for transplanted patients is greater than that for those remaining on the list only in the first few months post-transplant. Thereafter, long-term survival is significantly better for patients receiving a renal transplant.

O13

5 Year Results of Angioplasty and or Stenting of Transplant Renal Artery Stenosis

K Chan, M Willicombe, W Gedroyc, TDH Cairns, N Duncan, N Hakim, A Palmer, A Mclean, V Papalois and D Taube

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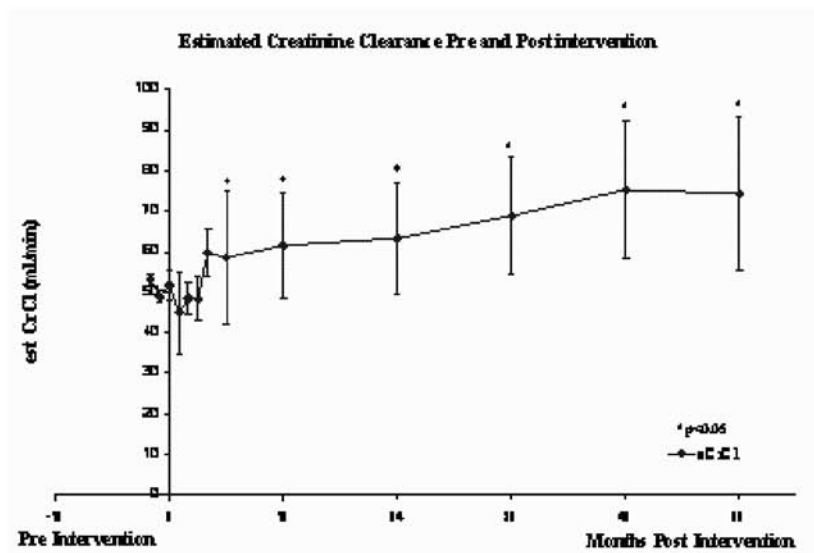
We report our 5 year experience with transplant renal artery stenosis [TRAS] in our kidney transplant programme.

421 kidney transplants [255m, 166f; age 44.6 ± 12.4 (1 SD)] were performed between June 1995 and October 2005 in our centre. All patients received a Tacrolimus based immunosuppressive regime. Patients with renal allograft dysfunction and or significant hypertension were screened for TRAS by MR angiography. If this was positive, patients proceeded to formal IA digital subtraction angiography [IADSA].

53 patients [42m, 11f; age 43.8 ± 12.4] were found to have TRAS on both MR angiography and IADSA. 39 patients underwent angioplasty [21 patients] and or stenting [18 patients]. Intervention was not thought to be necessary or clinically appropriate in the remaining 14 patients.

There were no graft losses as a result angioplasty or stenting. Following intervention, 5 year patient and allograft survival [Kaplan Meier analysis] was 92.8% and 91.8% respectively and not different to the patients without TRAS. Allograft function [estimated creatinine clearance by the Cockcroft Gault method] significantly improved following intervention as shown in the figure below, ($p < 0.05$, student paired t test). Patient and allograft survival in the group of patients with TRAS treated conservatively was 94.4% and 94.3%. No grafts were lost as a result of renal artery thrombosis. Allograft function remained stable.

This study shows that angioplasty and or stenting of renal transplant arteries is safe and is associated with improved allograft function



O14

What Effect Does 1 Year Renal Graft Function Have On Longer Term Post Transplant Haemoglobin, Bone Metabolism And Blood Pressure?

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²Royal Liverpool University Hospital, Prescott Street, Liverpool, L7 8XP, United Kingdom

Renal transplantation (Tx) restores kidney functions, improving haemoglobin, bone metabolism and blood pressure. It is unknown to what degree these changes are influenced by level of early graft function. The timing and the size of these changes related to level of graft function is not known

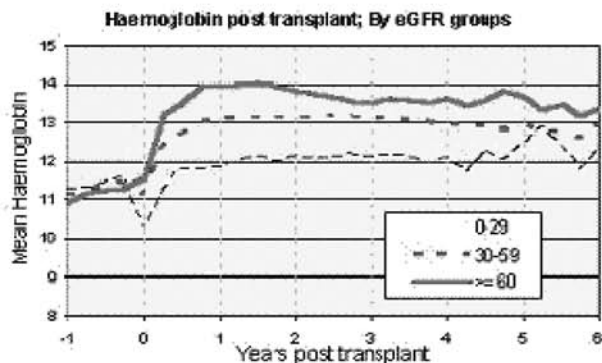
At 1 year post renal transplant, patients were categorised into 3 groups based on their eGFR by the abbreviated MDRD equation. These were low eGFR (<30ml/min/1.73m²), medium (30-59ml/min/1.73m²), and high (>=60ml/min/1.73m²). The sequential changes in quarterly data (eGFR, Hb, BP, calcium, phosphate, intact parathyroid hormone and bicarbonate) were then analysed for patients in these 3 categories. For patients previously on dialysis data is shown for the year prior to transplantation.

All patients on UKRR database between 01/01/1997 to 31/12/2002, who received a first Tx were analysed. The study included 1,123 patients of which 13% had a low eGFR, 65% a medium eGFR and 22% a high eGFR. The male : female ratio was 1.57. and 11% were diabetic. Patients who were lost to follow up within this period were excluded and in those patients that died, data from the quarter of death were excluded.

RESULTS: The 5y death censored graft survival was 74% for eGFR 0-29 group, 96% for 30-59 group & 92% for those with >=60. The 5y patient survival with a functioning Tx for three eGFR groups were 86%, 95% & 97% respectively.

The Hb rose more rapidly to a maximum by the end of 1y in high eGFR group & remained at that level. In the low group, the Hb rose more slowly and remained lower by almost 2 g/dl. Both systolic BP & diastolic BP were higher in pts with low eGFR when compared with those with a high eGFR (SBP:10mmHg, p=0.001; DBP: 8mmHg, p=0.003).

When diabetics were compared with non diabetics, significant differences were found for diastolic BP, cholesterol, ferritin and Po₄. In contrast, there were no differences in eGFR, systolic BP, Hb, Ca, iPTH, and bicarbonate.



O15

Postoperative Complication Profile And Donor Recovery Rates In A Consecutive Series Of 115 Laparoscopic Live Donor Nephrectomies

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Aims

Laparoscopic live donor nephrectomy (LDN) has yet to be widely adopted in the UK. This study presents the results of a consecutive series of 115 LDN from a single centre with an emphasis on postoperative complication rates and donor recovery times.

Methods

115 live donors (69 women and 46 men) underwent transperitoneal LDN. There was no selection on the basis of donor body mass index or because of difficult vascular anatomy. All patients received postoperative analgesia using a patient controlled analgesia system. Donors were allowed to resume normal activities, return home and return to work at their own discretion.

Results

There was no donor mortality or thromboembolic disease. Two operations were converted to open procedures for bleeding. The postoperative complications were: paraesthesiae of L1 dermatome 4 (3.5%) wound infection 5 (4.3%); unilateral pulmonary oedema 2 (1.7%); ileus 2 (1.7%); testicular pain 2 (4.4%); persistent wound pain 1 (0.9%) and incisional hernia 1 (0.9%). Two patients were re-laparoscoped for division of adhesions. Donor recovery rates (mean \pm SD) are shown in the table.

Conclusions

There is an appreciable morbidity in fit and healthy individuals undergoing LDN. LDN was associated with some unexpected complications such as L1 paraesthesia, testicular pain and pulmonary oedema. Nonetheless, donors return to the normal activities of life quickly following LDN.

In patient stay		4 \pm 1 days
Driving		2 \pm 2 weeks
Shopping		2 \pm 2 weeks
Exercising		4 \pm 3 weeks
Return to employment		6 \pm 2 weeks

Parallel Session 2(b)

Cardiac

Thursday 30 March

11.30 – 12.30

O16

Anti-Vimentin Antibodies Cause Accelerated Rejection Of Major Histocompatibility Complex (MHC) Identical Murine Cardiac Allografts

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Introduction

There is increasing evidence that non-MHC antibodies reduce graft survival. Among these, anti-vimentin antibodies (AVA) are significantly associated with human cardiac allograft vasculopathy. Here we examine mechanisms of damage caused by AVA in a murine model.

Methods

Wild type (WT) C57Bl6 (B6) recipients (H2b) were immunised with 400µg recombinant murine vimentin in 100µl complete Freund's adjuvant (CFA), followed by a booster 400µg vimentin 7days later, to generate high titers of IgG AVA. Vimentin Immunised (VIM) B-cell knockout mice on B6 background (IgH6) had high frequencies of interleukin-2 producing splenocytes, but **no antibodies**. Allogeneic or syngeneic control B6 WT recipients received 200µg hen egg lysozyme (HEL) or 400µg vimentin, respectively, in CFA. Two weeks following primary immunization, recipients received a vascularised 129/sv cardiac allograft [MHC identical (H2b), differ only in non-MHC loci] or B6 isograft.

Results

VIM B6 WT recipients showed accelerated rejection of allografts [8.4±1.5 days;n=26], compared to HEL-immunised B6 WT recipients [13.3±2.2 days;n=10;P<0.0001,Log-rank test]. In contrast, allografts in VIM IgH6 recipients were rejected with similar kinetics to unimmunised IgH6 controls [11.2±2.4 days vs 11.2±4.1 days;n=5;p=0.99]. Isografts in VIM B6 WT recipients continued to beat at 90days (n=11). At rejection, recipients did not produce anti donor-MHC antibodies [MHC-identical;H2b]. However, VIM WT recipients had high titers of AVA; greater amount of AVA could be eluted from cardiac allografts placed in VIM WT recipients at 2,4,6 and 8 days post-transplantation compared to control allografts and native hearts from WT recipients, as shown by binding of eluate to vimentin in western blots. There was significantly greater C3d deposition in allografts in WT VIM recipients at 4 and 8 days post-transplantation, compared to WT controls (18±6 vs 11±3pixel units at day-4; 21±7 vs 13±4 pixel units at day-8;P<0.0001). CD62P staining was greater in VIM WT allografts at day-4 post-transplantation (p=0.001), reflecting early activation of endothelial cells and platelets in VIM WT allografts.

Conclusion

The anti-vimentin response significantly accelerates rejection of cardiac allografts by antibody-mediated mechanisms in an MHC-identical murine model, suggesting a pathogenic role for autoantibodies.

O17

C3435T and G2677T Polymorphisms of the MDR1 Gene and Freedom from Biopsy Proven Rejection in Cardiac Transplantation

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Body: Variations in the expression levels and in the activity of the multidrug-resistance MDR1 encoded P-Glycoprotein (P-gp) have a major impact on the therapeutic efficacy of many drugs including immunosuppressants. We observed a significant association of polymorphisms in exon 26 (C3435T) and exon 21 (G2677T) of the MDR1 gene with increased incidence of biopsy proven rejection episodes in a cohort of 176 heart transplant patients.

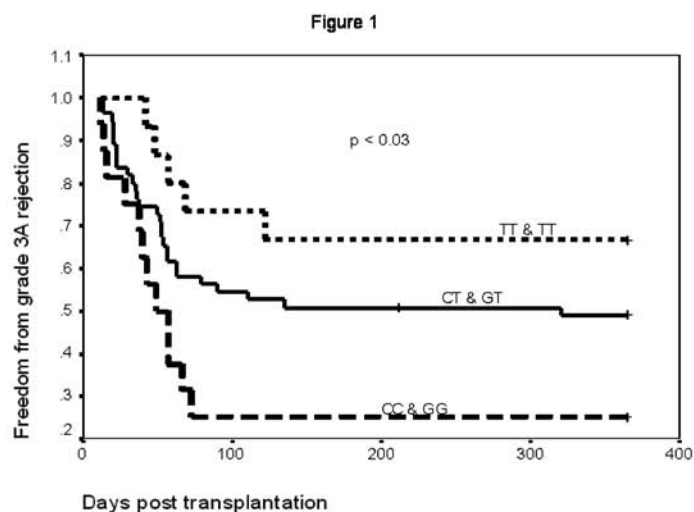
Methods: Using a previously described PCR method we characterized the C3435T polymorphism in exon 26 and the G2677T polymorphism in exon 21 of the MDR1 gene in 176 heart transplant patients. We assessed the relationship between these MDR1 polymorphisms and endomyocardial biopsy proven rejection (EBPR) determined by biopsy performed at set intervals according to a standard protocol.

Results: No significant differences in clinical variables were found between the 3 groups according to univariate analysis. A significant relationship was found between patient's exon 26 and exon 21 genotype and their freedom from first grade 3A rejection episode by Kaplan Meier analysis Figure 1. The effect of the MDR1 polymorphisms on increased likelihood of rejection is shown in Table 1.

Conclusions: These results highlight the importance of the MDR1 gene and P-gp in transplant rejection.

Table 1

	HR	95% CI	p-value
Exon 26 and Exon 21 Haplotype CC, GG	2.18	(1.21-4.26)	0.022
Exon 26 CC	1.8	(1.05-3.09)	0.034
Exon 21 GG	1.68	(1.01-2.92)	0.048
HLA 5 or 6 mismatches	1.18	(0.75-1.86)	0.47
HLA 3 or 4 mismatches	1.08	(0.70-1.75)	0.66
HLA 0, 1 or 2 mismatches	0.76	(0.28-2.08)	0.6



O18

Ischaemia Time In The UK Lung Transplantation Service

JC Hussey, RS Bonser, CJ Rudge and NR Banner

On behalf of the UK Transplant Cardiothoracic Advisory Group (CTAG), UK Transplant, Bristol, BS34 8RR, United Kingdom

Background: Whilst there is evidence that prolonged ischaemia time (IT) is detrimental to heart transplantation, the effect of IT on lung transplant outcome is less clear. We examined whether there was any trend in IT and its components in the UK lung transplant service.

Methods: Data were obtained from the National Transplant Database for 785 first adult cadaveric heartbeating lung (excluding double lung and heart/lung) transplants in the UK from 1 April 1995 to 31 March 2004. IT was analysed separately for the 371 single lung (SLT) and 414 bilateral sequential lung transplants (BSLT), where IT was based on reperfusion on the first lung (but in ten cases only the reperfusion time for the second lung was available, so this was used). Some centres reperfuse both lungs at the same time. Patient survival was summarised using Kaplan-Meier estimates of the survivor function.

Results: BSLT had a longer median IT (285 minutes (mins) vs 252 mins for SLT; $p < 0.0001$). The median transport times (donor cross-clamp to organ arrival) did not differ (143 vs 141 mins for SLT; $p = 0.89$), but the median implant time (organ arrival to reperfusion) for BSLT was longer (131 vs 102 mins for SLT; $p < 0.0001$). The median IT for SLT increased over the period, from 240 mins (IQR: 193-264) in 1995/6 to 275 mins (IQR: 225-315) in 2003/4 ($p = 0.03$). This was mainly due to an increase in median transport time (1995/6: 105 mins; 2003/4: 173 mins; $p = 0.0007$), as there was some evidence of a decrease in median implant time (1995/6: 115 mins, 2003/4: 97 mins; $p = 0.09$). There was no obvious trend in IT over time for BSLT. For both SLT and BSLT, median IT and its components differed across transplant centres ($p < 0.0001$). A smaller proportion of BSLT were from imported organs (52% vs 64% for SLT; $p = 0.001$). There was no significant difference in national short (30-day) or medium-term (1, 3 or 5 year) patient survival across ischaemia time groups (< 200 , 200-244, 245-299, ≥ 300 mins) for both SLT and BSLT. There was some evidence to suggest that 30-day survival was improving over the period (BSLT $p = 0.007$, SLT $p = 0.07$).

Conclusions: There was no evidence to suggest that IT influenced lung transplant outcome in the range observed. Centre differences in IT may be due to geography, transport methods or process diversity. The temporal trend in IT should be monitored to ensure there is no detriment to transplant outcome in the future.

Parallel Session 2(c)

Liver

Thursday 30 March

11.30 – 12.30

O19

Outcomes In Right Liver Lobe Transplantation: A Matched Pair Analysis

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BACKGROUND: Split liver transplantation has proven to be an effective technique of increasing the donor pool for paediatric recipients. There remains a concern regarding the outcome in adult recipients. Here we compare the results of split liver transplantation with matched whole liver grafts in all adult recipients.

METHODS: Twenty five adult recipients of split liver transplantations (SLTs) were matched to recipients of whole liver transplantations (WLTs) according to the following criteria: MELD score, recipient age, indication for liver transplantation, and year of transplantation. A WLT-recipient match was identified in 24 adult recipients of SLT.

RESULTS: Twenty four pairs of recipients were transplanted for chronic liver disease and one for acute liver failure. The overall 30 day mortality rates after SLT and WLT were 12% and 8% and 2 year survival rates after SLT and WLT were 72.7% and 91.7% respectively (log rank $p=0.126$). The median peak ALT during the first 14 days was 771 $\mu\text{mol/l}$ in SLT and 469 $\mu\text{mol/l}$ in WLT. One patient with a SLT developed hepatic artery thromboses with none from the WLT group. The prevalence of a biliary leak was higher among the SLT group (20.8%) compared with none in the WLT group. However the prevalence of biliary stricture was higher in the WLT group than that in the SLT (16.7% and 8.4% respectively; p value=0.333). Three patients who received split grafts were re-transplanted compared with none in the matched group. Patients with pre-operative hyponatraemia showed a trend toward lower 2 year survival after SLT compared with WLT (50% versus 100% respectively).

CONCLUSIONS: Our data suggests that Split Liver Transplantation with right hepatic lobes, although not significantly different to matched recipients of WLTs, shows a trend to a poorer outcome in adult recipients

O20

Prevalence And Outcome Of Cholangiocarcinoma In Patients With Primary Sclerosing Cholangitis Referred To A Regional Liver Transplant Unit

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BACKGROUND: Cholangiocarcinoma (CCa) is a recognised complication of primary sclerosing cholangitis (PSC) with prevalence rates of 8-18% reported from tertiary referral centres where screening protocols have lead to early identification of tumours. The aims of this study were to report the prevalence and outcome of CCa in PSC for a United Kingdom centre with a defined referral population.

METHODS: All patients referred to the unit over a 20 year period from 1985-2004 with a diagnosis of PSC were prospectively entered into a departmental database. The database was interrogated to determine all patients who had in addition a diagnosis of CCa either at presentation or subsequently. For this cohort, the mode of presentation, management and outcome were determined.

RESULTS: 370 patients (265 M and 105 F) with a median age of 50.5 years were referred with confirmed or suspected PSC of which 207 were subsequently transplanted. 48 patients (13%) developed a CCa with a mean interval from referral to tumour diagnosis of 4 months. The mode of presentation included: inoperable tumours at presentation (n=14); incidental findings in transplant hepatectomy specimens (n=13); PSC follow-up (n=9), transplant work-up (n=5), whilst on transplant waiting list (n=5), suspected tumour confirmed at transplant (n=1); and incidental finding at cholecystectomy. (n=1). The diagnosis was confirmed by: radiology-guided biopsy (n=27); MRI (n=2); CT (n=2); at laparoscopy/laparotomy (n=2); and by frozen section at transplant in 1 case. Management consisted of: transplantation (n=13, incidental on post transplant histology); hepatic resection (n=8); palliation through stenting (n=26); no treatment (n=1). The overall median survival was 5.3 months increasing to 7.6 months for transplant recipients and 52.8 months for patients undergoing resection. Survival for the palliation group was 2.8 months.

CONCLUSIONS: CCa is a common finding in PSC. Unfortunately, many patients with CCa/PSC will have inoperable tumours by the time they are referred and regular screening of PSC patients at referring centres is advocated to detect early tumours as resection offers significantly better outcomes for this cohort of patients.

O21

Simultaneous Liver Kidney Transplantation (SLKT) – Indications and Outcomes

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Introduction Patients with end-stage liver disease often have concurrent renal dysfunction. Liver transplantation can reverse renal dysfunction in patients with HRS whereas it has little impact on other causes of renal dysfunction. Pre-transplant renal dysfunction is a predictor of morbidity, mortality and post transplant renal replacement requirements. Hence, SLKT should provide an ideal solution for both problems. The aim of this study was to evaluate indications and outcome after SLKT.

Methods 15 adult patients have received SLKT in Leeds. Their demographic data, operative data and post transplant outcomes were collected. For comparison, two groups of patients, matched for age and sex were identified. These groups included patients undergoing liver transplant alone (LTA) without preoperative renal dysfunction, and liver transplant recipients with preoperative renal dysfunction (LTRI), defined as a creatinine >150 µmol/l. Patients with acute liver failure were excluded.

Results Each group contained 15 patients. The results are summarised in the table below. Survivals were calculated using Kaplan-Meier Survival curves.

[table nn here]

Conclusions Liver transplant recipients with renal impairment require more nursing care, more renal support and have significantly worse survival (p=0.02) than liver transplant recipients with normal renal function. Our data suggests SLKT eliminates these differences and is, therefore, a safe and effective treatment option for patients who have a combination of chronic hepatic and renal insufficiency.

	SKLT	LTA	LTRI
Median MELD score	24	17	29
Mean ITU stay (days)	1.7	1.3	4.1
Mean Inpatient stay (days)	22	17	26
Median Transfusion (units)	7	4	10
Post Operative Dialysis (%)	14	7	70
Dialysis at 1 year (%)	0	0	25
30 Day Mortality (%)	13	7	27
5 year survival (%)	67	79	27

Improved Availability Of Liver/Small Bowel Grafts For Children With Intestinal FailureV Mali¹, P Pocock², R Thakur¹, S Richards², S Falvey¹, A Millar¹, G Gupte¹, AD Mayer¹ and DF Mirza¹¹Liver Unit ,Birmingham Childrens Hospital , Birmingham, Birmingham, B4 6NH, United Kingdom and ²UK Transplant, Bristol, B, United Kingdom

Background: Children with intestinal failure associated liver disease (IFALD) have a high mortality on the waiting list. The Liver Advisory Group at UK Transplant in November 2004 proposed that paediatric recipients of liver/small bowel grafts would be prioritised nationally over non super-urgent paediatric liver recipients. We describe the impact of this on organ availability for this vulnerable subgroup.

Donors: Between 11/04 and 10/05, of a total of 31 paediatric heart beating donors (<17 years), 25 weighed <50 kg (74%) and liver donation was effected in all 25(100%). However, small bowel grafts were only offered in 16/25(64%) and effected in 10/16. Thus only 40% of these small paediatric donors resulted in bowel donation whereas 100% of livers were retrieved from this cohort. Super-urgent liver recipients were allocated 8/31 donor livers and none of these became bowel donors. The distribution of bowel donors was evenly spread across the different liver donor zones (see table).

IFALD Recipients: Between 11/2003 and 10/2005, 39 children with IFALD have been listed for transplantation. [image nn here]Table 2

Conclusions: Increased availability due to changes in liver allocation has resulted in increased paediatric bowel transplant activity. Children <10 kg are more disadvantaged in terms of risk of death on the waiting list (45% mortality vs. 0%), although waiting times are similar (approximately 2 months). Waiting times for isolated bowel grafts remain high. There remains potential for small bowel retrieval within the limited pool of smaller paediatric donors

	Paed donor <50 kg	liver donated	SB offered	SB retrieved
Cambridge	3	2	2	0
Birmingham	9	7	7	6
Kings	6	5	5	3
Royal Free	3	3	3	2
Leeds	7	6	6	3
Newcastle	1	1	1	0
Edinburgh	2	1	1	1
Total	31	25 (100%)	16 (64%)	10 (40%)

	Liver alone <10 kg n=10	Liver and bowel <10 kg n=20	Liver/bowel >10 kg n=7	Isolated Bowel >10 kg n=1
Died waiting	2	9	0	0
Median time to death	43 (34 and 52)	58 (1-295)	0	0
Transplanted	7	2 liver: bridge 7 liver and bowel	7	1
Median time to transplant	22 (4-71)	93 (39 & 97) 64 (27-244)	59 (30-123)	360
Still waiting	0	1	0	1
Median waiting time	0 (1 removed)	77 (1 removed)	0	262

O23

Does Parvus Tardus Waveform Accurately Predict Hepatic Artery Stenosis In Adult Orthoptic Liver Transplantation

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INTRODUCTION

Doppler ultrasounds are now used for post-transplant liver surveillance for vascular complications. Routine scans are performed on day 3 post-transplant and when clinically indicated in our unit. The aim of this study was to assess whether Parvus Tardus Waveform (PTW) accurately depicts hepatic artery stenosis and how it should effect management in Liver transplantation.

METHODS AND MATERIALS

An ultra sound (US) database was used to retrospectively analyse 1302 liver transplants between Jan 1988-Jan 2005. Paediatric transplants were excluded from the study. Patient reports with PTW as a primary finding were selected from the database. Serial ALT, Bilirubin, Alk Phos, Albumin, PT, INR and clotting were recorded for these patients at regular time intervals. The time points were 2 days prior to PTW being diagnosed, date of diagnosis, 1 week, 2 weeks, 4 weeks, 6 months and 1 year after diagnosis.

RESULTS

1302 liver transplants were carried out during the study period. 60 patients were identified as having Parvus Tardus waveform on Ultrasound. 29/60(48%) went onto have an Angiogram after the diagnosis of PTW while 31/60(52%) had a repeat US scan. 14/60(23%) had persistent PTW, and four of these patients were diagnosed with stenosis following an angiogram. PTW completely resolved in 17/60(28%) with no more PTW. The LFTs in this group were found to be normal on follow up.

18/60(30%) patients who had an angiogram were diagnosed with stenosis of the hepatic artery (3 stented, 2 regrafted, 3 hepatic artery thrombosis) while 11/60(18%) angiograms were negative for stenosis. The change in Bilirubin between date of diagnosis and 2 days prior to PTW being diagnosed, was significant between stenosis and no stenosis groups ($p=0.017$). No significant differences were seen between no stenosis and the stenosis groups versus time from transplant to examination, but the median number of days were found to be higher in the stenosis group (33 days) compared to the group where parvus tardus resolved spontaneously (13 days).

CONCLUSION

Parvus Tardus waveform alone was not found to be a predictor of stenosis, but the change in bilirubin and the Parvus Tardus Waveform together were found to be a good predictor of patients at increased risk of hepatic artery stenosis.

O24

The Role Of MELD And Sodium As Predictors Of Outcome In Potential Liver Transplant Recipients

R Rajaganeshan, S Asthana, A Young, P Lodge, G Toogood, S Pollard, M Davies, C Millson and R Prasad

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Introduction:

We have previously reported on the utility of MELD scores in predicting post transplant outcome after liver transplantation (OLT), as well as its accepted role in prioritizing patients awaiting OLT. Serum sodium levels have also been reported to predict the outcome for patients awaiting OLT. This study was conducted to assess whether a combination of the MELD score and serum sodium could better predict the outcome of all patients listed for liver transplantation at a single transplant unit.

Patients and Methods :

Four hundred and twenty-three patients listed for elective liver transplantation (OLTx) at a single unit between 1999 and 2004 were included in this study. Thirty-nine patients were removed from the list before receiving an OLTx. An analysis of this data was performed on an intention-to-treat basis. Recipient variables analysed included age at transplant, MELD at listing, MELD at transplant, ΔMELD (change in MELD), and Serum sodium and albumin levels. Graft failure, 90-day mortality, overall mortality or removals from the waiting list were the outcome variables studied. Univariate analysis was performed using chi-square test and 't' test as appropriate, and significant variables were further analysed using regression analysis. The patients removed from the list were further studied to identify factors predicting progressive liver dysfunction.

Results :

Of 423 patients included in the study, 384 proceeded to OLTx, while 39 were removed from the waiting list. MELD at transplant was an independent predictive factor for 90-day and overall mortality in this group, while serum sodium <130 mmol/L was associated with overall mortality. MELD at the time of removal from the list, ΔMELD, serum sodium <130 mmol/L significantly predicted the likelihood of not being offered a transplant on the waiting list. An equation using MELD –sodium equation predicted the risk of not proceeding to transplant better than MELD or sodium levels alone (c-statistic 0.61 and 0.67 respectively).

Conclusions :

Periodic review of MELD score, ΔMELD and serum sodium for patients on the transplant waiting list will help identify patients who would benefit from early transplantation, and potentially decrease the number of deaths on the waiting list.

Plenary Session 3

Medawar Medal

Thursday 30 March

14.00 – 16.00

O25

Outcome Of Marginal Liver Grafts Initially Refused By One Transplant Unit And Subsequently Transplanted Elsewhere

F Hanif, R Sivaprakasam, P Gibbs, NV Jamieson and RK Praseedom

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Aims: This study aimed to determine the outcome of cadaveric liver grafts which were initially refused on medical grounds or deemed unsuitable for transplantation by one centre but then accepted and transplanted by a different centre.

Methodology: The study was carried out in conjunction with UK transplant and is based on a retrospective data analysis of 34 cadaveric liver grafts which were initially refused by one centre on medical grounds and subsequently transplanted by another center over a period of one year from January 2004 to December 2004. The variables studied include the reason for initial refusal, donor factors, recipient demographics, rejection episodes, post transplant complications and three months graft and patient survival. (Wilson score method to calculate CI and multivariate Cox regression analysis of survival).

Results: The main reasons for the initial decision of refusal were fatty livers 9/34 (26.4%), elderly donors 5/34 (14.7%; Mean age 72.4 ± 7.23), anatomical problems 5/34 (14.7%), adverse past medical history 12/34 (35.2%), abnormal liver function tests 2/34 (5.8%) and prolonged ischaemia time 1/34 (2.9%). Mean recipient age was 53.9 ± 8.9 years. Three patients developed rejection which was treated successfully. 19/34 (55.8%) patients encountered complications including sepsis (41%), 2 hepatic artery thrombosis, one leading to immediate graft failure and death and the other requiring retransplantation, and 2 patients developed biliary strictures leading to graft failure. Three months graft survival was 79.4% (95% CI, 63.2 - 89.7) and three months patient survival was 76.5% (95% CI, 60.0 - 87.6). The best three months outcome was for livers refused on adverse past medical history (91.7% survival, 95% CI, 64.6 - 98.5) and the worst for fatty livers (55.56% survival, 95% CI, 26.7 - 81.1).

Conclusion: Marginal donor livers deemed unsuitable for transplantation by one centre were, when transplanted elsewhere, associated with a relatively poor outcome. However three-quarter of the grafts were successful at three months, highlighting a need for development of more robust nationally agreed criteria for organ selection and refusal.

O26

Nanoparticle Delivery Of siRNA Gene Knockdown To Reduce Pro-Inflammatory Gene Expression In The Donor Kidney

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RNA interference blocks gene expression according to small unique segments of gene sequence. This natural process can be exploited to reduce transcription of specific genes. In transplantation, it is established that donor derived complement C3 is rapidly upregulated in ischaemia / reperfusion injury (I/RI), contributing to tissue damage. This study sought to exploit siRNA to knock-down C3 gene expression in donor organs.

Renal epithelial cells in culture were stimulated with IL-1/IL-6 to upregulate C3 gene expression, and 72 hours later, were transfected with one of a panel of C3-specific siRNA. After 2 days, C3 expression was determined by Real-Time PCR. C3 expression was upregulated in non-transfected cells after stimulation, and by siRNA could be reduced by up to 60%, identifying the most effective siRNA sequence that did not non-specifically induce IFN γ upregulation, a potential off-target effect of siRNA. The most effective C3-siRNA was then packaged into synthetic polycationic nanoparticles that facilitate *in vivo* siRNA transfection. The nanoparticles were added to hyper-osmolar citrate perfusion fluid and administered to donor rat kidneys. After 4 hours of ischaemia, the kidneys were transplanted into syngeneic hosts, and 2 days later they were harvested and C3 gene expression determined by Real-Time PCR.

C3-siRNA reduced post-transplant C3 gene expression by a mean of 62.56% ($P < 0.05$, $n = 4$) compared to untreated transplants, to a level below that detected in normal kidney. When compared against scrambled-FITC labelled siRNA control, C3 gene expression was reduced by 73.34% ($P < 0.05$, $n = 4$). The FITC-labelled scrambled siRNA controls exhibited greater upregulation of C3 gene expression than untreated kidneys, suggestive of off-target effects. Histology showed C3-siRNA reduced I/RI, but fluorescence microscopy of cells and tissues perfused with FITC-labelled scrambled siRNA has not detected siRNA in tissues though more sensitive methods are being developed.

In conclusion, siRNA inhibition of C3 gene expression, effectively reduced local C3 activity compared to controls. The nanoparticle strategy appears to overcome the problem of effective siRNA delivery. It now appears possible to develop arrays of specific siRNA to diminish pro-inflammatory gene expression in donor organs as adjunct therapies to conventional immunosuppression or tolerance induction.

O27

T Cell Homeostatic Proliferation: Serious Implications For Allograft Survival

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Each individual maintains a diverse repertoire of naïve and memory T cells through thymic export of newly formed T cells and homeostatic proliferation of peripheral naïve and memory T cells. Tolerance protocols being tested clinically such as irradiation bone marrow chimera or depleting antibodies e.g. Campath 1H lead to recipient lymphopenia and exaggerated homeostatic proliferation of residual T cells. This can result in naïve T cells acquiring phenotypic and functional characteristics of memory cells, even without cognate antigen exposure. We hypothesise that naïve T cells that had undergone homeostatic proliferation can transform the characteristics of rejection and accelerate graft loss. When class II MHC mismatched BM12 kidney grafts were transplanted into wild-type BL/6 mice, biochemical and histological features of chronic allograft nephropathy developed over 70-80 days before death of recipients from graft rejection (MST=55d). Next, T cell deficient BL/6 RAG^{-/-} mice were reconstituted with 15x10⁶wild type T cells following transplantation of BM12 kidney allografts. Although CFSE labelling of transferred T cells demonstrated extensive homeostatic proliferation in the recipient host following adoptive transfer, the level of T cells in reconstituted recipients only amounted to a fraction of that seen in wild-type mice. Nevertheless, reconstituted RAG^{-/-} mice rejected BM12 kidneys in an accelerated fashion (MST= 11.5d) with histological features of acute rejection. This phenomenon was not restricted to fully MHC mismatched grafts but also seen in minor HY mismatched grafts: wild-type female BL/6 recipients do not reject male kidney grafts but reconstituted RAG^{-/-} mice rejected them acutely (MST=10d). Homeostatic proliferation is required for accelerated rejection as T cells injected into wild-type host (and therefore, did not undergo homeostatic proliferation) did not result in acute graft loss (MST=>57.5d). The ability to accelerate rejection was not limited to the early phase of homeostatic proliferation. BM12 allografts were also rejected acutely even if they were transplanted 50 days after reconstitution of RAG^{-/-} recipients (MST= 8d), suggesting that the repopulating T cells have true long lived “memory” function, even in the absence of cognate antigen. These findings have implications in tolerance protocols and lymphopenia induced by infections such as CMV, HIV.

O28

Outcome Of Renal Transplantation In Patients Of Indo-Asian Ethnicity: Leeds Experience
S Asthana, KV Menon, A Lewington, RJ Baker, L Sedgley, S Willis, JPA Lodge and N Ahmad

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Introduction: Indo-Asian population in the United Kingdom is disproportionately more likely to suffer from end-stage renal disease than the native British population. They are also less likely to receive cadaveric organs under the national organ allocation scheme, and may have a worse outcome after transplant. The economic burden to the NHS is significant and may increase substantially in the future. Comprehensive data on comparative outcome after renal transplantation between population groups is lacking. In the present study we have looked at the differences in graft and patient outcome between the Indo-Asian and native British population over a 20-year period in a single centre.

Methods : All white and Indo-Asian patients undergoing renal transplantation at the Leeds between 1985-2005 were included in this study . Data on recipient age, time on waiting list, cause of renal failure , HLA/DR mismatches and donor age were collected . Categorical data was analysed using the chi-square test while continuous data was analysed using the ‘t’ test. Significant variables were further analysed using logistic regression analysis.

Results : 1864 renal transplant recipients were included in this study, which included 164 Indo-asians (9%). The groups were well matched with respect to age, HLA /DR mismatches although Asian recipients had a significantly longer waiting time ($p<0.001$) [Table-I]. Graft half-life was significantly shorter in the Asian subgroup (67.2mths vs 42.2 mths, $p<0.001$), Time on the waiting list, number of HLA/DR mismatches and previous transplants were the only independent predictors for graft failure.

Conclusion :Graft outcomes after renal transplantation were worse among Asian recipients in this study, but were comparable when the groups were adjusted for waiting time for transplant. HLA-based organ allocation disadvantages recipients from ethnic backgrounds. Future strategies should include increasing awareness for organ donation within ethnic communities ,as well as modifying organ allocation protocols.

	White	Asian
Donor age	39 (5-75)	40.5 (2-75)
Recipient age	42 (3-79)	40.5 (3-71)
HLA mismatch	2 (0-6)	2 (0-4)
0 DR mismatch(%)	70.9%	65.9%
Time totransplant (mths)	9.1 (0-156)	16.9 (1-184.7)

O29

Small Patients Wait Longer For Liver Transplantation- A Case For Living Liver Donation?

CJ Peters¹, PV Pocock², AL Young¹, CE Millson¹ and KR Prasad¹

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Introduction

The number of patients on the UK Liver transplant list is increasing, but the organ donation rates remain fairly static. In addition, an unknown number of patients were either not assessed or assessed and considered unsuitable for listing due to the organ shortage, thereby keeping the mortality of patients on the liver transplant list artificially low. Accepting livers from non-heart beating donors, splitting livers and domino grafts are all attempts to increase the organ donor pool but they all have shortcomings and are insufficient to meet the shortfall. As size match is an important factor in organ allocation we studied the effect of recipient size on waiting time, death and removal from the transplant list.

Methods and Materials

This study utilized the UK Transplant Database to assess the difference in outcomes between adult patients weighing 40-60kg and those weighing >60kg. All adult patients registered between April 1999-March 2000 and April 2003-March 2004 were included in the analysis. The data were compared using the chi-squared statistical test.

Results

The results demonstrated consistent differences between the groups in both time periods. The proportions of patients weighing 40-60kg were similar [1999-2000 98 out of 429 (23%) ; 2003-2004 121 out of 560 (22%)]. Significantly fewer smaller patients were transplanted at 3 and 6 months [1999-2000 at 3 months 49% versus 69% ($p<0.01$) and at 6 months 65% versus 83% ($p<0.01$); 2003-2004 at 3 months 37% versus 67% ($p<0.01$) and at 6 months 55% versus 71% ($p<0.01$)]. The median waiting time for the smaller patients was longer [1999-2000 60 versus 45 days ; 2003-2004 77 versus 58 days].

Conclusion

We demonstrated nearly 1/4 of adult patients awaiting liver transplantation in the UK weigh 40-60kg. This group are significantly less likely to receive a transplant after 3 and 6 months on the transplant list when compared to larger patients. Our data demonstrates that small patients in the UK are being disadvantaged by the lack of size-matched organs.

Living liver donation provides a graft which is eminently suitable for the smaller recipient and is widely available throughout Continental Europe, North America and Asia. The widespread adoption of living liver transplantation in the UK is now overdue.

O30

Anti-CD4 And DST Treatment Abrogates Alloantibody-Mediated Rejection By Inducing B Cell Anergy And Regulatory CD4 T Cells With Indirect Specificity For Alloantigen

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Introduction

Alloantibody is now recognised as an important cause of acute rejection. B cells are solely dependent upon help from CD4 T cells that recognise alloantigen via the indirect pathway. We have shown in a rat model of alloantibody-mediated rejection that a combination of DST and anti-CD4 mAb induces tolerance. We examined the role of T cell regulation in abrogating the alloantibody response and preventing graft rejection.

Methods

PVG.RT1^u (RT1.A^u) rats were made tolerant to class I-disparate PVG.R8 (RT1.A^a) heart grafts by anti-CD4 (OX-38) and DST treatment (MST >100 days, n=35). The mechanisms responsible for maintaining tolerance were studied by a combination of adoptive transfer experiments and analyses of alloantibody responses following challenge with 24-mer peptide encompassing the immunodominant region of RT1.A^a.

