THE RENAL ASSOCIATION
founded 1950

LIVERPOOL 2009

BTS British Transplantation Society

RA BTS Annual Conference

ACC, Liverpool

21 – 24 April 2009

ABSTRACT BOOK

Welcome to Liverpool!

As Presidents of the Renal Association and the British Transplantation Society respectively, we are delighted to welcome you to Liverpool to the joint RA BTS Annual Conference 2009.

We hope that the meeting will be both an educational and enjoyable four days in the company of your colleagues from the UK and our visitors from overseas.

Following our successful joint meeting in 2005, the two societies have once again joined forces to provide an exciting scientific programme for our respective communities.

The first day (Tuesday) is a Renal Association stand-alone day and the final day (Friday) a British Transplantation Society stand-alone day. Members of the respective societies are of course welcome (indeed encouraged) to attend either or both of these stand-alone days. The Wednesday and Thursday offer both joint and parallel sessions.

We are very grateful to the members of the Programme Committee for their tireless work in putting together what promises to be a stimulating and diverse programme and to the local organisers for all their inputs. We also thank our corporate partners and other industry stakeholders whose support makes our meeting possible. Please take time during the meeting to visit the trade exhibition and talk to the company representatives about their products.

Yours sincerely,

Peter Mathieson
President of the Renal Association

Peter Friend
President of the British Transplantation Society

RA BTS Conference – Scientific Programme

Tuesday 21 April – RA Standalone day

	Clinical Pathway	Scientific Pathway	Miscellaneous	BTS Pathway
09:00	**Registration and Exhibition Open** **Arrival tea and coffee available in the exhibition hall**			
10:00	**Raine Award** (Hall 1A) Chair: Prof Peter Mathieson **The Pathogenesis of Haemolytic Uraemic Syndrome –** Dr David Kavanagh *4 x best abstracts*			
11.30	**Moderated Poster Session** (Hall 2 Exhibition Hall)			
12:30	**Lunch & Exhibition**	**Commercialisation & The Biotechnology Industry** (Hall 1C) **Chair: Prof Bruce Hendry & Dr Julie Williams** Prof Chris Gregory Dr Alan Boyd Prof Nick Bames **Packed lunch will be provided in the meeting room.	**Lunch & Exhibition**	
13:30	**Chandos Lecture** (Hall 1A) **Chair: Dr Steve Harper & Dr Simon Satchell** Prof Dontscho Kerjaschki	**Free Radical Session** (Hall 1B) **Chair: Dr Jeremy Hughes & Dr John Haylor** Prof Malcolm Jackson	**IgA Nephropathy and CKD** **Chair: Dr Alice Smith & Dr Neeraj Dhaun** Dr Ian Roberts	

	5 x abstracts	Dr Joles Jones Dr Rana Rustom	*6 x abstracts*	
15:00	**5 minute room change break**			
15:05	**CPD – Bone and Mineral Disorders Sponsored by the DGH Nephrologists' Society** (Hall IA) **Chair: Dr Paul Rylance & Dr Phil Kalra** Dr Markus Ketteler Dr Smeeta Sinha Dr David Goldsmith Dr Daniel Zehnder	**Renal Science CPD** (Hall 1B) **Chair: Dr Fred Tam & Dr John Haylor** Prof Philip Wright Dr Robert Edwards Prof Visith Thongboonkered	**Proteinuric and Glomerular Disease** (Hall 1C) **Chair: Dr Gordon Bell & Dr David Kluth** Prof Nigel Brunskill *6 x abstracts*	**Registration & Exhibition Open**
16:30	**Coffee Break**			
17:00	**Dialysis** (Hall 1A) **Chair: Dr Chris McIntyre & Dr Pearl Pai** Prof Simon Davis *6 x abstracts*	**Young Renal Science Forum** (Hall 1B) **Chair: Dr Tim Johnson** Prof Bernhard Moser Co-Judge – Prof Alison Eddy *6 x abstracts*	**Renal Registry/Clinical Trial** (Hall 1C) **Chair: Dr Lorraine Harper & Prof Terry Feest** Dr Charlie Tomson Prof Colin Baigent	**Registration & Exhibition Open**
18:30	**Osman Lecture – Chair: Prof Peter Mathieson** (Hall 1A) Prof Andy Rees			
19:00	**Exhibition Close**			
19:45	**Coach Transfer to the Crowne Plaza – RA Conference Dinner**			

Wednesday 22 April – Joint Day

	Transplantation Pathway 1	Clinical Pathway	Science Pathway	Transplantation Pathway 2
08:00	**Registration & Exhibition open**			
08:30	**Breakfast Symposium sponsored by Astellas & Novartis** (Hall 1) astellas Leading Light for Life NOVARTIS	**RA AGM** (Hall 11)		
09:30	**De Wardener Lecture** (Hall 1) **Chair Dr Kevin Harris** Prof Tim Goodship			**BTS/BASL Symposium** (Hall 12) **Chair: Prof Derek Manas & Dr Mark Houston** Dr Nick Torpey Dr Kosh Agarwal Mr Murat Akyol Mr Raj Prasad Mr Neville Jamieson
10:00	**Chronic Allograft Nephropathy** (Hall 1) **Chair: Dr Chris Dudley & Prof Paul Brenchley** Prof Michael Mengel *6x abstracts*	**Paediatric Adult Interface** (Hall 11) **Chair: Dr Nick Webb & Dr Brian Judd** Dr Janet McDonagh *6 x abstracts*	**Mechanisms of tissue healing** (Hall 3) **Chair: Dr Jeremy Hughes & Prof John Kirby** Prof John Kirby Prof John Iredale Prof Paul Martin	
11:30	**Manipulation of the Endothelium in Transplantation and Vascular Disease (Hall 1)** **Chair: Mr John Forsythe** Dr Anthony Dorling			
12:00	**Lunch & Exhibition** (Hall 2 – Exhibition Hall)			
13:00	**Moderated Posters** (Hall 2 – Exhibition Hall)			

14:00	**Long term Outcomes** (Hall 1) **Chair: Prof Andrew Bradley & Dr James Medcalf** Dr Charlie Tomson Prof James Neuberger 3 x abstracts	**Vascular Access Symposium** (Hall 11) **Chair: Dr Mick Kumwenda & Mr Gavin Pettigrew** Dr Justin Mason Mr Ali Bakran Mr David Mitchell Dr Andrew Frankel	**Transplant Immunology/Basic Science** (Hall 3) **Chair: Ms Lorna Marson & Prof Steven Sacks** Dr Christian Hugo Prof Dontscho Kerjaschki 3 x abstracts	**BTS/BASL Symposium** (Hall 12) **Chair: Dr John O'Grady & Mr David Mayer** Dr Richard Baker Dr Alex Gimson Case Presentation: Dr Mark Hudson Dr Chas Newstaed Mr Steve White Dr John O'Grady Prof Derek Manas Dr Graham Alexander
15:30	**5 minute room change**			
15:35	**Marginal Donors** (Hall 1) **Chair: Dr Phil Mason & Prof David Talbot** Mr Chris Watson *3 x abstracts*	**Recurrent Disease** (Hall 11) **Chair: Dr Ian Roberts & Prof Neil Turner** Dr Jonathan Barratt Dr Lorraine Harper Prof Peter Mathieson	**Transplant Immunology/Basic Science** (Hall 3) **Chair - Prof Graham Lord & Dr Anthony Warrens** Prof Frederic Geissman *3 x abstracts*	
16:35	**Coffee Break** (Hall 2 Exhibition Hall)			
17:00	**Transplanting the Difficult Patient** (Hall 1) **Chair: Mr Chris Watson & Dr Chas Newstead** Dr Rob Higgins Mr John Forsythe Dr Nick Torpey	**Kidney Transplantation - Clinical 1** (Hall 11) **Chair - Dr Paul Cockwell & Mr Neil Parrott** Prof Neil Sheerin *6 x abstracts*	**Renal Science Abstracts** (Hall 3) **Chair - Dr Alan Salama & Dr Lars Erwig** Prof Graham Lord *6 x abstracts*	**BTS/BASL Symposium** (Hall 12)
18:30	**Erythropoesis Stimulating Agents: from research to reality – Roche Sponsored symposium** (Hall 1) Roche			
19:30	**Exhibition close**			
19:45	**Social Evening – Pan Am Club**			