Results

Transfer of 1.5×10^8 naïve RT1^u splenocytes into RT1^u rats tolerant to an R8 heart graft did not cause rejection (MST >160, n=3), indicating that dominant tolerance maintains graft survival. Adoptive transfer of purified lymphocyte subsets from tolerant animals into CD4 T cell-reconstituted nude RT1^u recipients revealed that regulation resided in the CD4 T cell compartment (MST >50, n=6). This regulation could be broken by a sufficiently strong immunogenic stimulus, because 4 of 7 tolerant animals immunised with 100µg of allopeptide in CFA developed strong alloantibody responses. Surprisingly, the antibody response was directed against the 24-mer peptide and not against intact, conformational RT1.A^a antigen, suggesting that tolerance persists within the alloantigen-specific B cell compartment, even when T cell help is available. B cell anergy, rather than deletion, is the more likely mechanism as nude RT1^u rats that received DST were still able to develop alloantibody and reject R8 heart grafts after transfer of naïve RT1^u CD4 T cells (MST 13, n=5).

Conclusions

Anti-CD4 and DST abrogates alloantibody-mediated rejection by promoting the development of regulatory CD4 T cells with indirect allospecificity, and by inducing B cell anergy. Indirect allorecognition and alloantibody responses are significant factors in the development of allograft rejection and these results suggest that strategies to regulate indirect T cell allorecognition may have clinical potential.

O31

Adoptive Cell Therapy Using In-vitro Generated CD4⁺CD25⁺ Regulatory T Cells with Indirect Allospecificity to Promote Donor-specific Transplantation Tolerance

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The key goal in clinical transplantation is the induction of donor-specific tolerance to minimise the morbidity and mortality associated with long-term immunosuppression. CD4⁺CD25⁺ regulatory T cells (Tregs) play a crucial role in the prevention of autoimmunity, and appear to mediate transplantation tolerance, and these cells can have indirect allospecificity for donor antigens. Here we show that Tregs can be subverted into allopeptide specific cells in-vitro and expanded to large numbers, and importantly they were capable of inducing donor-specific transplantation tolerance. Using bone-marrow derived autologous dendritic cells pulsed with a peptide from H2-K^b, we generated T cell lines from purified CD4⁺CD25⁺ Tregs of CBA/Ca (H2^k) mice. The cell lines expressed high level of CD25 and Foxp3. They were more potent suppressors than freshly isolated Tregs. When co-injected with naïve CD4⁺CD25⁻ effector cells into CBA mice carrying a CBK (H2^k + K^b) skin graft, the K^b specific Tregs suppressed cytokine production of CD4⁺CD25⁻ cells. Importantly, they preferentially accumulated and divided in the graft draining lymph node, and could be found within the graft. The K^b specific Tregs prevented CBK but not third party B10.A (H2^k + D^b) or BALB/c skin graft rejection mediated by effector CD4⁺CD25⁻ cells. Finally, we extended this study in humans, we generated human Treg cell lines specific for an HLA-A2 peptide from purified peripheral blood CD4⁺CD25⁺ cells of DR0101⁺HLA A2⁻ individual. The specificity was demonstrated in functional assays and flow cytometry analysis using a fluorescent tetramer composed of HLA-DR0101 and the A2 peptide. Furthermore, these cells could be expanded to large numbers i.e. 1600-fold increase during a two-week period. The expanded cells maintained the expression of lymphoid homing receptor CD62L, suggesting that they were able to migrate to lymphoid tissues in vivo. Taken together, these data pave the way for clinical studies using CD4⁺CD25⁺ regulatory T cells with indirect allospecificity for the induction of donor-specific transplantation tolerance.

O32

Endothelial Injury and Proliferation: A Possible Mechanism for Macrophage Involvement in Renal Allograft Rejection

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Macrophages(M Θ) are implicated in both acute and chronic renal graft rejection but, the mechanisms remain unclear. We hypothesise that M Θ induce direct vascular endothelial cell(VEC) death and lymphatic endothelial cell(LEC) proliferation in this setting.

We performed immunohistochemical (IHC) studies on tissue from human non-functioning renal allografts(n=28) and control nephrectomy specimens(n=19). This shows significant reduction in the microvascular density of interstitial CD31 positive capillaries(p<0.001) and increased interstitial M Θ infiltration(p<0.001) compared to control tissue. IHC of control tissue with the LEC marker podoplanin demonstrated normal distribution of lymphatic vessels around large interlobular arteries. 13 grafts however exhibited increased lymphatic density p<0.001 and vessels within the interstitium; a finding verified with additional LEC markers(LYVE-1 & VEGFR-3). Importantly, double staining with podoplanin and CD68 demonstrated M Θ within lymphatic vessels indicating functionality.

The combined findings of increased M Θ infiltration, microvascular rarefaction & the de novo development of functional interstitial lymphatic vessels supports our hypothesis.

We then dissected the interaction between M Θ and microvascular endothelial cells (MEC) using established in vitro coculture techniques(Duffield et al J Immunol 2000). Coculture of cytokine activated bone marrow derived M Θ with MEC resulted in increasing MEC apoptosis and reduced cell number over a 24 hour time course. Non activated M Θ or cytokines alone were not cytotoxic. We performed cocultures in the presence of L-Nil, a specific inhibitor of inducible NO synthase (control D-Nil). L-Nil inhibited MEC apoptosis by 95+/-2.26% (p<0.001) and preserved cell number implicating a major role for NO in M Θ mediated MEC death. Importantly, L-Nil treatment did not affect TNF α production by M Θ suggesting that TNF α is not involved in MEC death.

Time lapse microscopy of activated cocultures demonstrated both contact dependant and independant MEC death.

Our ongoing work aims to explore the interaction between M Θ and LEC in vitro.

In conclusion, our work indicates a role for M Θ in the deletion of microvascular interstitial vessels with resultant tissue hypoxia and ischemia & supports the involvement of M Θ in the interstitial lymphangiogenesis that may occur in renal allografts.

Parallel Session 4(a)

Transplant Coordinators/Organ Donation

Thursday 30 March

16.30 – 18.00

O33

The Potential For Non-heartbeating And Heartbeating Organ Donation

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UK Transplant's (UKT) national potential donor audit (PDA) has been running since April 2003, as part of a series of measures to improve organ donation. Data on the potential for non-heartbeating (NHB) donation have been collected from January 2004.

An evaluation of 15 months of data has shown that, from January 2004 to March 2005, there were 2,520 patients for whom NHB donation was possible and in 1,552 (62%) patients active treatment was withdrawn making these patients potential NHB donors.

There was no record of discussion regarding NHB donation in 1,289 (83%) patients, mainly due to the lack of a NHB donor programme. Of the 263 patients for whom the possibility of NHB donation was known to have been suggested to relatives, consent for donation was given for 132 (50%) patients.

Of the 132 patients for whom consent for donation was given, 79 (60%) became deceased NHB solid organ donors. The overall refusal rate for NHB donation was 50% (95% confidence interval (CI): 44%-56%), and for males and females was 46% and 55%, respectively, $p=0.15$.

As far as heartbeating (HB) donation is concerned, an evaluation of 24 months of data (April 2003 – March 2005) has shown that there were 2,740 potential HB donors with no absolute medical contraindications. Of the 2,320 patients for whom the possibility of HB donation was known to have been suggested to relatives, consent for donation was given for 1,379 (59%) and not given for 941 (41%).

The overall refusal rate for HB donation is 41% (95% CI: 39%-43%), although there is considerable variability in the rate over time. The refusal rate was highest in April to June 2003, the first quarter of the audit (49%) and lowest in October to December 2004 (34%). There were no significant differences in the refusal rate between the different age groups or between male and female potential donors. For ethnicity, of 2,174 potential donors for whom data were complete, the refusal rates were 35% and 70% for white and non-white potential donors, respectively.

Using information provided by the PDA, an in-house coordinator scheme was piloted in two intensive care units (ICU). The coordinator was placed in the ICU to be available when a potential donor was identified. This pilot proved to be very successful in increasing the referral rate of potential donors and the scheme is now being implemented in other ICUs in the UK.

O34

Outcome of Living Donor Kidney Transplantation in the UK

S Armstrong, RJ Johnson, CJ Rudge, SV Fuggle and JLR Forsythe

On behalf of the Kidney and Pancreas Advisory Group, UK Transplant, Fox Den Road, Stoke Gifford, Bristol, BS34 8RR, United Kingdom

Background: This study investigates transplant and patient outcome after living related donor (LRD) and living unrelated donor (LURD) kidney transplantation in the UK between 1998 and 2004 and compares with outcome after deceased heartbeating donor (DHBD) transplantation. In particular, the potential influence of poor HLA matching in LURD transplants is investigated.

Methods: 1710 LRD, 479 LURD and 7143 DHBD transplants were analysed. Kaplan-Meier survival estimates were calculated and Cox regression models were used to analyse the combined effect of many factors on transplant survival (time from transplant to the earlier of return to regular dialysis or patient death) and patient survival after first living donor transplant.

Results: *Transplant survival* - Three-year transplant survival of LRD transplants (89%) and LURD transplants (91%) was comparable, but superior to that of DHBD grafts (82%), $p < 0.0001$. Cox regression modelling showed donor and recipient age, donor-recipient gender match and HLA-B+DR mismatches (0-3 vs. 4) significantly to influence survival after living donor transplant. Three-year transplant survival was 86% for both poorly matched (4 HLA-B+DR mismatches) LURD transplants and 000 mismatched DHBD transplants.

Patient survival - LRD transplants had significantly better three-year patient survival (97%) than both LURD transplants (94%), $p = 0.003$, and DHBD transplants (92%), $p < 0.0001$. Donor and recipient age influenced patient survival after living donor transplant. In addition, recipients of poorly matched LURD transplants (4 HLA-B+DR mismatches, 29% of LURD transplants) were associated with significantly inferior patient survival (relative risk of death=4.2, 95% CI 1.9-9.1). Three-year patient survival for these poorly matched LURD transplants was 90%, compared with 95% for 000 mismatched DHBD transplants ($p = 0.01$) and 92% for other DHBD grafts ($p = 0.3$). Further analyses are being carried out to investigate these outcomes.

Conclusion: Three-year transplant survival was comparable for LRD and LURD transplants and was superior to survival of DHBD transplants. Influential factors were donor and recipient age, donor-recipient gender match and degree of HLA mismatch. Three-year patient survival was significantly better after LRD transplant than after both LURD and DHBD transplant. Reasons for inferior patient survival after poorly matched LURD transplant are being investigated.

O35

The Potential for Paired Living Kidney Donation in the UK

RJ Johnson, JE Blackwell, L Burnapp, DC Pugh, SV Fuggle and CJ Rudge

On behalf of the UK Transplant Kidney and Pancreas Advisory Group, UK Transplant, Bristol, BS34 8RR, United Kingdom

ABO incompatibility and the presence of donor-specific HLA antibody preclude many potential living donor kidney transplants. From April 2006, the Human Tissue Act will enable paired donation in the UK, whereby incompatible donor-recipient pairs can exchange kidneys so that recipients can receive alternative compatible living donor organs. This study aims to identify the potential for establishing a paired kidney donation scheme in the UK.

All transplant centre based UK living donor transplant co-ordinators were contacted in Autumn 2005 and asked to provide data on living donor kidney transplants that could not proceed because of ABO or HLA incompatibility.

Information received from 13 centres relating to the last 2 years (290 pairs) showed 46% of potential donor-recipient pairs were ABO incompatible and 54% were HLA incompatible.

The demographics of the potential recipients were - age 43 ± 1.5 years, 53% female, 87% white. 20% were incompatible with more than one prospective donor. 61% of the potential recipients are on the deceased donor transplant list, 13% have received a deceased donor transplant and 3% have received an alternative living donor transplant. The mean age of the prospective donors was 44 ± 1.5 years and 32%, 28% and 19%, respectively, were spouse/partners, siblings or parents of the potential recipients. Blood group distributions of the potential recipients and their donors are different from those in normal donor and recipient pools, as shown below, and suggest that too few blood group O donors will be available to meet demand.

To inform discussion on the complex issues surrounding the establishment of a paired kidney donation scheme, the data collected will be used in computer simulation models developed to compare and contrast the effectiveness of alternative matching algorithms.

	Donor blood group (%)				Recipient blood group (%)			
	O	A	B	AB	O	A	B	AB
Blood group incompatible	0	61	27	12	79	11	10	0
HLA incompatible	62	29	8	1	38	41	17	4
All	33	44	17	6	57	28	14	2
Deceased donors/Tx list	48	39	10	2	50	33	14	3

O36

A National vs a Single Centre Approach to Kidney Paired Donation (KPD)

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KPD is a successful alternative treatment for recipients who have incompatibilities with their intended donors. Published data from nationally or regionally based programmes suggest that logistical issues can severely reduce the number of potential transplants. Would a paired kidney exchange programme therefore generate more compatible transplants if conducted in a single unit? We have examined the potential of a simple algorithm aimed at maximising KPD in our own unit.

We performed a retrospective review of all incompatible recipient-donor pairs from our own centre over a three year period. Data was compiled on recipients and their respective potential donors covering blood group, forbidden HLA class I and II antigens and sensitization history. A simple algorithm was constructed to maximise organ allocation by prioritizing couples with the smallest number of potential exchanges.

In total, 23 recipients were identified with 25 potential donors. All recipients were screened with flow cytometric beads and/or luminex techniques for anti-HLA class I and II antibodies. 10 recipients were identified with 1 or more ABO compatible and potentially crossmatch negative kidney exchanges. All 10 recipients could have been transplanted in this simulation.

KPD offers an incompatible donor/recipient pair the opportunity to match with another donor and recipient in a similar position. Whilst it is widely acknowledged that the potential for creating compatible transplants is vast, it has been shown that national programmes are encumbered by logistical issues. In this study, assuming no significant changes in recipient sensitization, donor medical status and donor willingness from initial assessment, paired donor exchanges could have represented a 25% increase in the rate of living donor renal transplantation. This could not have been improved upon if patients had been matched through a national programme. The implementation of the new Human Tissue Act may make paired exchanges a reality in the UK.

O37

Engaging Staff to Enable Improvement When Considering Organ Donation in the Critical Care Setting

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The Potential Donor Audit (PDA) UK has sanctioned detailed exploration of donation practice in Critical Care Units (CCU). Consistent negative trends impelled our Donor Transplant Coordinator (DTC) team to explore the donation process with staff, with the aim of improving this service.

In order to examine practice and design service improvement, discussions commenced in two Critical Care Units. It was agreed that the key measures for improvement would be staff and family satisfaction with the new process and staff adherence; not an increase in donation.

Unit One is a 10-bedded CCU/High Dependency Unit within a district general hospital. This CCU has a consistent 100% donor referral rate (5 potential donors per year) and a consistent 60% consent rate. Unit Two is a neurosurgical CCU based in a large teaching hospital. It has 14 beds with an average of 25 potential organ donors per year. Referrals are sporadic and the consent rate ranged from 50% to 30% during the first two years of audit.

Most staff were openly supportive of organ donation and were keen to embrace change in order to improve practice. Consensus was reached quickly that change was needed, but resistance was encountered over involving the DTC in initial family conversations.

In one CCU process mapping was agreed as the tool to ascertain current practice. All CCU staff were invited to participate over a one-month period. 80 responses were received. The main themes identified were that there was:

- No consistency in donor identification, management, the family interview, or utilisation of staff.
- Missed donors due to non or inappropriate approaches
- Delays in contacting the DTC

From this point further progress was made. Over time, the clinicians agreed to work in collaboration with the DTCs when initiating donation conversations with families. An evidence based guideline and pathway with audit tool has been devised. Both centres have commenced collaborative working when potential donors are identified. The regular legitimate presence of the DTC team on the CCU has led to acceptance of an In House Coordinator role, due to commence shortly.

The DTC team has also gained the support of the Critical Care Network and with the Network Service Improvement team, the guideline and pathway are to be developed into a Care Bundle and used throughout the Network.

O38

Living Donors Will Accept High Surgical Risks

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Introduction

This study was conducted to investigate risk perception within the context of living kidney donation. The study group consisted of previous donors as they were thought to have a clearer understanding of the risks involved. Focus was placed on how much risk to their own lives donors would tolerate. Risk communication was investigated to see whether different presentation methods had any impact on the acceptance of surgery.

Method

A questionnaire was sent to the 77 people who donated at Guy's Hospital, London between May 2003 and January 2005. Donors were asked to select the risk they would have accepted from a list of options. They were then guided through scenarios, each with a progressively worsening prognosis for the recipient, to determine whether prognosis had any influence. They were then asked about the likelihood of donation to a number of different potential recipients.

Risk communication was investigated by altering the way risk was presented. The donor sample was randomly divided into two groups. Group A were presented with a 'risk of death' (i.e. 1 in 3000) and group B were presented a 'chance of survival' (i.e. 99.99%).

Results

61 questionnaires were returned, 32 A and 29 B (79% response rate). The mean follow up time was 298 days.

58 would have still donated had the risk of death been higher. 25 would accept a 50% risk of death to donate to their closest relative. 72% of these were from group B. The modal risk accepted by group A was 1% and by group B was 50%.

28 participants gave identical answers for each scenario and of those whose answers changed, 26 would accept an increased risk as recipient's need increased.

As the donor-recipient relationship distanced donors were less inclined to donate. However, more were willing to donate to children over adults despite the distance in the relationship being the same.

Conclusion

Living kidney donors are willing to accept much higher risk to their own lives than the 1 in 3000 risk of death currently quoted. Almost half are willing to accept risks as high as 50%. Those donors presented with risk in terms of survival are often prepared to accept higher risks, suggesting communication methods do have an impact on the response. The study's findings have implications for those procedures carrying higher donor risk, such as kidney donation by marginal donors and living liver donation.

Parallel Session 4(b)
Renal Clinical Transplantation
Thursday 30 March

16.30 – 18.00

O39

Do Multiple Arteries In Kidneys Removed Laparoscopically Influence The Outcome Of Living Donor Transplantation?

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Objectives: Laparoscopic retrieved donor kidneys with multiple arteries can pose a technical challenge to the recipient surgeon. The objectives of this study were to review in a consecutive series of laparoscopic donor nephrectomies the types of arterial reconstruction employed; outcomes of multiple artery compared to single artery grafts; and the role of pre-operative radiology in defining the anatomy.

Methods: A retrospective case-note study of 75 consecutive laparoscopic retrieved living donor kidneys transplanted in the period 1999-2005 in a single center was undertaken.

Results: 75 kidneys retrieved laparoscopically [53 left and 22 right] were all transplanted. Anatomy at retrieval after stapler application showed a single artery in 56 [75%] and multiple arteries in 19 [25%]. Multiple vessels were found in 7/22 [32%] right sided kidneys. Reconstruction techniques of those with multiple arteries were as follows:

- 1 triple renal artery anastomosed to a gonadal vein patch;
- 5 double renal arteries joined side to side on the bench with a common ostium
- 6 double arteries with a significant polar vessel [5 lower, 1 upper] joined end to side onto main artery
- 1 double artery implanted separately onto external iliac artery
- 6 double renal arteries where a small upper polar vessel was ligated

There were two graft losses [one thrombosis and one hyperacute rejection] and one patient with ureteric stenosis. Comparison between multiple and single artery groups showed no significant differences in: patient survival at 1 year (100% for both), early graft loss 2(10.5%) vs. 0 ($p < 0.062$), immediate function-16 (84.2%) vs. 55(98.2%) ($p < 0.048$) and lymphocele-2 (10.5%) vs. 1(1.7%) ($p < 0.58$). There were no significant difference for post-operative length of stay, serum creatinine and GFR at 6 months. There were no significant differences in mean ischaemic times: 4.1 vs. 3.4 minutes for first warm time; 28 vs. 31.4 for second warm time; and 104 vs. 130 for cold time. Pre-operative radiological imaging failed to identify the correct anatomy in 15/19 (polar vessel in 12/12, second renal artery in 2/6, double renal vein in 1/1).

Conclusion: The outcome of laparoscopically retrieved kidney having multiple arteries is good, even if missed on pre-operative radiology. Multiple vessels should not be considered a contraindication in laparoscopic donor nephrectomy.

O40

Utility Of Cardiovascular Risk Profiling Of Potential Renal Transplant Recipients With Serum Brain Natriuretic Peptide And Cardiac Magnetic Resonance Imaging In High Risk Patients
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Background Potential renal transplant recipients are at high risk of cardiovascular (CV) disease. CV events are the leading cause of both early and late death with a functioning graft. Serum brain natriuretic peptide (BNP) is related to left ventricular (LV) function and can predict mortality and peri-operative outcome in other populations. We studied the relationship between CV risk factors, BNP, cardiac function and survival in potential renal transplant recipients.

Methods 254 (65.1% male; median age 53; range 24-73) patients from the renal transplant assessment clinic underwent CV risk profiling during the period January 2002-June 2005. High risk patients were defined by any of: age \geq 50, history of cardiac or vascular disease, diabetes or documented echocardiographic or ECG abnormalities. Cardiac function was assessed by cardiac magnetic resonance imaging (Siemens Sonata 1.5T). Serum was spun and frozen for measurement of BNP by radioimmunoassay (Shionoria).

Results 69 of these patients received a renal transplant. There were 42 deaths of which 5 were in patients with a functioning graft. Patients with ischaemic heart disease ($p<0.001$), diabetes ($p<0.01$), LV systolic dysfunction ($p<0.05$) and peripheral vascular disease ($p<0.001$) had significantly reduced survival. Renal transplantation was associated with improved survival ($p<0.01$) despite no significant difference in prevalence of ischaemic heart disease, LV systolic dysfunction or diabetes between patients who received a graft and those who did not. Although BNP correlated with cardiac mass and function (LV mass $R=0.374$, $p<0.001$, ejection fraction $R=-0.20$, $p<0.01$), it was unable to predict accurately mortality during this follow up period (sensitivity 76.9%, specificity 34.9%).

Conclusions Targeted screening can minimize early post transplant deaths. Patients with ischaemic heart disease or LV systolic dysfunction awaiting renal transplantation have a greater mortality and should be investigated for remediable coronary lesions. As transplantation is associated with improved survival, this remains the optimum treatment for end stage renal failure in appropriately selected high risk patients. The low specificity of BNP limits its diagnostic or prognostic value although a low serum BNP may be reassuring for listed patients.

O41

Predictors of Diabetes Mellitus and Stratification of Immunosuppression After Renal Transplantation

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The development of Post Transplant Diabetes Mellitus (PTDM) is a serious complication that is associated with an increased risk of chronic transplant dysfunction and cardiovascular morbidity and mortality. Identifying high risk patients would be beneficial and allow tailoring of immunosuppression and cardiovascular risk factor management in the hope of improving long term outcome. All patients who received a renal transplant between 1994 and 2004 and had at least one year of follow up were identified. Age, weight, Carstairs deprivation category, type of immunosuppression, pre transplant random glucose and post transplant random glucose concentrations were collected.

Seven hundred and eighty seven transplants recipients were identified. Seventy patients (8.9%) were known to have diabetes pre transplant, these were excluded from further analyses, and 55 developed PTDM (7%). Patients who developed PTDM were significantly older (49 vs 40 years, $p=0.001$), heavier (78 kg vs 69 kg, $p=0.001$), more likely to live in Carstairs deprivation categories 6 and 7 (42.9% vs 28.6%, $p=0.038$) and were more likely to be treated with tacrolimus (25.5% vs 11.8%, $p=0.006$). Mean glucose pre transplant (6.4 mmol/L vs 5.5 mmol/L, $p=0.002$) and the glucose within the first 24 hours post transplant (12.8 mmol/L vs 10.5 mmol/L, $p=0.047$) was higher in those who developed PTDM. There was no difference in sex or the use of high dose corticosteroids. By multivariate analysis, the predictors of PTDM were age (HR 1.04, 95% CI 1.008-1.073), weight (HR 1.032, 95% CI 1.006-1.059), mean glucose pre transplant (HR 1.60, 95% CI 1.18-2.169), glucose within the first 24 hours (HR 1.088, 95% CI 1.015-1.166) and the use of tacrolimus (HR 3.84, 95% CI 1.632-9.046). PTDM developed in 0.9% of patients under the age of 35 and who weighed less than 60kg and increased to 20.6% of patients over the age of 60 and who weighed more than 75kg. Factoring in a mean glucose concentration greater than 5.5 mmol/L increased the incidence of PTDM in those over 50 and who weighed more than 75 kg to 27.3%.

In conclusion, taking into account three factors, age, weight and glucose pre transplant we can predict those patients at higher risk. High risk patients should be considered for tailoring of immunosuppression and anti-hypertensive medication and cardiovascular risk factors should be managed intensively.

O42

DMSA Scan For Living Kidney Donors: Is It Necessary?

M Shehata, L Evans and D Green

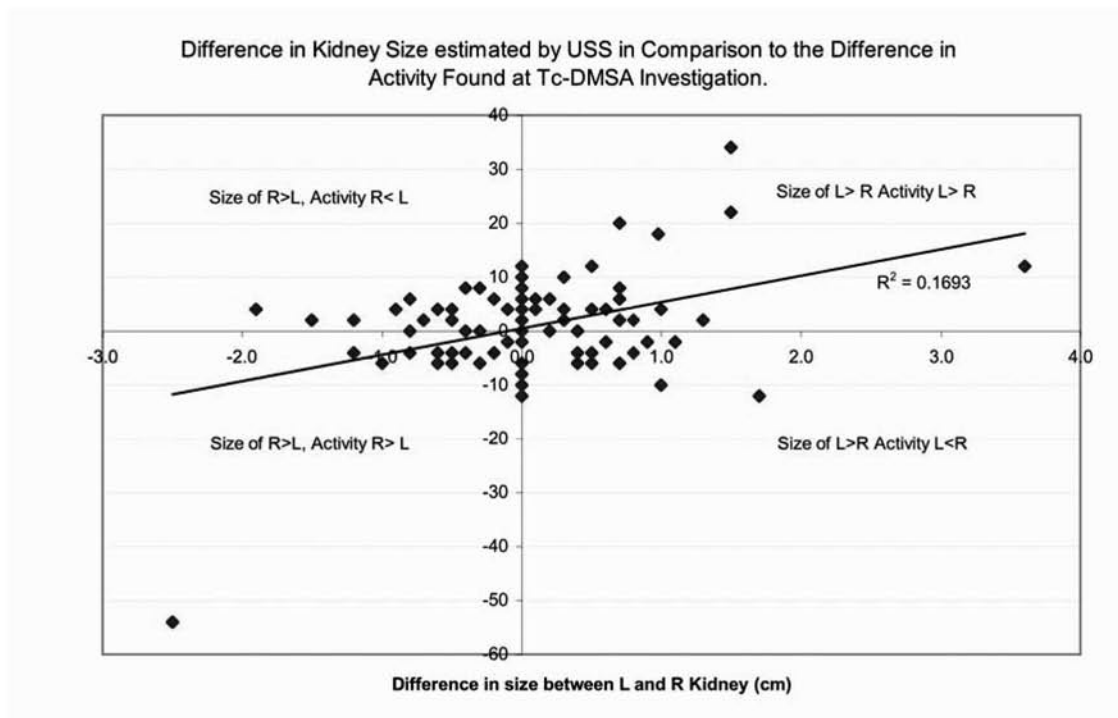
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The BTS recent guidelines for living donor kidney transplantation recommend that divided kidney function need only be assessed if there is a considerable disparity of size between the kidneys or anatomical abnormality is noted, but is otherwise not indicated. In our programme, all potential donors have their kidneys size measured by ultrasound scan and divided kidney function by TC-DMSA scan.

The aim of this analysis was to evaluate the correlation between kidney sizes and divided function.

The expected pattern of size and function being directly proportional was only seen in 45% of potential donors. Kidneys estimated as being equal size were seen in 23% of potential donors but only 11% of these had equal function. Of these 5% had divided function, which differed by at least 10% between kidneys. An inverse relationship between size and activity was seen in 30% of our potential donors. A scatter plot of the difference in size between left and right kidneys against difference between left and right activity failed to show a strong positive relationship with a correlation coefficient of only 0.4 ($r^2 = 0.2$)

Our data suggest that difference in kidney size on ultrasound scan alone is insufficient to determine divided function. The use of kidney size as a determinant of potential function may underestimate the effect of cortical scarring which DMSA scan measure (cortical activity). This is particularly important with marginal living donors.



O43

Do Failing Transplant Recipients Receive Optimum Care?

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In December 2003 the UK Renal Registry (UKRR) collected data from renal units covering 11,194 of the 17,500 transplant recipients. The UKRR receives quarterly biochemical data on these patients and 8,218 patients had a serum creatinine measured in the last quarter of 2003.

Using the abbreviated MDRD formula, 26% were in CKD stage 1-2, 56% stage 3, 15% stage 4 and 2.7% stage 5. Achievement of standards for haemoglobin, ferritin, BP, cholesterol, phosphate, calcium, iPTH, albumin and bicarbonate were analysed by CKD stage.

Haemoglobins fell with decreasing eGFR, such that of the 2.7% of transplant patients with eGFR < 15 ml/min 30% had an Hb < 10 g/dl and 51% < 11 g/dl. Accurate data on use of EPO in these patients was not available. The fall in haemoglobin contrasts with a rise in median serum ferritin from 89 to 212 g/L with decreasing eGFR. The reasons for this may be multi-factorial including decreased utilisation of ferritin with lower erythropoietin levels, ferritin acting as an inflammatory marker (as albumin also fell), iron infusions given for anaemia and lack of EPO provision for these patients.

Control of mineral metabolism also seems to be poor with almost ½ of Stage 5t and ¼ of Stage 4t having a PTH above the recommended limit. Phosphate control in these patients is also poor. Establishing vascular access in these patients is also important, although renal units are currently unable to provide this data.

The annual prevalent transplant failure rate in the UK is 2.3% and which is similar to most other countries. In the UK many patients with failing grafts remain under transplant clinic follow up rather than under CKD clinic protocols. The contribution of this to the poorer recognition and/or management of these patients needs to be explored, to see how access to these services can be improved.

	Transplant patients by CKD stage			
	Stage 1-2 (≥60)	Stage 3 (30-59)	Stage 4 (15-29)	Stage 5 (<15)
Number of patients	2,123	4,658	1,212	225
% of patients	25.8	56.7	14.8	2.7
eGFR Median	not calculated	45	25	12
Hb mean, SD	13.6 ±1.6	12.8 ±1.6	11.6 ±1.6	11.0 ±1.8
Hb % < 10g/dl	2	4	14	30
Hb % < 11g/dl	5	13	34	51
Ferritin median µg/L	89	111	168	212
Po4 % > 1.8 mmol/L	0.2	0.3	2.7	32.7
CaxPO4 > 4.4 mmol ² /l ²	0.2	0.1	2.8	28.3
iPTH % > 32 pmol/L	5	9	27	48
Albumin < 35 g/L	7	9	15	32

O44

Relative Insulin Resistance, Declining First Phase Insulin Secretion And Weight Gain Are Predictive Of Worsening Glucose Tolerance In Non-Diabetic Renal Transplant Recipients Treated With Tacrolimus

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Background New onset diabetes after transplantation is an important complication of renal transplantation. Our previous research has shown that even non-diabetic renal transplant recipients have lower first phase insulin secretion (FPIS) than healthy, non-diabetic controls, despite similar insulin sensitivity (SI) and second phase insulin secretion (SPIS). We followed these transplant recipients longitudinally for changes in fasting glucose and examined them for determinants of worsening glucose tolerance.

Methods 18 Caucasian renal transplant recipients 7 – 39 months post-transplantation treated with tacrolimus were examined with the frequently sampled intravenous glucose tolerance test to derive FPIS and SI, at two time points six months apart. SPIS was estimated from a meal tolerance test. Glucose tolerance status was defined using fasting glucose according to WHO criteria. BMI, Waist-Hip ratio (WHR), Glomerular Filtration Rate, tacrolimus levels, age, family history of Type II diabetes and corticosteroid therapy were also recorded.

Results At baseline all subjects had normal fasting glucose. 6 months later 4/18 subjects had a deterioration of glucose tolerance (1 with impaired fasting glucose, 3 with diabetes mellitus). Baseline SI was lower in the 4 subjects who had subsequent glucose intolerance (1.73 vs. 4.95 X – 10⁻⁴ min⁻¹.(pmol/L); P = 0.02). Although FPIS was similar at baseline (1192 vs. 1168 pmol/L; P = 0.93), subjects with worsening glucose tolerance experienced significant decline in FPIS, and not SI or SPIS between the two time points (-874 vs. +184 pmol/L; P = 0.006) than subjects who maintained normal fasting glucose. The 4 subjects with glucose intolerance also had significant rises in BMI (+1.4 vs. -0.46 kg/m²; P = 0.005) and WHR (+ 0.05 vs. +0.01; P = 0.042) between the two time points. None of the other factors were significantly different between the two groups.

Conclusions 4/18 subjects showed worsening glucose tolerance after only 6 months of follow up. These subjects had a lower SI at baseline associated with marked decline in FPIS during the study period. In addition body weight represented as BMI and WHR increased significantly in the group with glucose intolerance. These traits closely mimic the pathophysiology of Type II diabetes.

O45

Factors Influencing Five-Year Paediatric Renal Transplant Survival In The UK

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Transplant and follow-up details for all UK paediatric renal transplants are reported to the National Transplant Database held by UK Transplant. Analysis of 596 first paediatric kidney only transplants from cadaveric heartbeating donors in the UK, 1995-2001, was undertaken to investigate the influence of various factors on five-year transplant survival. These factors included donor and recipient demographics, year of graft, HLA match and kidney exchange. Deaths with function were treated as transplant failures. Patients were defined as under 18 years at time of transplant. Cox regression models were fitted to analyse the combined effect of factors on transplant outcome.

Five-year transplant survival of paediatric patients was 72% (95% CI 68-76%). Investigation showed year of graft, donor age and recipient primary renal disease to have a significant influence on transplant survival, while HLA match did not influence outcome significantly.

Five-year transplant survival has improved year-on-year for paediatric patients transplanted in the period analysed (RR 0.9, 95% CI 0.8-1.0, $p < 0.05$). Very young donors confer an increased risk of failure compared with donors aged 18-29 years, while donors aged over 40 years are associated with the greatest risk of transplant failure for paediatric patients (RR 2.2, 95% CI 1.0-5.1, $p < 0.1$). Investigation of primary renal disease found that glomerulonephritis was associated with poorer outcome than other renal diseases.

In order to compare risk-adjusted outcome of paediatric and adult patients, a combined model for five-year transplant survival was investigated. The risks of transplant failure relative to that for recipients aged 24-39 years were

1.8 (95% CI 1.2-2.9, $p = 0.01$) <5 years

1.1 (95% CI 0.7-1.7, $p = 0.7$) 5-10 years

1.3 (95% CI 0.8-1.9, $p = 0.3$) 11-13 years

1.9 (95% CI 1.4-2.5, $p < 0.0001$) 14-17 years

1.3 (95% CI 1.0-1.7, $p = 0.04$) 18-23 years

Thus the risk is comparable for those recipients aged 5-13 years, but significantly worse for those aged <5 or 14-23 years.

Transplant outcome for 14-17 year-olds was in fact comparable with that for patients aged 60 years and over, although death-censored graft survival was poorer in 11-17 year-olds than in any other age group.

Transplant survival is improving in paediatric recipients, however adolescents have a worse transplant outcome than other paediatric and adult recipients.

O46

**Paediatric Kidney Transplantation into the Abnormal Urinary Tract:
A UK survey on behalf of the 'Surgical Challenges in Paediatric Transplantation' forum**
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Introduction

The optimal pre-transplant management of the paediatric urinary tract is a matter of ongoing debate. There is a spectrum of outcomes reported for children with so called 'bad bladders'. In order to review contemporary UK practice, we surveyed the units represented by members of the 'Surgical Challenges in Paediatric Transplantation' forum of the BTS.

Methods

A questionnaire was issued to UK centres with paediatric kidney transplant programmes. Information on 5 years' activity (2000-2004) was requested on unit structure, recipient demographics, diagnoses, pre-transplant workup including urinary tract surgery, graft outcome and post-transplant management.

Results

Details for 74 patients were acquired from 8 centres. There were 62 boys and 12 girls. 39/74 had posterior urethral valves (PUV), 14/74 had neuropathic bladders, 5/74 had prune belly syndrome. 16 had other uropathies. The median age at transplant was 12 years (range 1-17), and the median follow-up was 36 months (range 6-69). There were 78 kidney transplants within the five year period. Ten were re-transplants.

Ten children had undergone proximal diversion (vesicostomy or ureterostomy) at some point. Thirteen had undergone augmentation or substitution cystoplasty. Urinary drainage was by intermittent catheterisation (ISC) in 26/74 (14 via Mitrofanoff stomas). Transplants were into native bladders in 61, augmented systems in 13, ileal conduits in 3, and into a cutaneous ureterostomy in one.

Seven grafts were lost: 3 early, and 4 late. One child died with a functioning graft. Graft function was specified in 57 children: 18 had deteriorated, and 15/18 were in children with PUV. Recurrent UTI (commonest), chronic allograft nephropathy and acute rejection were the factors identified in deteriorating grafts.

In the PUV group, 9/39 had no documented pre-transplant urodynamics: 8/9 had deteriorating function. 10/15 with deteriorating graft function emptied by ISC. 8/15 had recurrent UTI.

Conclusions

The children with PUV give most cause for concern in this series. The need for ISC seems to predict deterioration in graft function in this group, but the reasons are likely to be multifactorial. Urodynamic studies are mandatory in the pre-transplant workup of these children.

O47

Successful Transplant Of Adult-Size Kidneys For Low-Weight Children – Effect Of Size Mismatch

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Objectives: Pediatric renal transplant outcomes remain significantly worse than adult transplants, with higher technical complication and rejection rates. Low-weight children are particularly disadvantaged due to scarcity of suitable donors. Adult-size-kidneys (ASK) have been successfully used for pediatric recipients. A larger nephron mass provides a significant reserve of renal function and may be protective against rejection. We present our experience with ASK transplants for pediatric recipients with a significant weight mismatch.

Methods: All pediatric transplants performed for low-weight recipients (<20kg) at our centre between 1999 and 2005 were included in this study. In the initial part of the study, only donors <55kg in weight were considered for this patient subgroup. However, this criterion was relaxed in 2004. Recipient weight, indication, type of anastomosis, cold and warm ischemic time and donor weight and size were studied. Graft status was the primary outcome measure. Outcomes for large body weight donors (>55kg) and large donor/recipient weight mismatch were compared to those receiving kidneys with smaller donor/recipient weight mismatch.

Results: Of 51 pediatric transplants performed in the study period, 16 recipients weighed <20kg. Nine recipients received kidneys from donor <55 kg with a mean weight discrepancy of 34Kg. Seven recipients received kidneys from donors >55 Kg with mean weight discrepancy of 54Kg. Two grafts (one in each group) were lost in the study period within the first 2 months (unknown -1, renal vein thrombosis- 1). ASK from larger body-weight donors were more commonly anastomosed to the aorta and the IVC, with a slightly longer warm ischemia time (p=0.6, NS). All transplants except 1 (<55Kg group) were extra peritoneal. 14 of 16 transplants were functioning at last follow-up.

Conclusions: Adult-size-kidneys can be safely transplanted into small pediatric recipients with comparable outcomes to size and body-weight matched grafts.

Table-I Comparison of groups based on donor weight

	Donor weight <55kg	Donor weight >55kg
Number of children	9	7
Recipient age	4 (3-15)	4 (3-10)
Recipient wt (kg)	15.5 (12-20)	16.3 (13-20)
Donor weight (kg)	50 (20-55)	70 (60-96)
Warm ischemic time (min)	35 (30-45)	42 (30-50)
Early graft failure	1	1

Figures are expressed as Median value (Range)

Parallel Session 4(c)
Ischaemia Reperfusion Injury
Thursday 30 March

16.30 – 18.00

O48

Reducing Prolonged Kidney Cold Storage Time Before Transplantation : A Single Centre Prospective Audit.

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Purpose: Prolonged cold storage (CS) of donor kidneys is a major risk factor for the need for post-transplant dialysis (DGF), rejection and reduced early survival. UK Transplant data show that 3 month transplant survival is reduced by 9% for kidneys transplanted after 29h CS contrasted with kidneys transplanted in less than 20h CS

Objective: A prospective audit of adult, heart-beating deceased donor kidney transplants between Jan 2003 & February 2005 to initiate changes to reduce CS.