Thursday 23 April – Parallel Day

	Transplantation Pathway 1	Clinical Pathway	Science Pathway	Transplantation Pathway 2	Donation Pathway
08:00	**Breakfast Symposium sponsored by Wyeth (Hall 3)** **Immunosuppression-Optimising Renal Function** Wyeth	**Breakfast Symposium sponsored by Bristol Myers Squib & sanofi-aventis (Hall 11)** **Managing Diabetic Renal Disease** Bristol-Myers Squibb sanofi aventis		**Registration & Exhibition opens**	
09:00	**Chronic Graft Injury** (Hall 1A) **Chair: Prof Steve Powis & Mr Marc Clancy** Prof Michael Mengel Prof Steve Wigmore Dr Daniel Kreisel	**Science for Clinicians** (Hall 11) **Chair: Dr John Reynolds & Dr David Game** Prof Graham Lord Prof Andrew George Pof Charles Pusey	**Stem Cells** (Hall 3) **Chair: Mr Paul Shiels & Ms Eleanor Bolton** Prof Terry Cook Dr Wilson Wong *3 x abstracts*	**ITNS/BTS Nurses Symposium** (Hall 4) **Chair: Ms Moira Perrin & Mrs Jane Smith** Ms Denise Roberts Ms Dawn McPake Ms Joanne Routledge	**Organ and tissue donation in 21st Century, "are we there yet?"** (Hall 12) Mrs Sally Johnson Dr Paul Murphy Miss Sue Falvery
10:30	**Coffee Break** (Hall 2 – Exhibition Hall)				
11:00	**Ischaemia Reperfusion Injury** (Hall 1A) **Chair - Prof Steve Wigmore & Prof Magdi Yaqoob** Prof Steven Sacks Dr David Kluth *3 x abstracts*	**Diabetes and Transplantation** (Hall 11) **Chair: Mr Murat Akyol & Dr Menna Clatworthy** Prof Jiten Vora Dr Richard Smith Prof Nadey Hakim *3 x abstracts*	**Renal Fibrosis** (Hall 3) **Chair - Dr Jill Norman & Dr Mark Dockrell** Prof Alison Eddy *6 x abstracts*	**ITNS/BTS Nurses Symposium** (Hall 4) **Chair: Mr Chris Rudge** Mr David Mayer	Mr Anthony Clarkson Ms Ella Poppitt, Ms Heather Small Dr Paul Rooney Mr Andrew Broderick

12:30	**Lunch & Exhibition** (Hall 2 – Exhibition Hall)	**Workforce planning and renal trainees** (Hall 4) Dr David Game	**Lunch & Exhibition** (Hall 2 – Exhibition Hall)		
13:30	**Moderated Posters** (Hall 2 – Exhibition Hall)				
14:30	**Medawar Medal Session (Hall 1A)** **Chair: Prof Peter Friend & Mr Keith Rigg** *8 x abstracts*	**CPD- Quality of Care** (Hall 11) **Chair: Mr Gabriel Oniscu & Dr Iain MacPhee** Prof Alan Jardine Prof John Cunningham Dr David Goldsmith Dr David Wheeler	**Immunological Renal Disease** (Hall 3) **Chair - Prof Caroline Savage & Prof Charles Pusey** Prof Sir John Savill *6 x abstracts*	**BTS/BSHI Symposium** (Hall 4) **TransitionalTechniques Applied to Transplantation** Mrs Rachel Johnson Dr Susan Fuggle Dr Craig Taylor Dr Paul Sinnott Mr John Smith Dr Robert Vaughan	**Best Abstracts (Hall 12)** 14:30 – 15:30 **Debate (Hall 12)** 15:30-16:00
16:30	**Coffee Break** (Hall 2 – Exhibition Hall)	**Transplant Surgeon's Chapter** (Hall 11)	**Coffee Break** (Hall 2 – Exhibition Hall) **RA Meeting Close**		Session Ends
17:00	**Kidney Transplantation – Clinical 2** (Hall 1A) **Chair - Dr Richard Baker & Prof Phil Dyer** Dr Rana Rustom *6 x abstracts*	**Chair – Mr Derek Manas & Mr Peter Veitch** Prof Niaz Ahmed Prof Derek Manas Mr Hany Riad Mr Raj Prasad Mr Neil Parrott Mr Raaj Praseedoom Mr David Stell	**Experimental Models of Organ Transplantation** (Hall 3) **Chair: Dr Wilson Wong & Dr Julian Pratt** Prof Andrew George Prof Daniel Kreisel Prof Margareet Jonker	**BTS/BSHI Symposium** (Hall 4) Ms Lisa Burnapp Mr David Curran Dr Anthony Dorling Dr Raj Thuraisingham	

18:30	**Exhibition Closes**
19:45	**Coach Transfer to the Crowne Plaza – BTS Conference Dinner**

Friday 24 April – BTS Stand Alone Day

	Transplantation Pathway	**Science Pathway**
08:00	**Registration & Exhibition Open** (Hall 2 – Exhibition Hall)	
08:30	**BTS AGM** (Hall 1B)	
09:30	**NHSBT Session** (Hall 1B) **Chair: Mr Murat Akyol & Prof Phil Dyer** Mrs Rachel Johnson Ms Joanne Allen Ms Marina Knight Mr Alex Hudson Dr Dave Collett Miss Claire Hamilton Mrs Kerri Barber	**Basic Science** (Hall 1C) **Chair: Prof Anthony Warrens & Dr Nick Jones** Mr Gavin Pettigrew *6 x abstracts*
11:00	**Coffee Break** (Hall 2- Exhibition Hall)	
11:30	**Ethics of Organ Allocation - Balancing Utility, Equity & Science**(Hall 1A) **Chair: Dr Antonia Cronin & Miss Laura Buist** Panel Discussions: Prof Gurch Randhawa Dr Sue Fuggle Prof Bobbie Farsides Mr John Forsythe Prof Steve Sacks	