Method: Data was collected from 204 consecutive medical notes and from the National Transplant Database. A series of logical time points was established and reasons for delays were recorded. Outcome measures were creatinine and survival at 3 months and DGF.

Results: Two time intervals were found to have a linear correlation with prolonged CS. The first was the time of kidney removal to time of UK Transplant offer (linear association, $R=0.6$). The second was the interval of waiting for access to theatre following crossmatch ($R=0.6$). Transplanting kidneys with CS over 15 hours versus below 15 hours was shown to have a significant effect of an increased incidence of DGF ($p = 0.027$) and a striking influence on three month transplant survival in that no kidneys stored less than 15h were lost ($p = 0.147$).

Outcome: Anaesthetic & theatre staff were educated of the need to minimise CIT though update sessions and audit reports. The Trust Management Board have been informed of need and responded by agreeing a “twilight theatre session” (16:00 to 24:00) dedicated to transplantation 5 days per week . This is programmed to increase to 7 days then to 24 hours, 7 days a week. The cost of £290K for phase 1 has been met from the Commissioning PCT in response to our Renal Transplant Surgery Strategy. The “historic culture” within our Trust that kidneys can be stored for over 24h has been addressed. Some influential clinical managers with past experience in transplantation were unaware of recent developments emphasising the need to minimise CS.

Conclusion: This prospective audit highlighted the importance of reducing CS to improve outcomes and significantly reduce expenditure. By transplanting all kidneys within 15 hours the NHS will save on average 3 bed days and £538 in dialysis costs per patient transplanted

O49

Hsp90-Binding Agents Improve Outcome In Kidney Ischemia-Reperfusion Injury

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Background Stress proteins are cytoprotective and may be useful in limiting the ischemia/reperfusion injury associated with transplantation, yet safe and efficacious strategies of induction remain elusive. Hsp90-binding agents are potent inhibitors of Hsp90, which represses HSF1. We hypothesised that Hsp90 inhibition would stimulate the stress response through the release of HSF1, prompting transcription of stress proteins with consequent renal protection.

Methods Male BALB/c mice were injected with geldanamycin, 17-AAG or 17-DMAG (all 1 mg/kg) and subjected to renal pedicle clamping for 30 min or sham-procedure followed by 24 h recovery. Major outcomes measured were urine output and LDH, serum urea and creatinine, renal histological injury and caspase 3/7 activity. Hsp70 and HO-1 real-time PCR, Western blotting and ELISA were also performed.

Results Hsp70 and HO-1 gene and protein expression were raised 6 h following Hsp90-binding agent treatment and remained elevated for at least 24 h ($p < 0.05$). Urea and creatinine ($p < 0.01$), histological injury ($p < 0.05$) and caspase 3/7 ($p < 0.05$) activity were all lower following ischemia/reperfusion injury in groups pre-treated with Hsp90-binding agents. Creatinine was significantly lower in 17-DMAG treated groups compared with geldanamycin ($p < 0.05$).

Conclusions Hsp90-binding agents significantly increase expression of protective proteins in mouse kidneys. This is associated with improved outcome following renal ischemia/reperfusion injury. Hsp90 inhibition represents a novel protective strategy with wide-ranging clinical potential, including kidney transplantation.

Hsp, heat shock protein; HSF1, heat shock transcription factor-1, HO-1, heme oxygenase-1; 17-AAG, 17-(Allylamino)-17-demethoxygeldanamycin; 17-DMAG, 17-dimethylaminoethylamino-17-demethoxygeldanamycin.

O50

The Potential Influence Of Ischaemic Epigenetics On The Transplanted Kidney

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Cytosine methylation in Cytosine-Guanine (CpG) dinucleotides is believed to be important in gene regulation, and is associated with reduced levels of transcription. Methylation-mediated gene silencing involves a series of DNA-protein and protein-protein interactions initiated by binding of methyl-CpG binding proteins (MBP's). The methylation of even single CpG sites in gene promoters has profound biological effects on gene expression. The impact of oxidative damage to methyl-CpG sites on MBP was investigated (1) and showed that oxidation of a single 5-methyl Cytosine (5mC), significantly inhibited binding of MBP to DNA by at least an order of magnitude. Progressive oxidation of 5mC may therefore lead to replacement of 5mC with an unmethylated cytosine and hence diminish gene regulation in tissues that have endured highly oxidative environments, e.g. the post-ischaemic, transplanted kidney.

We sequenced a region of DNA, equating to the complement C3 gene promoter in normal rat renal tissue and identified putative cytokine response elements and transcription factor binding sites by sequence homology. To identify methylated cytosines in this region, we further sequenced bisulphite modified genomic DNA extracted from normal rat kidney to produce an epigenetic map of the promoter region of the rat kidney C3 gene. This epigenetic map identified regulatory methylated CpG sites localised within cytokine response elements for IFN γ , IL-1 & IL-6 and in two NF- κ B binding sites, one of which resided within exon-1. Similar analysis of kidney tissue perfused with Marshall's solution for 24hrs cold ischaemia, suggested some demethylation had occurred which, we hypothesise may be even more pronounced after reperfusion.

In conclusion, epigenetic mapping of gene promoters in transplanted organs may provide insight on the extent that ischaemia / reperfusion injury (I/RI) may lead to aberrant demethylation and hence persistent dysregulation of gene expression. Whilst aberrant demethylation in the C3 promoter may influence local C3 synthesis, known to contribute to transplant injury (2), these epigenetic changes are thought to be irreversible and inheritable to daughter cells upon mitosis which leads us to speculate that ischaemic epigenetics may have profound influence on transplanted organs.

1. Valinluck et al. *Nucleic Acids Research*. 32(14):4100-8, 2004.
2. Pratt et al. *Nature Medicine*. 8: 582-87, 2002

O51

Ischaemic Preconditioning Protects Human Liver Sinusoidal Endothelial Cells From Cold Preservation Injury

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Background Apoptosis of sinusoidal endothelial cells is believed to be a key component of hepatic cold preservation injury. Ischaemic preconditioning (IPC) reduces the severity of this injury in animal models of liver transplantation. The aims of this study were to confirm that apoptosis occurs in human liver sinusoidal endothelial cells (HuLiSEC's) undergoing cold preservation, to assess any beneficial effects of IPC, and finally, to investigate a potential mechanism of IPC, activation of the phosphoinositide 3-kinase (PI3-K) cell survival pathway.

Methods Primary cultures of HuLiSEC's were obtained from hepatic resection specimens. Cells underwent cold preservation in University of Wisconsin solution at 4°C for 12 hours and were reoxygenated at 37 °C, simulating storage and reperfusion of a transplanted liver. In one arm of the study, cells underwent IPC – 10 minutes hypoxia and 10 minutes reoxygenation at 37 °C - prior to cold preservation. A cell death detection ELISA using anti-DNA antibodies was performed to quantify apoptosis. Western blotting and colorimetric assay for caspase-3 activation were performed to determine if IPC reduces the rate of apoptotic cell death. Western blotting for Akt was performed to ascertain if the PI3-K pathway mediates IPC.

Results Cell death ELISA demonstrated that cells undergoing 12 hours of cold preservation alone did not experience a significant increase in apoptotic cell death. However, following 2 hours of reoxygenation at 37 °C, there was a 3-fold increase in the rate of apoptotic cell death ($p < 0.04$). Both western blotting and colorimetric assay demonstrated a reduction in caspase-3 activity in cells undergoing IPC prior to cold preservation-warm reoxygenation, by a mean of 36% and 42% respectively ($p < 0.02$). Western blotting for Akt revealed an increase in phosphorylation of Akt in cells undergoing IPC prior to cold preservation-warm reoxygenation, by a mean of 35% ($p < 0.02$).

Conclusions This study confirms that human liver endothelial cells undergo apoptosis in response to cold preservation-warm reoxygenation injury. Ischaemic preconditioning is demonstrated to significantly decrease the rate of apoptosis in response to this injury. This is associated with an increase in Akt phosphorylation, implicating the phosphoinositide 3-kinase signalling pathway in the underlying mechanism of ischaemic preconditioning.

O52

A Comparison of Nonpulsatile and Pulsatile Hypothermic Machine Perfusion (MP) of Non Heart Beating Donor Kidneys(NHBDs)

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Introduction

MP of NHBD kidneys provides better preservation, helps to assess the viability and aids the selection process. Nonpulsatile MP (NMP) subjects the kidney to higher mean pressures that may impair viability. We aimed to determine whether there was any difference in organ preservation between the two modalities.

Methods

Kidneys were retrieved according to standard NHBD protocols. One kidney from each donor was commenced on either NMP or pulsatile (P) MP at a peak pressure of 30mmHg. Perfusion parameters were recorded hourly for 4 hours and fluid samples were drawn at each interval for glutathione-S-transferase (GST, a marker of tubular cell injury), pH and lactate measurements. MP continued until implantation.

Results

In 1 year there were 17 NHBDs (mean D age 50, range 17-66 years, 9MC2, 7MC3, 1MC4). P and NMP occurred in 14 kidney pairs (6 dual and 12 single transplants, 2 pairs discarded).

After 3 hours, NMP produced significantly better flows and pressure flow indices (PFIs). GST levels from NMP kidneys were higher but there were no differences in pH, lactate levels or weight gain post MP (Table1).

For single transplants, cold ischaemia times were similar for N and PMP kidneys (23 hrs 56 mins±218 mins NMP vs. 24 hrs 15 mins± 457 mins, P=0.92). There was no difference in length of DGF (4 vs 4 days, range 0-17, P=0.82).

Conclusion

The higher GST levels from NMP may result from higher flows and greater washout of GST or it may reflect endothelial injury. The equal weight gains suggest NMP does no more damage than PMP. Also, immediate function appears to be unaffected by NMP.

Perfusion Characteristics	NMP (mean ± SD)	PMP (mean ± SD)	P value (t-test)
Flow (ml/min/100g)	39.5 ± 14.9	29.9 ± 11.0	0.0003
PFI (mmHg/(ml/min/100g)	1.4 ± 0.6	1.1 ± 0.5	0.0008
GST (IU/100g)	179 ± 115	154 ± 113	0.02
pH	7.20 ± 0.07	7.21 ± 0.06	0.31
Lactate (mmol/L/100g)	0.98 ± 0.51	0.95 ± 0.42	0.61
Weight Gain (%)	17.7 ± 8.0	16.2 ± 9.4	0.67

O53

Ultrastructural Resolution of Complement Deposition in Renal Allograft Rejection

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The finding of complement C4d in peritubular capillaries of renal transplant biopsies is a useful surrogate marker for humoral rejection. This study sought to aid the interpretation of published reports describing C4d in peritubular capillaries by examining the distribution of complement in rejecting renal transplants at ultrastructural resolution. A rare archive of formalin fixed, and LR-Gold resin embedded biopsy samples was used for Silver Enhancement-Controlled Sequential Immunohistochemistry (*SECSI*), a method of double-labelling immunoelectron microscopy developed in-house.

From a cohort of 22 patients whose transplanted kidneys were biopsied for suspected rejection, 6 were found to be C4d positive in peritubular capillaries. The *SECSI* method assessed the distribution of C4d & C3d, and C1q & C9 in these 6 samples. The data showed at ultrastructural resolution a more detailed pattern of complement activation than has previously been reported. The study confirmed finding C4d in peritubular capillaries is indicative of complete classical pathway activation since C1q, C3d and C9 were found in equivalent distribution to C4d. That C3d was not found in the absence of C4d suggested little role for the alternative pathway in these tissues. *SECSI* staining also revealed complement deposition in glomerular capillaries and epithelial cells of the renal cortex. In particular, *SECSI* analysis revealed new findings of complement fixation on mitochondria, and condensed chromatin in the epithelial nucleus and nucleolus suggesting putative non-HLA targets of an alloantibody response. These findings were validated by a rigorous series of controls. These included Ig staining which was found in a similar distribution to complement in samples analysed, and biopsies from cases of membranous nephropathy and minimal change disease which exhibited predicted patterns of positive and negative control labelling.

In conclusion, this study confirmed that C4d deposition is indicative of classical pathway complement activation from C1 to C9, that the predominant sites of detected product are basement membranes rather than the luminal surface of endothelial cells or glomerular capillaries, and this study provided evidence of previously unrecognised non-HLA targets of humoral alloimmunity. The study may assist interpretation of C4d staining in transplant biopsies, and perhaps help to inform clinical practice.

Parallel Session 1(a)

Pancreas

Friday 31 March

09.00 – 10.00

O54

Sensitised Patients: Prospects for Pancreas Transplantation?

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In recent years there has been a rapid increase in pancreas transplant activity in the UK. Donated pancreata are offered first to the local designated transplant centre and, if declined, offered according to the Balance of Exchange to the other designated centres. Now that transplant activity is sufficient, the Pancreas Task Force (PTF) reviewed access to transplantation for sensitised patients.

Data analysed included patients actively registered on the pancreas transplant list (1 June, 2005) and the outcome of patient registrations during calendar years 2001-04.

95/121 (79%) patients registered on the pancreas transplant list were unsensitised and the remaining 26 (21%) had varying levels of HLA antibody reaction frequency (%RF). In terms of registration outcome, the likelihood of transplant decreases with increasing levels of %RF. Waiting times to transplant were estimated and the results showed that unsensitised patients (%RF<10%) are significantly more likely to be transplanted within one year of listing compared with patients with a RF>30% (Log-rank p=0.04). 52% of unsensitised patients were still awaiting transplant one year after registration, compared with 68% and 78% of patients with a %RF of 10-30% and >30%, respectively.

Analysis of recipients transplanted (2001-04) showed that the majority of transplants were performed in unsensitised patients 207/240 (86%) with only 8/240 (3%) in sensitised patients with a RF>30%.

To assess the chance of finding pancreata for sensitised patients, the number of acceptable (crossmatch negative) pancreata was calculated for sensitised patients (%RF>10%) where the antibody profile was defined into unacceptable specificities. The blood group compatible, HLA acceptable pancreata count from a pool of 348 actual pancreas donors (2001-2004) was calculated. The data show that in the pool of national donors available within a four-year period, there were less than 25 acceptable donors for patients with a RF>70%.

In summary, sensitised patients wait longer and have a lower chance of a pancreas transplant than unsensitised patients. Results indicate that organ sharing is necessary to find suitable organs for these patients. Following PTF discussions two pilot schemes for organ sharing have been agreed, the results of which will inform discussion on mechanisms to increase pancreas transplantation in sensitised patients.

O55

Pancreatic Islet Transplantation In The UK: A Single Centre Experience

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Background: In North America, clinical islet transplantation is an accepted treatment for the secondary complications of type 1 diabetes, especially hypoglycaemic unawareness. Despite the recent improvements in clinical outcomes, the UK has lagged behind the rest of the world in the uptake of this valuable treatment modality. We have established the technique within our unit and have performed islet alone transplants in three patients with hypoglycaemic unawareness.

Methods: Pancreases were retrieved from brain dead heart beating donors and digested with collagenase. Islets were purified on a Ficoll density gradient, cultured overnight and transplanted into the portal vein of recipients via a percutaneous injection under ultrasound control. Immunosuppression was with daclizumab induction followed by sirolimus and low dose tacrolimus maintenance. All patients received standard prophylaxis.

Results: From November 2000, 64 pancreases were received at our unit, of which 58 were processed for islet isolation. An average yield of 378,049 ±38,796 islet equivalents (IEq) was isolated from processed pancreases, with yield increasing over time. Three patients with type 1 diabetes and hypoglycaemic unawareness were transplanted with four preparations and have been followed up for a median of 5.9 months. They were transplanted with 11,793 ±332 IEq/kg, resulting in a reduction of insulin requirements from 29 to 14 IU/day, with one patient becoming insulin independent after a single transplant. Mean HbA1c fell from 9.8 to 7.7% and two patients regained their hypoglycaemic symptoms. All patients experienced leukopenia, anaemia and mild abdominal pain associated with a temporary rise in liver enzymes. There were two episodes of bacterial sepsis and one patient required blood transfusion for an intra-abdominal bleed. There have been no episodes of CMV, PCP or malignancy. One potential recipient died from hypoglycaemia while awaiting a suitable organ for transplantation.

Conclusions: Islet transplantation is an effective treatment for severe hypoglycaemic unawareness, with associated improvement in metabolic control. We have shown that islet transplantation can be established in the UK but the treatment is expensive and centralised funding will be crucial to the establishment of this treatment modality.

O56

Pancreatic Transplantation; Is Manpower And Resource A Limiting Factor?

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The Renal Transplant Unit, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, United Kingdom

Background: Manchester Royal Infirmary has one of the highest rates of pancreas transplantation in UK, but despite this, we have been conscious of the amount of ‘wasted resource’ arising from this programme. This study has therefore examined the potential pancreatic offers, the transplants, and the outcome of all offers and transplants.

Methods: All pancreatic offers (donors or imports) from 1st August 2004 to 31st October 2005 (15months) were examined using our own data base. Donor demography, and medical details of all offers were recorded prospectively, and the reasons for refusal of the offer, or failure to transplant were also noted.

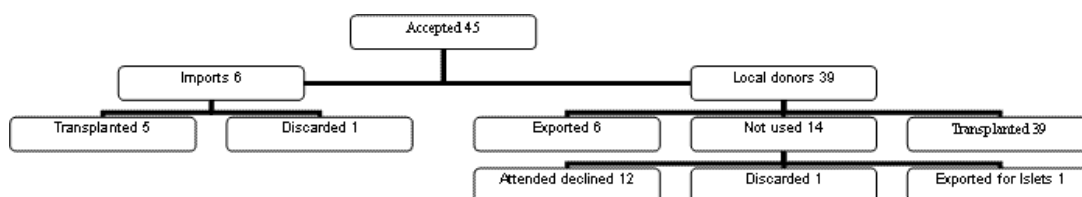
Results: During the time of the study, 113 potential pancreas offers were identified, 68(60%) were declined, and only 45 donors or imports were accepted (40%).

Diagram 1

Thus, 39 ‘local retrievals’ resulted in just 19 transplants (48% use).

During the same period, there were 68 offers of either imports or local retrievals that were declined. A highly significant number of these (15%) were declined due to lack of resource (medical, nursing, theatre or HDU). A number were considered ‘inappropriate referrals’ due to donor factors such as known hepatitis, IV drug abuse etc, no recipient in 10 (15%) and in a further 41% the declined offer was due to donor factors that may have contraindicated pancreatic donation. Within the ‘other’ group, there were also at least 4 additional pancreata that were probably refused because of resource limitations. Thus, there were at least 14/68 declined offers that occurred for this reason (around 20%).

Conclusion: The potential complications of pancreatic transplantation have such devastating consequences that careful donor selection is essential. This study highlights the magnitude of work undertaken to achieve just 24 transplants in a 15 month period. Less than half of all retrieved pancreata were re-implanted because of medical contraindications. More worrying is the high number of lost pancreatic transplants that are declined through lack of resources and manpower. The study also highlights the fact that were it not for limited manpower and beds, this unit might have increased it’s successful pancreas transplant rate from 24 to 38, an increase of 58%.



O57

Preliminary Experience With Serial Thromboelastography In Pancreas Transplantation – The Way Forward?

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Introduction:

Graft thrombosis accounts for 6 – 9% of pancreatic graft loss in kidney-pancreas transplantation (SPK), and is the leading non-immunological cause for graft failure in the first year following transplantation. Thromboelastography (TEG) directed anticoagulation in the postoperative period has been successful in preventing graft loss due to thrombosis. The present study was conducted to identify the trend in TEG variables over the first two weeks following transplantation.

Materials and methods:

The study included 18 patients with Type 1 diabetes and end-stage renal who underwent simultaneous kidney-pancreas transplantation: one patient received a pancreas after kidney transplantation. The subjects were studied pre-op, and daily for the first 14 days postoperatively. TEG was performed using Haemoscope 5000 (Haemoscope Inc, USA) using fresh venous blood activated with kaolin and analyzed using heparinase coated cups. The common TEG parameters R time, K time, Angle, Maximal Amplitude (MA) and Coagulation index (CI) were analyzed.

Results:

Mean recipient age was 39.5 (SD 5.01). Male: female ratio 11:7. Normal values: R 4-8 min; K 1-4 min; Ang 47-74 deg; MA 55-73 mm; CI -3 - +3. The median values of the various TEG variables are displayed in table 1. The K time and the MA show a biphasic trend with an initial prolonging of the K time coupled with a reduced MA by day 2, which reflects as a low CI in the first 6 days. By day 10, the K time begins to shorten, the MA increases and this reflects on the CI, which enters the hypercoagulable spectrum after day 10. R time and Angle remained within normal range throughout the period of study. The increase in CI by day 10 is associated with hypercoagulable TEG tracings, and as a result of serial observations of the TEG variables, 10 out of 17 (58.8 %) of the patients were commenced on warfarin for a period of 3 months. No episodes of graft thrombosis occurred during this study.

Conclusion: The results of the present preliminary study show that the coagulability changes considerably over the postoperative period, and serial thromboelastography could prove to be a useful tool to monitor the coagulation status in kidney-pancreas recipients.

	day 0	day 1	day 2	day 3	day 4	day 5	day 6	day 7	day 8	day 9	day 10	day 11	day 12	day 13	day 18
CI	2.1	0.4	-0.3	-1.3	-0.2	-1.0	-1.5	2.3	1.7	1.5	3.1	3.0	2.8	3.3	3.2
R	5.2	4.7	5.1	6.1	5.9	7.1	7.0	5.1	6.1	6.3	4.4	3.8	5.5	5.8	5.7
K	1.3	1.5	2.0	2.3	2.1	2.4	1.8	1.6	1.7	1.8	1.3	1.1	1.3	1.4	1.2
Ang	68.9	67.8	62.9	58.4	60.5	58.5	64.3	67.0	69.3	69.7	71.1	74.0	72.0	70.4	73.9
MA	68.5	60.4	53.8	55.4	58.5	62.9	67.1	69.7	74.0	70.9	74.3	74.5	74.0	72.0	76.2

O58

Alemtuzumab Induction Therapy & Steroid-Free Immunosuppression In Pancreas Transplantation – Early Experience

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Introduction

Alemtuzumab (Campath-1H) is a humanised anti-CD52 antibody, which has a powerful lytic effect on T & B lymphocytes and is known to have clinical activity in a number of conditions mediated by lymphocytes. The impact of Alemtuzumab induction and steroid-free immunosuppression in pancreas transplantation was evaluated.

Patients & Methods

Over a 11-month period, (January to November 2005), 23 consecutive patients underwent either a simultaneous pancreas kidney (SPK) or pancreas after kidney (PAK) transplant. They received 30 mg of Campath on day 0 and 1, with tacrolimus (trough levels of 10-15ng/ml) and 1g mycophenolate mofetil for maintenance immunosuppression. Patient and graft survival, rejection rate and adverse events were obtained prospectively by review of charts and case notes.

Results

There were 15 males and 8 females in the group with a median age of 39.5 years (range 31-51 years). Nineteen patients underwent a SPK while 4 patients had a PAK. The median length of follow-up was 4 months (range 1-10 months). All allografts are currently functioning, with all patients being insulin-free and off dialysis. Thirty-day mortality in the group was 0%.

One patient who underwent a SPK has sub optimal kidney function (median creatinine - 335), a renal biopsy showed evidence of BK virus Nephropathy. Three patients (17.3%) were treated for rejection episodes, on the basis of graft dysfunction with steroid pulse therapy. One male recipient (4.3%) had treatment for cytomegalovirus infection. Seven patients had reoperations (30%, range 0-2 operation); the causes included abdominal wall dehiscence, bleeding, perforated gall bladder, renal vein thrombosis and abdominal compartment syndrome. Two patients (8.6%) were commenced on steroids after a rejection episode, however only one patient (4.3%) remains on prednisone.

Conclusion

Our early results suggest that Alemtuzumab is safe and efficacious, with low incidence of rejection despite a steroid free immunosuppression in 96% of patients.

O59

Early Neural Regeneration After Pancreas Transplantation Detected By Corneal Confocal Microscopy: A Pilot Study

S Mehra¹, M Tavakoli², A Palmer¹, A Tavakoli¹, R Pararajasingam¹, N Parrott¹, R Malik² and T Augustine¹

¹Renal and Pancreas Transplant Unit, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9WL, United Kingdom and ²Academic Department Of Medicine, Manchester Royal Infirmary and University of Manchester, Manchester, M13 9WL, United Kingdom

Background: The most effective treatment for insulin-dependent diabetes mellitus currently is whole organ pancreas transplantation (PTx). PTx with sustained euglycemia has been shown to ameliorate secondary complications including retinopathy, nephropathy and neuropathy. Nerve conduction studies (NCS) and quantitative sensory testing (QST) have been used to evaluate neuropathy but are insensitive tests and do not test small neural fibres which may be earliest to regenerate. Corneal confocal microscopy is a rapid, non invasive in vivo clinical examination technique which defines the extent of corneal nerve damage and repair which acts as a surrogate measure of somatic neuropathy in diabetic patients. **Methods:** 20 pancreas transplant recipients were recruited since January 2004 (M: F-11:9, median age- 42years). A baseline corneal scan was done within one month of transplantation .Repeat scans were done at 6monthly intervals in 7 patients with normal functioning grafts and the study continues. Nerve fibre density (NFD), nerve fibre length (NFL), nerve branch density (NBD), nerve fibre tortuosity (NFT), corneal sensitivity with non contact corneal aesthesiometer (NCCA) and Cochet-Bonnett aesthesiometer (C-BA) are the parameters assessed. **Results:** Corneal NFD (13.41 ± 8.88 patient v control 51.95 ± 10.27 , $p=0.000$), NBD (3.70 ± 6.35 v 28.93 ± 14.31), NFL (2.19 ± 1.18 v 9.12 ± 6 , $P=0.001$), NFT (15.14 ± 3.07 v 24.38 ± 10.50 , $p=0.026$) were significantly reduced in diabetic patients prior to transplantation. 7 patients underwent a repeat scan 6-12 months after transplantation. There was an improvement in NFD (18.50 ± 4.00 v first scan 7.74 ± 7.26), NBD (3.08 ± 5.34 v 1.98 ± 3.38), NFL (4.23 ± 2.30 v 1.79 ± 1.25) and NFT (11.86 ± 1.40 v 15.34 ± 2.63). Corneal sensitivity improved significantly in the second scan after 6 months. The study continues to rescan the rest of trial. **Conclusion:** The early phase of this study shows that neural regeneration starts within 6-12 months of Pancreas transplantation and corneal confocal microscopy is a novel non-invasive technique to assess corneal nerve damage and repair of small nerve fibres.

Parallel Session 1(b)
Corneal Transplantation

Friday 31 March

09.00 – 10.00

O60

Outcomes Of Penetrating Keratoplasty In Patients With Pseudophakic Bullous Keratopathy
MNA Jones¹, PD Jaycock², DM Tole² and J Males²

¹On behalf of the Ocular Tissue Advisory Group, UK Transplant, Bristol, BS34 8RR, United Kingdom and ²Division of Ophthalmology, Bristol Eye Hospital, Lower Maudlin Street, Bristol, BS1 2LX, United Kingdom

Background: Pseudophakic Bullous Keratopathy is one of the main indications for corneal grafting in the UK. However graft survival is poorer for Pseudophakic patients, compared with the other main indications for corneal grafting. It is hypothesised that one of the reasons for poor graft survival may be that previous intraocular inflammation has resulted in these eyes being 'immunologically primed' and thus require long-term topical steroids post-operatively.

Methods: This study considers Pseudophakic patients receiving a first Penetrating Keratoplasty (PKP) in the UK between April 1999 and March 2004. There were 1274 first PKP grafts for Pseudophakic Bullous Keratoplasty reported to UK Transplant in this time period, of which 1184 (91%) were grafted for visual reasons. Of these 1184 grafts, follow-up has been reported in 1033 instances (87%). Kaplan-Meier survival curves were used to illustrate differences in three-year transplant outcome between the main indications. A Cox regression model was fitted, to investigate the effect that pre-operative factors and post-operative medications have on graft survival.

Results: Three-year graft survival for Pseudophakic patients was 65% (95% CI: 59-70), whereas the graft survival rates for Keratoconus and Fuchs' patients were much higher at 96% and 92% respectively. Steroids were still being used 18 months post-operatively in 378 of the 1033 (36%) corneal grafts included in this study. Patients receiving steroids for longer than 18 months were half as likely to fail, and this was highly significant in the final model ($p=0.0002$, 95% CI 0.3-0.7).

Of the pre-operative factors considered, donor age ($p=0.01$), HLA matching ($p=0.008$), trephine size ($p=0.02$), recipient age ($p=0.03$), corneal vascularisation ($p=0.02$) and surgeon activity levels ($p=0.01$) were all found to affect graft survival. There were also statistically significant associations between graft survival and the post-operative use of glaucoma medication ($p=0.001$) and other immunosuppressants ($p=0.03$).

Conclusions: The use of long-term postoperative steroids improved graft survival, even when taking account of other factors that may affect graft survival. Thus the use of long-term steroids should be considered post-operatively following penetrating keratoplasty for Pseudophakic Bullous Keratopathy.

O61

Influence Of Advanced Recipient Age On Corneal Grafts And Factors Affecting Graft Survival
MNA Jones¹, D Collett¹ and SB Kaye²

¹On behalf of the Ocular Tissue Advisory Group, UK Transplant, Bristol, BS34 8RR, United Kingdom and ²St Paul's Eye Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP, United Kingdom

Background: There has been a significant increase ($p < 0.0001$) in the proportion of corneal transplants performed on elderly recipients (aged ≥ 80 years at surgery) since the start of the Corneal Transplant Service in 1983. The proportion of elderly cornea recipients has risen from 7% in 1983-85 to 18% in 2004-05. The aim of this study was to compare graft survival rates and investigate factors affecting corneal graft survival in this subset of recipients.

Methods: This study only considers elderly patients receiving a first penetrating keratoplasty (PKP), in the UK between April 1999 and March 2004. There were 6200 first PKP reported to UK Transplant in this time period, of which 1142 (18%) were aged 80 years or over at transplant. Follow-up of the graft has been reported in 1043 instances (91%). Kaplan-Meier survival curves were used to illustrate differences in three-year transplant outcome for different age groups. A Cox regression model was fitted, to investigate the effect that pre-operative factors had on transplant survival in recipients over 80 years of age.

Results: Three-year corneal transplant survival for elderly recipients was 79% (95% CI: 75-83), which was only slightly lower ($p=0.14$) than the survival rate for recipients aged less than 80 years (81%, 95% CI: 79-82). By excluding transplants performed for keratoconus (a condition mainly affecting younger recipients) however, the survival rate for elderly recipients was slightly higher than younger recipients (75%, 95% CI: 73-77).

Of the pre-operative factors considered in the analysis, indication for PKP ($p=0.001$), suturing method ($p=0.001$), whether or not cataract surgery was performed at the time of the transplant ($p=0.02$), donor gender ($p=0.002$), HLA matching ($p=0.02$), perforation of the cornea ($p=0.03$) and whether the patient had chronic glaucoma ($p=0.02$) were all found to affect graft survival among elderly recipients.

Conclusions: The difference in survival rates between elderly recipients and those aged less than 80 years was not statistically significant. The CTS Eye Banks attempt to match recipients with corneas from similarly aged donors and as a result neither recipient age nor donor age were found to affect graft survival. Indication for transplant, suturing method and donor gender were the main explanatory factors that affected graft survival in elderly recipients.

Wednesday 29 March
Moderated Poster Session
Laboratory

P1

THIS ABSTRACT HAS BEEN WITHDRAWN

P2

Development Of Transplanted Metanephroi: Evaluation Of Glomerular Number And Expression Of Key Transporters

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Transplantation of embryonic kidneys has been proposed as a potential solution to the problem of kidney donor shortage. We have reported previously that rat metanephroi transplanted into a host of the same species have glomerular filtration rates (GFR) comparable with those achieved by dialysis and have reported, for the first time, estimates of renal blood flow (RBF) and renal vascular resistance (RVR) within these transplanted metanephroi. Here we estimate glomerular numbers within these metanephroi and examine expression of transporters central to urinary concentration. Metanephroi from E15 Lewis rat embryos were transplanted adjacent to the abdominal aorta of adult female Lewis rats under isoflurane anaesthesia. Transplanted metanephroi were explanted between 21 days and 3 months following transplantation and fixed in 4 % PFA. Glomeruli in transplanted metanephroi, embryonic day 21 (E21) and postnatal day 1 (PN1) Lewis rat kidneys were counted using a non-biased stereological counting technique. Number of glomeruli in transplanted metanephroi (4131 ± 299 , $n = 5$) were significantly lower compared to PN1 kidneys (7023 ± 587 , $n = 5$, $P < 0.05$) but not E21 kidneys (2578 ± 358 , $n = 5$, $P > 0.05$). Aquaporin 1 and 2 (AQP 1 and 2) and urea transporters A-1,2 and 3 (UT-A1,2 and 3) were localised by immunohistochemistry. Most metanephroi expressed AQP1 (5/6), AQP2 (4/5) but not UT-A1,2 or 3. This pattern of expression was also observed in E21 and PN1 Lewis rat kidneys. These results provide evidence that transplanted metanephroi, up to 3 months following transplantation, are at a stage of nephrogenesis comparable with kidneys at around the time of birth in the rat. Transporter expression indicates an immature urine-concentrating mechanism exists within these transplants.

P3

Breaking Tolerance To Vimentin – Are B-Cells Required For Antigen Presentation?

B Mahesh, A McCormack, A Holder, M Jacovides, P Sarathchandra, JD Smith and ML Rose

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Introduction

Non-Major Histocompatibility Complex antibodies, such as anti-vimentin antibodies (AVA) are significantly associated with human cardiac graft vasculopathy. Furthermore, conflicting data is available in literature about role of B-cells as antigen presenting cells (APC) to CD4 T-cells. We describe a murine model with high titres of AVA produced by breakdown of peripheral tolerance to vimentin (VIM), and examine importance of B-cells as APC. Mycobacterial components in Complete Freund's adjuvant(CFA) promote T-Helper Cell-1 responses through Toll-Like Receptor-2 signalling in professional APC; their role in modulating breakdown of tolerance to VIM is described

Method

Wild type (WT) C57Bl6(B6), 129/sv, B-cell knockout mice on B6 background (IgH6), were immunised with 400µg murine VIM in 100µl CFA or IFA, followed by a booster 400µg VIM 7days later. Control mice received 100µl urea vehicle(Vcl) in CFA or IFA. Mice were sacrificed for sera and spleens at 2,4,6 and 12weeks (n=4/group). Production of interferon-γ(IFNγ),IL-2,IL-4 and IL-5 by stimulated splenocytes was measured in Elispot assays. AVA titres were measured by ELISA. Low splenocyte numbers permitted measurement of only IFNγ and IL-2 in IgH6 mice. Results were analysed by independent sample T-tests; p<0.05 was considered significant

Result

VIM/CFA B6 and 129/sv had high titres of IgG AVA at 2weeks, which remained persistently elevated upto 12weeks compared to Vcl/CFA controls. Similarly, production of IFNγ,IL-2,IL-4 by splenocytes from VIM/CFA B6 and 129/sv was significantly higher than Vcl/CFA controls upto 12weeks. In contrast, **VIM/IFA** B6 had high IgG AVA titres at 2weeks, but titres dropped subsequently and were not higher than Vcl/IFA B6 at 4-12weeks. Production of cytokines by splenocytes from VIM/IFA B6 was not higher than Vcl/IFA B6 at 2,4,6 or 12weeks. Splenocytes from **VIM/CFA** IgH6 showed higher IL-2 but not higher IFNγ production compared to Vcl/CFA IgH6. However, splenocyte IL-2 response from VIM/CFA IgH6 was 36±9%, 30±1% and 39±20% of VIM/CFA WT B6 splenocytes at 2,4 and 6weeks, suggesting that B-cells maybe needed for adequate antigen presentation to CD4 T-cells

Conclusion

CFA is required in murine models to produce sustained breakdown of tolerance to VIM, and to generate high titres of anti-VIM antibodies and T-cell responses. B-cells may play an important role in presentation of this particular autoantigen

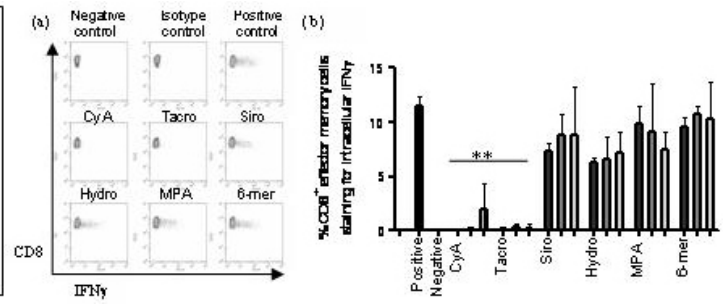
Controlling The Generation & Function Of Human Memory T Cells *In Vitro*

D Jones, S Sacks and W Wong

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Memory T cells play a pivotal role in acute and chronic rejection of organ grafts. However, it has only been recognised recently that their responses are not controlled in the same manner as naïve T cells. Studying this in humans *in vivo* is not possible. Therefore we have established an *in vitro* model of CD8⁺ effector memory T cell (T_{em}) generation and function to test the influence of immunosuppressive drugs on this. PBMCs were stimulated with anti CD3 and anti CD28 mAb for 5 days followed by resting in culture for a further 9 days. Changes from a naïve phenotype (CD45RA⁺, CCR7⁺) to T_{em} phenotype (CD45RA⁻, CCR7⁻) was assessed by flow cytometry. Naïve CD8⁺ T cells became blastoid (as evident by an increase in FSC-H) and upregulated CD25 expression after 5 days of stimulation. After 9 days of rest in culture, they returned to their resting state but acquire the cell surface phenotype of T_{em} cells. All commonly used immunosuppressants at therapeutic levels prevented the formation of T_{em} *in vitro*. The mechanisms for their action was investigated by CFSE and Annexin V staining. Some acted through inhibition of proliferation: ciclosporin, tacrolimus and mycophenolic acid (MPA); while others through activation induced cell death: MPA, 6-mercaptopurine and hydrocortisone. By contrast, the function of pre-existing T_{em} cells was not uniformly suppressed by all immunosuppressants. When stimulated with anti CD3 mAb alone, only calcinerin inhibitors were able to suppress intracellular IFN γ production by CD8⁺ T_{em} when analysed by flow cytometry (figure 1). These differences may shed light into the tailoring of immunosuppressants for transplant recipients, particularly those with pre-existing immunological memory.

Figure 1
 (a) Representative flow cytometry dot plots illustrating the detection of intracellular IFN γ within CD8⁺ CD45RA⁻ CCR7⁻ (T_{em}) cells following stimulation.
 (b) Ciclosporin and tacrolimus completely inhibited the production of intracellular IFN γ while sirolimus, hydrocortisone, mycophenolic acid and 6-mercaptopurine were relatively ineffective.
 (** p<0.01 Paired t test)



P5

Relationships Between Haematopoietic and Epithelial Lineages in Human Fetal Liver

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Introduction

In developing human liver, hepatoblasts generate hepatocytes and cholangiocytes. Haematopoietic progenitors generate lymphoid and myeloid precursors. Recent studies indicate that phenotypic haematopoietic stem cells may give rise to liver epithelial cells, an observation which questions the lineage relationship between haematopoietic progenitors and hepatoblasts in developing liver. Understanding this may prove critical in the generation of cell therapies for liver disease. To examine this relationship, haematopoietic, epithelial and mesenchymal lineages were immunostained in human fetal liver.

Methods

Monoclonal antibodies were applied to first trimester human fetal liver sections (week 8). Thy-1 and CD34 indicated putative haematopoietic stem cells and CD45 and glycophorin-A were used as blood lineage markers. Epithelial (albumin, cytokeratins 18 and 19) and mesenchymal (vimentin) lineages were also labelled.

Results

Thy-1 labelled portal vein endothelium and portal tract mesenchyme. CD34 was expressed in portal and hepatic venous and sinusoidal endothelium. Intensely positive CD34-labelled cells were also scattered throughout the liver. Cytokeratin 18 labelled the epithelial compartment, whereas cytokeratin 19 and albumin staining was pronounced around portal structures. CD45 and glycophorin-A expression was seen within the presumptive sinusoidal compartment. Vimentin expression was pronounced on all endothelium and sinusoids.