13:00	**Lunch & Exhibition** (Hall 2 – Exhibition Hall) **PLEASE NOTE THAT THE EXHIBITION HALL CLOSES AT 14:30**
13:45	**BTS Fellows** (Hall 1A) **Chair: Mr Chris Watson** Mr David Vass Mr Tony Rostron
14:15	**Best Abstracts** (Hall 1A) **Chair: Mr Keith Rigg & Ms Sue Fuggle** *6 x abstracts*
15:30	**What's Hot, What's New** (Hall 1A) **Chair: Ms Lorna Marson** Dr Matthew Howse Prof John Kirby
16:30	**Meeting Close**

Acknowledgements

A formal thank you to the Programme Committee, Prof Phil Dyer, Prof Marlene Rose, Mr Abdul Hammad, Prof Derek Manas, Ms Lorna Marson, Prof John Dark, Dr Iain MacPhee, Dr Tim Johnson, Dr Jeremy Hughes, Dr Lorraine Harper, Dr Gordon Bell and Prof Bruce Hendry for putting together an educational and enjoyable programme.

The CPD sessions have been organised by Dr Phil Kalra, Dr Steve Riley, Dr John Reynolds, Dr David Game, and Dr Tim Johnson. The Bone and Mineral Disorder CPD session has been sponsored by the DGH Society.

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

The British Transplantation Society

Clinical	Laboratory	Coordinator
Dr Ian MacPhee	Dr Nick Jones	Miss Jayne Fisher
Miss Lorna Marson	Dr Wilson Wong	Ms Jacqui Spencer
Prof Derek Manas	Dr Sue Fuggle	Ms Deirdre Walsh
Mr Vassilios Papillois	Prof Marlene Rose	Ms Moira Perrin
Dr Richard Baker	Prof Phil Dyer	Ms Sue Moore
Prof Mike Nicholson	Prof John Kirby	Ms Jane Smith

The Renal Association

Clinical Abstracts

Peritoneal Dialysis	CKD (Primary Care)	Haemodialysis
Dr Simon Davies	Mr Charile Ferro	Dr Richard Fluck
Dr Martin Winkle	Prof Paul Roderick	Dr Stuart Lambie
Dr Graham Woodrow	Prof Alison Mc Leod	Dr Graham Warwick
Dr Steve Holt	Dr Peter Topham	Dr Chris McIntyre
Dr Edwina Brown	Dr David Wheeler	Dr David Goldsmith

Clinical Nephrology	Acute Kidney Injury	CKD (Progression & risk)
Dr Lorraine Harper	Dr Gordon Bell	Mr Charlie Farro
Dr Jonathan Kwan	Dr David Goldsmith	Dr Chris McIntyre
Dr Mark McGregor	Prof Magdi Yaqoob	Prof Daniel Zehnder
Dr Richard Fluck	Dr Andrew Lewington	Dr Phil Kalra
Dr Mark Taylor	Dr Chris McIntyre	Prof Alan Jardine

Complications of CKD	Complications of RRT	Registry & epidemiology
Mr Charlie Ferro	Dr Ian McDougall	Dr Charlie Tomson
Dr Chris McIntyre	Dr Edwina Brown	Dr David Ansell
Prof Daniel Zehnder	Dr Rob Lewis	Dr Janice Harper
Dr Phil Kalra	Dr Aine Burns	Dr David Wheeler
Prof Alan Jardine	Dr Gordon Bell	Dr Mark McGregor

Transplantation	Conservative & Pallative Care for ESRF
Prof Steve Powis	Dr Laurie Solomon
Dr Richard Borrows	Dr Lorraine Harper
Dr Rob Higgins	Dr Lindsey Barker
Prof David Taube	Dr Edwina Brown
Dr Paul Cockwell	

Science Abstracts

Prof Robert Unwin	Prof Robert Unwin	Dr Jeremy Hughes
Dr Stan White	Dr Stan White	Dr Alan Salama,
Dr David Marples	Dr David Marples	Prof Caroline Savage
Dr Steve Harper	Dr Steve Harper	Prof Magdi Yaqoob
Dr David Shirley	Dr David Shirley	Prof Andy Rees
Professor Adrian Woolf	Professor Adrian Woolf	Prof Bruce Hendry
Prof Patrick H. Maxwell	Prof A. Peter Maxwell	Dr Moin Saleem,
Dr Albert C. M. Ong	Dr Albert C. M. Ong	Prof Nigel Brunskill,
Prof Robert Unwin	Prof Tim H. J. Goodship	Dr Mark Dockrell
Dr Stan White	Dr David A. Long	Dr Donald Fraser,
Dr David Marples	Prof Robert Unwin	Dr Tim Johnson
Dr Bryan Conway	Prof Aled Phillips	Dr Jill Norman

We would also like to thank the following organisations for their contributions to the conference:

Astellas & Novartis Breakfast Symposium on 22 April

Astellas

Poster Boards
Internet Café
Badge Lanyards
Conference Bags
Conference Pens & Pads
Abstract Book & CD

Roche:

Evening Symposium on 22 April
Coffee Breaks

Wyeth:

Breakfast Symposium on 23 April

Bristol-Myers Squibb & sanofi-aventis Breakfast Symposium on 23 April

The British Transplantation Society

Company and Charity Annual General Meeting

Friday 24th April 2009 08.30 to 09.30hrs

Liverpool Conference Centre, Liverpool

1. Welcome
2. Apologies
3. Minutes of AGM on 18th April 2008, SECC, Glasgow (held as BTS registered Charity No 1098584)
4. President's Report
5. Vice President's Report
6. General Secretary's Report
7. Treasurer's Report
8. 13th Annual Congress
9. Any other business
10. Next meeting: Friday 19th March, Kensington Town Hall, London
11. Closure of meeting

By order of the Board of Directors

Date 18th March 2009

BRITISH TRANSPLANTATION SOCIETY

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

Friday 18th April 2008 at 08.30, The Lomond Auditorium, Scottish Exhibition Conference Centre, Scotland

1 PF welcomed the members present to the Annual General Meeting

2 No apologies had been received. 24 members were in attendance.

3 The minutes from the last AGM of the charity held on 29th March 2007 were approved and accepted as a true record of the meeting.

3.1 The Bursary payments have been suspended for the international meeting's this year, due to the fact that Astellas and Novartis believe that the initiative could only work with the support of all the Corporate Partners

4 President's Report

4.1 The BTS bid for ESOT 2011

Successful. The meeting will be held in Glasgow, but is hosted by the BTS and is a wonderful opportunity to showcase BTS.

4.3 Organ Retrieval

Launched a working Party to look at developing a national organ retrieval service. Lots of work done so far, proposal written and approved by the council of BTS.

4.2 Retiring members of council

Chris Dudley has served his term on council, and has been responsible for running the bursary scheme. Thanks were given for his commitment. Steve Wigmore, chair of Ethics Committee is also retiring from the committee, and from council, and thanks were given for all his hard work.

5 Vice President's Report

5.1 Liverpool 2009

Programme currently being developed. Joint meeting with the Renal Association. Plan is to run as joint programme on the Wednesday and Thursday and have the Friday as a BTS day, with a joint social event on the Wednesday evening.

5.2 2010 congress

To be held in London at Kensington Town Hall

5.3 2011 Congress.

Congress strategy to change, in particular to reflect need for it to become financially neutral. Currently looking at a central venue for a rolling 3 years. There will be a national organising committee, with local support.

5.4 IT strategy.

The council and executive have recognised the need to update the whole IT infrastructure including the membership database and website. Looking at re-branding the website and back office functions. Website needs to be the first port of access for members and public with interest in transplantation, and there needs to be member only areas. The Council has agreed to move ahead with this and have appointed Luke Devey to be web manager who has agreed to provide his time free of charge. Web editorial sub committee to sit alongside.

6 General Secretary's Report

6.1 Elections

817 voting codes distributed, only 184 online votes cast (23%). This compares poorly to 2007 when 272 votes were cast (~33%). The plan is to continue with electronic voting system in the future. There were a few teething problems and two candidates had incorrect statements published. As a consequence Electoral Reform Services (ERS) re ran the election for councillor without portfolio without charging as this was their error. The following positions have been filled.

Mr Hany Riad – Councillor without Portfolio

Dr Iain MacPhee – Councillor representing Nephrology

Mr Derek Manas – Councillor representing Liver Transplantation

Dr Sue Fuggle – Councillor representing Histocompatibility

Mr Luke Devey – Training Committee Member

Mr Vasillios Papalois – Ethics Committee Member

Dr Paolo Muiesan – Ethics Committee Member

6.2 A public apology was made to Cinzia Sammartino as an error was made over her abstracts. The council agreed that a full refund would be given for congress fees.

6.3 Congress Abstracts

A total number of 205 Abstracts were submitted for the congress of which 65 were accepted for oral presentation and 125 were accepted for posters.

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

6.5 Roy Calne award to Kathryn Brown

Clinical Training Fellowships to David Vass, Edinburgh: Astellas

Tony Rostron, Newcastle: Novartis

6.6 Presumed Consent survey

119 responses. 70% were in favour of presumed consent; 48% in favour of a soft opt out.

86% were in favour of required referral.

6.7 Rule 5: Associate Membership. There are two ways of achieving this membership, Council have proposed that the names are changed to: International associate member and Commercial Associate member (for CP). All agreed in favour of this. New rule reads as follows:

"Commercial Associate Members shall have the same privileges as Members but shall not be members of the company; they shall not pay membership fees and shall not attend the Company Annual General Meeting.