Conclusions

Phenotypic haematopoietic stem cells, which give rise to liver epithelium, may be derived from portal vein endothelium. Conversely, isolated CD34+ cells in the developing liver are probably haematopoietic stem cells. Common markers could reflect a common derivation of both cell types from embryonic haemangioblasts. This study has revealed a novel and unexpected portal endothelial compartment bearing haematopoietic stem cell markers in human fetal liver. Previous work suggests this compartment may provide liver epithelial cells in vitro.

Wednesday 29 March

Moderated Poster Session

Chronic Allograft Nephropathy

P6

Natural History Of Chronic Allograft Nephropathy: Assessment By A Structured Protocol For Histological Examination In A Mouse Kidney Allograft Model

VF Moxham¹, AB Fogo², J Karegli¹, KL Brown¹, SH Sacks¹ and W Wong¹

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The natural history of chronic allograft nephropathy (CAN) is poorly defined. While mice represent good in vivo models for human diseases, there are fundamental differences in the anatomical ultrastructure of the kidney, particularly the glomeruli. Extrapolation of the Banff criteria for use in mice is therefore unsuitable. Here we define the natural history of CAN by devising a standardised classification of murine renal allograft pathology.

Transplantation of kidney allografts from MHC class II mismatched BM12 donors to BL/6 recipients reliably resulted in biochemical features of CAN: slow rise in blood urea nitrogen from normal (<15) to >70mmol/L over 70d without immunosuppression. Donor kidneys were harvested at 14d intervals to study the natural history of CAN and scored (both descriptively and numerically from 0 – 4) in 4 categories: **Glomeruli** (sclerosis, hyalinosis, endocapillary hypercellularity). **Tubules** (tubulitis, atrophy/fibrosis), **Interstitialium** (cellular infiltrate), and **Vascular lesions** (endothelialitis, hyalinosis, intimal proliferation). Two to 4wks following transplantation, features of acute rejection predominates (tubulitis and cellular infiltrate [predominantly lymphocytic with some plasma cells], cuffing of the arteriolar vessels [without endothelialitis or adherence] and glomerular cellular proliferation). By the 6th week, chronic damage (marked tubular damage, fibrosis and atrophy) were seen. Mild tubular fibrotic/atrophic lesions could be seen with basement membrane thickening which confirms an obliterative process rather than an acute lesion, such as necrosis. Tubulitis was also reduced by this point. Interstitial infiltrates was more generalised and no longer cuffed arterial vessels, although endothelialitis became prominent. Glomerular sclerosis and hyalinosis became the predominant lesion along with tubular atrophy, further confirming the chronic nature of the late lesions.

The natural progression of CAN is described in detail using a standardised method to quantify histological lesions. CAN in mice display similar histological features to human but emphasis on various lesions differ, such as the predominance of glomerular sclerosis and endothelial lesions with less vascular lesions. The new scheme allows for quantification of CAN and impact of intervention in murine models.

P7

Antibodies in Renal Transplantation: Correlation with the Development of Chronic Allograft Nephropathy

D Besarani¹, J Procter¹, M Barnardo¹, L Cerundolo¹, J Smith², P McShane¹, I Roberts¹, A Handa¹, PJ Friend¹, ML Rose² and SV Fuggle¹

¹Oxford Radcliffe Hospitals NHS Trust, Oxford Transplant Centre, Churchill Hospital, Oxford, OX3 7LJ, United Kingdom and ²Heart Science Centre, Harefield, UB9 6JH, United Kingdom

Background:

An association between the production of anti HLA-antibodies and renal allograft failure has been described. However, the role of non-HLA antibody is a matter of debate. Antibody may act as a critical trigger for rejection of allografts and may serve as an early indicator of a slow progression of chronic allograft nephropathy (CAN). In this study we have explored the role of HLA and non-HLA antibodies in the development of CAN.

Methods:

The study group comprised 70 recipients of primary deceased donor renal transplants at our Centre, Jan 1991-Dec 2001. The primary endpoint was biopsy confirmed CAN (n=30) or in the control group creatinine clearance of ≥ 40 mls/min at 5 years (n=40). Serum samples from renal transplant recipients were assayed in an ELISA for IgM and IgG antivimentin antibody (AVAb). Samples tested included 2 samples prior to transplantation and 4 samples/year thereafter until biopsy confirmed CAN or up to 3 years in the control group. Pre and post transplant HLA antibody-screening profiles were analysed. The patients received triple immunosuppression therapy regime of cyclosporine, azathioprine and prednisolone.

Results:

We have demonstrated de novo production of antibody in sera of renal transplant patients. In the CAN group 16/30 (53.3%) of patients developed AVAb and 22/30 (73.3%) HLA antibodies, whereas in the control group 15/40 (37.5%) made AVAb and 11/40 (27.5%) HLA antibodies. Overall analysis shows that percentage of patients who developed (AVAb and/or anti-HLA antibody) antibody was significantly higher in the CAN than in the control group (89.6% vs. 50% p value <0.0001).

Conclusion:

The results demonstrate a strong correlation between the development of antibody post transplant and CAN and illustrate the value of screening for anti-vimentin and HLA antibodies. In the control group, 50% of patients had increased antibody levels. It is possible that, despite no deterioration of function as assessed by biochemical markers, these patients may be at risk of development of CAN, but longer follow up will be required. Detection of a rise of antibody offers an opportunity for clinical intervention and modification of immunosuppression, which may be beneficial for long-term renal transplant outcome.

This work was supported by Proteome Sciences plc, Coveham House, Downside Bridge Road, Cobham, Surrey, KT11 3EP.

P8

Albumin Overload Induces Oxidative Stress In Human Proximal Renal Tubular HK-2 cells: Implications For Chronic Allograft Nephropathy

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After the first year of transplantation, chronic allograft nephropathy (CAN) is the major cause of renal transplant failure. The pathogenesis, however, remains unclear. Proteinuria occurs commonly with CAN. Proteinuria may be directly pathogenic at the level of the renal proximal tubular cell (PTC). Increased oxidative metabolism and oxidative stress may lead to maladaptive responses and gene expression. The fatty acids (FA) attached to albumin (the predominant protein in the urine) may further modulate these responses.

The aim of this study was to investigate the potential role of albumin overload (0-30 mg/ml) on oxidative stress in a cell culture model. The separate effects of the attached FA to albumin were also determined. Two human serum albumin (HSA) preparations were used: globulin free/FA free (GF/FAF) and globulin free HSA with attached FA (GF). Markers of PTC hyperfunction, oxidative stress, adaptive cellular responses, transcription factor activation (AP-1), and changes in gene expression were measured.

Lysosomal NAG activity was significantly increased in a dose-dependent manner by GF/FAF HSA. By contrast, a dose-dependent increase in ammonia generation was induced by GF HSA. Total glutathione content was only significantly decreased following exposure to GF/FAF HSA. However, oxidized glutathione was increased with either HSAs but maximal effects occurred with GF HSA. Superoxide dismutase (SOD) zymography demonstrated that MnSOD activity was significantly increased only in cells treated with GF/FAF HSA. Cu/ZnSOD activity remained unaffected regardless of the HSA used. Electrophoretic mobility shift assays revealed the activation of AP-1 with both HSAs, with maximal response following GF HSA exposure. HSAs modulated the expression of various stress-related genes analysed using Human Stress Arrays (Clontech, UK), particularly those involved in cell signalling (ERK6), cell stress or antioxidant defences (HSP90, α -crystallin A, extracellular SOD) and DNA repair (DNA ligase I).

Our results demonstrate that HSA overload is associated with complex effects in terms of oxidative stress and gene expression in HK-2 cells. FA attached to albumin also modulate these responses. These results may provide important insight into the pathogenesis and prevention of CAN in proteinuric patients.

P9

The Contribution Of Indirect Allorecognition To The Development Of Autoantibody In Chronic Allograft Rejection

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Introduction

B lymphocytes play an important role in the development of chronic rejection and recent studies have highlighted that allo- and auto-antibody may be involved. The generation of alloantibody requires help from T cells that recognise alloantigen via the indirect pathway but it is unclear how T cell recognition of alloantigen provides help for generating autoantibody. This study examines the link between indirect allorecognition and the development of autoantibody in a model of chronic heart graft rejection.

Methods

B6 recipients were grafted with Bm12 hearts, a strain combination that differs at only 3 a.a residues within the I-A class II antigen. Serial development of allo- and auto- antibody in recipients was assessed by labelling test sera against either target Bm12 thymocytes or nuclear-antigen-expressing HEp2 cells. The role of indirect T cell allorecognition was examined by immunizing B6 mice, 14 days prior to transplantation, with a synthetic 20mer peptide that corresponds to the disparate region of the I-A^{Bm12} antigen.

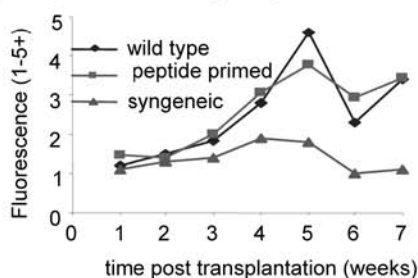
Results

B6 animals rejected Bm12 hearts slowly (MST=95, n=13). Histological examination of hearts harvested at day 50 suggested a vascular humoral component, yet surprisingly only autoantibody, and not alloantibody, was detectable in the sera of transplanted animals. Neither CD4 T cell deficient recipients nor control animals grafted with syngeneic hearts developed autoantibody, suggesting its development is dependent upon CD4 T cell recognition of alloantigen. To test this, B6 mice were primed for indirect allorecognition by immunising with Bm12 allopeptide. Peptide-primed recipients rejected their grafts more rapidly (MST=35, n=6), but the rate of autoantibody development was comparable to that of WT controls.

Conclusion

Humoral vascular rejection may be effected by autoantibody in the absence of a demonstrable alloantibody response. Although priming for indirect T cell allorecognition accelerated rejection, this was not due to an augmented autoantibody response. Exactly how the T cell recognition of alloantigen results in the activation of autoreactive B cells remains unclear.

Figure 1: Autoantibody response after heart grafting



Wednesday 29 March

Moderated Poster Session

Histocompatibility & Immunogenetics

P10

Antibodies To DPB In Patients Awaiting Renal Transplantation – A Significant Problem?
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We regularly audit positive flow-cytometric crossmatches that occur in our cadaver and living donor renal transplantation program to attempt to elucidate the antibody specificities involved. With the advent of specific antigen beads we have become more adept at defining these specificities, however we still get unexpected positive crossmatches that cannot be ascribed to autoantibodies.

One possible explanation for the unexplained positive crossmatches is HLA-DPB. We have used Flow PRA DP single antigen beads (One Lambda) to detect DPB antibodies, and have found that the results correlate well with the DP types of the sensitising donor and do not react with self DP. In addition the DPB reaction patterns are predictable based on our knowledge of the pattern of DPB1* variable regions defined by nucleotide sequences.

Of 473 patients on our active renal transplant waiting list 65 (14%) showed verifiable DPB antibody specificities. This is higher than a previous estimate for the prevalence of DP antibodies detected using an antigen capture assay (Pfeiffer et al 1995). In addition, of 200 unexplained positive crossmatches 19 (9.5%) could be ascribed directly to a DP antigen mismatch.

We conclude that DP antibodies are more prevalent than previously estimated and they make a significant contribution to the positive crossmatch seen using flow cytometry. We suggest DP typing of cadaver donors should be introduced to avoid shipping their organs to DP sensitised recipients.

(1) Pfeiffer K, Vogeler U, Albrecht KH, Eigler FW, Buchholz B, Grosse-Wilde H. HLA-DP antibodies in patients awaiting renal transplantation. *Transpl Int.* 1995;8(3):180-4.

P11

The Clinical Relevance of DRB3 Allele Specific Alloantibody in Renal Transplantation

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Introduction: Donor HLA-specific alloantibody present at transplantation can cause graft rejection. This can be avoided by the use of a pre-transplant crossmatch, yet despite a high degree of donor-recipient matching, unexpected positive crossmatch still occurs. Often such results have been attributed to uncharacterised HLA-C and/or HLA-DP specific antibodies however, we have previously identified DRB3 allele specific alloantibody as an alternative explanation. Kidneys from deceased donors are allocated on the basis of HLA-A, -B and DRB1 only and so may be matched with a DRB3 mismatched and potentially incompatible recipient. We now show that the presence of DRB3-specific antibody has clinical importance and significance.

Methods: Two patients received DRB3 mismatched renal allografts and a third was crossmatched against a DRB3 donor. HLA specific antibody characterisation was determined using luminex and flowbead microarrays. Pre-transplant crossmatch was performed by flow cytometry, whilst histological investigations of rejection were performed according to previously published protocols

Results: See table

Conclusions: Since DRB3 allele specific alloantibodies are associated both with renal allograft rejection and unexpected positive crossmatch they are clinically relevant. Approximately 5% of the West Midlands transplant waiting list have these antibodies. There is currently no means of listing allele specific antibody with UKT and neither are DRB3 alleles considered for organ allocation. These deficiencies need to be addressed.

	Recipient DRB3 Type	Donor DRB3 Type	DRB3 specific antibody	Observations
1	0202/05-08	0101-03	DR52*01	DRB3 0101 allele only mismatch. Rejection episode 1 year post-transplant; biopsy C4d +ve; no other HLA Ab in patient's serum
2	0301/02	1) DR52 2) 0202	DR52*02	Sensitised via primary transplant. 2nd graft transplanted unknowingly in the presence of DRB3*0202 antibody; rejected after 1 month
3	0202/05-08	0101-03	DR52*01	DRB3 allele only mismatch, Imported kidney, positive crossmatch, re-exported

P12

Multi Drug Resistance Gene 1 (MDR-1) Haplotypes Have Only A Minor Influence On Tacrolimus Dose Requirements In Renal Transplant Patients

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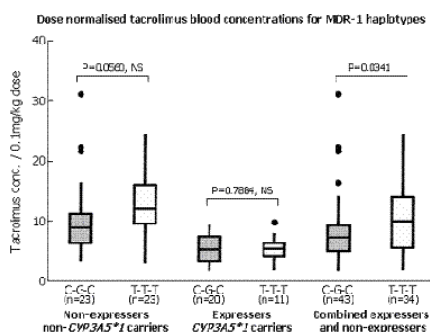
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Renal transplant recipients identified as non-expressers of the drug metabolising enzyme cytochrome (P450 3A5), by the *CYP3A5*1* genotype, have been shown to have lower dose requirements of tacrolimus. However, the influence of genetic polymorphisms of the multi drug resistance-1 gene (MDR-1), which codes for the drug transporter P-glycoprotein (P-gp), on the dose requirements of this drug remains controversial. It has been suggested that haplotype analysis of MDR-1 is a strong predictor of drug dose requirements in this patient group.

Dose normalised tacrolimus blood concentrations of 206 renal transplant patients were related to MDR-1 genotypes of single nucleotide polymorphisms (SNPs) C1236T, G2677T/A and C3435T, and combined haplotypes of these SNPs: C-G-C and T-T-T predictive of high and low levels of P-gp expression respectively. This is the largest cohort of tacrolimus treated patients genotyped for MDR-1, to date.

Lower dose normalised blood tacrolimus concentrations were achieved for: 2677 GG genotype patients, as compared to 2677 TT ($p=0.003$), and 3435 CC patients as compared to 3435 TT patients ($p=0.002$). There was also a small but significant difference in dose requirements between haplotypes C-G-C and T-T-T patients, which was not significant between these two haplotype groups when further sub classified as expressers and non expressers of *CYP3A5*, based on *CYP3A5*1* genotype. A highly significant difference was observed in tacrolimus blood concentrations between expressers and non expressers of *CYP3A5*.

The sub group of *CYP3A5* expressers contained a higher proportion of the C-G-C haplotype, as compared to the non expressers. Our data, when related to the *CYP3A5* genotype suggest that the MDR-1 genotype has only a minor influence on tacrolimus dose requirements and published data suggesting a more significant association may be due to linkage of the high P-gp expressing MDR-1 genotypes with *CYP3A5* expression.



P13

Multi Drug Resistance Gene-1 (MDR-1) Haplotypes And *CYP3A5*1* Genotypes Do Not Influence Ciclosporin Dose Requirements In Stable Renal Transplant Recipients

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The bioavailability of ciclosporin and tacrolimus are potentially influenced by the intestinal expression of the drug efflux pump P-glycoprotein (P-gp), the product of the polymorphic multi drug resistance-1 (MDR-1) gene. Three linked single nucleotide polymorphisms (SNPs) in exons 12, 21 and 26 are associated with P-gp activity. MDR-1 SNPs have a minor but statistically significant influence on tacrolimus dose requirements. The *CYP3A5*1* genotype, a SNP that influences the activity of the cytochrome P4503A enzymes has a major effect on tacrolimus dose requirement. Ciclosporin is also a substrate for this enzyme subgroup. However, the influence of individual SNPs or haplotype combinations of these SNPs in the MDR-1 gene and *CYP3A5*1* genotype on ciclosporin dose requirements is less clear.

Dose-normalised whole blood ciclosporin concentrations from trough (C0) and two-hour (C2) post dose sampling were used to assess the ciclosporin dose requirement in 190 stable renal transplant recipients. The Local Research Ethics Committee approved this study, and all subjects gave written informed consent. This is the largest cohort of ciclosporin patients genotyped for MDR-1 and *CYP3A5*1* to date. Dose-normalised ciclosporin blood concentrations were related to MDR-1 genotypes of SNPs C1236T, G2677T/A and C3435T, as well as homozygote based haplotype combinations: C-G-C and T-T-T, predictive of high or low levels of P-gp expression, respectively. No significant differences were found in dose normalised blood ciclosporin concentrations between different genotypes for any of these SNPs using both C0 and C2 based measurements. Haplotype analysis comparing patients with C-G-C (n=32) and T-T-T (n=35) haplotypes also showed no significant difference in dose requirements of ciclosporin. Similarly, there was no significant difference in dose-normalised blood concentrations of ciclosporin between carriers and non-carriers of the *CYP3A5*1* allele.

Although it has been suggested that MDR-1 haplotype analysis is an important predictor of ciclosporin dose requirement we did not find this in our cohort. We conclude that neither MDR-1 genotyping nor haplotyping are useful predictors of ciclosporin dose requirement in renal transplant recipients as is the case for *CYP3A5*1* genotyping, in contrast to observations with tacrolimus.

Ciclosporin blood concentration to dose ratio for each genotype group and homozygote based haplotypes for MDR-1 (µg/L/mg/kg)

	C1236T			C2677T/A						C3435T			Haplotypes	
	CC	CT	TT	GA	GG	GT	TA	TT	GA	CC	CT	TT	C-G-C	T-T-T
n	56	87	44	9	53	76	7	46	6	60	68	72	31	35
C0: Mean (SD)	42 (17.7)	51 (8.9)	61 (33.8)	38 (17.5)	43 (17.7)	52 (19.4)	47 (18.9)	59 (33.6)	38 (17.5)	43 (17.5)	50 (19.6)	57 (29.1)	42 (16.0)	55 (22.5)
C2: Mean (SD)	276 (75.3)	313 (39.1)	347 (121.7)	266 (109.3)	286 (75.9)	313 (98.3)	315 (113.6)	340 (2.1)	265 (109.3)	283 (74.5)	307 (106.1)	325 (109.6)	266 (72.7)	335 (103.9)

P14

The Cadaveric Donor Crossmatch Using Peripheral Blood Lymphocytes

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The traditional method of crossmatching cadaveric renal donors in this laboratory uses cells extracted from splenic samples obtained at retrieval. To identify recipients with negative crossmatches before retrieval, we have performed crossmatches using donor peripheral blood lymphocytes (PBL) and compared these results with those of our standard method.

50ml blood samples in EDTA were taken from potential donors and separated using lymphoprep. On receipt of the donated organs, crossmatches using splenocytes and PBLs were performed in parallel. The calculated relative median fluorescence (RMF) values that determine a positive or negative result were compared for each crossmatch. Standard statistical analysis was used to identify significant differences.

20 donors were used in this study, with 131 crossmatches performed and 238 samples tested. There was no significant difference between the mean of the median fluorescent values by splenocyte or PBL crossmatching for T-cells ($p>0.91$) or B-cells ($p>0.88$). There was no significant difference between the mean of the RMF values by splenocyte or PBL crossmatching for T-cells ($p>0.77$), but the RMF values with PBLs was 22% lower than that of splenocytes for B-cells ($p<0.05$). This was due to the median fluorescent value of the negative control being 20% higher for PBLs than splenocytes ($p=0.05$). However, titration of positive controls indicated that the end point was the same for both PBLs and splenocytes, implying equal sensitivity. The outcome of the T-cell crossmatch was the same by both methods and only 3 of 131 crossmatches were B-cell positive using splenocytes and negative using PBLs.

The cadaveric crossmatch using PBLs is a suitable alternative to using splenocytes in identifying crossmatch negative recipients prior to organ retrieval. After discussion with users we have introduced the PBL crossmatch to the South Thames regional sharing scheme to attempt to reduce the CIT for locally retrieved kidneys.

Wednesday 29 March
Moderated Poster Session
Kidney 1

P15

Prospective Study Comparing NASBA and quantitative PCR in Diagnosis and Monitoring Treatment of Human Cytomegalovirus Infection in Kidney Transplant Recipients

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Objectives:CMV infection maybe diagnosed by quantitative PCR (Polymerase Chain Reaction-LightCycler system) to detect DNA copies or by Nuclisens CMV pp67 mRNA assay using NASBA technique (Nucleic Acid Sequence Based Amplification). Aim of study was to compare diagnostic accuracy of NASBA and PCR in detecting CMV (Cytomegalovirus) infection and monitoring treatment in kidney transplant recipients.

Methods:Blood samples were collected prospectively from 47 kidney transplant recipients pre-transplant and at regular intervals post transplant. Further samples were collected for monitoring treatment and on clinical suspicion at subsequent follow-up visits. Clinical data, NASBA and PCR results were compared in all the patients.

Results:Data on NASBA was complete in 26 patients, and for PCR in 36 patients. Diagnostic accuracy for NASBA was: sensitivity 76.4%, specificity 100%, positive predictive value (PPV) 100%, and negative predictive value (NPV) 69.2%. PCR had sensitivity of 100%, specificity 86.9%, PPV 81.2% and NPV 86.9%. Both NASBA and PCR positivity preceded clinical features in most patients who developed active CMV disease. PCR preceded clinical features in 8/12(66.6%) cases, with a mean lead-time of 28.6 days (SD 16.1days). In contrast, NASBA was positive in 9/11 cases (81.8%), with average lead-time of 42.7 (SD 46.3 days). NASBA tended to become positive when DNA copies of CMV on PCR were exponentially raised on consecutive tests, with an average multiplication factor of 16 times (SD 16.3, range 7-28). NASBA reverted to negativity once the consecutive fall in DNA copies was logarithmic by mean of 11 times (range 5-28). There appeared to be no correlation between NASBA positivity and actual copy number of DNA.

Of 12 patients with follow-up data following treatment of active CMV disease, NASBA and PCR remained positive in 10(83.3%) despite cessation of symptoms. Further episodes of active CMV disease were seen in 80% of these patients.

Conclusion:Both NASBA and PCR techniques detect CMV before clinical features. PCR is more sensitive, but NASBA is more specific. NASBA is cheaper and quicker to perform. Adopting better techniques to improve its sensitivity maybe useful. Both techniques have a role in monitoring treatment, and viral replication should be tested before stopping anti-viral treatment.

P16

The Use Of Oral Glucose Tolerance Tests To Determine The Prevalence Of Post-Transplantation Diabetes Mellitus (PTDM): An Under-Diagnosed Phenomenon

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Aims. Current opinion suggests that PTDM is under-diagnosed in the renal transplant population despite routine glucose monitoring. Fasting glucose measurements may be insensitive in detecting PTDM and will ignore the diagnosis of impaired glucose tolerance (IGT). Both PTDM and IGT confer a higher risk of developing cardiovascular disease. Early recognition of these patients allows for optimisation of their management. The aim of this study was to use OGTTs to help identify the prevalence of PTDM and IGT in renal transplant recipients.

Methods. Renal transplant recipients with 2 consecutive fasting blood glucoses < 7.0 mmol/L and not currently diagnosed with either pre-transplantation diabetes mellitus or PTDM underwent an OGTT. The diagnosis of PTDM, IGT and impaired fasting glucose (IFG) were based upon WHO guidelines. Epidemiological data on each patient was also collated to identify individual risk factors.

Results. In this on-going study, 66 patients have undergone an OGTT. Please refer to table below.

Discussion. Fasting glucose underestimates PTDM and ignores IGT. OGTTs identify clinically significant but unrecognised PTDM and IGT. Clinical parameters do not help in the identification of abnormal glucose tolerance. In agreement with other studies, abnormal glycaemic status is associated with hyperlipidaemia (¹PTDM vs. normal OGTT = 5.8 vs. 4.5; P<0.05 and ²abnormal OGTT vs. normal OGTT = 5.0 vs. 4.5; P<0.05).

Conclusions. Over half of renal transplant recipients were found to have an abnormal glycaemic status. These results confirm that the use of routine glucose levels underestimates the prevalence of PTDM and ignores the prevalence of IGT. These findings would suggest the routine use of OGTTs in renal transplant recipients is a valuable clinical tool to identify and treat those with an abnormal glycaemic status.

OGTT status	Normal	PTDM	IFG & IGT	IFG alone	IGT alone
Patients	47%	14%	15%	20%	4%
Fast. Glu.	5.6 ± 0.1	6.7 ± 0.2	6.4 ± 0.1	6.6 ± 0.2	5.8 ± 0.1
BMI	27 ± 1	28 ± 1	30 ± 2	30 ± 3	24 ± 3
W/H ratio	0.93 ± 0.03	0.96 ± 0.02	0.96 ± 0.07	0.94 ± 0.03	0.84 ± 0.05
Chol.	4.5 ± 0.2	5.8 ± 0.5 ^{1,2}	5.0 ± 0.3 ²	4.5 ± 0.3 ²	5.1 ± 0.2 ²
Systolic BP	138 ± 4	149 ± 8	143 ± 7	134 ± 3	142 ± 12
Diastolic BP	80 ± 2	83 ± 4	78 ± 4	78 ± 2	66 ± 6

Data expressed as mean ± std. error mean.

P17

Transplanting Patients Repeatedly: Is It Worth Doing?

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INTRODUCTION

Kidney transplantation is quite challenging in patients who have had a transplant before, as these patients may have altered anatomy and immune status. Reported series thus show inferior outcome in re-transplants compared with first transplants. However, it is not clear whether outcome worsens with multiple attempts at transplantation.

We analysed data from 197 multiple transplants and compared graft and patient survival between patients with different number of transplants.

Methods

Patients included had two or more kidney transplants at our centre between 1993 to 2004. Patients in group I had two, in Group II three and in Group III > three transplants. Along with number of re-transplants, impact of donor type (whether deceased or living), the HLA mismatches and recipient sensitization on graft survival were analysed. Survival estimates were done by Kaplan- Meier method and log-rank test and multivariate analysis by Cox regression.

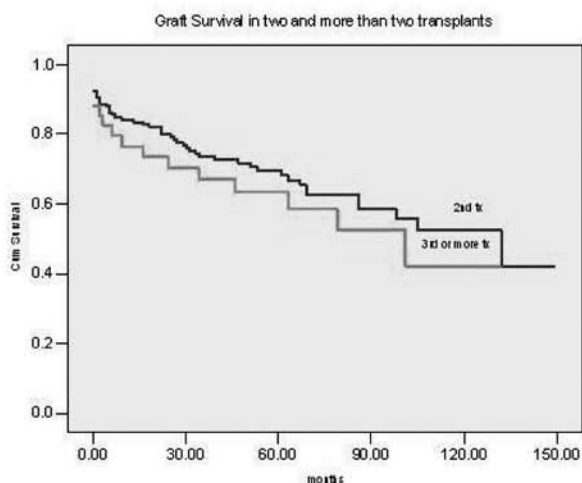
Results

197 cases were analysed (mean age 36 ± 16 years). The number in group I, II and III was 163(83%), 25(13%) and 9(5%) respectively. 88% (173) were deceased donor and 12% (24) living donor transplants. Mean HLA mismatches were 2.2 and mean panel reactive antibodies 43.3%. Mean follow up was 55 months. 68(34%) grafts failed- 53(33.1%), 12 (48.0%) and 3 (33.3%) in group I,II and III respectively. 38(19%) patients died - 28 (17.5%), 5 (23.8%) and 2 (22.8%) in respective groups. One and 5 year graft survival in group I was 85% & 65%; in group II 75% & 59%; and in group III 77% & 63% (P= 0.45). One and 5 year patient survival rates in group I, II and III were 95% & 85%, 90% & 78% and 88% & 77% respectively(P=.86). On multivariate analysis, only living donor transplants independently correlated with better outcome (P=0.03).

CONCLUSION

Graft survival is not significantly affected by number of re-transplants although there was a trend towards better outcome in group I than others. Living donation seems to be more important than the number of previous transplants in determining the outcome.

Figure:1



P18

Creatinine Drop in the First Week is an Important Predictor of Graft Survival in Renal Transplantation

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Background: DGF is traditionally defined as need for dialysis in the first week post transplant and has long term prognostic significance. In UK it affects around 13% of recipients.

Aim: To see if Creatinine (Cr) fall by Day 7 post transplant is an independent predicting factor for graft survival and 5 year kidney function, irrespective of the need for dialysis. To establish if the effect of rejection was significant in patients whose Cr did not fall more than 30% by the 7th day.

Methods: 455 cadaveric kidney transplants performed in a 6-year period were included in the study. Patients with thrombosis in the first week were excluded from further analysis. Patients whose Cr had not fallen 30% by the 7th day or needed dialysis constituted Group A. Patients with more drop of their Cr were group B.

Results: 94 patients (20%) had a drop of their creatinine of less than 30% by day 7 (group A). Group A patients were more likely to have any rejection than group B (CI for Risk ratio 1.1-2.8, p=0.010) and also more likely to have vascular rejection (CI for Risk ratio 1.1-3.6, p=0.013). The presence of any rejection had no effect on graft survival but patients with vascular rejection had worse graft survival at 1 year (80 vs. 92%) and at 5 years (57 vs. 76%) compared to patients without vascular rejection (p=0.002).

Patients in group A had worse survival than patients in group B (78 vs. 94% at 1y and 62 vs. 76 at 5y, p=0.0005). Stratified analysis showed that vascular rejection had a greater impact on graft survival in patients in group B (5y survival 60 vs. 78% in those without vascular rejection within that group, p=0.006) than in patients in group A where the effect was non significant (p=0.7).

Creatinine in the surviving grafts was worse at 5 years in group A compared to group B (187 vs. 145, p=0.05).

Conclusions: The drop of Creatinine by the end of 1st week by at least 30% is an independent factor for better graft survival and kidney function 5 years post transplant. Vascular but not cellular or borderline rejection, affects long term graft survival. The relative effect of vascular rejection although detrimental in both groups is more pronounced in grafts that initially functioned well. The drop of Creatinine by the end of the first week, compared to the traditionally used need for dialysis, is a broader but equally important factor for long term outcome.

P19

Short-Term Changes in Growth, Bone Mineral Content and Biochemical Markers in Children Post-Renal Transplantation

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In the early stages following renal transplantation children receive high dose steroids. In a LREC approved study, we examined short-term changes in growth, bone mineral content and biochemical markers in 10 children (6M:4F) immediately following renal transplantation (median age:12.0yrs,10th,90thcentiles:5.2,13.9). Baseline immunosuppression was with oral prednisolone, tacrolimus and azathioprine. 6 children had previously received peritoneal dialysis for a median duration of 2.5 years (1.3,6.3). At 0 and 6 months post-transplantation growth was measured by routine anthropometry and bone mineral content (BMC), measured by dual energy x-ray absorptiometry, was calculated for total body (TB) and Lumbar spine (L2-L4) (LS). BMC was adjusted for height age and expressed as percentage predicted Height BMC (ppHBMC). Biochemical markers bone specific alkaline phosphatase (bAlkP) and total deoxypyridinoline for Creatinine (DPD/Cr) were measured and expressed as percentage change over the 6 month period.

Median Ht SDS and Ht velocity at 0 months were -1.7(-3.0, -0.7) and 3.4 cm/yr(1.4, 6.1) and at 6 months -1.8(-2.9, -0.8) and 4.8 cm/yr(3.2, 8.1) respectively. Median GFR at 6months was 56ml/min/1.73m² (46, 68). Median total steroid and tacrolimus dose (mg/kg/day) over the 6 month period were 0.6(0.4,0.8) and 0.25(0.1,0.4) respectively. There were no correlations between GFR, steroid & immunosuppression doses and BMC or bone markers. There was a significant decrease (p<0.05) in LSppHBMC at 0 and 6 months, 99%(90,112) and 85%(81,87) but not for TBppHBMC, 86%(75, 107) and 81%(75, 86) respectively. Median % change bAlkP over the study period was not significant, -2%(-12, 5.1). % change DPD/Cr from baseline significantly increased over the study period 92.2% (51.3, 109) (p<0.05). There were significant inverse correlations between % change TB and LS ppHBMC and % change DPD/Cr (p<0.05, r,-0.6) over the study period.

Short-term assessment of Tx children shows that although growth is relatively normal, there is a decrease in LS BMC and correspondingly, a rise in DPD/Cr. There was no clear correlation with steroid dose. Factors affecting BMC over short and long-term post renal transplantation need further evaluation.

Wednesday 29 March

Moderated Poster Session

Kidney 2

P20

Successful Early Radiological Intervention After Renal Transplantation

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Introduction: Vascular complications following renal transplant is well recognised leading to deterioration of graft function, hypertension, allograft nephropathy and graft loss. Vascular problems may exist in the donor or recipient artery pre-transplant. Early vascular complications such as anastomotic and donor or recipient stenosis may be amenable to treatment with radiological intervention with satisfactory outcome. Radiological intervention very early after transplant are avoided by most centres due to perceived risks of bleeding, anastomotic disruption, thromboembolism, groin haematomas, pseudo aneurysm formation and traumatic arterio-venous fistulation. We describe our experience with early radiological intervention.

Method: All patients who received renal transplant in 2004 and 2005 were reviewed. Patients who had ultrasound (US) and magnetic resonance (MR) scanning evidence of renal artery or vein stenosis within 30 days of transplantation were included. Angiography procedures and follow-up imaging and renal function was reviewed

Results: 311 patients received renal transplants in the study period. 10 patients had US and MR evidence of transplant artery or vein stenosis (median age = 38, range = 5-59) within 30 days of renal transplantation (mean= 8 days). All patients underwent angiography (one venography). 5 patients showed significant arterial stenosis which was successfully plastied or stented. One patient with renal artery thrombosis was surgically explored and subsequently had nephrectomy. One patient had significant renal vein kinking which was successfully stented.

Conclusion: Early radiological intervention in renal transplant is safe and avoids morbidity of surgical re-exploration with satisfactory graft and patient outcome.

Table: Results of early radiological intervention for renal vascular problems after transplant

No	Days post transplant	USS ± MR Diagnosis	Intervention	Complication	Function
1	4	Anastomotic stenosis	Stent	Nil	Good
2	8	Anastomotic stenosis	Stent	Nil	Good
3	21	Segmental RA stenosis	Stent	Nil	Good
4	8	Anastomotic stenosis	No	Nil	Good
5	1	RA thrombosis	No	Nil	Nephrectomy
6	30	Anastomotic stenosis	No	Nil	Good
7	10	RA kinking	Balloon plasty	Nil	Good
8	3	Recipient IIA stenosis	No	Nil	Good
9	7	Renal Vein Kink	Stent renal vein	Nil	Good
10	3	RA kinking	Stent	Nil	Good

P21

Exclusion from the Waiting List for a Kidney Transplant Based on Body Mass Index (BMI) Alone is Inconsistent

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The aims of this study were (1) to determine the number of our patients with stage V chronic kidney disease excluded from the transplant waiting list (TWL) on the basis of their weight who were otherwise eligible, and (2) to determine if the practice of using body mass index (BMI, Kg/m²) as an exclusion criteria from the TWL was consistent.

Poorer graft and patient survival after kidney transplantation has been described in obese patients. A BMI > 30 is considered to be a relative contraindication. However, recent evidence suggests obesity results in increased wound complications but overall these patients do as well as the non-obese.

All patients (n=371) in the low clearance clinic (LCC), on haemodialysis (HD) and on peritoneal dialysis (PD) were categorised according to their weight, BMI, suitability for transplantation (eg absence of co-morbidity, age) and transplant status.

41% (152/371) of these patients had a normal BMI of 19-25, 3% (12/371) BMI <19 and 29% (106/371) BMI 26-29. 27% (101/371) were obese with a BMI >30 and comprised 34% LCC, 25% HD and 23% PD patients. Of those with BMI 30-34 (n=61), 29/61 were otherwise suitable for a kidney transplant. Of these, 3/29 were excluded from TWL because of their weight, 14/29 were on TWL and the remainder were under assessment. Of those with BMI 35-39 (n=27), 11/27 were otherwise suitable for transplantation. Of these, 3/11 were on TWL and 6/11 had been refused because of their weight (the remainder pending a decision). Of those with BMI >40 (n=13), 10/13 were otherwise eligible for transplantation. Of these, 8/10 had been refused because of their obesity and 2/10 were on the TWL. Cardiac disease, diabetes mellitus nor age explained the exclusion/inclusion of obese patients who were otherwise suitable for transplantation.

In summary, 34% (17/50) of patients with a BMI >30, who were otherwise suitable for transplantation, were refused a kidney transplant because of their weight, although 38% (19/50) in the same BMI range had been accepted. Our current practice of listing a patient for a kidney transplant with respect to BMI is inconsistent and not explained by patient age or co-morbidity.

P22

The Hidden Danger Of Post Transplant Erythrocytosis

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Background :

Post transplant erythrocytosis remains an enigmatic condition which can lead to serious thromboembolic events. The risk factors identified are: diabetes, male gender, retention of native kidneys, polycystic kidneys, adequate erythropoiesis prior to transplant, smoking, transplant renal artery stenosis, hypercalcemia and rejection free well functioning graft.

Aim: To identify the risk factors and outcome of various therapeutic modalities.

Methods:

Data of 2044 renal and pancreatic-renal recipients from 1979 up to October 2005 was retrieved. Patients with persistently elevated haematocrit for more than a month were identified. Males with a haematocrit ≥ 0.5 and females with a haematocrit ≥ 0.48 were selected.

Results:

46 patients, M:F = 23:23 were identified. Nine patients were diabetic and 7 had polycystic kidneys as their original disease. Thirty patients did not require Erythropoietin while on dialysis. Immunosuppressive medications consisted of Mycophenolate Mofetil =12, Azathioprine =7, Cyclosporine =34, Tacrolimus = 9. Twenty four patients did not have any episode of rejection while 20 had at least one rejection episode and 2 patients had 2 rejection episodes. The median serum creatinine was 148 mmol/litre while the serum calcium was 2.49 mmol/lit. The median time interval to develop erythrocytosis was 9.4 months. (1.4 – 131.9) Twenty patients were treated with both ACE Inhibitors and venesection, 6 were treated with ACE Inhibitors alone, 8 with venesection alone, and 12 did not get any treatment. The median time taken for the haematocrit to fall below 0.450 was 70.07 wks. (6-677) In eight patients the haematocrit did not fall below the recommended value of 0.450. Three were treated with venesection and Enalapril, 2 with Enalapril alone and 2 with venesection alone and one patient did not receive any treatment. Three incidents of thromboembolism were noted which occurred during the period of risk. All incidents occurred in women. One patient had recurrent deep vein thrombosis and one developed venous thrombosis with pulmonary embolism.

Conclusion :

Erythrocytosis was seen in upto 2.2% of transplant recipients of which 23% showed spontaneous resolution. 17.4% of patients did not respond favourably and remained at risk of thrombosis. Although rare, erythrocytosis can lead to life threatening complications specially in women who have a higher risk for venous thrombosis.

P23

Asymptomatic Coronary Artery Disease In Candidates For Renal Transplantation: Cardiac Risk Stratification By Myocardial Perfusion Scan

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Objective : To look for significant silent coronary in patients referred for renal transplantation.

Methods: Asymptomatic patients referred for renal transplantation whose exercise tolerance was unchallenged with two or more clinical risk factors for coronary artery disease undergo a stress myocardial perfusion scan.

Results: July 1999 and December 2002, 553 patients were referred for renal transplantation. 88 had unchallenged exercise tolerance and ≥ 2 risk factors for coronary artery disease. 14 patients had lethal or life threatening cardiac event.[please refer to table]

High Calcium-phosphate product (>4.5) along with high PTH was noted in 5/31 patients in group I Vs 7/22 in group III, though $p > 0.05$.

Conclusions: Significant silent coronary disease is present in 2.5% (14/553, only 4 of these were diabetic) of renal transplant referrals. Stress myocardial perfusion scanning is a sensitive non-invasive method of identifying such patients.

MIBI scan	Age (mean)	Follow up (months)	Dead on dialysis	Transplant and alive	transplant and dead	Alive on HD/PD
Group I: (n= 31)	53.6	23.5	Total: 8	10	3 of them transplanted	Total: 10
Normal			4 were listed for transplantation		<u>Cause of Death:</u>	
			<u>Cause of Death:</u>		Non-cardiac 3	7 were listed for transplantation
			Cardiac : 1			
			Non-cardiac: 7			
Group II (n=35)	53.6	31.3	Total: 8	11	0	Total: 16
Includes fixed defect (n=32), or dual positivity (n=3)			5 were listed for transplantation			7 were listed for transplantation
			<u>Cause of Death:</u>			9 were not listed: among them (2 had angiogram, and one had poor EF had cardiac event)Two of them had angioplasty
			Non cardiac 7			
			Cardiac: 1			
Group III: (n=22)	57.1	26.7	Total: 7	2	Total: 4	Total: 9
			2 were listed for transplantation: both died	One of them had angiogram	<u>Cause of Death:</u>	
			<u>Cause of Death:</u> cardiac		Non-cardiac 3 (one of them had angiogram)	3 were listed for transplantation (angiogram in one of them)
Reversible ischaemia,			5 not listed:		Cardiac 1 (had angioplasty)	6 not on list
			<u>Cause of Death:</u>			(Angiogram in 2 Angioplasty in one developed ischemic event)
			Cardiac 3, Cancer lung			
			2 (one of them had angio, both with abnormal ECG)			

P24

Oxford Experience Of NHB & HB Renal Transplant

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Aim: To review outcome and renal function in consecutive of non-heart beating (NHB) and heart beating (HB) renal recipients in Oxford Transplant Centre from 2002 to 2005.

Methods: During the 3-year period, a total of 123 HB renal 54 NHB transplants performed. The last 24 NHBD procured kidneys were preserved by continuous hypothermic pulsatile perfusion using UW machine perfusion solution in the (Life Port™) transporters. Renal function and allograft survival rates for kidneys from machine perfused, static cold stored NHB and HB donors were compared at 3, 6, 12, and 24 months.

Results: The mean age of HB, machine perfused, and non-machine perfused NHB recipients were (47.88±12.51), (45.5±14.7) and (53.65±9.8) years respectively. The mean of CIT for HB was (1056.54±330.47) min in comparison to (1154.8±327.4) min for machine perfused and (1168.5± 297.5) min for static cold perfusion NHBD kidneys. After transplantation the incidence of delayed graft function was 39% (48//123) in HB graft, 41% (10/24) in machine perfused and 86% (26/30) in static cold preservation NHB graft (p value< 0.001). Primary non-function in HB, machine perfused and non-machine kidneys were (7/123) 6%, (2/24) 8% and (3/30) 10% respectively. The serum creatinine level at 12 months for HB, machine perfused, and non-machine perfused NHB recipients were 147±62.8, 174±48.8 and 194.3±120.6 (µmol/L) (p value <0.001) respectively.

Conclusion: Non-heart beating donor kidneys represent a valuable mean to decrease the waiting time for organ transplantation. Machine perfused kidneys from non-heart beating donor have an acceptable graft function comparable to cadaveric renal transplant. A decreased rate of DGF in the machine-perfused kidneys is encouraging but randomised controlled trial comparing machine-perfused and static preservation of NHBD kidney is important.

P25

Subclinical Recurrence Of Iga Nephropathy Following Renal Transplantation: Evidence From Early Protocol Biopsies

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Clinical recurrence of IgA nephropathy (IgAN) accounts for 40% of all recurrent disease following renal transplantation and may result in graft failure. However, the incidence of subclinical recurrent IgAN (IgA deposits on histology without clinical evidence of glomerulonephritis) is unknown. The aim of this study was to determine the frequency and clinical significance of early histological recurrent IgAN by analysis of 1 month protocol biopsies, performed routinely on our unit, irrespective of graft function.

Search of nephrology (1985-97) and pathology records (1998-2005) revealed 53 patients transplanted for IgAN on our unit. Of these, 35 had an adequate early protocol biopsy (1 month) and were eligible for inclusion. Mean follow-up was 10.5 years (range 3-19). Staining for IgA was performed retrospectively on all biopsies, including the 1 month protocol biopsies.

Thirteen (35%) patients developed recurrent IgAN. Two patients were diagnosed at 2 and 2.4 months post-transplantation; both showed glomerular IgA deposits in the 1 month protocol biopsies, but not in biopsies at implantation and 1 week. Ten patients developed late clinical recurrence at a median of 72 months (range 40-219), none of these showing IgA deposits in the 1 month protocol biopsies or later clinically indicated biopsies performed in 6 of the 10 patients during the first 3 years post-transplantation. The final patient is having annual protocol biopsies as part of a trial, and has histological recurrence in the 3 year biopsy. The remaining 22 patients have not developed disease recurrence, after being followed for a median time of 148 months; all their 1 month protocol biopsies were negative for IgA. In those patients showing early subclinical recurrence, IgA positivity was initially focal, involving only a proportion of the glomeruli, becoming diffuse with clinical recurrence.

In conclusion, most recurrent IgAN occurs late post-transplantation (>5 yrs). However, IgA positivity in 1 month protocol biopsies predicts early clinical recurrence. There is a short time period between histological and clinical recurrence. All transplanted IgAN patients with no clinical recurrence had negative IgA staining in the 1 month biopsies; therefore, at least in early protocol biopsies there is no evidence of histological recurrence without subsequent clinical recurrence.

Wednesday 29 March
Moderated Poster Session
Donor Care

P26

The Impact of In House Donor Liaison Schemes- The Bristol Experience

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An in House Transplant Co-ordinator can significantly increase Organ Donor numbers. Studies from both Spanish & American 'In House' approaches have demonstrated their impact on organ donation rates. With this evidence UK Transplant implemented Donor Liaison schemes (DLS). This abstract demonstrates the success of the DLS in Bristol's Neuro-surgical ICU & recommends the need to continue this approach.

Bristol obtained funding for a DLS in July 2002. Historically the majority of organ donor referrals came from the Neuro-surgical ICU. This changed during 2000, & donor numbers fell dramatically. An audit of ICU deaths highlighted some key changes that were needed. Priorities were to improve staff awareness of organ donation, increase relative consent & to implement a Controlled Non Heart Beating Donor programme (NHBD). It was felt these objectives could be best achieved through an 'In House' Donor Liaison approach.

In 3 years, the DLS has transformed organ donation rates & led to a 60% increase in Deceased donors, & a 73% conversion of potential to actual donors, one of the highest in the U.K. Family consent for donation is above the UK national average at 73%. Furthermore controlled NHB Donors contribute significantly towards the total number of Organ donors from the Neuro-surgical ICU.

Organ Donation is now perceived as an important part of bereavement care within the ICU & feedback from staff & donor families has been positive. In the absence of a DLS it is unlikely that this level of commitment towards organ donation would have been achieved.

In the U.K, the DLS as a whole has not increased organ donor rates. However it is important to demonstrate the individual success of this scheme in Bristol & highlight the need to continue to support this programme. A clinically credible in-house co-ordinator can champion organ donor programmes, & support the introduction of NHBD scheme. In light of this evidence Bristol aims to implement an in House Transplant Co-ordinator, & evaluate if this can match the success of an effective DLS.

P27

In House Coordination (IHC) the First UK Experience

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Introduction

This was a pilot scheme to establish IHC's in two London NHS Trusts. Following a period of observation within both units the IHC developed objectives to facilitate the referral, approach and request donation from families of all potential multi organ donors.

Objectives

The objectives were:-

- To establish 100 % referral of all potential multi organ donors.
- To increase the number of organs available for transplantation.
- Develop a long contact model with next of kin.
- Understanding relative refusal rates.
- Development of policies and guidelines to support the organ donation.
- To a deliver a seamless process from approach, consent to donation.
- Support staff working on I.T.U's and Theatres.
- Provide education and analysis of PDA data.

Design:

Following negotiation with key stakeholders, UKT and North Thames Coordinators, the pilot was commenced in October 2004 and funded for 2 years. Two experienced Coordinators were appointed into the posts. The IHC's role and results are continually being evaluated; referral rate, relative's refusal and conversion rate data is collected.

Outcomes:

There has been an increase in the referral rate of potential donors to the IHC. The relative's refusal rate remains static but insight into reasons for relative's refusal has increased. Since commencing the IHC scheme the conversion rate has increased from potential to actual organ donors. During the first year the IHC have integrated within the I.T.U's and developed a long contact model with bereaved families.

Conclusion:

Following this pilot scheme and evidence from the U.S.A and Spain, UKT have agreed to fund a further fourteen additional IHC posts nationwide. The objective is to have an IHC in each Neuro Intensivist care unit in the U.K. The involvement of the IHC brings an enhanced quality of service to the Intensive Care Unit and allows information to be given to bereaved families at a critical time.

P28

5 Years Of Hepatocyte Banking: The UK Human Tissue Bank Experience

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The UK Human Tissue Bank has been established for 5 years, accepting and promoting the expanding need for good quality human tissue for research. The donation of both surplus surgically resected tissue and non-transplantable organs from cadaveric donors for this purpose is actively encouraged. All tissue donation and subsequent distribution is with the approval of NHS Multi-centre (MREC) and Local Research Ethics Committees (LREC).

The majority of work at our tissue bank involves hepatocyte isolation and subsequent research. Human hepatocytes are used in a multitude of research projects including pharmacotoxicological research, transplantation and bioartificial liver development. They may be isolated from multi-organ donor tissue or more commonly from surgically resected specimens, the latter being obtained most commonly as a consequence of major liver surgery for malignant disease.

Hepatocyte work is often conducted during antisocial hours due to the timing of donation and evidence suggests reduced ischaemic time positively affects yield and viability. Additionally, supply of liver is often erratic and geographically challenging with demand presenting similar difficulties. To alleviate the nocturnal aspect of hepatocyte biomedical research, to ensure maximal use of each donation and to build a bank of hepatocytes, one of our interests is the development of successful cryopreservation techniques.

This presentation reviews the work of the UK Human Tissue bank over the previous five years; reviewing the outcomes of over 300 donations, commenting on changes in donation pattern and discussing the challenges and recent changes within this field.

Comparative Efficacy Of Renal Preservation Solutions To Limit Functional Impairment After Warm Ischaemic Injury

N Ahmad¹, JR Pratt¹, DJ Potts² and JPA Lodge¹

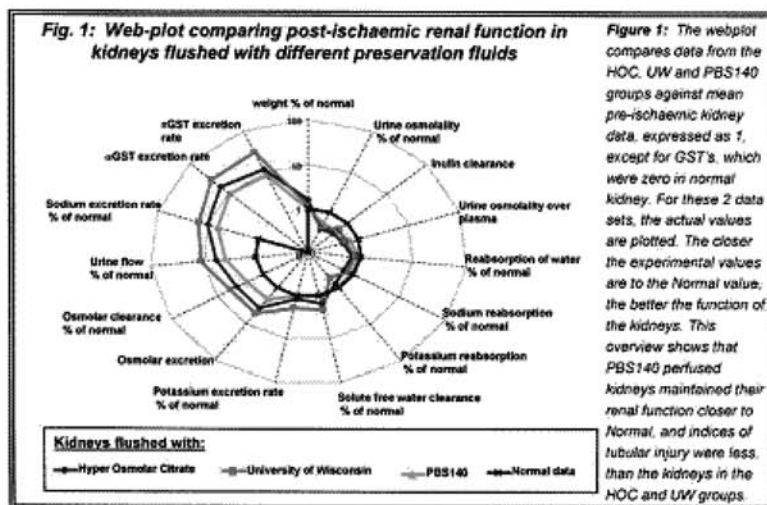
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Tissue damage at the time of preservation for transplantation has a negative impact on the success of the procedure. Preservation fluids limit damage during ischaemia as their core components prevent electrolyte imbalances that lead to fluid influx and cellular oedema. However, there is little information on the influence of these fluids on physiologic consequences of warm ischaemia alone, or on the comparative ability of preservation fluids to limit warm ischaemic injury.

Warm ischaemia was induced in rat kidneys by cross-clamping the left renal pedicle for 45 minutes with contralateral nephrectomy. The ischaemic kidneys were flushed with either: Euro-Collins (EC), Hyper Osmolar Citrate (HOC), University of Wisconsin (UW) or Phosphate Buffered Sucrose solution (PBS140). Over two hours after reperfusion, urine and blood samples were collected and glomerular and tubular function were assessed, as were markers of tubule damage (urinary α and π glutathione-s-transferase), and histology at the end of the experimental period.

The data show that warm ischaemia induces severe injury and that parameters of post-ischaemic renal function were significantly influenced by the choice of preservation fluid used. Essentially, the continued use of EC as a renal preservation solution finds no support in these data. HOC and UW solutions were better able to limit the decline in renal function after warm ischaemia, but the solution most able to limit functional impairment after warm ischaemia was PBS140 (see **Figure 1**), a solution under development in our centre. These data were validated by histopathological analyses which showed acute post-ischaemic changes were limited most by the use of PBS140.

In conclusion, this analysis compared the efficacy of preservation solutions with an improved fluid and ultimately may permit development of an optimum platform for improved preservation.



Wednesday 29 March
Moderated Poster Session
Immunosuppression 1

P30

Anthracycline-based chemotherapy as first-line treatment in adults with malignant Post Transplant Lymphoproliferative Disorder (PTLD) after solid organ transplantation

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Background

The recommended first-line treatment for post-transplant lymphoproliferative disorder (PTLD) is reduction in immunosuppressive therapy, irrespective of histopathological type. Second line treatment with chemotherapy is generally reserved for patients whose tumours fail to respond to reduced immunosuppression. Because of the similarities between high-grade malignant PTLD and non-Hodgkin's lymphoma in the general population, our policy has been to treat this type of PTLD with anthracycline-based chemotherapy as a key component of first line treatment.

Methods

A retrospective single centre analysis of 20 patients who developed PTLD following liver or kidney transplantation between 1993 and 2005 was undertaken, with particular emphasis on tumour histology, treatment received and clinical outcome.

Results

Of the 20 patients presenting with PTLD, thirteen had high-grade malignant lymphoma on initial diagnostic biopsy and all received anthracycline-based chemotherapy and reduction in immunosuppression as first line therapy. Nine (69.2%) of the thirteen patients achieved complete remission and seven of these remained in complete remission 5 years after diagnosis of PTLD; two patients died in remission of unrelated causes. Six of the 20 patients had non-malignant PTLD on initial diagnostic biopsy (of which three were subsequently re-classified) and all were treated by reduction in immunosuppression (+/- antiviral therapy and/or surgery). All six patients achieved complete remission without chemotherapy and five were alive at a median of 31 months (range 10 – 123) after diagnosis; one patient died in remission of unrelated disease. Overall, sustained complete remission was seen in 16 out of 20 patients (80%) at one year following diagnosis.

Conclusion

The use of chemotherapy combined with reduction of immunosuppression as a first-line treatment of high-grade malignant PTLD achieves sustained complete remission in around 70% of patients. In patients with non-malignant PTLD, complete remission can be achieved by using reduction of immunosuppression (and in some cases anti-viral agents or surgery) as first-line treatment without the need for chemotherapy.

P31

New Onset Diabetes After Transplantation [NODAT]: A Single Unit's Experience Over 7 Years
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OBJECTIVE: NODAT is associated with significant morbidity and mortality. The aim of this study was to audit the incidence, impact, management and outcomes of NODAT in a single centre over the last 7 years.

METHODS: A retrospective audit of 256 adult patients was undertaken to identify those patients who had developed NODAT. Data collected were time of onset post-transplant, any possible triggering factors, management and glycaemic control, regression or permanence, infections and other complications, impact on patient and graft survival, and relation to CMV and different immunosuppression regimes.

RESULTS: There were 27/256 [10.5%] patients with NODAT. The median period of onset was 120 days post-transplant (range 10-660), but 21(77.7%) occurred in the first 6 months. Regression was seen in 11(40.7%) and occurred at a median time of 185 days post onset (range 90-1080). Treatment was diet control in 7; oral hypoglycaemic agents (OHA) in 5; progression from OHA to insulin in 6; and insulin only in 9. Glycaemic control was very poor in 7/27(26%). Possible immediately preceding events for hyperglycaemia were: - treatment of acute rejection in 8; CNI toxicity in 13; over immunosuppression with reduced white cell count in 8. There was no identifiable preceding factor in 9 patients. Tacrolimus was used in 16 cases, of which 8 had toxicity, and cyclosporine was used in 12, of which 5 had toxicity. Asymptomatic CMV IgG positivity seen in 11(40.7%) of patients with NODAT. The following infections occurred in the NODAT group: CMV disease in 7 patients; serious bacterial septicaemia in 10 of which 6 were two or more episodes; recurrent UTI in 14; candida UTI in 4; herpes simplex infection in 2; BK virus in 2; chest infection in 2; and diarrhoea in 4 [clostridium difficile = 3]. After diagnosis of NODAT the prednisolone dose was reduced by half and then tapered off in 3 patients; gradual reduction according to protocol in 6 and no steps taken in 18. There was only one graft failure with a follow up period of 7 years, although 6 patients has a 20% reduction in their GFR. There was one patient death after 4 years.

CONCLUSIONS: NODAT carries a significant morbidity due to infection. Timely recognition of this with modification of immunosuppression should be undertaken.

P32

Revisiting Immuno-Suppression In Non Heart Beating Kidney And Pancreatic Transplantation (SPK Or PAK)

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Introduction

Calcineurin inhibitors have a known nephrotoxic action. One way to minimize this effect is to reduce their dose and use adjuvant induction therapy. Long term steroids apart from being diabetogenic are a detrimental factor in patient survival and quality of life. Due to increasing numbers of patients waiting for renal transplant non-heart beating donation is becoming more widely accepted. There is also a growing interest in UK in pancreas transplantation with its life enhancing and life changing potential. Our aim was to evaluate a thymoglobulin (ATG) induction regime with low dose tacrolimus in non-heart beating kidney (NHB)and pancreas (either SPK or PAK) transplants with steroid withdrawal or avoidance.

Methods

A Prospective study of all transplants having the following immuno-suppression regime: Induction with ATG 1.25mg/kg for five days starting at transplantation, Tacrolimus 0.1mg/kg/day to maintain a trough level of 5 to 8 µg/l, Mycophenolate 2g/day, Prednisolone in NHB kidneys 20mg tapered to withdrawal in three months and complete avoidance in pancreas transplants.

Results

We followed up 18 renal transplants with ATG induction. 10 NHB, 5 SPK and 3 PAK. Recipients mean age was 48.3y. Donor mean age was 37.8y. Mean cold ischaemic time was 15h 42min. The average HLA mismatches were 3.4 in NHB kidneys and 4.2 in pancreas transplants. All NHB kidneys suffered from delayed graft function. None of the SPK had DGF. At 30 and 90 days the creatinine was 159 and 119 in NHB, 115 and 117µmol/l in SPK. Only one renal transplant had biopsy proven borderline rejection. A second case was treated with prednisolone due to deterioration of renal function, however, renal biopsy was negative. One case of PAK had raised amylase, lipase and CRP was treated successfully with 3 doses of OKT3. Two cases were readmitted for infection. One was CMV infection and the other a case of fungal peritonitis. There was one death in SPK transplant due to fatal ventricular arrhythmia 14 days post transplant. The rest of pancreas patients have controlled blood sugar without insulin.

Conclusion

Induction with ATG is a reliable and safe method to minimize tacrolimus dose in NHB and pancreas transplants with a high number of HLA mismatches. It also allows for safe withdrawal or total avoidance of steroids in such patients that are usually seen as high risk.

P33

Solid Organ Malignancies After Renal Transplantation: Oxford Experience in the Last 3 Decade
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Aims: Immunosuppression in solid organ recipients is associated with an increased risk of de novo malignancy following transplantation. The aim of this study is to report Oxford immunosuppression regime and cancer results in the last 30 years.

Methods: We examined the incidence of cancer among 2100 renal recipients from 1975 to 2005. For the purpose of analysis we have divided the patients into to 3 groups according to the year of transplant. Group I (479) recipients transplanted between 1975-1984, group II (806) recipients between 1985-1994 and group III (815) recipients between the periods of 1995 to 2005. The Oxford Transplant database was used to identify patients who developed post-transplant lymphoproliferative diseases (PTLD) and solid organ malignancies after transplantation. Skin cancer has been excluded in this study. Different immunosuppression regimes were followed in the three eras in particular time. Since late 2003, induction therapy with Basiliximab or Campath has been introduced in our unit.

Results: The mean age of donor in the group I, II and III was 28.3±14.0, 36.6±15.3 and 44.0±14.4 years and the mean age of transplant recipients was 38.1±11.3, 45.2±13.9 and 44.7±13.0 years respectively. A total of 49 patients developed PTLD in which 9/479 (1%) occurred in group I, 24/806 (3%) in II and 16/815 (1%) PTLD in-group III. Solid organ cancer was diagnosed in 29/479 (6%) in-group I, 60/806 (7%) in-group II and 21/815 (2%) in group III. In group I; patients received steroids, CYA and or AZA. The majority of group II, III received ATG and triple immunosuppression therapy.

Conclusions: De novo malignancy in transplant recipients is a challenging event after solid organ transplantation. Regular surveillance to diagnose early occurrence and adjustment of immunosuppression may be beneficial. In addition, there is as yet no evidence that our recent powerful immunosuppression strategy has had any detrimental effect.

P34

Pattern of Post-renal Transplant Hyperlipidemia In Patients on Steroid-free Maintenance Immunosuppression

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BACKGROUND

Hyperlipidemia is a common risk factor for graft dysfunction and premature atherosclerotic cardiovascular disease after transplantation.

OBJECTIVES

To compare the effect of steroid avoidance in immunosuppressive drug regimes on the prevalence and pattern of hyperlipidemia in renal allograft recipients with stable function.

PATIENTS & METHOD

Retrospective data on lipid profiles of 209 patients after renal transplantation between January 2001 and December 2004 was collected. The pre-transplant profiles served as controls. Values in mmol/l were obtained for total cholesterol (TC), Low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG). Adult Treatment Panel III (ATP III) guidelines were used to define dyslipidemia. Exclusion criteria: Proteinuria >3g/24hrs, acute graft dysfunction at the time of follow-up. Patients were divided into four groups on the basis of immunosuppressive maintenance regime after transplantation.

Group I (n=85) – Cyclosporine without corticosteroids

Group II (n=54) – Tacrolimus without corticosteroids

Group III (n=51) – Tacrolimus or Cyclosporine with corticosteroids

Group IV (n=19) – Sirolimus with corticosteroids

RESULTS

The cohort of 209 patients (M/F: 124/85; median age 44 yr) with a median follow-up of 15 months was studied. The prevalence and trend of post-transplant dyslipidemia compared to pre-transplant state in the four patient groups is shown below (Table 1).

The median values of TC, TG, LDL-C, HDL-C and risk ratio TC/HDL in four groups were similarly compared pre- and post-transplant. (Table 2).

According to ATP III definition, groups I and II showed favourable lipid profiles.

Hypertriglyceridemia was the main feature in group 3 and 4.

CONCLUSION:

Hypertriglyceridemia is the commonest type of post transplant lipid abnormality in our set up. Corticosteroides in combination with either calcineurine inhibitors or Sirolimus is associated with hypercholesterolemia. The requirement of statins is increased with addition of corticosteroids and sirolimus to the immunosuppressive drug regimen.

Wednesday 29 March
Moderated Poster Session
Immunosuppression 2

P35

FTY720 Reduces Renal Fibrosis Induced By Ischaemia-Reperfusion Injury In A Rat Model

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Background

A key histological feature of chronic allograft nephropathy (CAN), one of the commonest causes of late graft loss, is tubulointerstitial fibrosis (TIF). One of the most prominent non-immune factors in the development of CAN is ischaemia-reperfusion injury (IRI), which induces cellular infiltration.

Although, traditionally the macrophage was thought to stimulate fibroblast activity in CAN, recent evidence supports a role for lymphocytes. FTY 720 is a new immunosuppressant that promotes lymphocyte sequestration into lymph nodes and Peyer's patches. This study investigated the effect of FTY 720 on the renal fibrosis in the rat following an ischaemia-reperfusion insult in the absence and presence of cyclosporine.

Methods

A rat model of IRI was used in which male Sprague-Dawley rats (under isoflurane anaesthesia) underwent bilateral flank incision with removal of the right kidney and clamping of the left renal hilum for 45mins. Five groups of animals were studied (n=4), nephrectomy only, IRI only, IRI + FTY720 (1mg/kg/d, IRI + cyclosporine (15mg/kg/d) and IRI + FTY 720 (1mg/kg/d) and cyclosporine (15mg/kg/d). Animals were sacrificed at 30 days.

Results

Fibrosis was assessed using Masson's trichrome (MT) staining and an image analysis system. IRI alone produced a significant increase in MT staining compared with nephrectomised animals (16.08% v 0.29%, P<0.05). This effect was potentiated by treatment with cyclosporine ((20.62% v 16.08%, P = 0.022). Treatment with FTY 720 significantly reduced the level of MT staining in rats following IRI alone (7.45% v 16.08%, P <0.05) and in rats following IRI + cyclosporine (7.45% v 20.62%, P <0.05). Parallel changes were seen in the serum creatinine (SCr). IRI alone produced a significant increase in SCr compared with nephrectomised animals (138 mmol/l v 55mmol/l, P <0.05). This effect was potentiated by treatment with cyclosporine (173 mmol/l v 55mmol/l, P <0.05). Treatment with FTY 720 significantly reduced SCr in rats following IRI alone (81 mmol/l v 138 mmol/l, P <0.01) and in rats following IRI + cyclosporine (98 mmol/l v 173 mmol/l, P < 0.014).

Conclusion

Our study shows that treatment with FTY720 can reduce renal fibrosis as a result of ischaemia-reperfusion induced injury; this suggests that lymphocyte infiltration has an important role in the pathophysiology of CAN.

P36

Does Conversion From Mycophenolate (MMF) To Myfortic (EC-MPS) Allow An Increase In Mycophenolic Acid (MPA) Exposure In Patients On Reduced Doses Of MMF?

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The benefits of MMF have not yet been fully achieved in transplantation due its gastrointestinal (GI) side effects. These have been reported in up to 40% of kidney transplants recipients on MMF. GI symptoms are managed by dose splitting, reduction or by drug discontinuation. Recent US registry data suggest that MMF dose alterations result in inadequate graft protection, increased late acute rejection rate and decreased long-term graft survival.

In this study we investigated whether conversion to an enteric-coated MPA,(EC-MPS) would allow higher MPA exposure in patients with GI side effects and reduced doses of MMF.

15 patients, on reduced dose MMF were initially converted to equimolar dose of EC-MPS. After 2 weeks an increase in EC-MPS dose was attempted according to GI symptoms. GI symptoms were assessed using gastrointestinal rating score (GSRs) and gastrointestinal quality of life index (GIQOL). Changes in kidney function was also recorded pre and post conversions and after dose alterations. Data are expressed as mean \pm SEM.

All patients were on MMF and prednisolone alone for management of chronic Allograft nephropathy. The mean follow up period post conversion was 192 ± 36 days (44-584). Following conversion to EC-MPS, there was no overall significant change in serum creatinine(SCr)(197 ± 26 mmol/l vs. 191 ± 27 mmol/l, respectively), however, there was a trend towards improved SCr in patients who tolerated an increased dose of EC-MPS (194 ± 26 mmol/l vs. 177 ± 12 mmol/l, $p=0.57$). An increase in EC-MPS dose was achieved in 60% (9/15) of patients. No episodes of rejection were observed during or after conversion.

All patients experienced an overall reduction in GI symptoms rating score. Using GSRs questionnaire, symptoms score declined from 26 ± 6 to 14 ± 7 , whereas GIQOL score improved from 77 ± 6 to 95 ± 5 .

In conclusion, patients on reduced dose MMF for management of GI symptoms can be safely switched to an equimolar dose of EC-MPS with an overall improvement in symptoms. An increase in MPA exposure can be achieved in over 50% of patients with sustained improvement in GI symptoms. Our preliminary data suggest that an increase in MPA exposure may associated with an improvement in kidney function. Further studies with a larger cohort of patients are needed to validate our data.

P37

Poor Tolerance Of Sirolimus In A Steroid Avoidance Regime

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Background: Concerns over vascular disease and chronic allograft nephropathy have prompted many centres to re-evaluate the roles of both steroids and calcineurin inhibitors (CNIs). Despite a number of potentially serious adverse effects, sirolimus (SRL) has commonly been used to facilitate early CNI withdrawal. From January 1st 2004 we initiated the Early CNI and Steroid Elimination in Leeds (ECSEL) study. Here we report the poor tolerability of SRL in our patients.

Methods: 64 patients were recruited and received basiliximab 20mg IV (Day 0 & 4) and methylprednisolone 1000mg IV (at induction) followed by 2 months of immunosuppression with tacrolimus (TAC) and mycophenolate mofetil (MMF). 51 patients were randomised to either continue TAC/MMF (controls) or to switch to SRL/MMF. In the first phase patients were immediately switched from TAC to SRL at 2 months (10 patients - ECSEL 1), and in the second phase SRL was introduced between months 4 and 6 with gradual tapering of TAC (13 patients - ECSEL 2). 13 patients were not randomised. Median follow up was 440 days (ECSEL 1) and 246 days (ECSEL 2).

Results: All 10 ECSEL 1 and 10/13 (77%) ECSEL 2 patients discontinued the study due to adverse events. Adverse effects included: ECSEL 1 - leucopenia (n=5,50%), rash (8, 80%), mucosal ulceration(3,30%) and one case each of pneumonitis, angioedema, arthralgia and shingles; ECSEL 2 – leucopenia (6,46%), rash (10,77%), arthralgia (3,23%) and one case each of hypoglycaemia, mucosal ulceration, and possible pneumonitis. Rashes and mucosal ulceration responded well to topical steroid therapy. 3 episodes of rejection occurred (2 vascular in ECSEL 1, 1 cellular in ECSEL 2). Patient and graft survival were 100% and renal function was good – ECSEL 1 Mean creatinine at 12 months 158.1 ± 34.1, ECSEL 2 Latest mean creatinine 143.0 ± 39.7.

Conclusions: Sirolimus was poorly tolerated in a steroid free immunosuppression regime for renal transplantation.

P38

Comparison Of Outcomes Over 6 Years Of Renal Allograft Recipients Receiving Neoral Or Tacrolimus-Led Immunosuppression

SB Roberts, JE Pearce, W Metcalfe and CE Whitworth

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This single centre retrospective study compared the outcomes over 6 years of consecutive patients treated with Neoral or Tacrolimus-led immunosuppression between June 1995 and June 1998, bridging a change in unit protocol.

63 patients started Neoral (N) and 45 Tacrolimus-led (T) therapy. Donor and recipient demographics and graft matching were comparable between the groups.

Outcome measures were graft survival and function, patient survival, number of rejection episodes and incidence of post-transplant diabetes, hypertension, CMV disease and malignancies. Data were collected at 1, 3, 6, 12 months and annually thereafter. Analyses were on an intention to treat basis, patients were censored at time of change of calcineurin phosphatase inhibitor (11 patients), loss of graft or death.

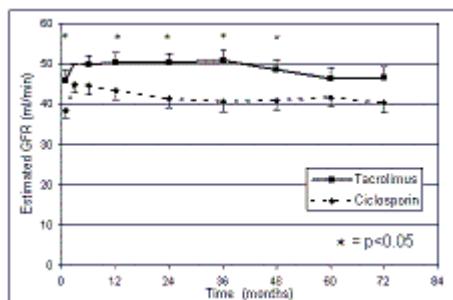
At 6 years follow-up there were no differences between the 2 groups in terms of graft survival (73% N: 71% T) or patient survival (95% N: 93% T). Estimated GFR (abbreviated MDRD) was consistently higher in the T group at all census points. The rate of decline in GFR from baseline (3 months post-transplant) was not significantly different between the two groups (Graph).

Biopsy proven rejection was more common in the N group with 44.8% of patients experiencing at least one episode compared with 25.6% in the T group ($p=0.03$).

CMV disease was more common in the T group (22.2%T: 10.9%N); skin malignancies were also more common in the T group, but neither difference reached statistical significance. There was a higher incidence of CMV D+/R- in the T group.

There was no difference between the two groups in the incidence of post-transplant diabetes (10.9%N: 6.7%T) or the attained mean arterial BP at each census point.

Tacrolimus-led immunosuppression has reduced the incidence of acute rejection and resulted in improved graft function in our unit.



P39

Tacrolimus Dose In Black Renal Transplant Recipients

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It is well established that black patients require higher doses of tacrolimus than other ethnic groups to achieve target blood concentrations. Low tacrolimus concentrations in the first post transplant week have been associated with increased rejection rates. In 2002 we changed our immunosuppressive protocol to give black patients an initial dose of tacrolimus two fold higher than our standard protocol. All black renal transplant recipients transplanted in our centre between 1995 and 2004 were studied. All were given 500mg of methylprednisolone and from July 2002 basiliximab at induction. Prednisolone was given at an initial dose of 20mg daily. A loading dose of 0.2 mg/kg tacrolimus was given pre-operatively followed by 0.1mg/kg twice daily prior to July 2002 (n=23). Patients transplanted after this date (n=10) were given a loading dose of 0.4 mg/kg followed by 0.2 mg/kg twice daily. Subsequent drug doses were aimed at achieving a target 12 hours post-dose whole blood concentration of 15-20 ng/mL during the first week and then 10-15 ng/mL until ninety days after transplantation. A small number of patients were given azathioprine or mycophenolate mofetil.

Giving black patients two fold higher than standard doses of tacrolimus avoided the problem of failing to achieve target blood concentrations early after transplantation but did result in an increase in the number of measurements in the toxic range (Table). The rate of acute rejection prior to the protocol change was 60.8% (14/23) and was 40% (4/10) afterwards (not statistically significant). A daily tacrolimus dose of 0.4 mg/kg allowed achievement of minimum target blood tacrolimus concentrations in all black patients but may, in fact be too high a dose. A daily dose of 0.3 mg/kg may be more appropriate.

Tacrolimus dose			
	0.2mg/kg daily	0.4mg/kg daily	P
Mean conc. days 1-7 (median,IQR)	14.98 (10.33-17.57)	25.14 (21.64-28.49)	<0.0001
Mean conc. days 8-14(Median,IQR)	12.62 (10.3-14.93)	17.63 (17.1-23.7)	0.037
Any low day 1-7	20/23 (87%)	2/10 (20%)	<0.03
All low day 1-7	6/23 (26%)	0/10 (0%)	0.08
Any low day 8-14	11/23 (48%)	2/10 (20%)	<0.03
All low day 8-14	2/23 (9%)	1/10 (10%)	0.90
Any high day 1-7	9/23 (39%)	10/10 (100%)	<0.04
Any high day 8-14	13/23 (57%)	8/10 (80%)	0.45

Thursday 30 March
Moderated Poster Session
Live Donation

P38

Comparison Of Outcomes Over 6 Years Of Renal Allograft Recipients Receiving Neoral Or Tacrolimus-Led Immunosuppression

SB Roberts, JE Pearce, W Metcalfe and CE Whitworth

Renal Unit, Royal Infirmary of Edinburgh, Little France, Edinburgh, EH16 4SA, United Kingdom

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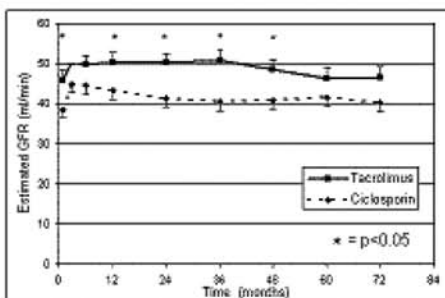
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Tacrolimus-led immunosuppression has reduced the incidence of acute rejection and resulted in improved graft function in our unit.



P41

Is Quality Of Life Better After Laparoscopic Living Donor Nephrectomy?

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Purpose

Laparoscopic live donor nephrectomy is considered to be superior to open surgery due to shorter convalescence and less wound pain. However little is known about the influence of minimally invasive surgery on quality of life after the initial recovery period. We conducted a quality of life assessment on living kidney donors from 2003 to 2005. We aimed to determine if there was any significant difference in medium term quality of life for the donor between a laparoscopic and open incision.

Method

The subjects were taken from the living donor transplant programme at Guy's Hospital, London. The short form-36, version 2, a standardised measure of health related quality of life was sent to 77 subjects; 37 were laparoscopic (hand-assisted technique) donors and 40 were open. The groups were well matched for age, sex and time since nephrectomy.

The outcome measures were the scores for the eight dimensions of the UK SF36-II. These are physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The mean scores were compared and an unpaired t-test done for each category. The mean follow up from transplant was 289 days.

Results

The survey was completed by 61 (30 lap, 31 open) living kidney donors (78% response rate). For both groups, the quality of life exceeded that of the UK population normative values throughout the categories. In the category of general health, the UK norm was 71.06, the lap group 87.57 and the open group 86.70. An unpaired t-test for each category showed no significant difference between the groups undergoing surgery with a p value greater than 0.05 for each dimension. Mean bodily pain score was 88.31 for lap and 87.10 for open ($p = 0.85$).

Conclusion

Quality of life after living kidney donation is better than for the general population. There is no significant difference in this study between medium term quality of life when comparing open and laparoscopic living kidney donors.

P42

Minor Blood Pressure Abnormalities Pre-Donation: Major Concern Post-Donation

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Introduction

Hypertension is a significant prognostic factor for cardiovascular morbidity and mortality. The long term effects on blood pressure from unilateral nephrectomy are small in healthy individuals. With increasing pressure on the cadaveric pool of organs, individuals with ongoing cardiovascular risk factors are now being considered for donation and the outcomes for these more marginal donors is less certain.

Methods

We present data on 31 cases of patients who had 'abnormal blood pressure' pre-donation with a follow up of one year. 'Abnormal blood pressure' is defined as an individual with a history of managed hypertension (but no end organ damage) or with an 'office' blood pressure reading of 140/90 or above at any point in the pre-operative work up.

Results

160 cases of live donation were reviewed at Guy's Hospital. 31 cases (19%) had hypertension pre-donation - 7 cases (4%) had managed hypertension, 24 cases (15%) had abnormal office blood pressure but were not on treatment.

Outcome for those with managed hypertension: 3 out of 7 cases (43%) required an increase in antihypertensive medication at one year follow up. Outcome for those with abnormal office blood pressure: 13 out of 24 cases (54%) needed further review for abnormal blood pressure post donation. 3 cases (12.5%) commenced antihypertensive treatment at one year follow up.

Evidence of minimally abnormal blood pressure pre-donation predicts the need for antihypertensive treatment post-operatively (6 out of 31 v 5 out of 129, $p < 0.05$ Fischer's exact test)

Discussion

In this study of 160 cases followed up to a year, 81% had a normal blood pressure profile. For those with pre-existing hypertension, donation carries a significant (43%) risk of worsening the blood pressure profile. For those with an episode of 'office' hypertension which has not required treatment there is a major (12.5%) risk of requiring hypertensive medication at one year follow up. This is significantly higher than if there has been normal blood pressure pre-donation.

P43

Donor Renal Function Post Laparoscopic Nephrectomy - No Cause For Alarm

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Introduction

Live donor renal transplantation provides the optimum renal replacement therapy. The current trend is for most donors to request laparoscopic donation where available. Experimental work and some clinical studies have suggested that laparoscopic nephrectomy has a deleterious effect on renal function. If true, what are the implications for the donor's remaining kidney?