International Associate Members shall have limited privileges of Membership. They shall not be members of the company; they shall not attend the Company Annual General Meeting and shall not be entitled to vote. They shall pay a reduced membership fee and they shall not be entitled to apply for fellowships or bursaries"

6.8 Rule 3: member of good standing – James Douglas' points were outlined.

Two options discussed: one to revert to original phraseology, the other to adopt the phrase used by the Transplantation Society. Members pointed out initial indication for changing rule, and recommended legal opinion before further changes were made.

6.9 Directed Donation, Laura Ashworth Case.

Council proposed that the BTS write a letter to HTA stating the BTS position. Propose that the society support directed donation in exceptional circumstances, but not conditional donation. The AGM is happy for a letter to be written.

7 Treasurer's Report

7.1 Finances of Society are currently in good shape. Income over the last two years is almost identical. Saved approx £80k over the past two years. Fall in restricted income, however slight increase in the unrestricted funds. Need to reserve a certain amount of funds. Increased that from £80k to £100k.

8 12th Annual Congress

Liverpool 22-24th April 2009.

9 Any other Business

There was no other business raised

10 Next Meeting

Scheduled for Friday 24th April 2009 – Liverpool.

11 The AGM was closed at 09:15am

Annual General Meeting

Hall 11, ACC Liverpool

Wednesday 22nd April 2009

08.30 – 09.30am

AGENDA

1. Present
2. Apologies
3. Minutes of last meeting
4. Matters not covered in this agenda
5. President's report
6. Treasurer's report
7. Hon Secretary's report
   - 7.1 Annual report 2008
   - 7.2 New members to approve
   - 7.3 60th anniversary celebrations - annual meeting Manchester 2010
8. Clinical Vice President's report covering Clinical Affairs Board (CAB)
   - 8.1 Clinical Services Committee
   - 8.2 Clinical Practice Guidelines Committee
   - 8.3 Renal Registry
   - 8.4 Renal Patient View

9. Academic Vice President's report covering Academic Affairs Board (AAB)

    9.1 Education and Training Committee

    9.2 International Committee

    9.3 Research Committee

    9.4 Clinical Trials

10. Elections

    10.1 President-elect

    10.2 Executive positions

    10.3 Terms of reference trustees

11. Green Nephrology

12. AOB

13. Date and time of next AGM

Breakfast will be served.

The Renal Association welcome all delegates to attend, however only those who are Renal Association members will be eligible to vote.

Abstracts

Plenary Session

Tuesday 21 April 2009

Raine Award

10:00 – 11:30

O1

Outcomes of ABO incompatible live donor renal transplantation in West London

Jack Galliford, Kakit Chan, Rawya Charif, Marina Loucaidou, Terry Cook, Candice Roufosse, Anthony Warrens, Nadey Hakim, Adam McLean, Tom Cairns, Vassilios Papalois, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

ABO incompatible live donor [ABOiLD] renal transplantation is now an accepted therapy for end stage renal failure.

We present the medium term outcomes of 42 patients [27m, 15f, mean age 48.7±11.9 years] who entered our ABOiLD programme, the largest single published experience in Europe.

Between 2003 - 8, 27 patients received Tacrolimus [Tac], Mycophenolate Mofetil [MMF], plasmapheresis and ivIg [100mg/kg] until blood group IgG titre $\leq$ 1/4. 26/27 patients received Rituximab [RTX] and 22 patients were transplanted [14/17m, 8/9f; mean age 45.4±12.0 years]. Post transplant all received Daclizumab [DAC] and steroids for 1 week unless previously steroid dependent.

From 2008, 14/15 patients were similarly transplanted [8/9m, 6/6f; mean age 54.2±10.4 years] using Alemtuzumab, Tac and no MMF, RTX, DAC or steroids.

5/42 [11.9%] patients were not transplanted because we could not lower pre transplant blood group IgG titres below 1/4.

Patient survival is 100% and not statistically different to 303 ABO compatible living donor transplants [ABOcLD] at 6, 12, 24, 36 and 48 months performed in the same period [99.25%, 98.85%, 98.40%, 98.40% and 98.40%; Logrank p=0.5].

Censored allograft survival is 94.59% at 6, 12, 24, 36 and 48 months which is also similar to the ABOcLD group [p=0.7829].

2/37 [5.4%] ABOiLD allografts have been lost, both in the RTX group; 1 technical failure [haemorrhage] and the other antibody mediated rejection with no detectable blood group antibody but a de novo donor specific anti-HLA antibody.

Rejection free survival at 6, 12, 24 and 36 months is 69.38%, 65.52%, 56.16% and 56.16%, which is significantly higher than the ABOcLD programme [p=0.001], but has not impacted significantly on allograft function in the same period at any time point [MDRD eGFR; 51.5±1.9 vs 53.7±1.0, 51.9±2.5 vs 53.3±1.1 and 46.7±2.5 vs 52.2±1.4 and 49.6±3.4 vs 49.9±1.8 mls/min/1.73m^2; p=0.24].