This study examines the recovery of renal function in the contra-lateral kidney after live donor nephrectomy by comparing open donor and laparoscopic donor techniques at one centre.

Methods

Data was collected retrospectively on 48 consecutive hand-assisted laparoscopic donor nephrectomies and 41 open donor nephrectomies performed at Guy's Hospital. The patient selection criteria for living donation was the same for both groups. Open donor nephrectomy continues according to patient choice and where logistically necessary. Both groups receive the same peri-operative management. Patients were followed up at regular intervals to one year post-donation.

Results

Patient demographics

There are no significant differences between the open and laparoscopic groups ($p>0.5$).

Serum Creatinine

There is a significant difference in serum creatinine between the two groups at day 2, 1 week, 2 weeks and 1 year post donation with open donors having a lower creatinine level ($p<0.5$).

Estimated GFR

There is no significant difference at any interval between the two groups up to one year follow up (Cockcroft-Gault measurement) ($p>0.5$).

Delta estimated GFR

There is no significant difference at any interval between the two groups up to one year follow up ($p>0.5$).

Discussion

Experimental evidence shows that a pneumoperitoneum affects renal blood flow and cortical perfusion. Clinical studies have shown that recovery of donor renal function after laparoscopic donation is slower compared to open. In this study, whilst serum creatinine was significantly elevated in the laparoscopic group post surgery, there was no difference in donor renal function assessed by estimated GFR or Delta estimated GFR at any point post operatively. These findings are reassuring, and may be attributed to the critical importance of careful peri-operative management.

Open Versus Laparoscopic Live Donor Nephrectomy: A Meta-Analytical ComparisonT Nanidis¹, D Antcliffe¹, K Kokkinos¹, P Tekkis¹ and V Papalois²

¹Department of Surgical Oncology and Technology, Imperial College London, 10th Floor, QEOM Wing, St Mary's Campus, Praed Street, London, W2 1NY, United Kingdom and ²The West London Renal and Transplant Centre, Hammersmith Hospital, Du Cane Road, London, W12 0HS, United Kingdom

Background: There is lack of randomized controlled trials to allow a comprehensive comparison of open versus laparoscopic donor nephrectomy. The aim of this study is to compare the two methods using meta-analytical techniques.

Methods: A literature search was performed for studies comparing open to laparoscopic and hand assisted laparoscopic donor nephrectomies. A total of 87 comparative studies published between 1997 and 2005 matched the selection criteria. The studies included 6475 patients, of whom 2761 (43%) underwent open and 3714 (57%) laparoscopic nephrectomy. The following end points were evaluated: operative and warm ischaemia times, estimated blood loss, donor complications, donor length of hospital stay, time taken by donors to return to work, delayed graft function, recipient ureteric complications and graft survival rates.

Results: Total operative and warm ischaemia times were significantly shorter for open nephrectomy by 51.2 minutes ($p<0.001$) and 84.6 seconds ($p<0.001$) respectively. The intra-operative blood loss was less for the laparoscopic group by 76.4 ml ($p<0.001$) with no difference in the overall donor complication rate ($p=0.45$) between the two groups. The laparoscopic group displayed shorter hospital stays and a faster return to work than the open group by 1.6 days ($p<0.001$) and 2.2 weeks ($p<0.001$) respectively. There was no difference in the incidence of delayed graft function between the two groups ($p=0.19$). Likewise, the incidence of post-transplant ureteric complications was not different for the two groups ($p=0.12$ overall, $p=0.48$ and $p=0.92$ for leaks and strictures respectively). Finally, the graft survival rates were similar between the two groups ($p=0.15$).

Conclusion: Classic open nephrectomy allows shorter operative and warm ischaemia times while laparoscopic nephrectomy is associated with reduced blood loss, shortened hospital stay, and faster return to work. The overall incidence of donor complications, delayed graft function and the graft survival rates were similar between the two groups. The technique of open donor nephrectomy via a small incision using laparoscopic instruments combines the advantages of both methods although not enough studies are published to allow a separate meta-analytical comparison with the classic open or laparoscopic methods.

Thursday 30 March
Moderated Poster Session
Laboratory

P45

The Penta-Nucleotide Repeat In The Promoter Of The *LPA* Gene Is Linked To Survival After Renal Transplantation

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Serum Lipoprotein(a) [Lp(a)] is an independent risk factor for atherothrombotic disease. Most variation in Lp(a) levels is controlled by polymorphisms within the Lp(a) subunit apolipoprotein(a) encoded by *LPA*. An inverse relationship exists between the number of penta-nucleotide repeats (PNR) in *LPA* and Lp(a) concentration. High levels of Lp(a) are associated with nephrotic syndrome and various renal disorders.

We developed a fluorescence based fragment analysis assay to genotype the *LPA* PNR in 225 Caucasian renal transplant recipients and 96 controls matched for age, gender and ethnic origin. Allele distribution in controls was identical to published frequency data. Patient genotypes were compared to 10 year clinical outcome data and the contribution of individual PNR alleles analysed using 2x2 contingency tables. Alleles were also analysed in groups according to the number of repeats.

In transplant recipients the 10 repeat allele was significantly increased (30% vs. 12%; $p < 0.0000009$) and the 8 allele significantly decreased (46% vs 72%, $p < 0.001$) compared to controls. At 10 years post-transplant the 8 repeat allele was increased in deceased patients compared with those still living (67% vs. 37%; $p < 0.001$). A compensatory decrease in the incidence of the 10 repeat allele was also associated with mortality (19% vs. 35%; $p = 0.004$). When alleles were grouped according to repeat number the distribution of longer (10-13) and shorter (7-9) repeat alleles is approximately equal (52% vs 48%). In those who have died the distribution is skewed towards the shorter alleles (80% vs 20%). Transplant recipients with a 7-9 PNR repeat, regardless of the presence of a longer allele, were less likely to survive >10 years post-transplant than patients homozygous for 10-13 repeat alleles ($p = 0.0000003$).

Shorter (7-9) PNR repeats carry a higher risk of atherothrombotic events which may reflect this poorer prognosis. Higher incidence of atherothrombosis would be a contraindication to transplantation, and would suggest that the increase in longer (10-13) PNR repeats seen in the transplant population reflects clinical selection. Further investigations correlating cause of death with PNR genotype are in progress.

P46

FTY720 Reduces Ischaemia-Reperfusion Induced Injury In Rat Kidneys

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Background

The current shortage of organ donors has led many centres to use marginal and non-heart-beating donors (NHBD), where limiting the ischaemia-reperfusion injury (IRI) is paramount to successful graft function.

Recent research into the pathophysiology of IRI has implicated the infiltration of lymphocytes as an important mediator. FTY720 is a new immunosuppressant that promotes lymphocyte sequestration into lymph nodes and Peyer's patches. The purpose of this study was to examine the potential for FTY720 induced lymphopaenia to abrogate IRI when subjected to an increasing ischaemic time.

Methods

A rat model of IRI was used in which male Sprague-Dawley rats (under isoflurane anaesthesia) underwent bilateral flank incision with removal of the right kidney and clamping of the left renal hilum, groups were divided into an ischaemia time of 45, 55 and 65mins. At each ischaemic time the groups were further divided into a control group (IRI only), IRI + FTY720 (1mg/kg/d) and IRI + cyclosporine (15mg/kg/d). There were 4 animals in each group.

Results

Serum creatinine (SCr) was significantly elevated above baseline (62 ± 3 vs 476 ± 20 μ mol/l, $P < 0.001$) 3 days after 45 min ischaemic clamping. The increase in SCr was potentiated by cyclosporine 15mg/kg/d (697 ± 32 μ mol/l) but reduced by pre-treatment with FTY720 1mg/kg/d (156 ± 9 μ mol/l, $P < 0.001$). A similar pattern was observed with an ischaemic time of 55mins. The beneficial effect of FTY720 1mg/kg/d (655 ± 32 μ mol/l) was still observed when the ischaemic clamp time was further increased to 65min, either IRI only (777 ± 20 μ mol/l, $P = 0.023$) or following cyclosporine 1mg/kg/d (1037 ± 35 μ mol/l, $P < 0.05$). FTY720 treated animals recovered from the 65mins ischaemia whereas control and cyclosporine treated animals needed to be sacrificed between day three and five. Treatment with FTY720 reduced renal damage assessed histologically, including the tubular necrosis score and dilation. FTY720 treatment also reduced apoptosis and increased cell proliferation.

Conclusion

In our model of IRI, FTY720 reduced the severity of injury. Increasing ischaemia potentiated the degree of injury in FTY720 treated animals but did not lead to acute renal failure as in the control and cyclosporine treated groups. This study suggests that FTY720 may help improve the quality of grafts from NHBD and marginal donors thus increasing the availability of organs.

P47

Leeds Solution: Optimised Preservation For Intra-Abdominal Organs

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During transplant ischaemia, hypothermia in combination with an adequate preservation fluid are the principal elements used to prolong organ viability *ex vivo*. Common practice in the UK is the combined use of Marshall's hyper-osmolar citrate (HOC) solution for renal preservation with UW for hepatic preservation. Leeds Solution (LS), a fluid under development in our centre, has been shown to provide improved hepatic preservation. In a bid to unify intra-abdominal organ retrieval strategies, we developed an isolated perfused rat kidney model to evaluate the effectiveness of LS as a renal preservation medium.

Male Wistar rat kidneys were harvested and flushed with LS, or a conventional preservation solution (PBS140, HOC or UW), and were stored at 4°C for 24 hours ($n = 6$ in each group). The kidneys were then maintained for 2 hours on an *ex vivo*, oxygenated reperfusion circuit at 37°C. Physiological analyses of reperfusion fluid and urine were performed at 30 minute intervals to assess organ function. At the end of the reperfusion period the kidneys were immediately fixed for histological analysis.

To optimise the reperfusion medium, organic solutes (oxalate & formate) were added at physiological concentrations to support renal function. This significantly improved urine flow rate by 58% ($P < 0.05$) and increased glomerular filtration rate by 61% ($P < 0.05$). Using this optimised *ex vivo* model, preservation with LS produced significantly improved urine flow rate (29% increase), GFR (44% increase) and percentage Na⁺ reabsorption (25% increase) when compared against organs preserved in PBS140, HOC or UW ($P < 0.05$). The data suggested reduced tissue damage in the glomerulus, the proximal tubules and the collecting system that was supported by histological observation.

In conclusion, the model developed here provides a valid tool for physiological assessment of the response of whole organs to preservation solutions. Optimisation of the reperfusion circuit assisted in prolonging functional viability of organs maintained *ex vivo*. In addition, the data presented suggests that LS reduces functional impairment after prolonged cold ischaemia coincident to reduced tissue damage in the kidney. Finally, taken with our data in the liver, it is reasonable to propose that LS could provide a single preservation medium for intra-abdominal organs, thus minimising organ damage and potentially improving transplant outcome.

P48

Indices Of Immunological Tolerance In Renal Transplantation: Interim Analysis

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Induction of tolerance is a desired long-term outcome for renal transplant patients. However in order to manipulate the immune response to achieve tolerance, we first need to identify the specific immunological characteristics which describe the tolerant phenotype. This ongoing study scrutinizes the cellular basis of tolerance in terms of specific anti-donor responses and regulatory activity of CD4+CD25+ Tregs in 4 specific groups (n = 20 per group) of renal transplant recipients (1) Stable renal function with a non-CNI based immunosuppressive therapy, (2) Stable renal function with a CNI based therapy, (3) Patients undergoing chronic rejection and (4) drug-free Tolerant recipients. Quantitative assessments of recipient responses to donor and 3rd-party antigens were made by IFN γ and IL-4 ELISpot analysis. Donor-specific responses generated by the indirect pathway were prepared by stimulating recipient PBMCs with a preparation of solubilised donor membrane proteins. Frequencies of direct pathway donor-reactive CD8 and CD4 T cells were studied by stimulation with APCs purified from donor PBMCs or spleen. Direct pathway T cell responder frequencies were also estimated by CFSE analysis. Depletion of CD4+CD25+ cells from responder populations in ELISpot and CFSE assays further allowed detection of Treg-mediated regulation of anti-donor responses. Interim data analysis shows that using these assays donor-specific hypo- and hyper-responsiveness is detected, along with donor-specific Treg activity. By performing these assays in parallel on each patient group, we aim to detect immunological differences which may govern the tolerant state. We expect that with more patients analysed by the study end-point, a clinically important answer should be obtained. Donor-specific assays developed for this study provide an insight into the development of recipient responses following transplantation and will help to elucidate the governing role of Tregs in immune tolerance and chronic rejection. In addition, combined with data from molecular and genetic studies (in vivo DTH, Micro-array, TCR-Landscaping) on these same patients, this data should significantly further our understanding of regulatory mechanisms and provide an immunological 'fingerprint' of tolerance.

T-Cell Epitope Dominance In Transplantation

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Indirect allorecognition is important for alloantibody production. We have previously mapped T cell epitopes involved in the provision of help for generating alloantibody against a single disparate class I antigen. Several peptide epitopes, derived from regions of the donor antigen and which shared sequence homology with the recipient, were able to provide help. Here we extend this work and examine how priming a response against such cryptic self epitopes alters the T cell response to a subsequent heart graft.

Rejection of class I disparate RT1^a grafts by RT1u recipient rats occurs rapidly and is antibody mediated. The T cell epitopes involved in the provision of help were analysed by immunising RT1^u recipients with allopeptide corresponding to hypervariable region of the RT1^a antigen (P7) or to a sequence of amino acid homology between donor and recipients (P1). Rats were challenged with an RT1^a heart graft and alloantibody production measured. 10 days after grafting, the epitope specificity of the T cell response to donor antigen was assessed by CD4 T-cell ELISPOT assay.

Alloantibody production and allograft rejection was more rapid in rats primed with either P7 or P1 compared with control peptide primed rats (MST 4, 5 vs 6 days). Following grafting, the T-cell response to the hypervariable region was greatest in those animals primed with P7. Interestingly, priming with P1 did not enhance the *in vitro* T-cell response to P1 but instead augmented the response to P7.

The ability of priming with self peptide to accelerate the alloantibody response suggests that auto-reactive T cells can provide initial B-cell help. As the rejection process continues, the normal pattern of T cell hierarchical dominance to the hypervariable region is re-established.

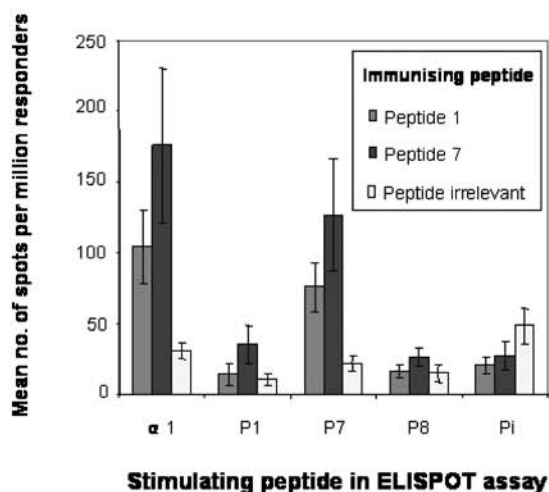


Figure 1. Influence of peptide immunisation on post-transplant CD4 T-cell responses

Thursday 30 March
Moderated Poster Session
Thoracic

P50

Pulmonary Transplant Recipients CC Homozygous for the C3435T Polymorphism of the MDR1 Gene Undergo Rapid Decline in FEV1

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Introduction: The MDR gene encodes the ABC cell membrane transporter P-Glycoprotein (P-Gp) which is the transporter of immunosuppressants including Cyclosporine (CyA), azathioprine and Prednisolone across the cell membrane. The C3435T polymorphism of the gene at Exon 26 is known to correlate with high and low P-Gp production. Our hypothesis is that CC homozygous individuals are high P-gp producers, likely to pump immunosuppressants out of target leukocytes more rapidly and are more likely to display a drug resistant phenomenon in the guise of more rapid rejection.

Methods: We genotyped 60 lung transplant patients transplanted between Jan 1990 and Feb 2003 and correlated their outcome according to genotype. We followed their FEV1 compared with baseline values, BOS score and acute rejection episodes.

Results: Patients were similar between groups in terms of demographic details and pre – transplant diagnosis. Genotype followed the Hardy-Weinburg distribution, 14 CC homozygous, 30 CT heterozygous and 16 TT homozygous. We observed a more rapid decline in FEV1 in patients who are CC homozygous for the MDR gene (51% decline) in comparison to the CT (43% decline) and TT (33% decline) genotypes $p < 0.017$. Differences in BOS grade and acute rejection episodes did not reach statistical significance.

Conclusions: Patients who are CC homozygous for the MDR1 gene are susceptible to a more rapid decline in function of the transplanted lung. We believe that this is due to the effect of P-gp on intracellular leukocyte immunosuppressant levels and that this manifests as decreased organ function. This phenomenon is indicative of a multidrug resistance in transplant patients akin to tumour resistance to chemotherapy agents in the field of oncology.

P51

Peripheral Blood Mononuclear Cell Expression of P-Glycoprotein and Outcome Following Cardiac Transplantation

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Objectives: P-glycoprotein (P-gp), the membrane bound efflux pump encoded by the multi drug resistance (MDR1) gene may be one reason for poor response to immunosuppression in heart transplant recipients. This study set out to test the hypothesis that peripheral blood mononuclear cell (PBMC) expression of P-gp is associated with increased levels of biopsy proven rejection, cyclosporine levels and nephrotoxicity in heart transplant recipients.

Methods: Using a flow cytometric method with directly conjugated monoclonal antibody to P-Gp, we assessed peripheral blood mononuclear cell expression of P-Gp in terms of mean fluorescence intensity in a group of 68 heart transplant recipients. 10 of the 68 patients were in the early post-operative phase. We tested for any correlation with biopsy proven rejection, difficulty obtaining Cyclosporine A (CsA) levels, and creatinine clearance.

Results: There was a strong correlation between PBMC P-gp expression and biopsy score of endomyocardial rejection, Pearson correlation 0.428, $p < 0.001$. This correlation remained when controlling for time, cyclosporine and Prednisolone levels. There was no correlation between P-gp and creatinine clearance, cyclosporine levels, or days post transplantation. P-Gp measurements were no different between the early group (first 90 days post op) and the late group (greater than 90 days post op). An unexpected increase in P-Gp levels was found in patients who were CMV positive or who received an organ from a CMV positive donor.

Conclusions: High P-gp expression is associated with an increased level of biopsy proven rejection independent of cyclosporine doses and serum trough levels. These results highlight the significance of P-gp in mediating transplant rejection and suggest that the use of immunosuppressive agents which are not handled by the P-gp efflux pump would be useful in patients who display high P-gp expression.

P52

Combined Use Of C2 And C0 Monitoring Results In Improved Efficacy Versus C0 Monitoring Alone In Cardiac Transplant Patients

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Background. Cyclosporine (CsA) level at two hours post-dose (C2) is a more sensitive marker for rejection risk than trough (C0) level. A combination of C2 and C0 monitoring may prove optimal.

Methods. We compared efficacy and safety outcomes among 28 de novo heart transplant patients in whom both C2 and C0 monitoring were undertaken (Group 1), with a single CsA profile at weeks 2-6, versus 28 historical controls monitored by only C0 (Group 2). Patients received ATG induction with CsA, steroids and azathioprine maintenance therapy.

Results. CsA-ME dose was significantly higher in Group 1 than Group 2 to three months post-transplant. Mean C2 values in Group 1 at 3 and 12 months were 1248+328ng/mL and 1039+362ng/mL, respectively. One patient in Group 1 and seven in Group 2 (25%) discontinued CsA, either due to CsA-related neurotoxicity or >2 episodes of early rejection. At 12 months, graft and patient survival were 100% in both groups. Six patients in Group 1 (21%) and 11 in Group 2 (39%) experienced at least one episode of biopsy-proven acute rejection (n.s.). Over the first 12 months post-transplant, the proportion of biopsies showing grade 3 rejection was 5% in Group 1 and 11% in Group 2 (p<0.002). GFR was significantly lower in Group 1 than Group 2 at both three and 12 months.

Conclusions. Combined use of C2 and C0 monitoring results in improved efficacy versus C0 monitoring alone. Regular measurement of C2 levels should be undertaken in de novo heart transplant recipients.

P53

Hpatocyte Growth Factor Is Associated With Rejection Following Cardiac Transplantation - A Preliminary Report

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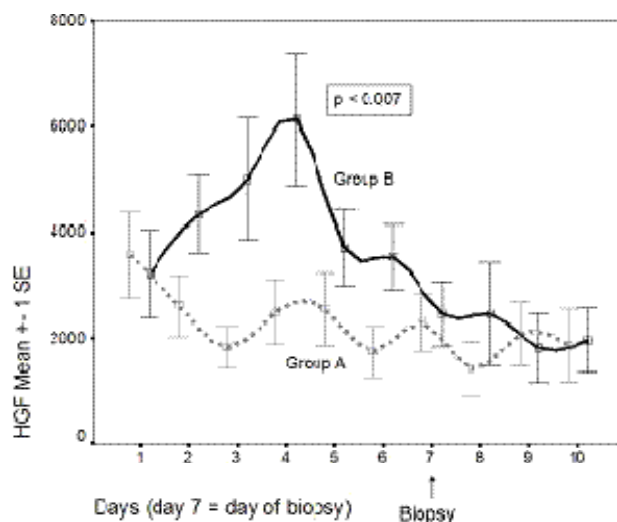
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Background: The incidence of acute graft rejection following cardiac transplantation is 37% in the first year. The current diagnostic technique to determine acute rejection is endomyocardial biopsy, which is both expensive and high risk. Hepatocyte growth Factor (HGF), a pleotropic cytokine with anti-apoptotic and cardioprotective properties, has been shown to correlate with acute rejection following renal transplantation. We hypothesised that HGF may be a putative marker of acute rejection following cardiac transplantation.

Methods: 297 serial samples were taken (at daily intervals) and analysed using ELISA. Patients were biopsied at weekly intervals over the follow-up period of 1 month post transplantation according to ISHLT guidelines.

Results: Patients with biopsy proven rejection (group B) had significantly higher serum HGF concentrations three days prior to biopsy compared to those who had no rejection (group A) $P=0.007$ (Figure 1). A significantly higher mean serum HGF concentration was observed in group B (3634 pg/ml) compared to group A (2308pg/ml), $P=0.001$.

Conclusions: We believe this could open a new and exciting chapter in the non-invasive diagnosis of acute rejection. HGF could be used as a therapeutic predictor of rejection via serum monitoring, and could be of great benefit to patients during the early postoperative period when acute rejection is most likely.



P54

The Role Of HLA Antibodies In Lung Transplantation

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INTRODUCTION : The role of pre-formed HLA antibodies in hyperacute and accelerated acute rejection of organ transplants is well established. Recently it has been suggested that antibodies produced post transplant may play a role in long-term graft rejection. Long-term graft dysfunction is a particular problem in lung transplantation. Data from UKT show five-year graft survival following first cadaveric lung transplants of 42% against 72 % and 73% for comparable kidney and heart transplants.

METHODS : The sensitivity of techniques for detection and definition of HLA antibodies has increased dramatically over recent years. This study utilised the Luminex 100 Lifecode Class I ID Class II ID system (Tepnel) to establish the role of HLA antibodies in long-term rejection in 36 lung transplant recipients, classified by diagnosis at sample collection. 12 patients had acute rejection, 13 had chronic allograft dysfunction or bronchiolitis obliterans syndrome (BOS), while 11 were stable. All diagnoses were biopsy proven. Patients were free from HLA antibodies prior to transplant by complement dependent cytotoxicity (CDC), with negative retrospective cytotoxic crossmatches. A control population consisted of 30 untransplanted patients listed for heart and /or lung transplantation.

RESULTS : The proportion of patients with HLA antibodies was considerably higher in the transplanted population compared to the controls ($p = 0.0001$). When the various groups within the transplanted population were compared, a significant association between acute rejection and production of HLA antibodies post transplant was noted ($p = 0.02$).

DISCUSSION : A significant association between lung transplantation and the production of HLA antibodies was found. The presence of such antibodies, particularly those specific for donor antigens appears to be highest in the group with acute rejection. Although there is some question as to whether the formation of such antibodies is causative of, or merely indicative of subsequent rejection episodes, early antibody detection facilitates their prompt treatment. Current BTS/BSHI guidelines recommend 'regular monitoring' of post transplant patients for HLA specific antibodies. This and other recent studies would suggest that a definitive protocol should be established for monitoring of HLA antibody status of thoracic organ recipients for a substantial period post transplant.

P55

Cardiac Resynchronization Therapy as Bridge to Alternative for Heart Transplantation in Patients with End-stage Heart Failure

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Heart transplantation is considered the gold standard treatment for terminal heart failure refractory to treatment, but the supply of donor hearts is inadequate. Since asynchrony is frequent in advanced heart failure, cardiac resynchronization therapy might offer an adjunctive or alternative to heart transplantation. The present study retrospectively analyzed the impact of cardiac resynchronization therapy on freedom from transplantation and death in a selected group of patients with end-stage heart failure listed for heart transplantation.

Patient characteristics : From April 2001 till May 2004 109 patients referred for heart transplantation screening, dilated cardiomyopathy of ischemic (n=79) or nonischemic (n=30) etiology were listed for heart transplantation. Patients with asynchrony(CRT+) (n= 24) were treated with resynchronization therapy. Compared to those without asynchrony(CRT-) no differences in hemodynamic parameters such as EF, LVEDVI, PCWP and mean PA was noted. However CRT had more pronounced asynchrony on TDI echocardiography as well as on standard ECG. Time to death or Tx was significantly retarded in the CRT+ pts (Figure 1) and 19 CRT+ pts (79%) were removed of the list because of improved hemodynamics. NYHA class improved significantly in the CRT+ group. On the contrary all CRT-pts remained listed for Tx. Two CRT+ pts died, 1 sudden cardiac death, 1 non-cardiac death whereas 3 CRT-pts, 1 sudden cardiac death, 2 nonsudden cardiac death.

Conclusion: Biventricular pacing/ICD proofs to play a role in heart transplantation and can be implemented as an alternative for or bridge to heart transplantation with an acceptable risk.

Thursday 30 March
Moderated Poster Session
Liver

P56

Pattern Of Infection Following Liver Transplant: 12 Year Results From A Single Centre
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Introduction: Liver transplant is the only proven treatment permitting long-term survival for patients with end-stage liver disease. Infection is one of the most common complications and is a major determinant in the successful outcome of liver transplant. Despite this, there is little prospectively collected data on rates of clinically significant infection following liver transplant. This study analyses infections in all liver transplants performed in the Scottish Liver Transplant Unit from 1992 to February 2005.

Methods: Since the unit opened in 1992, a database has been prospectively maintained which includes details of all post-operative infections judged to be of clinical significance. This was interrogated to determine the rates of infections, their sites and the causative organisms, trends over time and effect on survival. Infections were divided into those occurring during the initial transplant admission ('early'), and those occurring during subsequent admissions ('late'). Causes of death were defined by UK Transplant criteria. Univariate analysis was performed by Chi-square and survival analysis by Kaplan-Meier.

Results: 418 patients received 559 transplants. The early and late infection rates were 49.1% and 24.5%, respectively. MRSA accounted for 12.4% of early and 6.1% of late infections. VRE accounted for 3.1% of early and 1.7% of late infections. The incidence of CMV infection was 2.6%. The number of transplants per recipient was associated with an increased risk of infection ($p < 0.05$). Patients with early infection had a 40% increased risk of late infection (RR 1.4, 95% CI 1.04, 1.89). Survival to 5 years was analysed according to the presence or absence of infection and was not different between the 2 groups. 134 patients died, and the most common cause of death was septicaemia (12.7% of all deaths).

Conclusion: The rates, sites of infection and causative organisms are broadly similar to those reported elsewhere, although the incidence of CMV is lower. Early infection predisposes to late infection. Although septicaemia is the commonest cause of death, overall survival is not determined by infection alone.

Children With IFALD Require Higher Volumes Of Blood Products At Transplantation Than Those With Biliary Atresia

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Introduction: Children with IFALD undergoing organ transplantation are at high risk due to liver failure, subclinical sepsis and intra-abdominal adhesions. Their blood product requirements at transplantation were compared with patients undergoing liver transplantation for biliary atresia. All patients undergoing liver or liver and small bowel transplantation at BCH are anaesthetised by one of 4 anaesthetists. Intraoperative blood product administration is guided by in theatre assessment of Hb, PT and Thromboelastograph results. Packed red cells are transfused to an end Hb of 7 – 8 g/dl. PT is kept at between 15 – 20 seconds unless there is active clinical bleeding.

Methods: Data was collected about diagnosis, organs transplanted, demographics and volume of different blood products transfused. Preoperative haematology, clotting, bilirubin and albumin results were used to create simple morbidity scores (range 0 – 6) to give an assessment of severity of liver disease and associated haematological abnormalities.

Results: The 2 groups were age and weight matched. There was no significant difference in blood product use between those patients with IFALD receiving either isolated liver transplants or liver and small bowel transplants. See Tables of Kruskal-Wallis Chi statistical analysis

Conclusions: IFALD patients require significantly more blood products at surgery than children with EHBA despite similar clinical history and no statistical difference in severity of liver disease. Children with IFALD have significantly more abnormal haematology results. This is likely to be due to their requirements for an indwelling venous access device, parenteral nutrition and long periods of in patient care. The combination of liver failure and the above factors is associated with increased blood product requirements during transplantation

Blood product	Diagnosis	n	Median (ml/kg)	Range (ml/kg)	Mean (ml/kg)	P (Kruskal-Wallis, Chi squared)
Packed cells	IFALD	21	47	15 - 199	63	
	EHBA	37	33	0-99	40	0.06
FFP	IFALD	21	40	0-160	59	
	EHBA	37	15	0-110	25	0.02
Cryo	IFALD	21	3	0-21	5	
	EHBA	37	0	0-17	1.5	0.01
Platelets	IFALD	21	20	0-89	27	
	EHBA	37	0	0-27	3	<0.01
Total volumes	IFALD	21	120	20-392	155	
	EHBA	37	50	0-218	61	<0.01

Diagnosis	n	Median	Range	Mean	p (Mann-Whitney)	
IFALD	Age (mths)	21	11	8-138	31	
	Wt (kg)		8.4	5.8-36	12.4	
EHBA	Age (mths)	37	10	5-173	22	0.15
	Wt (kg)		8.0	4.5-47	10.8	0.70

P58

Prevalence And Management Of Anaemia After Liver Transplantation

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Background: Anaemia is well recognised after solid organ transplantation. Specific data on its prevalence in adults after liver transplantation is not available and little is known about how to manage anaemia during long term follow up post-liver transplant.

Aims: To investigate the prevalence of anaemia in our post-transplant population during long term follow up. To establish a pragmatic algorithm for the management of this anaemia and to assess whether our current practice approximates to this algorithm.

Methods: We identified all post transplant patients under follow up in this institution who were more than 6 months post transplant. We included them in our analysis if they were found to be anaemic. We defined anaemia as Hb<12g/dl in males, Hb<11g/dl in females, persisting for 6 months or more. Patients' notes were examined to determine the following: 1. Has the anaemia been noted? 2. Have relevant aspects of the history been sought? 3. Have basic blood tests been performed? 4. If iron deficient, have endoscopic investigations been considered? 5. Has a referral to a haematologist been made?

Results: 65 patients fulfilled criteria. This represents 14% of the total post transplant population of 456. The average age was 52 years (range 27-78 years). Mean Hb = 9.8g/dl. The anaemia was noted in 36/65 (55%). All 65 patients were on potentially myelosuppressive medications. Haematinics were measured in 22/36. 24/36 underwent endoscopic investigations. 7/36 patients were referred for a haematological opinion. The aetiology of the anaemia was multifactorial and included; myelosuppressive medications, iron deficiency and hypersplenism.

Conclusion: Anaemia after liver transplant represents a significant problem in our institution with a prevalence of 14%. Our review identifies shortfalls in our current approach to these patients, probably due to the lack of existing information about how this problem should be managed. We intend to implement the management algorithm used in our study in the out patient setting.

P59

Technical Complications After Split Liver Transplantation. Is There A Learning Curve?

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Introduction: Split liver transplantation was developed to increase the donor pool. It allows sharing grafts between adult and paediatric recipients to reduce the gap between the demand and supply of available organs. However, some centres have reported high incidence of technical complications and a learning curve that might affect the outcome.

Methods: We started our split liver program in December 2000. We analysed our results for the first 30 cases that were performed in the first 2 years (Period A) and compared them with the last 36 cases that were done subsequently in our centre (Period B). Our objective was to look for the early technical complications including; hepatic artery thrombosis, biliary leak, biliary stricture and whether there is a learning curve that might affect the outcome of this procedure.

Results: A total of 66 split liver transplantations were performed. Forty paediatric and 26 adult split liver transplantations were performed. The median age of paediatric was 1 year and for adult was 51 years. We had 4 perioperative deaths (6%), 3 adults and 1 paediatrics. Three of the deaths occurred in the first period and only one death in the second period. Hepatic artery thrombosis was found in 3 cases, 2 in period A giving overall incidence of 4.5 % (A = 6.7% & B = 1.8 %). Biliary leak was observed in 7 (10.6 %) of cases (A= 10% & B=11.1%). Biliary intervention was performed endoscopically or percutaneously in 3 (4.5 %) of cases and reoperation for biliary complications was performed in 4 (6.1%). Biliary stricture rate was found in 1 (1.5%) of cases in the first period, but no strictures were found in the later period. The overall 3 year patient survival was 88.5%. Three year patient survival was 97.5% in the paediatric group and 74.3 % in the adult group.

Conclusions: Our technical complication rate following split liver transplantation is low. Our overall biliary complication figures (12.1 %) are significantly lower than some other published series. We found no statistically significant difference in the early technical complications between the 2 time periods and the effect of the learning curve was not observed in this study.

P60

A Modified Technique For Reduced Left Lateral Segment As An Alternative To Monosegmental Liver Transplantation

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Introduction: One of the main technical challenges in paediatric liver transplantation is to tailor the graft size to the recipient size. We have developed a reduced left lateral segment as an alternative to monosegment transplantation for small size recipients.

Methods: A reduced left lateral segment was fashioned by non anatomical resection of parts of segment 2 & 3. The inflow and outflow for these reduced segments remains the same as in the left lateral segmental grafts.

Results: The median weight was 4.9 Kg (range 2.9-7.8). Average age was 5 weeks (range 2 weeks-9 months). The indications were neonatal haemochromatosis, biliary atresia and metabolic liver disease. The median age for the donor liver was 46.5 years. The average warm ischaemia time was 53.5 minutes. The median weight of the liver tissue was 264 gm. The average blood transfusion requirement was 548.3 ml. The median levels of peak ALT were 1473 $\mu\text{mol/l}$, INR was 2.2 and bilirubin was 293 $\mu\text{mol/l}$ in the first 2 weeks following surgery. There was one early mortality at day 5 due to massive intracranial haemorrhage and the patient died with a functioning graft. Hepatic artery thrombosis was found in one patient and the patient was retransplanted successfully. No biliary or venous out flow complications were found in this group of patients.

Conclusions: This new modified technique of reduced left lateral segmental liver transplantation as an alternative to monosegments allowed transplanting very small recipients successfully with good results and minimal technical complications.

Friday 31 March

Moderated Poster Session

NHBD/Deceased Donation

P61

Bacterial Contamination Of Machine Perfusate Samples From Non-Heart Beating Donor (NHBD) Kidneys: A Prospective Audit

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Introduction

The incidence of contamination of perfusion fluid in cadaveric kidney transplants varies between 3 to 23% and most often by non-significant pathogens. To our knowledge there isn't enough evidence about the incidence or type of organisms that can potentially contaminate during non-heart beating cadaveric donation or machine perfusion

Aim

To determine the frequency of contamination and its relevance to the subsequent transplant

Methods

Since March 2005, 13 machine perfusate samples were collected from 13 NHBD kidneys before implantation. All samples were collected aseptically and processed by direct and enrichment culture.

Results

Organisms were grown in 7 (54%) perfusate samples. The isolated pathogens were coagulase-negative staphylococcus (1), Brevibacterium Sp (1), Enterobacter cloacae (2), E coli (1), Enterobacter faecalis (1), lactobacilli (2), and Streptococci pneumoniae (1). Two recipients have grown corresponding pathogens in the urine postoperatively. The most serious infection was the streptococci pneumoniae which was derived from the unsuspected cause of death in a maastricht category II donor (sterptococcal pneumonia). Very severe re-perfusion syndrome was encountered which later caused the grafts to fail after implantation despite full course of appropriate antibiotics which were administered later.

Conclusion

The incidence of contaminating organisms is much higher in organs retrieved from NHBD's. Predominance of bowel organisms signifies active translocation of gut organisms due to longer ischemic times in this group of donors. in most cases however they do not produce significant morbidity.

P62

Potential Damage To The Renal Artery Patch Due To Retrieval Of The Superior Mesenteric Artery With An Aortic Patch: A Survey Of Surgical Opinion

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Background:

In cadaveric renal transplant, the renal artery (RA) is retrieved from the donor with a patch of aorta (Carrel's patch). The patch facilitates implantation, reduces the risk of RA stenosis and improves graft outcome. Recently, we have seen an increased incidence of deficient or damaged aortic patches in cadaveric kidneys. An informal survey of the registrars and clinical fellows performing the liver retrieval has identified one recurring reason: The perceived need to take superior mesenteric artery (SMA) with an aortic patch in case of an accessory right hepatic artery (HA) arising from the SMA. This can potentially damage the aortic patch on the anterosuperior aspect of the renal artery.

Consultant liver transplant surgeons in UK and Ireland were asked for their opinion regarding the need for SMA retrieval with or without an aortic patch.

Methods:

A questionnaire was sent to all the consultant liver transplant surgeons asking the following three questions (each requiring a yes/no answer):

1. The SMA should always be retrieved in liver retrieval
2. The SMA should always be retrieved with an aortic patch
3. Do you perform renal transplants in addition to Liver Transplants?

Results:

Out of thirty three questionnaires sent, twenty (64%) replies were received.

- 67% of liver transplant surgeons believed that the SMA should not be retrieved in liver retrieval except where there is a right accessory HA from the SMA the remaining 33% believe that the SMA should always be retrieved.
- However, in cases where the SMA needs to be retrieved 81% of liver transplant surgeons believed that the SMA need not be taken with an aortic patch.
- 76% of the surgeons who replied to our questionnaire did both liver and kidney transplants while the remainder only did liver transplants.

Conclusion:

Retrieval of an aortic patch with the SMA during liver retrieval increases risk of damage to the RA and according to majority opinion can be avoided.

P63

Outcome Of Kidney Transplantation From Non-Heart-Beating Versus Heart-Beating Cadaveric Donors

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Background: Kidney transplantation from non-heart beating (NHB) donors is one of the solutions for the ever developing problem of organ shortage. Although many centres develop NHB kidney transplant programmes, there is still a lot of skepticism regarding the outcome of those transplants. The aim of this study was to assess short and long term outcomes of kidney transplants from NHB compared to heart-beating (HB) cadaveric donors, using meta-analytical techniques.

Methods: A literature search was performed for studies comparing outcomes of kidney transplants from NHB vs. HB cadaveric donors. Nineteen comparative studies published between 1988 and 2005 matched the selection criteria. The studies included 111,146 patients, of whom 1,923 received a kidney transplant from a NHB and 109,223 from a HB donor. The following end points were evaluated: warm ischaemia time, cold ischaemia time, primary non-function, delayed graft function, post-transplant need for dialysis, length of hospital stay, incidence of rejection, patient and graft survival and post-transplant serum creatinine.

Results: Warm and cold ischaemia times were significantly longer for the NHB group ($p < 0.05$). The incidence of primary non-function, delayed graft function and need for post-transplant dialysis was higher for the NHB group ($p < 0.001$). The length of hospital stay was also longer for the NHB group by 4.6 days ($p < 0.001$). The incidence of acute rejection was not significantly different between the two groups ($p = 0.45$). Long-term patient survival was similar between the two groups but graft loss at 3 months was less for the HB group (OR=1.42; $p < 0.001$). The initial graft survival advantage in favour of the HB group diminished over time. A similar trend in serum creatinine level was evident at 3 months (WMD=12.34; $p = 0.08$) and 12 months (WMD=5.86; $p = 0.24$) post-transplantation.

Conclusion: Non-heart-beating donors carry the potential of expanding the kidney transplant pool. Recipients from NHB donors appear to have an initial disadvantage which may partly be attributed to the prolonged graft ischaemic times, but the long-term outcomes are comparable.

P64

Marginal Kidneys; Extending The Pool Or Expanding The Complications?

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Aims: The use of less-optimal (marginal) kidneys is one way to expand our donor pool and overcome graft shortages. We prospectively assessed the 1 year outcome of transplantation in recipients who had marginal kidneys (group1) by comparing them with those who received optimal kidneys (group2).

Methods: A cohort of 203 cadaveric kidney recipients, transplanted between 2001 and 2004, were included. Grafts were considered marginal if they fulfilled one or more of the following: Cold Ischaemic Time (CIT) >24hrs, donor age >60yrs, kidneys from non-heart beating (NHB) donors, or donors with history of hypertension (HTN) or Diabetes.

Outcome measures were: delayed graft function, 1-yr patient survival, number of rejection episodes during the first year, 1-yr graft survival, & eGFR 1 year post implantation (MDRD).

106 patients were identified in group 1 & 97 in group 2. Chi-Square test was used for categorical variables & t-test/Mann-Whitney test for numerical data.

Results: Mean recipient age at transplantation was 52 ± 13 y for the group 1 vs 49 ± 13 y for group 2 ($p=0.1$). Mean donor age was 55 ± 13 y (gr1) vs 43 ± 12 y (gr2) ($p<0.001$). CIT mean was 24 ± 9 h (gr1) vs 19 ± 3 h (gr2). 51(48%) out of 106 pts in group 1 had more than one marginal criterion: 25(23.6%) received kidneys from NHB donors, 40 from hypertensive and 8 from diabetic donors. Post implantation, 36(40%) recipients in group 1 had delayed graft function vs 23 (23.7%) in group 2 ($p=0.035$), & the median [IQR] days required before cessation of dialysis were 10.5(7-16.5) [gr1] and 9.5(5-21)[gr2], $p=0.007$. There was no statistically significant difference in the incidence of rejection episodes during the first year ($n=24$ [gr1], $n=29$ [gr2], $p=0.17$), or in the proportion of patients who died in each group during the first year ($n=5$ [gr1], $n=5$ [gr2], $p=1$). Graft failure developed in 12(11.3%) marginal and 14(14.4%) non marginal patients ($p=0.65$). eGFR at 1 year post implantation was significantly lower in group 1 (38 ± 15 mls/min vs 46 ± 15 mls/min respectively, $p<0.001$).

Conclusions: While the utilization of expanded criteria donors does not seem to pose a significant detrimental effect on 1 year graft and patients' survival, recipients of marginal kidneys not only have more delayed function, but also worse renal function after 1 year. Longer follow up is needed to determine the late effects on graft survival.

P65

First Simultaneous Pancreas-Kidney (SPK) Transplant From A Controlled Non-Heart-Beating Donor (NHBD) In The UK — A Case Report

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We report the first SPK from a controlled non heart beating donor (NHBD) in the UK. Liver, pancreas and kidneys were retrieved from a 17 yr old female donor who had succumbed to RTA. Retrieval was done using the standard technique and UW solution aortic perfusion. Warm ischemia time was 12 minutes.

The recipient was fifty year old female, who had been diabetic for 45 yrs. She had her first kidney transplant in 1988 with deteriorating graft function, significant autonomic neuropathy and multiple coronary stents. The grafts were 111 mismatched. The pancreas was transplanted intraperitoneally through a midline incision with exocrine drainage to the bladder. A transplant nephrectomy of her first kidney transplant was done simultaneously before the kidney implantation on the left. Immunosuppression with Basiliximab induction followed by Tacrolimus, Mycophenolate Mofetil and steroids was commenced. She achieved primary pancreas function with delayed kidney function of 10 days. Total cold ischemia time was 13 hrs and 31 minutes. Four months post transplant she is insulin independent with normal HbA1C.

Sollinger et al have shown no difference in patient survival, pancreas and renal allograft survival between organs from non heart beating donors and standard donors. The increasing NHBD pool in the UK could be a useful source of pancreata for transplantation.

Renal Vasospasm During Intra-Arterial Cooling Is Extracellular Calcium DependentCH Wilson¹, N Carter², AC Cunningham², D Vijayanand¹, H Wyrley-Birch¹, SO Aliu¹ and D Talbot³¹School of Surgery and Reproductive Sciences, Newcastle University, NE2 4HH, United Kingdom,²Applied Immunobiology Group, Sunderland University, SR2 7EE, United Kingdom and ³The Liver/

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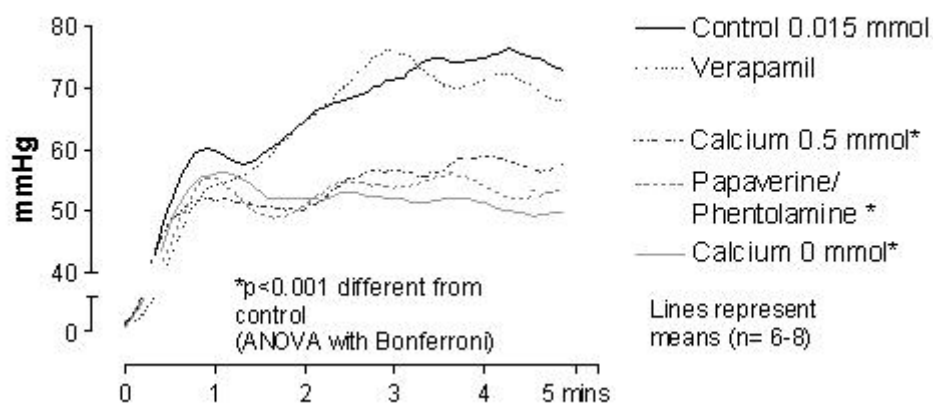
Introduction. Effective intra-arterial cooling (IAC) of non-heart beating kidneys requires large volumes of preservation solution to be flushed through the microcirculation at high flow rates. Renal vasospasm compromises cooling and strategies to reduce vascular smooth muscle contraction could increase the number of useable kidneys retrieved.

Methods. Rodent kidneys were exposed to 30 minutes warm ischaemia, cannulated and flushed with streptokinase before perfusion at a fixed flow rate with a chilled (4°C) low viscosity preservation solution (HTK, Histidine-Tryptophan-Ketoglutarate). In separate experiments either the preflush was supplemented with vasodilators or the calcium concentration of the preservation solution was altered.

Results. Within 2 minutes there were differences in the perfusion pressures (Figure 1). Kidneys flushed with HTK at the standard concentration of 0.015 mmol/l or with verapamil added to the preflush had a perfusion pressure of c.70 mmHg. In contrast, the addition of papaverine or phentolamine to the preflush, removing calcium or adding *more* calcium (0.5 mmol/l) significantly reduced the perfusion pressure to approximately 55 mmHg.

Discussion. These results suggest that during kidney perfusion vasospasm is prominent and mediated by intra-cellular calcium released in response to extra-cellular concentrations of calcium. Blockade of alpha-adrenergic receptors or myosin light chain kinase, but not voltage gated calcium channels, reduces the vascular resistance during perfusion: alternatively 10 mls of calcium gluconate could be added to each 5 L bag of HTK.

Figure 1. Perfusion pressures during IAC with HTK



Friday 31 March

Moderated Poster Session

Laboratory

P67

Pathfinder Cells: A Cellular Therapy For Diabetes

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Cellular therapies have real potential for the treatment of diabetes. Evidence that cells, which might fulfill this role, reside in the pancreatic ducts, has been provided by rodent models of pancreas regeneration . We have previously isolated a novel cell type from adult rat pancreatic ducts, termed Pathfinder Cells that can fulfil this role. We have presented the first evidence of highly successful diabetes treatment by direct intravenous injection into STZ diabetic mice and demonstrated that the Pathfinders contribute to the recovery process by stimulating host tissue. We have also investigated whether the efficacy of the Pathfinder cells is affected by murine immune responses. Significantly, immunosuppression appears not to improve the efficacy of these cells, whereas repeat dosing with higher cell numbers does ameliorate blood glucose levels. Crucially, the insulin produced by these animals is both rat and mouse in origin.

These results demonstrate the feasibility of using intravenous administration of adult cells to regenerate damaged tissue. Critically, they enhance our understanding of the mechanisms relating to such repair and suggest a means for novel therapeutic intervention in diabetes.

Unlike stem cell therapies, which entail an elevated risk of cancer following transplantation, we observe no tumourogenesis post transplant with Pathfinder cells. Significantly, in contrast to stem cell therapies, Pathfinders exhibit sensitivity to oxidant stress. We have utilised this to evaluate telomere dynamics, senescence associated gene expression (p21,p16,XRCC5, hPOT1, Sirtuins 1-7) and cellular markers of senecence (Senescence associated beta galactosidase, lipofuscin) to demonstrate the effect of age and the safety of using Pathfinder cells in transplantation.

P68

The Effect of MICA mismatch following Lung Transplantation

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Background

MHC Class I related Chain A (MICA) is a polymorphic gene in the MHC class I region. MICA is constitutively expressed on the surface of certain cell types predominantly epithelial cells, endothelial cells and fibroblasts making this polymorphic molecule a possible target for immune responses during graft rejection. In addition to this the evidence for heat and viral upregulation of MICA cell surface expression suggests that MICA is a marker of stress in cells. Our initial objective was to type a cohort of thoracic organ donors to determine the frequency of MICA alleles in our donor population, to assess the extent of MICA mismatching and its effect on graft survival.

Methods

A PCR-SSP based typing system for MICA alleles was established and 142 consecutive donors and 52 lung transplant recipients were typed. The frequency of MICA alleles was determined in the two populations. Matching between donor/recipient pairs and mean survival post-transplant by Kaplan-Meier survival curves was analysed.

Results

Allele frequencies for both populations are detailed in Table 1 below. No significant differences were seen between the two groups.

Mismatch data were available for 46 donor recipient pairs, 19 of which had one or more MICA mismatches. The 1 year graft survival of recipients with 0 MICA mismatches (MM) was 83% (n=12) vs 1 MICA MM 58.8% (n=17) vs 2 MICA MM 57.1% (n=7). These findings were not significant, although a trend towards improved survival with 0 MICA MM can be seen.

Discussion

The frequencies of alleles in the donor population are comparable to published findings We also noted a distinct trend towards longer survival in 0MM donor/recipient pairs and this study needs to be expanded to further investigate this phenomenon.

MICA allele	Recipient	Donor
	Allele	Allele
	Frequency (%)	Frequency (%)
*002	13.2	23.2
*004	14.1	6.3
*007	8.8	6.3
*008	48.1	54.2
*009	6.6	3.5
*010	3.7	5.6
other	2	0.7
n=	104	52

P69

Association Of HLA Phenotypes Of Patients On Waiting List With Sensitization And Waiting Time For Renal Transplantation

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Aims

There is some evidence that HLA phenotype may be associated with sensitization in renal failure patients (Heise E, 2001). Our primary aim was to compare the HLA phenotypes of highly-sensitized patients (PRA>85%) on the waiting list for renal transplantation (group1) with that of unsensitized patients (group2). The secondary aim was to investigate whether particular alleles are associated with the length of time waiting for a transplant.

Methods

Data for all current patients on the local waiting list for renal transplantation were collected. The 10 most frequently occurring HLAs were identified. The association between HLA type and sensitization status of patients, and between HLAs and waiting times for transplantation, were explored. Chi-square test and Fisher's exact test was used for analysis of categorical data and Mann-Whitney test for numerical data.

Results

There were 109 patients in the unsensitized group (53F, 56M, mean age 43, mean waiting time 601 days) and 19 in the highly-sensitized group (12F, 7M (p=0.357), mean age 49 (p=0.117), mean waiting time 2188 days (p<0.001)). There was no statistical difference in ethnicity in either group. The five most common alleles in both groups were Bw4, Bw6, Cw*07, DQB1*03 and DQB1*06. In the unsensitized group A*02, DQB1*02, DRB1*03, DRB3*01 and DRB4*01 were also very common. Only DQB1*02 and DRB1*03 were significantly different between the two groups (p=0.014 & p=0.038; OR=0.23 & 0.29 respectively). That is, patients with these HLAs were 77% and 71% less likely to be highly-sensitized as compared to patients without these HLAs.

The presence of either DQB1*02 or DRB1*03 alleles was also significantly associated with less waiting time for transplantation (p=0.001 & p=0.005 respectively). The mean waiting time if the DQB1*02 allele was present was 604 days vs 996 days if it was not present, whereas if the DRB1*03 allele was present the mean waiting time was 525 days vs 1012 days if it was not present.

Conclusions

DQB1*02 and/or DRB1*03 alleles were more frequently found in unsensitized, than highly-sensitized patients. The same alleles were also associated with less waiting time for transplantation in this group of patients. These findings should be explored further in larger studies, but an important implication may be that these HLAs are a predictor of level of sensitisation and waiting time.

Friday 31 March

Moderated Poster Session

Pancreas

Anatomical Variations In The Superior Mesenteric Artery, And Its Implications In Pancreas Retrieval

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Introduction:

Pancreas transplantation has gained popularity in the United Kingdom. This has led to the emergence of dedicated pancreas retrieval teams. The key to successful retrieval of a pancreas lies upon a detailed orientation of the superior mesenteric artery (SMA) and its anomalies. This abstract suggests solutions for safe removal of transplantable pancreata in donors having anatomical variations in the superior mesenteric artery.

Materials and methods:

From April 2004 to November 2005, the Oxford Transplant Centre performed 41 pancreas retrievals. All retrievals were heart beating, multiorgan retrievals in conjunction with a regional liver team within the Oxford Pancreas retrieval zone. Standard single perfusion through the aorta was instituted for majority of the donors. Anatomical variations of the SMA were noted, as were the graft outcomes. Reported variations in anatomy were studied from Netters' Anatomy and Gray's Anatomy.

Results:

Six donors had anatomical variations in the SMA. Of these six, three had an accessory right hepatic artery; two had a replaced right hepatic artery giving origin to the inferior pancreaticoduodenal artery (IPDA), one had a complete replaced hepatic artery from the SMA. One pancreas was lost due to uncontrolled haemorrhage from an unrecognized IPDA that originated from the replaced right hepatic artery, leading to rapid flushing by the liver team. Five pancreata were transplanted successfully.

Discussion:

[table here]

GDA- gastroduodenal a.; RHA – right hepatic a.; Ac.HA- Accessory hepatic a.

Conclusion: Despite anatomical variations, pancreata with complex anatomy can be transplanted safely if the liver and pancreas transplant teamwork in tandem bearing these anatomical variations in mind.

Common	Variation	Solution
Hepatic artery (CHA)	Ac.HA from SMA	Cut SMA high in pancreas; Aortic cuff to liver
	RtHA from SMA	Same as above
	CHA From SMA	Same as above
Celiac Axis	Common origin of Celiac & SMA	Save aortic patch with CHA, to liver
	Splenic A & CHA from SMA	Either liver or pancreas team could get aortic patch
	Splenic A from SMA	Both liver & pancreas team get aortic patch
	Replaced RHA from SMA & IPDA from it	Aortic patch with SMA essential for pancreas team
	Accessory Rt HA from SMA & IPDA from it	Same as above. Liver team gets celiac trunk & reconstruct using GDA.

P71

Kidney Survival in Simultaneous Pancreas/Kidney and Kidney Only Transplants

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Background

When no suitable 000 mismatched highly sensitised adult or 000 mismatched paediatric patients are listed for a kidney transplant, donated kidneys are offered first to patients awaiting a simultaneous pancreas/kidney (SPK) transplant and then to those awaiting a kidney only (KO) transplant. We have therefore investigated whether kidney graft and patient survival in SPK transplants is comparable with that of KO transplants, using a paired kidney study.

Data

Data were obtained from the National Transplant Database on 224 first adult SPK transplants performed in the UK between 1 January 1995 and 31 December 2004, and the corresponding 224 first adult KO transplants performed using the other kidney from the pancreas/kidney donors.

Methods

Risk adjusted Weibull survival models were developed to model the hazard of graft failure and patient death following transplantation. A variable identifying the transplant type (SPK or KO) was added to a risk-adjusted model that accounted for other factors known to affect kidney transplant outcome. This allowed the effect of transplant type on post-transplant graft and patient survival to be explained once other influential donor and recipient factors had been adjusted for. An additional term was added to the model to account for each pair of recipients having a common donor.

Results

Statistically significant differences in recipient demographics across the two groups of recipients were found: SPK recipients were generally younger, had waited fewer days to receive their transplant and had inferior HLA mismatching. After allowing for donor and recipient factors known to affect kidney transplant outcome, there was no statistical evidence to suggest that kidney graft survival in SPK transplants differs from that in KO transplants ($p=0.58$). There was, however, strong statistical evidence to suggest patient survival was inferior for SPK transplants compared with KO transplants ($p=0.004$). A higher proportion of patient deaths occurred within the first three months post SPK transplant, largely attributable to myocardial ischaemia and infarction, and septicaemia.

Conclusions

There is no evidence to suggest that kidney graft survival in SPK transplants differs to that in KO transplants, but there is strong statistical evidence to suggest that patient survival for SPK transplants is inferior.

P72

An Audit Of The Pancreas Retrieval Programme In Oxford

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Background:

In April 2004 Oxford became a NSCAG designated regional center for pancreas transplantation. Since then there has been a steady increase in the solid organ pancreas transplant and pancreas retrieval activity. This is an audit of the pancreas retrieval programme in our unit.

Methods:

The donor coordinator team collected the data prospectively from 1st April 2004 to 30th September 2005 (18 months). All referrals for a potential pancreas donor were included. Data was analyzed looking at a number of variables including the referral pattern, retrieval activity, percentage of successful retrieval and reasons for declining a retrieval offer. In addition, an attempt was made to identify the pattern of organ sharing amongst the regional units.

Results:

Over this 18-month period there were 201 referrals in all. There were 80 zonal referrals (39.8%) and 121 out of zone referrals (60.2%). 51.25% of the zonal offers were accepted for retrieval and 40(98%) pancreases were retrieved successfully. The reasons for declining the organ included a lack of a blood compatible recipient (n = 22, 57%), an unsuitable donor (n=14, 36%) and lack of intensive care beds.

We transplanted 22 patients (55%) with organs retrieved by our team. The organ was exported to another center on 14 occasions (35%). 10% (n=4) of organs were not transplanted as were found to be unsuitable. During this period we exported 14 organs while we used 8 organs (29%) retrieved by other teams.

Conclusion:

We have provided a reliable and effective retrieval programme to our allocated zone. 98% organs were retrieved when accepted for retrieval. The reasons for declining an organ had bearing on factors other than the retrieving team. There is an encouraging trend of exchange of organs between centres.

P73

A Single Centre Comparitive Morbidity Analysis Of Bladder Drained Versus Enteric Drained Pancreas Transplants

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BACKGROUND: Pancreas transplantation is still associated significant morbidity. Debate continues regarding the optimum technique of exocrine drainage.

METHOD: A retrospective study to investigate the morbidity following pancreas transplantation and to compare the differences between enteric versus bladder drained pancreata. Parameters evaluated included rates of radiological interventions, re-exploration/laparotomies, fistulation, sepsis, hospital stay, graft and patient survival.

RESULTS: Between June 2001 and November 2005, 66 patients underwent pancreas transplantation (53 SPK, 13 PAK). 32 had bladder drained (BD) transplants whereas 32 had enteric drainage (ED). 2 grafts thrombosed intraoperatively. Radiological drainage of collections occurred in 10 (31%) BD and 2 (6%) ED patients. Surgical re-explorations were required in 19 (59%) and 15 (47%) patients with a mean of 1.5 and 2.6 procedures per patient (range 0 to 5 and 0 to 6) in BD and ED patients respectively. Reasons for re-operations were as follows: transplant pancreas thrombosis 6 in BD and 5 ED, bleeding in 4 and 1 in BD and ED respectively. 9 (28%) of BD patients required inpatient treatment for excessive bicarbonate loss and dehydration. There were 7 bowel fistulae in ED compare to 2 urinary fistulae in BD. Sepsis was similar in BD and ED patients (47% vs. 44%, respectively). There were differences between the rate of wound infections (12.5% and 41%) peritonitis (9% and 16%) urinary tract infection (44% and 31%) and abdominal abscess (28% and 25%) in BD and ED patients respectively. There were three hospital deaths in ED and one in BD group. The rejection rate was similar in either group (22%). Median initial hospital stay was 17 (range 14-200) and 19 days (range 10-90) in BD and ED patients respectively. 7 (22%) patients were discharged in less than 14 days in ED were as no BD patients discharged in less than 14 days. At discharge all patients with functioning grafts were insulin free. Current graft survival for BD and ED remains 72% and 81% respectively.

SUMMARY: The initial 14 patients had enteric drainage while the subsequent group had varied drainage. ED patients had a higher incidence of hospital death and surgical procedures per patient but slightly better graft survival. Seven of ED patients were discharged in less than two weeks. The incidence of readmission for dehydration was significantly less in the ED group. There were higher incidence of invasive interventions in BD patients.

P74

Thrombocytosis In Pancreatico-Renal Transplant Recipients

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Background: Pancreas transplant recipients have an increased risk of post-operative thrombosis involving coronary, cerebral, retinal and graft vessels. Furthermore, fine control of blood sugar by insulin pump infusion in non-transplanted diabetics has been associated with initial deterioration in retinopathy. Could euglycemia in angiopathic diabetes alter platelet numbers or function and thereby raise the risk of thrombosis?

Objective: To assess the degree and duration of thrombocytosis in pancreas transplant recipients.

Method: Platelet counts were performed in the following patient groups: Group 1 (n= 61) euglycemic pancreas transplant patients; Group 2 (n=27) diabetics with renal transplant alone; Group 3(n=47) non-diabetics with renal transplant and Group 4 (n=28) diabetics who have undergone major surgery.

Results: (censored for pancreas transplant failure)Platelet count x 10⁻³ / mm³ [please refer to the table]

Conclusion: Euglycemic pancreas graft recipients exhibit a marked relative thrombocytosis which persists longer (up to 3 months) than in other groups; requiring routine anti-thrombotic prophylaxis.

Group	0 day	1 d	3 d	7 d	10 d	14 d	17 d	21 d	24 d	28 day	1 mo	3 mo	6 mo	1 yr	3 yrs	5 yrs	10 yrs
1	244	189	174	290	421	477	449	442	387	386	358	323	288	273	232	240	220
2	265	206	202	252	341	369	336	308	268	235	252	302	244	244	215	188	----
3	200	169	184	225	365	310	299	258	232	233	259	271	246	237	202	232	223
4	256	263	----	280	305	288	386	293	269	264	268	240	228	249	----	----	----

Friday 31 March

Moderated Poster Session

Immunosuppression

P75

Ciclosporin and Tacrolimus cause a Genotype-Dependent Effect on Endothelial Nitric Oxide Synthase Expression with the T-786C Polymorphism

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Nitric oxide (NO), derived from endothelial nitric oxide synthase (NOS3), plays an important role in endothelial function. The calcineurin inhibitors, ciclosporin and tacrolimus, have been associated with endothelial dysfunction by altering expression of NOS3. A T-786C substitution in the NOS3 promoter is associated with reduced expression. The aim was to determine whether the calcineurin inhibitors exert a genotype-dependent effect on NOS3 expression in patients with the T-786C polymorphism.

Hepatoma (HepG2) cells were transfected with a vector containing a luciferase gene and a 866 base-pair segment of the NOS3 promoter with either -786TT or -786CC. Luciferase activity was recorded, with and without incubation with ciclosporin or tacrolimus in doses of 50, 100, 200 and 400ng/ml for 48 hours. Percentage change in activity from baseline (no drug) was calculated.

An increase in NOS3 expression was noted for -786CC with ciclosporin, but a decrease was noted with -786TT. Tacrolimus caused a dose dependent increase in expression with both -786TT and -786CC (see table below).

Our results demonstrate that calcineurin inhibitors cause a genotype-dependent alteration in NOS3 expression. Potentially, tailoring of immunosuppressive therapy to the NOS3 T-786C genotype could reduce complications such as chronic allograft nephropathy.

Dose (ng/ml)	Genotype	Mean % change with ciclosporin	N	Mean % change with tacrolimus	N	Sig.
50	-786TT	-7.7 (± 50.4)	6	3.9 (± 15.0)	6	P<0.0001
	-786CC	68.7 (± 50.1)	6	29.7 (± 44.1)	6	
100	-786TT	-9.4 (± 53.3)	6	11.3 (± 17.8)	6	
	-786CC	67.7 (± 49.1)	6	58.4 (± 64.5)	6	
200	-786TT	-9.5 (± 48.5)	6	19.7 (± 9.9)	6	
	-786CC	68.5 (± 27.7)	6	76.8 (± 27.8)	6	
400	-786TT	-12.4 (± 50.7)	6	19.4 (± 7.6)	6	
	-786CC	63.8 (± 33.2)	6	86.7 (± 43.1)	6	

P76

Campath And Medium Dose Tacrolimus Monotherapy In Renal Transplantation: One Year Pilot Study

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We report our experience with Campath 1H induction and medium dose Tacrolimus monotherapy in kidney transplantation.

56 patients [32m, 24f; mean age 45.3 ± 12.5 yrs (1 SD); 31 live donor recipients, 25 deceased donor recipients] received an immunosuppressive regime consisting of 30mg Campath 1H iv, prednisolone [60mg daily for 4 days and 30mg daily for 3 days] and Tacrolimus, 0.15 mg/day [12 hr trough level 5 - 8 ng/L (LCMS)]

99 patients [51m, 48f; age 45.1 ± 12.5 yrs (1 SD); 45 live donor recipients and 54 deceased donor recipients] receiving our previous immunosuppressive regime acted as controls. These patients received 2 iv doses of Daclizumab [2mg/kg, day 0 and day 14], prednisolone [60mg daily for 4 days and 30mg daily for 3 days], Tacrolimus, 0.15 mg/day, [12 hr trough level $8 \hat{=} 11$ ng/L (LCMS)] and Mycophenolate Mofetil 1.5g/day [12 hr target trough level $1.5 \hat{=} 3.0$ mg/L]. Rejection was diagnosed by allograft biopsy and treated with iv methyl prednisolone [x3] and reinstitution of oral steroids.

Mean follow up in the Campath group was 6.4 ± 4.3 months and 21.1 ± 9.4 months in the Daclizumab group.

At 1 year, patient survival in the Campath group was 100% and 96.8% in the Daclizumab group. At 1 year, graft survival was 94.3% in the Campath group. There were 2 technical failures and 1 graft was lost as a result of atypical HUS. Allograft survival was 93.6% in the Daclizumab group. There were 3 deaths with a functioning graft [2 sepsis, 1 cardiac]; there was 1 technical failure and 2 grafts were lost, 1 from chronic rejection and 1 from pyelonephritis.

Only 1 case of rejection was observed in the Campath group whereas there were 12 cases of rejection in the Daclizumab group [chi test $p=0.026$].

Estimated creatinine clearance [Cockcroft Gault] was similar in both groups as shown in the table below.

Although these are early data, this pilot study with Campath 1 induction and medium dose Tacrolimus produces similar outcomes to a conventional immunosuppressive regime with a lower incidence of rejection.

Table 1. Allograft function at 3, 6 and 12 months

		Campath			Daclizumab			p
		Mean	+ 1SD	n	Mean	+ 1SD	n	
3 months	Creatinine nmol/L	148.47	\pm 64.97	41	151.26	\pm 63.93	96	0.41
	eCrCl ml/min	55.19	\pm 19.94	36	54.93	\pm 22.06	93	0.48
6 months	Creatinine nmol/L	156.07	\pm 66.24	27	151.73	\pm 67.65	90	0.38
	eCrCl ml/min	54.03	\pm 18.89	27	55.56	\pm 20.49	90	0.36
12 months	Creatinine nmol/L	159.90	\pm 53.49	14	143.41	\pm 52.89	83	0.14
	eCrCl ml/min	56.02	\pm 20.16	14	56.77	\pm 20.61	81	0.45

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Low Incidence Of Infection With Campath And Medium Dose Tacrolimus Monotherapy In Renal Transplantation

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Campath 1H induces temporary lymphopenia and there is concern that this may be associated with a higher incidence of infection following renal transplantation. We present our experience here with infection in patients receiving Campath 1H induction and medium dose Tacrolimus monotherapy in kidney transplantation.

56 patients [32m, 24f; mean age 45.3+12.5 yrs (1 SD); 31 live donor recipients, 25 deceased donor recipients] received an immunosuppressive regime consisting of 30mg Campath 1H iv, prednisolone [60mg daily for 4 days and 30mg daily for 3 days] and Tacrolimus, 0.15 mg/day [12 hr trough level 5 - 8 ng/L (LCMS)]

99 patients [51m, 48f; age 45.1+12.5 yrs (1 SD); 45 live donor recipients and 54 deceased donor recipients] receiving our previous immunosuppressive regime acted as controls. These patients received 2 iv doses of Daclizumab [2mg/kg, day 0 and day 14], Prednisolone [60mg daily for 4 days and 30mg daily for 3 days], Tacrolimus, 0.15 mg/day, [12 hr trough level 8 - 11 ng/L (LCMS)] and Mycophenolate Mofetil [MMF] 1.5g/day [12 hr target trough level 1.5 - 3.0 mg/L].

Positive urine, bronchiolar lavage, drain fluid, ascites and blood cultures constituted significant episodes of bacterial infection. CMV pcr positivity [> 1000 copies/ml] and BK viral nephropathy were considered to be significant markers of viral infection.

Mean follow up in the Campath group and the Daclizumab group is 6.4 + 4.3 and 21.1 + 9.4 months respectively. 1 year patient survival was 100% in Campath group and 96.8% in the Daclizumab group, of which 2 recipients died from sepsis.

% Mean lymphocyte counts [+1SD] in the Campath group at 1, 3 and 6 months were 0.1 [0.3], 0.22 [0.2] and 0.59 [0.4] respectively.

Within the first 12 months post transplant, a total of 128 significant microbiological diagnoses were recorded and expressed as episodes per patient month. The incidence of urinary tract infection was similar in the 2 groups [Campath 0.062 episodes vs Daclizumab 0.065 episodes per patient month], (p = NS). The incidence of bacteraemia was significantly higher in the Daclizumab group [0.027 per patient month than the Campath group [0 per patient month], (chi test p=0.002). No CMV infection was diagnosed in the Campath group. There was 1 episode of BK viral nephropathy in each of the 2 groups.

This study shows that the lymphopenia in patients treated with Campath 1H is not associated with a higher incidence of infection compared with patients receiving Daclizumab and MMF.

P78

Steroid Avoidance In Renal Transplantation: Analysis By Donor Source

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Background: Since January 2004 we have used a steroid avoidance (SA) regime in all low and medium risk renal transplants. Early metabolic benefits and good levels of graft function have been described previously. During this period there has been a steady decline in Heart-Beating Cadaveric donors (HBC). However our programme has continued to grow by increasing the numbers of both Living (LD) and Non-Heart Beating Cadaveric (NHBC) donors. Accordingly the quality of donor organs has become more heterogenous thus merits separate analysis.

Methods: Data was obtained from case notes and from our PROTON database. All patients received 1g methylprednisolone intra-operatively and basiliximab 20mg (Days 0&4) followed by tacrolimus and mycophenolate mofetil maintenance.

Results: Up until August 2005, 216 transplants have been performed, 169 having been treated with the SA regime. Excluded patients were either high risk or involved in trials. At a mean follow up of 378 days (214-524) overall patient survival was 96.4% (163/169) and graft survival 92.9% (157/169). Patient data is shown in the table below. Causes of death were 2 infective, 3 cardiovascular and 1 calciphylaxis. Graft loss was due to 2 primary non-function (both CAD), 1 CAN, 2 Acute rejection, and 1 graft thrombosis. Side effects were minor and occurred in small numbers in all groups.

Conclusions: Steroid avoidance leads to good early outcomes in all groups of patients, irrespective of donor source.

	CHB	CNHB	LD	Overall
N	101	32	35	169
Patient Survival	98.00%	93.90%	94.30%	96.50%
Graft Survival	93.10%	90.10%	94.30%	92.90%
BPAR Banff (1,2/3)	8.1%(6,1,2,0)	15.2%(12,1,3,0)	14.3%(8,5,5,7)	10.7%(7,7,2,9)
DGF	41.50%	73.50%	8.60%	41.40%
Creat/GFR 6M	158.8/44.8	165.1/47.0	147.6/49.8	157.7/46.3
Creat/GFR 12M	158.6/43.3	150.8/45.2	138.6/53.9	153.4/45.6
CIT	18.9	16.5	1.7	
Donor Age	49	45.9	47.7	
A/B/DR MM	0.8/0.8/0.2	1.0/1.3/0.6	0.8/0.8/0.8	
Steroid free	87.2%(82/94)	90.0% (27/30)	90.1% (30/33)	88.5%(139/157)

P79

Incidence Of New Onset Diabetes After Transplantation [NODAT] In A Steroid Avoidance Renal Cohort Taking Tacrolimus

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Background

Renal transplants performed in Leeds since January 2004 have received a steroid avoidance [SA] maintenance immunosuppression regime of mycophenolate mofetil and tacrolimus.

Recent literature has highlighted the increased incidence of NODAT in patients receiving tacrolimus over cyclosporin. This data however uses a suboptimal definition of diabetes based on insulin requirement rather than WHO guidelines.

A more precise way to assess the development of diabetes is to look at blood glucose concentration and perform glucose tolerance tests [GTT]. We analysed our SA patients using these techniques looking for cases of NODAT.

Methods

Proton© computer database was used to identify all SA patients. The highest random blood sugar for each individual in the period between three months post-transplant to present day was recorded alongside a current medication list.

NODAT was diagnosed in patients with random blood sugars above 11.1mmol^{-1} , and in those started on oral hypoglycaemic agents or insulin post transplant.

GTTs were performed on forty-six SA patients at six weeks and thirty patients at six months post-transplant.

Results

143 patients were identified (mean period from transplant 427 days). Nineteen (13.29%) had pre-transplant diabetes. Three NODAT cases were identified (2.10%), one treated with gliclazide, one with insulin and the other by diet. One case had received prednisolone 5mg daily due to azathioprine and mycophenolate intolerance. None had been pulsed with methyl-prednisolone.

Six week GTTs showed that 10.87% (n=5/46) met diagnostic criteria for diabetes and 41.3% (n=19/46) had impaired glucose tolerance. This fell to 3.33% (n=1/30) and 6.67% (n=2/30) at six months.

Conclusion

The incidence of NODAT in our SA cohort was 2.10% at a mean follow up of 427 days post-transplant. By using GTTs the detection of post-transplant diabetes is greater but after six months the relative numbers still remain small.

Friday 31 March

Moderated Poster Session

Desensitisation/Live Donation

P80

ABO Incompatible Live Donor Transplantation With Rituximab

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We present our experience with Rituximab in place of surgical splenectomy in ABO incompatible [ABOi] live donor kidney transplantation.

5 patients [3m, 2f, age: 37.8 ± 8.9 years] underwent ABOi live donor kidney transplantation. Single dose Rituximab at $375\text{mg}/\text{m}^2$ was administered immediately post transplantation in the first 2 cases. Thereafter, two doses of Rituximab were administered, at the same dose, at the start of the antibody removal treatment [mean time prior to transplant 13.3 ± 2.08 days] and immediately post transplantation.

Prior to plasma exchange, all patients were immunosuppressed with Tacrolimus [$0.15\text{mg}/\text{kg}$ daily, 12 hr target trough level 8-11 ng/L (LCMS)], Mycophenolate Mofetil [1.5g daily, 12 hr target trough level $1.5 \text{--} 3.0$ mg/L]. Post transplantation, 4 patients also received Prednisolone for 1 week [60mg for 4 days and 30mg 3 days]; the 5th patient with a cardiac allograft received steroids for 6 months. All patients were treated with Daclizumab [$2\text{mg}/\text{kg}$ day 0 and 14]. Cases 3, 4 and 5 underwent a further 2.33 ± 0.47 post transplantation plasma exchanges.

Pre-transplantation each patient undertook 8.5 ± 1.76 antibody removal treatments with plasma exchange alone [4 patients] or immunoadsorption and plasma exchange [2 patients] prior to transplantation. The frequency of these treatments was determined by antibody titre as shown in the table below. No side effects were recorded as a consequence of antibody removal therapy.

Mean follow up is 11.5 ± 10.8 months. Mean length of in patient stay after transplantation was 8.6 ± 3.57 days.

One year cumulative patient and graft survival is 100%. There was only 1 episode of rejection, patient 4, which was successfully treated with plasma exchange, iv immunoglobulin and iv methyl prednisolone [$0.5\text{g} \times 3$]. There were no cases of infection requiring hospital admission. Estimated creatinine clearances [Cockcroft and Gault] at 1, 3, 6 months respectively are 63.03 ± 12.18 , 61.57 ± 23.05 and 49.11 ± 10.37 mls/min.

This study shows that ABOi live donor transplantation can be safely and successfully accomplished with Rituximab rather than surgical splenectomy.

Table 1. Recipient Demographics

No	Age	Sex	Aetiology of CKD	No. Txp	Blood Group (Donor)	Blood Group (Recip)	Titres pre therapy IgM/G	Titres pre TxP IgM/G	No. Ig removal treatments
1	24.7	M	CNI toxicity	1	A	B	16 / 2	4 / 0	8
2	45.0	F	DM	1	B	O	8 / 4	0 / 0	10
3	38.8	F	DM	1	A	O	64 / 32	8 / 4	11 + 2
4	24.5	M	MCGN	1	A	B	128 / 32	16 / 2	9 + 2
5	41.2	M	APKD	1	B	A	16 / 4	2 / 0	6 + 2

P81

Resynthesis Of Donor Specific HLA Antibody After Living Donor Kidney Transplantation In Highly Sensitised Patients

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Successful antibody incompatible kidney transplantation is associated with both modulation of donor specific antibody (DSA) production, and accommodation of the graft, but the rate of change in these variables is not fully described.

We report 8 highly sensitised patients who had living donor transplantation after a course of high volume double filtration plasmapheresis (PP). Three cases had +ve complement dependent cytotoxic (CDC) crossmatch (XM) before PP (titres 1:128, 1:32, 1:1 respectively), 4 had +ve flow cytometric (FC) XM, and 1 had DSA detectable by Luminex bead analysis only. Post-transplant, antibody levels were monitored daily for the first 2 weeks by Luminex.

Six patients achieved a –ve FC and CDC XM after PP. The two patients with high pre-treatment CDC XM titres had residual DSA at the time of transplantation, 1 at a level compatible with a +ve CDC XM (DR53 antibody), and one with antibody detectable by Luminex only. All patients had good early graft function and none required early dialysis.

One patient did not resynthesise DSA in the early post-operative period, and another maintained a steady level of DSA, both of these had good urine output and graft function throughout. There was resynthesis of DSA in the other 6 patients, at a median of 7.5 days post-transplant. In each case, there was a concomitant rise in serum creatinine (median increase from best to peak 58.5 umol/l). There was also a fall in urine output (from above 2000ml/24hr to below 1500ml/24hr in all patients, and below 1000ml/24hr in 4 patients). One patient required temporary haemodialysis.

Patients were treated with PP and methyl prednisolone, 1 received IVIg and rituximab. Improvement in urine output and creatinine were established at a median of 9 days after resynthesis of DSA. DSA were still at high levels in 4 cases when graft function improved. There was then a variable rate of decline in DSA levels that was not associated with graft function.

Neither the specificity of DSA for Class I or Class 2, nor the strength of the XM before PP, predicted the clinical course of these patients.

In summary, resynthesis of DSA occurred in the first 10 days after HLA incompatible transplantation in the majority of cases, and was associated with a fall in urine output and rise in serum creatinine. Both accommodation by the graft and modulation of antibody synthesis were observed.

P82

Comparison Of Laparoscopic Versus Hand-Assisted Live Donor Nephrectomy

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Background: Hand- assisted laparoscopic nephrectomy is a bridge between laparoscopic and open techniques with limited information regarding the pro and cons of each technique. The aim of the present study was to compare hand-assisted laparoscopic live donor nephrectomy to the classic laparoscopic method, using meta-analytical techniques.