This paper shows that ABOiLD transplantation is successful and associated with excellent medium term outcomes comparable to those with ABOcLD transplants.

O2

Pivotal Role for $CD4^+$ T cells in Renal Fibrosis

Thomas Tapmeier[1], Paramit Chowdhury[1], Julieta Karegli[1], Neil Sheerin[2], Steven Sacks[1], Wilson Wong[1]

[1]MRC Centre for Transplantation, King's College London School of Medicine at Guy's, King's and St Thomas' Hospitals, London, United Kingdom, [2]Institute of Cellular Medicine, Medical School, Newcastle University, Newcastle upon Tyne, United Kingdom

A diverse range of kidney diseases leads to end stage renal failure, requiring renal replacement therapy, with tubulointerstitial fibrosis as a common end point. The severity of renal fibrosis closely correlates with leukocyte infiltration in the kidney, suggesting a role for macrophages and lymphocytes in fibrosis. However, it remains unclear which leukocyte population is responsible for injury. We hypothesise that $CD4^+$ T cells play a pivotal role in UUO induced injury. To dissect the roles of different T cell subsets in renal fibrosis we used the UUO model in Recombination Activating Gene-1 knockout ($RAG^{-/-}$) mice reconstituted with different T cell populations. UUO was performed in WT (n=5) or $RAG^{-/-}$ mice reconstituted with 1.5 x 10^7 syngeneic splenocytes (n=5), 5 x 10^6 $CD4^+$ T cells (n=9) or 5 x 10^6 $CD8^+$ T cells (n=9). A control group received PBS (n=9). After 14 days of UUO kidneys were harvested and interstitial expansion and collagen deposition quantified. Infiltration of T cells and macrophages was analysed by immunohistochemistry. RT-PCR was performed to quantify TGF-β and α-SMA expression in fibrotic and contralateral kidneys, and the expression of IFN-γ, IL-4, T-bet and GATA-3 was analysed to characterise the infiltrating T cells. After 14 d of UUO $RAG^{-/-}$ mice showed significantly less interstitia expansion (23% vs 36%, p=0.0443) and collagen deposition (26% vs 41%, p=0.0043) than WT mice. Reconstitution of $RAG^{-/-}$ mice with WT splenocytes two weeks before UUO restored the level of injury to that seen in WT mice. Macrophage infiltration was equivalent in all groups. Reconstitution with $CD4^+$ T cells but not with $CD8^+$ T cells resulted in increased interstitial expansion compared with PBS injected controls (41%, 26% and 24% respectively, $p \leq 0.0001$ $CD4^+$ vs PBS). Interstitial collagen deposition was increased in $CD4^+$ $RAG^{-/-}$ mice compared to PBS injected controls (40% vs 28%, $p<0.0006$) but not after $CD8^+$ reconstitution (29%). Expression of TGF-β and α-SMA was significantly higher in obstructed kidneys from WT, splenocyte and $CD4^+$ reconstituted mice compared to contralaterals ($p \leq 0.05$) but not after $CD8^+$ or PBS reconstitution. Expression of IFN-γ in absence of IL-4 expression suggests a T_H1 skewing environment in fibrotic kidneys. Our results in the UUO model clearly demonstrate a critical role for $CD4^+$ T cells in renal fibrosis.

O3

Clinical outcome of systemic AL amyloidosis affecting the kidneys

Jennifer Pinney[2], Helen Lachmann[1], Janet Gilbertson[1], Philip Hawkins[1], Julian Gillmore[1]

[1]National Amyloidosis Centre, UCL Medical School, Royal Free Campus, London, United Kingdom, [2]UCL Centre for Nephrology, Royal Free Hospital, London, United Kingdom

Background: Systemic AL amyloidosis frequently presents with proteinuric renal dysfunction which may progress to end-stage renal disease (ESRD). Predictors of ESRD are poorly characterised in this disease but outcomes with all modalities of renal replacement therapy (RRT) have traditionally been poor.

Methods: All patients with renal AL amyloidosis who were prospectively followed at the UK National Amyloidosis Centre (NAC) between 1990 and 2008 were identified from the NAC database. We evaluated clinical features, renal outcomes, and patient survival with RRT.