Methods: A literature search was performed for studies comparing hand-assisted laparoscopy to classic laparoscopy for live kidney donation between 1999 and 2005. The following end points were evaluated: operative time, warm ischaemia time, length of hospital stay, intra-operative adverse events, and donor and recipient post-operative complications.

Results: Eleven comparative studies matched the selection criteria, reporting on 423 patients, of whom 228 (54%) had hand-assisted laparoscopic nephrectomy and 195 (46%) had the classic laparoscopic technique. Conversion to open surgery was 2.63% in the hand-assist group and 4.10% in the laparoscopic group, $p=0.35$. Total operative and warm ischaemic times were significantly shorter for hand-assisted laparoscopy by 39.69 minutes ($p<0.001$) and 1.5 minutes ($p<0.001$) respectively. The intra-operative blood loss was less for the hand-assisted laparoscopy group by 29.41 mls ($p=0.02$), although intra- and post-operative complications, including delayed graft function and primary non-function, were similar between the hand assisted and laparoscopic groups (3.95% vs 6.67%, $p=0.33$ and 6.14% vs 10.26%, $p=0.30$ respectively).

Conclusion: In live donors, hand-assisted laparoscopic nephrectomy appeared to have the same donor and recipient complication rate with standard laparoscopy but offered substantial advantages in terms of shortened operative and warm ischaemia time as well as decreased intra-operative bleeding.

P83

Review Of Outcome In Single Centre Of Modified Use Of Dacluzimab Compared To Basiliximab In Renal Transplant Patients

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Introduction

The use of anti-IL-2 receptor antibodies for the prevention of acute rejection is common practice. The protocol in our centre based on a previous trial using Dacluzimab in non heart beating patients, involves the administration of a single dose at induction followed by further doses at 2 weekly intervals if indicated by delayed graft function. We report the presence of acute rejection, infection and delayed graft function in patients administered standard dose baxiliximab or daclizumab (modified regime) to determine if this resulted in an increase in adverse clinical outcomes.

Methods

Data was collected prospectively on clinical outcome on all patients in a single centre following treatment protocol. All patients who underwent live related and non heart beating were routinely given IL-2 receptor antibodies. The IL2 antibody used was allocated on an alternate month basis from Jan 2005.

Results

In the period January 2005- October 2005 55 patients were treated with IL2 receptor antibodies. In the case of Daclizumab the majority had double dose at induction and in no case was the full five doses according to license administered.

Conclusion

The outcome for significant adverse outcomes despite the use of daclizumab in an unlicensed dose appears to be comparable to baxiliximab at the recommended dose. The high incidence of delayed graft function in the dacluzimab group probably reflects sample size.

D	Dax	Bax	P Values
Number (n)	28	27	
Delayed function	10	5	0.023
Significant infections	4	5	0.4
Biopsies	8	12	0.13
Acute rejection	5	4	0.5

P84

Hand-Assisted Laparoscopic Donor Nephrectomy: Results from First 40 Cases

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Background:

Live kidney donation is increasingly required to meet the demand for renal transplantation. To reduce the morbidity associated with traditional open donor nephrectomy (ODN) a shift towards minimally invasive donor procedures has occurred. In this presentation we compare our experience with hand-assisted laparoscopic donor nephrectomy (HALDN) and ODN.

Methods:

Data were prospectively collected from 40 HALDNs and outcomes compared against 35 historic ODNs. All procedures were performed by the same surgeon (ARR). HALDN was introduced in early 2004 and offered to all donors thereafter irrespective of factors such as body habitus and vascular anatomy. SPSS package was used to determine t test and chi square test ($p < 0.05$ was considered significant).

Results:

All ODNs were left sided. One right and 39 left HALDNs were performed. Right HALDN was performed due to the presence of a left-sided inferior vena cava. Both groups were matched for mean age (45.9 vs. 44.2 years), weight (76.8 vs. 72.3kg) and preoperative haemoglobin (14.2 vs. 14.3g/dL) and creatinine (91.6 vs. 90 μ mol/L). Between the groups, there was no statistical difference in operative time (90 vs. 105 minutes), haemoglobin drop (3.30 vs. 3.09g/dL) or delayed graft function (11.5% and 14.3%). However, the mean hospital stay was 2.6 days shorter for HALDN ($p < 0.05$), which was also associated with less pain, faster return to normal activity and higher levels of patient satisfaction. This has led to an increase in donors presenting to the programme.

Conclusion:

HALDN is as effective as ODN in providing good allograft outcomes but has the benefits of shorter hospital stay and more rapid return to normal. HALDN is applicable to most donors, makes donation more attractive and helps promote living donor transplantation.

Friday 31 March

Moderated Poster Session

Live Donation

P85

Radiological Evaluation Of Donor Anatomy Prior To Laparoscopic Nephrectomy

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Accurate Radiological Evaluation Of Donor's Arterial And Venous Anatomy Is Critical In Laparoscopic Nephrectomy. Anatomical Evaluation May Be Achieved By Arteriogram, Mri Angiogram Or Ct Angiogram.

In This Analysis We Describe The Anatomical Variations Reported In A 100 Ct Angiogram And Compare It To Operative Findings.

All Potential Donors Had Ct Angiogram Combined With 3 Dimensional Post-Processing Of Images. The First 42 Scans Were Done On A Single Slice Scanner And Subsequent Scans On A Multi-Slice Scanner. One Consultant Radiologist Reported All The Scans. Prehilar Branching Was Documented In All Cases And Measured From The Aortic Margin On The Left And From The Aortic Margin And Ivc Margin On The Right. Only Prehilar Branching Within 2 Cm Of The Aorta On The Left And 4 Cm On The Right Were Analysed.

Single Renal Artery And Vein Were Reported In 42% Of Donors. Multiple Arteries Were Reported In Both Kidneys In 7% Of Cases; Multiple Arteries Were More Common In Left Kidney Compared To Right Kidney (18% Vs. 14%, Respectively). Prehilar Branching Was Seen In Both Kidneys In 30% Of Cases. Again They Were More Common In The Left Renal Artery Compared To The Right (39% Vs. 31%).

Most Donors Had Single Renal Vein (92%). Duplicate Renal Vein In Both Kidneys Was Encountered In 1% Of Cases. There Was Similar Incidence Of Duplicate Left And Right Renal Veins (5%). Retroaortic Left Renal Vein Was Reported In 7% Of Cases And Left Circumaortic Vein Was Reported In One Donor.

At Surgery, Both Single- And Multi-Slice Scanners Were 100% Accurate In Detecting Venous Anatomy. Accuracy Of Single Slice Scanner In Detecting Accessory Arteries And Prehilar Branching Was Around 82% Compared With 100% Accuracy Noted With Multi-Slice Scanner.

In Conclusion, Spiral Ct Angiogram With Multi-Slice Detection Provides Greater Spatial Resolution And Increased Contrast Enhancement Of Renal Vessels And Therefore Images Produced Are More Accurate. It Has 100% Correlation With Surgical Findings.

Mri Has The Advantages Of No Ionising Radiation And No Need For Iodinated Contrast. However, Ct Is Quicker To Perform And Has Higher Spatial Resolution. Compared With Angiography, It Performed As An Outpatient Procedure And Is Non-Invasive.

P86

Ten Year Single Centre Experience Of Pre-Emptive Living Donor Kidney Transplantation

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Pre-Emptive Kidney Transplantation, Prior To The Recipient Starting Dialysis, Avoids The Need For Expensive, Invasive And Potentially Hazardous Interventions Associated With Dialysis, And May Also Reduce The Cardiovascular Risk Associated With End-Stage Renal Failure. Pre-Emptive Transplantation Is An Especially Attractive Option If A Suitable Living Kidney Donor Is Available. We Report Ten Years Of Experience In A Single Large Renal Transplant Unit Serving A Population Of 2.2 Million. Between April 1995 And March 2005 We Performed 146 Living Kidney Donor Transplants. Of These, 44 (30%) Were Pre-Emptive. In Paediatric Recipients The Proportion Of Pre-Emptive Transplants Was Even Higher (8 Of 19, 42%). The Proportion Of Transplants That Were Pre-Emptive Has Risen Steadily During This Ten Year Period, But Only In Living Donor Operations: For Deceased Donors The Pre-Emptive Rate In Our Unit Stayed Approximately Constant At Around 5-8%. 36 Of The 44 Patients Receiving Pre-Emptive Transplants Were Not On The National Waiting List, Allowing Other Patients More Equitable Access To The Limited Pool Of Deceased Organ Donors. Graft Survival At One Year In Those Patients Transplanted Pre-Emptively Was 93% And In Non-Pre-Emptive It Was 98 % (Overall Our Unit's Figure Is 95 % (Same As The National Average). Mean Creatinine At One Year Was 138 Mmol/L, Range 83-232 For Pre-Emptive Living Donor Transplants; 136 Mmol/L, Range 67-202 For Non-Pre-Emptive. Three Early Graft Failures Occurred In The Pre-Emptive Group, All Due To Acute Rejection: One Of These Recipients Admitted Non-Adherence To Immunosuppressive Therapy.

We Consider That Pre-Emptive Living Donor Kidney Transplantation Should Be Increasingly Utilised Because Of The Theoretical, Practical And Economic Advantages. The Outcomes Are Comparable To Those Of Transplants To Patients Already On Dialysis, And There Is No Threat To Equitable Access To Deceased Donors For Those Patients Already On Dialysis.

P87

Laparoscopic Donor Nephrectomy For Paediatric Recipients

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Introduction

Although Laparoscopic Donation Has Become The Method Of Choice In Living Donor Transplantation, Few Data Exist About Its Efficacy In Paediatric Recipients. A Recent Study Of 34 Patients (Singer Am J T 2005) Found No Difference In Graft Outcomes When Compared With Open Techniques, But Previous Data From Unos Has Suggested A Higher Incidence Of Rejection In Laparoscopically Procured Kidneys.

Methods

We Examined Recipient Outcome In Paediatric Patients With Laparoscopic Living Donor Kidneys At Guys And Great Ormond Street Hospitals.

Of 71 Laparoscopic Donor Operations, 22 Were For Paediatric Recipients. The Hand-Assisted Laparoscopic Technique Was Used In All Cases.

Donor Outcome

Median Length Of Stay For The Donor Was 4 Days (2-5). Mean Operating Time Was 215 (S.E. 8) Minutes, Mean Warm Ischaemic Time Was 205 (S.E. 40) Seconds. One Patient Was Converted To Open Surgery Due To Bleeding, But Did Not Require Transfusion. One Patient Had A Wound Infection And Subsequent Incisional Hernia And One Patient Complained Of Transient Testicular Engorgement; There Were No Other Donor Complications.

Recipient Outcome

Median Recipient Age Was 8 (2-17). One Patient Had Delayed Graft Function; All Other Grafts Functioned Immediately. One Patient Developed Ptld And Grade 1 Cellular Rejection But Has Maintained Graft Function At 1 Year. Two Other Patients Also Had Mild Rejection Requiring Steroid Treatment. Thus, At A Mean Follow-Up Of 9 Months There Is 100% Graft Survival And A 14% Incidence Of Rejection.

Conclusion

Our Experience Of Laparoscopic Kidney Donation For Paediatric Recipients Suggests That Recipient Outcome Is Excellent. Laparoscopic Donation Remains The Optimum Method Of Kidney Procurement.

P88

Establishing A Living Renal Transplant Program In Sudan And Nigeri, Portsmouth Initiative
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Introduction: Renal Transplantation Is The Gold Standard, As A Renal Replacement Therapy For End Stage Renal Failure, In View Of The Long-Term Economic Benefit Over Dialysis And The Improved Quality Of Life. Approximately I Million Patients Worldwide Are Eligible For Renal Transplant; Where As Only 91 Thousand Patients Are Transplanted Each Year. Out Of 198 Countries, Renal Transplantation Is Performed Only In 91. Developing Countries Are Least Privileged

Methods: Transplant Surgeon, Nephrologist, Anaesthetist, Transplant Nurses, Renal Theatre Scrub Nurse And Tissue Typing Clinician From Portsmouth And Southampton Embarked On Multiple Journeys To Sudan And Nigeria To Perform And Train Local Medical Personnel On Live Renal Transplantation. 162 Renal Transplant Were Performed In Sudan And 19 In Nigeria In The Past 46 Months. Tissue Typing, Cytotoxic Cross Math, Virology Screening Including Hiv, Donor Renal Angiographies As Well As Donor And Recipients Selection Has Been Worked Up By The Local Surgeons And Nephrologests In Consultation With Portsmouth Team Over The Internet. Standard Immunosupretion (Cyclosporine, Prednisolone And Azathioprine) Was Used, As Well As Prograf And Mmf When Indicated. Malaria Prophylaxis Was Given To All Recipients. Tb Prophylaxis Was Given To People With Past Infection Only. 14 Transplants Were Performed Under Spinal Anaesthesia. Results: Donor Survival Was 100% In Both Centres With No Major Complications. One-Year Recipients Survival Was 90.2% In Sudan And 91.3% In Nigeria. One-Year Graft Survival Was 92.4% In Sudan And 93.1% In Nigeria. 3 Transplant Centres Has Been Established In Sudan And One In Nigeria They Are Now Up And Running And Performing Transplant Independently.

Conclusion: It Is Feasible And Safe To Establish Renal Transplant Centres In Developing Countries. Help From Centres In The Develop World Is Needed To Establish Much Needed Such Centres. Bts May Have A Role To Play In Co-Ordinating Such Efforts For Inclusion Of More Developing Countries.

P89

Attitudes Of Medical And Nursing Staff Regarding Ethical Issues In Live Kidney Donation

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The development and acceptance of live donor kidney transplantation as the treatment of choice for end stage renal failure have intensified the debate regarding the ethical issues in live kidney donation.

We aimed to survey the views of the medical and nursing staff of the West London Renal and Transplant Centre on ethical issues in live kidney donation when the donor and the recipient are blood related relatives (live related donation), non-blood related relatives or friends (live unrelated donation) and strangers (non-directed donation). The participants were invited to complete an anonymous and confidential questionnaire.

108 members of staff completed the questionnaire (46% response). Live related, unrelated and non-directed donation were considered as ethically acceptable by 100%, 92% and 48% of the participants respectively. 92%, 82% and 12% of the participants were willing, if needed, to donate a kidney to a blood related relative, a non-blood related relative or friend and a stranger respectively while, if they had renal failure, 92%, 85% and 44% were prepared to accept a kidney from each of those three donor categories respectively. For live related and unrelated transplantation, 34% of participants thought that the donor should have no financial reward, 56% thought that the donor should be compensated for travel, accommodation or loss of work-days expenses and 8% thought that there should be a direct financial reward for the donor. For non-directed donation, 32%, 50% and 18% were in support of no financial reward, compensation reward and direct financial reward respectively.

Our study demonstrated that live related and unrelated kidney donation are widely considered as ethically acceptable procedures and that non-directed donation is gaining support since almost half of the participants believed that it is ethically acceptable. Interestingly, those who were prepared to accept a kidney from a stranger were about four times more compared to those who were willing to donate a kidney to a stranger. The majority of the participants were against direct financial rewards for the donors. However, a not negligible minority was prepared to accept the idea of direct financial reward for the donor (especially in the case of non-directed donation) providing that this is being done not in an "open organ market" but under tight government regulations and monitoring.

P90

Comparison Of Techniques Of Vascular Control In Laparoscopic Donor Nephrectomy – The Leicester Experience

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Introduction

Laparoscopic donor nephrectomy (LDN) has the potential to overcome some of the disincentives to live kidney donation but there have been concerns about the safety of the operation and the quality of the retrieved kidney. One of the challenges of LDN is to obtain maximum length of the vessels for transplantation of the kidney. The objective of this study was to compare the safety and vascular lengths using a stapling device, metal clips and polymer clips (Hem-o-lok).

Patients and Methods

We compared the vascular length in kidneys of 106 patients of LDN who had vascular control with either a stapling device or hem-o-lok clips for renal vein and a stapling device, endoclips or hem-o-lok clips for the artery. The length was measured after perfusing the kidney.

Results

106 patients underwent LDN (right = 25, left = 81). The length of renal vein was compared in the stapling device (n= 74, mean = 36mms; range 15-60) and hem-o-lok (n=23, mean = 37mms; range 15-55) group. This was not significant (p=0.46).

The renal artery length in the stapling group (n=56) was 30 ± 8 mms, in hem-o-lok group (n=24) 34 ± 9 mms and in the endoclip group (n=20) 35 ± 6 mms. Statistical analysis with unpaired t test, in the stapler vs hem-o-lok group was very significant (p=0.03). However, in the endoclip and hem-o-lok group it was not significant (p=0.85). In 1 patient the stapler did not fire properly. In 1 another case the endoclips slipped from the artery and the surgery had to be converted to open to control haemorrhage.

Conclusions

Our experience has shown that hem-o-lok effectively lengthens renal artery length and is safer to use in patients undergoing LDN. However, we did not find a significant difference in renal vein length in the two methods.

Friday 31 March

Moderated Poster Session

Ischaemic Reperfusion Injury

P91

Senescence Associated Gene Expression Is Correlated With Cold Ischemic Damage, Donor Sex And Predicts The Development Of Late Graft Dysfunction In Human Renal Allografts

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Cellular stresses at the time of transplantation can predispose to post transplant graft dysfunction. Typically, ischemia-reperfusion injury can super impose upon normal ageing processes in the graft and accelerate them, thus impacting upon organ function as a direct consequence. Assessment of these effects at the time of transplantation is problematic. We have investigated the expression of senescence associated genes involved in cellular damage and stress responses, in pre transplant human renal biopsies from donors ranging from 9 to 78 years old. We have correlated the expression of these genes with chronological age, cold ischemic time and post transplant creatine clearance at 6 and 12 months as a measure of graft function.

Significantly, we observed an increase in p16 with increasing chronological age in time zero biopsies ($p < 0.007$), but no association was observed between p16 expression and age in post perfusion biopsies. A significant difference in expression was observed between p16 expression and cold ischemic time ($p < 0.046$). The expression of the telomeric protein hPOT 1 was highly significant with respect to the subsequent development of late graft dysfunction and the sex of the donor ($p < 0.009$). The expression of this gene was significantly elevated in late graft dysfunction versus peri-transplant biopsies ($p < 0.002$). A sex related difference in expression was also observed for the mitotic checkpoint regulator SIRT 2 ($p < 0.046$) in samples from kidneys undergoing late graft dysfunction. The DNA damage repair gene XRCC5 and SIRT 2 showed a trend correlated with creatine clearance at six months post transplant, indicative of extant ischemic cell damage and loss. In total, these data indicate that accelerated senescence as a result of peri-transplant stress, affects graft function and predisposes to graft loss.

Our observations provide important pre transplant prognostic indicators for renal allografts and indicate the potential for novel interventions.

Homozygous But Not Heterozygous Deletion Of HO-1 Increases Susceptibility To Hepatic Ischaemia Reperfusion Injury

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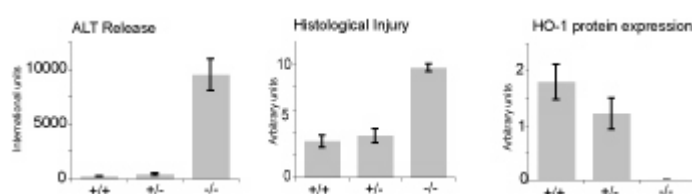
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BACKGROUND: Previous data using pharmacological up or down regulation of HO-1 has demonstrated protection or increased susceptibility to IRI respectively. Pharmacological manipulations of the HO-1 system are limited by non-specific effects upon parallel enzyme systems for example iNOS.

METHODS: HO-1 gene deleted animals were bred from heterozygotes imported from Birmingham Alabama. Littermate +/+, +/-, -/- animals underwent isoflurane anaesthesia, laparotomy, and selective occlusion of the vascular pedicle to the hepatic left lobe, followed by recovery and cull at 24 hours. Blood was taken for ALT, and separate left and right lobe liver tissue samples were taken for Western blot and histology.

RESULTS: Preliminary experiments established that +/+ littermates tolerated a maximum of 40 minutes lobar ischaemia without substantial injury (n=6, ALT 214 +/- 28, histological injury 3.2 +/- 0.54). There were no deaths in HO-1 +/+ or HO-1 +/- groups. HO-1 +/- animals tolerated the insult with no significant difference to wildtypes (n=6, ALT 403 +/-99 p=.095, histological injury 3.7 +/-0.61, p=0.556). Two of five HO-1 -/- animals died following insult, and the survivors were severely injured compared to +/+ or +/- littermates (ALT 9515 +/- 1437 p=0.0001, histological injury 9.3 +/- 0.33 p=0.0001). HO-1 protein was absent from the HO-1 -/- group. HO-1 expression did not differ significantly between HO-1 +/- and HO-1 +/+ animals (p= 0.683).

CONCLUSION: HO-1 -/- animals are more susceptible to ischaemia reperfusion injury than wildtype littermate controls in terms of mortality, ALT release and histological injury. We were unable to detect a difference in the susceptibility of heterozygous animals compared to wildtypes, reflecting similar expressions of HO-1 protein.



P93

Peptide Inhibition Of Heparan Sulphate (HS) - Chemokine Interaction: A Potential Molecular Target To Ameliorate Renal Ischaemia / Reperfusion (I/R) Injury

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Introduction

Leukocyte infiltration is a characteristic feature of an inflammatory process triggered by I/R injury. Chemokines (chemoattractant cytokines), are the primary motivators for the vectorial recruitment of specific leukocyte populations from the circulation. Association of chemokines with HS enhances its biological activity and facilitates to form chemotactic gradients along the endothelial surface, providing directional cues for migrating leukocytes. This interaction between chemokines and HS are ionic in nature, basic amino acids within the protein tertiary structure interact with the anionic sulphate groups along the HS polymer. We propose that blocking HS - chemokine interactions may prove a more effective molecular target to ameliorate I/R injury

Aim

To design a peptide that mimics the putative HS binding sites of human CC chemokine RANTES (CCL5) to inhibit the formation of HS - chemokine complexes.

Methods

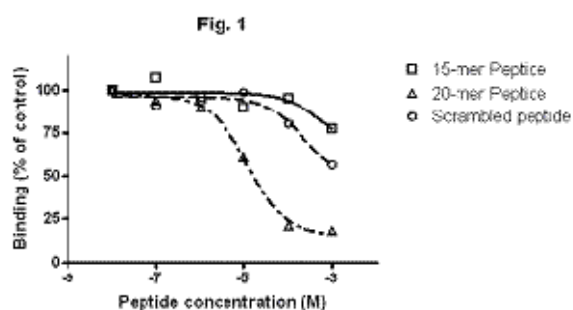
A custom synthesised 15-mer peptide which incorporates the primary high affinity basic cluster (⁴⁴RKNR⁴⁷) was tested initially. Latter a 20-mer peptide was generated to include the secondary low affinity basic cluster (⁵⁵KKWVR⁵⁹) to the 15-mer peptide. The effects of these peptides were assessed in vitro by Ligand binding competitive assay using a [¹²⁵I] labelled RANTES. In-order to assess the specificity of binding sites a scrambled version of a site specific 20-mer peptide was also studied. Currently a third peptide is being generated to include only the secondary low affinity binding site.

Results

Significantly less radiolabelled RANTES bound to heparin with 20-mer peptide as compared to 15-mer peptide (see fig. 1). The secondary low affinity binding cluster effectively reduces the residual binding activity of RANTES. Scrambled sequence confirms the binding activity were sequence specific.

Conclusion

Our preliminary results indicate that peptide containing both high and low affinity basic clusters effectively competed against formation of HS – RANTES complexes. Functional assays and in vivo studies are ongoing.



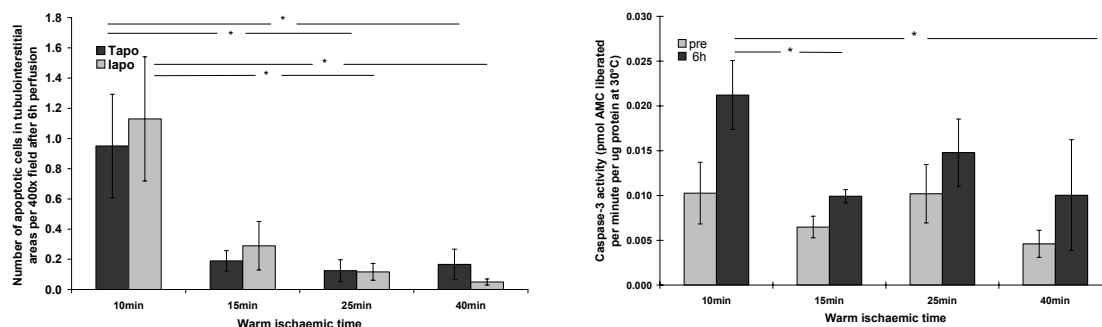
Apoptosis and Caspase-3 in Prediction of Viability of Isolated Kidneys after Different Warm Ischaemia Time and Six-hour Normothermic Reperfusion

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Ischaemia/reperfusion (I/R) injury is important in kidney transplantation. Prolonged warm ischaemia (WI) occurs in non-heart-beating donor (NHBD) kidneys and is one of the major causes of delayed graft function and primary non-function. The loss of graft cells may be due to apoptosis and/or necrosis depending upon the severity and duration of injury. Apoptosis is a programmed cell death and consumes energy. Caspase-3 plays a central role in apoptosis, although it has pleiotropic functions. However, the mechanisms of I/R injury are far from clear and there is no satisfactory method to identify the viability of NHBD kidneys. In this study, we evaluated the value of apoptosis and caspase-3 in an ex vivo renal I/R injury model. Porcine kidneys were subjected to 15, 25 and 40 minutes WI (n=6), while control kidneys had approximately 10 minutes WI. After 2-hour cold storage, kidneys were perfused with oxygenated autologous blood containing 1000 mmol/L of creatinine on an isolated organ perfusion system at 37°C. Physiological and biochemical parameters were measured throughout 6-hour perfusion period. After 6-hour perfusion, the number of apoptotic cells (in situ end labelling fragmented DNA) in both tubular and interstitial areas was peaked at 10 minutes, decreased with WI time and significantly lowered at 25 and 40 minutes. Caspase-3 activity (enzyme cleavage assay) at the end of 6-hour perfusion was also peaked at 10 minutes, gradually decreased in time and particularly significant at 15 and 40 minutes. At all WI times, there was a trend for increased caspase-3 activity at the end of 6-hour perfusion compared with pre-perfusion and their pattern of change was consistent. Further more, tubular and interstitial apoptosis was positively correlated with renal function (GFR, $r=0.689$ or 0.845 respectively, both $p<0.01$). Caspase-3 activity was closely associated with not only GFR ($r=0.498$, $p<0.05$), but also renal blood flow ($r=0.695$, $p<0.01$) and renal vascular resistance ($r=0.448$, $p<0.05$). In conclusion, detecting the level of apoptosis and caspase-3 activity might be helpful to estimate the degree of ischaemic damage and effect of reperfusion, and subsequently predict the viability of NHBD kidneys and renal function.

Fig.A Fig.B



P95

Thromboxane A₂ Inhibition In Experimental Liver Ischaemia/ Reperfusion Injury

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Primary non-function accounts for up to 10% of liver graft failure and disturbance in the microcirculation is thought to be one of the major mechanisms implicated in ischaemia-reperfusion injury (I/RI). A cascade of events initiated by the activation of phospholipases leads to the production of cyclo-oxygenases and activation of thromboxane A₂ (TXA₂), ultimately producing platelet aggregation and microthrombi. We investigated the addition of aspirin and a more specific TXA₂ inhibitor to Leeds Solution (LS), an improved, phosphate buffered sucrose based perfusion fluid under development in our centre, in order to protect donor livers from I/RI.

Rat livers were flushed via the aorta and portal vein in vivo with either LS, with or without a form of TXA₂ inhibition, i.e. aspirin (targeting COX inhibition), or Piracetam (targeting TXA₂ receptor and synthetase inhibition) in varying concentrations (n=5/group). The aim was to augment platelet disaggregation and vasodilation and enhance this further with TXA₂ inhibition to permit sparing of prostacyclin. After 24hrs cold preservation, livers were reperfused on an *ex-vivo* isolated circuit for 2hrs at 37°C to measure functional parameters (bile flow and serum enzymes). Tissues taken pre-preservation, post preservation and post reperfusion were analysed for histology.

The data shows that addition of aspirin or piracetam produced significant (P<0.05) dose-dependent modulation of lactate dehydrogenase (LDH) compared to livers perfused with LS lacking TXA₂ inhibition. Elevation of LDH was indicative of irreversible hepatocellular damage. Tissue damage was also evident in histology following 24hr preservation where portal vein and sinusoids were filled with proteinous material with loss of sinusoidal spaces and bile duct constriction in the absence of TXA₂ inhibition. Although bile flow and liver enzymes (AST/ALT) were comparable upon reperfusion between LS containing aspirin and variable concentrations of piracetam, the maintenance of liver architecture was most improved with LS containing 0.38mM/L aspirin.

In conclusion, TXA₂ inhibition in a perfusion fluid during cold ischaemia may confer significant benefits in organ function upon reperfusion. The data suggest that there is clear clinical potential for LS containing aspirin to reduce primary non-function following liver ischaemia in transplantation.

Friday 31 March

Moderated Poster Session

Liver

P96

Does Laparoscopy And Intra-Operative Ultrasound (Ious) Have A Role In The Assessment Of Patients With End Stage Liver Disease(Esld) And Hepatocellular Carcinoma (Hcc) For Liver Transplantation(Lt)

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Background

Lt Is The Treatment Of Choice For Patients With Esld And Early Hcc Within The Milan Criteria. Routine Laparoscopy With Ious Has Been Used In Our Centre In All Patients With Hcc Being Considered For Transplantation, In Whom No Contraindication On Cross-Sectional Imaging (Ct, Mri Or Both) Could Be Identified.

Aim

Assess If Laparoscopy And Ious Had Any Impact On The Selection Of Patients With Esld And Hcc Being Considered For Transplantation.

Methods

The Clinical Notes And Transplant Database Details Of All Patients With Esld And Hcc, Being Assessed For Lt, From Jan 2000 To April 2005 Were Retrospectively Reviewed. The Data Collected Included: Findings On Cross-Sectional Imaging, Findings At Laparoscopy And Ious, Findings At Transplantation And Pathological Details From The Explanted Liver.

Results

Twenty-Five Patients With Esld And Hcc Underwent Assessment For Lt. 8 Patients Were Deemed Un-Transplantable On Cross-Sectional Imaging Alone. 17 Patients Met Transplant Criteria. 16 Patients Underwent Laparoscopy And Ious. One Patient Had Undergone A Previous Segmental Hepatectomy And Laparoscopy Was Not Technically Feasible. At Laparoscopy All 16 Patients Were Found To Be Free From Extra-Hepatic Disease And Major Vascular Involvement. All 16 Patients Went Forward For Transplantation. The Median Waiting Time Was 88 Days. One Patient Was Found To Have Extra-Hepatic Disease At Time Of Transplantation And The Procedure Was Abandoned. One Patient Was Found To Have Lesser Curvature Lymphadenopathy Which Was Confirmed Post Operatively To Be Positive For Metastatic Disease. Two Patients Had Major Vascular Involvement Found In The Explanted Liver. All These Findings Were 'Missed' On Pre-Transplant Imaging And At Laparoscopy With Ious.

Conclusions

In 25% Of The Patients Undergoing Lt For Hcc, Laparoscopy And Ious Failed To Identify Features That Could Have Changed Patient Management. As An Additional Investigation It Did Not Improve Staging Or Alter The Management Of Patients With Hcc Being Assessed For Lt. Since July 2005 The Newcastle Liver Transplant Unit Has Stopped Routine Laparoscopic Assessment Of These Patients Prior To Listing. The Decision To Laparoscope Patients Is Now Being Taken On A Case-By-Case Basis. We Plan To Re-Audit The New Policy In The Future.

P97

Psc: Edinburgh Liver Transplant Experience 1992 - 2005

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Introduction: Primary Sclerosing Cholangitis (Psc) Is A Chronic Progressive Cholestatic Liver Disease Of Unknown Aetiology. It Is Characterised By Inflammation, Strictureing And Fibrosis Of The Biliary Tree. 70-80% Of Patients Have Concomitant Inflammatory Bowel Disease (Ibd), Usually Ulcerative Colitis (Uc). The Median Survival Is 12 Years From Diagnosis. Liver Transplantation Is Performed In Patients With End Stage Liver Disease And Has A Reported 5 Year Survival Of 85%.

Methods: 55 Patients (37m) That Underwent Liver Transplantation For Psc Were Identified. Demographic Data, Disease Characteristics, Treatment Interventions & Survival Post Transplant Was Collected. Kaplan-Meier Analysis, Log Rank Test & Multiple Logistic Regression Was Used To Identify Independent Factors Associated With Disease Recurrence.

Results: 61 Liver Transplants Were Conducted For 55 Patients In The Study Period. The Median Follow-Up Time Was 4.89 Years During Which 7 Patients Died. Patient And Graft Survival At 1, 5 And 10 Years Was 94%, 86%, 79% And 89%, 82%, 74% Respectively. 12 Patients Had Psc Recurrence With A Median Time To Recurrence Of 45 Months. Cumulative Psc Recurrence Rates At 1, 5 And 10 Years Were 2%, 34% And 45% Respectively. Multivariate Analysis Identified Pre-Transplant Therapy Of Cyclical Antibiotics (P=0.04) And Pre-Olt Uc (P=0.03) As Independent Predictors Of Recurrence. 77% Of Patients Had Concomitant Ibd (33uc / 7cd) At Time Of Liver Transplantation. 9 Patients Had Total Colectomies Prior To Transplant And 10 (18%) Had Colectomies Post Transplant (3 Neoplastic Disease). Of Those That Had Pre-Transplant Colectomies None Developed Recurrence Of Psc (P=0.14, Log Rank Test).

Conclusion: Liver Transplantation Is An Effective Treatment For Psc With A 5 Year Survival Rate Of 86%. Psc Recurrence Developed In 21.8% Of Patients With A 45% Cumulative Risk Of Developing Psc At 10 Years. Pre-Transplant Therapy With Cyclical Antibiotics And Uc Are Independent Predictors Of Psc Recurrence. Pre-Olt Total Colectomy May Protect Against Recurrent Psc After Successful Liver Transplantation.

P98

Risk Factors For Biliary Complications After Liver Transplantation

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Introduction: Biliary complications remain a major cause of morbidity and mortality in patients following liver transplantation (OLT). We aimed to identify possible risk factors predisposing to biliary complications after OLT with duct-to-duct biliary reconstruction.

Materials and Methods: Five years of prospectively collected donor and recipient data between April 1999 and April 2004 were retrospectively reviewed. The presence of a biliary complications, donor and recipient age, cold ischaemic time (CIT), hepatic artery thrombosis (HAT), whether the donor was non-heart beating (NHBD) and graft steatosis (>30%) was assessed. Results were compared to a control group of OLT patients without biliary complications.

Results: 173 OLT recipients were identified. Biliary complications occurred in 28 patients (16.2%), of which 12 were leaks, 15 biliary strictures and 1 non-anastomotic intra-hepatic stricture. Mortality following biliary complications was 11%, compared to 6% in the control group. The risk factors considered are shown in the table below.

Conclusion: Biliary complications still remain a persistent problem in OLT. Analysis of risk factors has identified HAT and steatosis as predisposing factors. With greater experience, NHBD livers may also prove to be at risk of biliary complications.

Risk Factor	Biliary Complications (n=28)	Controls (n=145)	OR	p=
NHBD	2 (7%)	3 (2.1%)	3.64	0.190
CIT (hr:min)	10.44 ± 2.58	10.51 ± 2.55		ns
Recipient age (years)	47.9 ± 14.7	48.7 ± 14.7		ns
Donor age (years)	46.7 ± 13.4	44.0 ± 14.0		ns
Graft steatosis	10 (36%)	27 (19%)	2.33	0.078
Inotrope usage	27 (96%)	116 (84%)	4.57	0.130
HAT	5 (18%)	0 (0%)		<0.001

Mean ± standard deviation. OR: odds ratio.

P99

Our Experience of Liver Transplantation of patients with Budd-Chiari Syndrome

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Background:

Budd-Chiari Syndrome (BCS) occurs as a result of obstruction of venous outflow at any level from the small hepatic veins to the junction of the inferior vena cava with the right atrium and occurs in 1/100,000 of the general population worldwide. The most common presentation is with ascites, but can range from fulminant hepatic failure to asymptomatic forms. The traditional classification of BCS – as fulminant, acute or chronic – is not prognostically useful. This makes assessing the benefit of therapy difficult especially as there is no evidence from randomized studies.

Methods:

We reviewed our experience of 9 adult patients who presented to our liver unit from January 1999 to August 2005 and were diagnosed with BCS and then underwent Orthotopic Liver Transplantation (OLT). We assessed their short-term and long-term outcomes, including specific complications with regards to their interventions.

Results:

Ascites was the commonest clinical feature on presentation (7 patients). At presentation predisposing factors included, Benign Myelodysplasia, Myeloproliferative disease, Pregnancy, and idiopathic factors.

Five of the nine patients were initially managed medically (e.g venoplasty, stent, or TIPSS) and the remaining four required immediate liver transplants. The median survival is 35 months (range 1-71) with 2 patients developing post operative complications (one patient developed a wound infection and the second required a laparotomy for bleeding). BCS eventually reoccurred in 2 cases post-OLT and this has been managed satisfactorily with non operative management (Venoplasty in one case and TIPSS in the other). No graft failures and two deaths have been reported, one due to peritonitis (2 and half years after transplant) and the second two days after transplant due to multi-organ failure.

Conclusion:

Liver transplantation for BCS provides good long-term survival with acceptable morbidity. Patients with BCS should be managed in a centre with access to all modalities of therapy including medical, interventional radiological techniques and surgical intervention because improvement or progression of the liver disease is unpredictable and worsening liver failure can occur.

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C4d Immunohistochemistry In Liver Allografts

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C4d immunopositivity helps recognition of humoral rejection in renal allografts, but is little studied in liver allografts. We asked if C4d positivity could be used to recognise and study humoral rejection in dysfunctional liver allografts. In a pilot evaluation, 2 of 7 biopsies selected from 129 as suspicious on morphology for humoral rejection showed C4d positivity, so we were encouraged to continue.

Methods. We retrospectively evaluated monoclonal anti-C4d immunopositivity in selected categories of biopsies from first liver allografts: pre-perfusion, primary non-function (PNF), protocol early biopsies, lymphocytotoxic crossmatch-positive patients, moderate/severe early acute rejection, centrilobular necroinflammation (CLNI), biliary obstruction and chronic rejection.

Results. C4d staining was reliable in needle biopsies, but more capricious in sub-optimally fixed explants. Three patterns of staining were encountered. Staining was counted positive when there was at least moderately strong staining of portal vascular plexus walls in 4 portal areas, or in 25% of lobular sinusoid walls. Cytoplasmic staining of isolated or zone 3 hepatocytes was considered non-specific related to necrosis and not counted positive.

C4d positivity was not encountered in 10 preperfusion or 15 consecutive early protocol biopsies. However, 3 of 12 early protocol biopsies from crossmatch-positive patients were C4d-positive. In allograft dysfunction, C4d was positive in 2 of 16 early acute rejection, 3 of 14 CLNI, and 3 of 11 biliary obstruction, and 2 of 13 chronic rejection explants. One PNF showed C4d positivity and morphology suggesting humoral rejection. Two patients in whom successive needle biopsies were evaluated showed persistent C4d positivity. Morphologic associations with C4d positivity resembled those reported in lymphocytotoxic crossmatch +ve patients.

Conclusion. C4d immunopositivity is uncommon in protocol-biopsied liver allografts. There is a weak positive correlation with patients having had a positive lymphocytotoxic crossmatch, and with some patterns of allograft dysfunction. Positivity manifests in the portal venular plexus or in lobular sinusoid walls. The specificity for humoral rejection and the practical utility of C4d immunostaining is not made clear by this study, although it is tempting to speculate that a small subgroup of individuals have humoral microvascular injury that contributes to allograft dysfunction.

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