Results: One thousand and twenty-three of 1918 (53%) patients with AL amyloidosis had renal involvement at presentation as defined by international consensus criteria. Median patient survival among those with renal amyloidosis was 35 months, not significantly different from those without renal involvement. Among 753 patients with eGFR >50 ml/min at presentation, only 36 cases (5%) reached ESRD by censor/death, with median follow up from diagnosis of 22 months (0-193). Significant predictors of ESRD were low serum albumin and heavy proteinuria; liver involvement by amyloid and total body amyloid load by SAP scintigraphy were not significantly associated with risk of ESRD. A total of 256 patients reached dialysis-dependent ESRD and were followed for a median of 36 months (0-256) from commencement of RRT. Median patient survival from start of dialysis was 41 months and was substantially different between those commencing dialysis pre- and post-2000; 26 and 50 months respectively (P=0.0002). Dialysis modality and amyloid load did not affect survival on dialysis. Twenty-two patients underwent renal transplantation. There were no graft failures but 20 of 22 patients (91%) were alive at 1 year, and 4 of 9 (44%) patients were alive at 5 years from transplantation, with a strong suggestion of improving long-term survival among recently transplanted patients, who were very carefully selected.

Conclusions: Renal involvement, present in ~50% of patients with AL amyloidosis at diagnosis, does not substantially influence patient survival. Severity of nephrotic syndrome correlates with renal outcome. Survival on dialysis in this cohort was markedly better than that previously reported in AL amyloidosis and has improved substantially in recent years. Renal transplantation is feasible and long-term outcomes after transplantation do appear to be improving with careful patient selection.

O4

SOCS3 expressing macrophages as a target for treatment of glomerulonephritis

Carylyn Marek, Eileen Bishop, Yu Liu, Andrew Rees, Heather Wilson

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Macrophages are a key feature in renal disease where they can exacerbate or alleviate progressive renal injury. SOCS are inducible intracellular proteins that regulate the cytokine and TLR intracellular signalling pathways that direct macrophage pro- or anti-inflammatory function. We have previously shown that the majority of macrophages infiltrating inflamed glomeruli exclusively express either SOCS1 or SOCS3; and enhanced SOCS3 macrophage expression *in vitro* is associated with a pro-inflammatory phenotype with potential to drive tissue injury. (JI 2008;180:6270). The aim of this study was to determine the role of SOCS3 expressing macrophages in mediating the severity of immune-mediated glomerulonephritis and to address the molecular mechanisms by which SOCS3 controls macrophage pro-inflammatory potential *in vivo*.

Triple immunohistochemistry determined the number of CD68 positive macrophages exclusively expressing SOCS1 or 3 in kidney sections of animals with nephrotoxic nephritis. The correlation between the number of SOCS3 (but not SOCS1) expressing glomerular macrophages and severity of nephritis, as assessed by albuminuria, was highly significant supporting their pro-inflammatory role in *vivo*. siRNA mediated knockdown of SOCS3 in macrophages adoptively transferred and conditioned in the inflamed peritoneum had an impaired ability to develop pro-inflammatory properties. Instead they exhibited enhanced anti-inflammatory characteristics including increased expression of mannose receptor, arginase, IL-10 and notably SOCS1 that we have shown previously to be associated with anti-inflammatory, reparative macrophages. Knockdown of macrophage SOCS3 *in vitro* not only increased STAT3 activity but also decreased NFκB activity and prevented IκBα degradation on activation by pro-inflammatory mediators. This provides an intriguing mechanism by which SOCS3 controls macrophage pro-inflammatory properties.

These data demonstrate the importance of SOCS3 in directing and maintaining macrophage activation to a pro-inflammatory phenotype and emphasise that decreasing macrophage SOCS3 expression has potential to down regulate renal inflammation.

Plenary Session

Tuesday 21 April

Chandos Lecture

13:30 – 15:00

O5

Interaction between kidney anion exchanger (kAE1) and nephrin in glomerular podocytes leads to proteinuria in distal renal tubular acidosis

Moin Saleem[1], Fiona Wu[1], Lan Ni[1], Tibor Toth[1], Ros Williamson[1], Seth Alper[2], Carsten Wagner[3], Ash Toye[1]

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Protein filtration in the kidney is controlled at the level of the podocyte, in the glomerulus. Nephrin (NPHS1) is a podocyte junctional slit diaphragm (SD) protein, providing a physical framework for the glomerular filter, connecting the SD to the cell cytoskeleton, and participates in cellular signaling. The tubular-cell membrane protein kidney AE1 (SLCA4) is a HCO_3/Cl^- exchanger crucial for distal tubular urinary acidification, mutations in which result in recessive dRTA. Presence of kAE1 in the glomerulus has not previously been reported. The N-terminus of AE1 was recently shown to bind Integrin Linked Kinase (ILK). We report a novel interaction between the kAE1 cytoplasmic C-terminus and nephrin by yeast two-hybrid assay, and studied the functional significance of this interaction.

Glomerular kAE1 expression was confirmed by western analysis and confocal imaging of human kidney. In normal glomeruli, kAE1 staining partially colocalised with that of nephrin. Strikingly, kAE1 protein was absent in glomeruli homozygous for human nephrin (*NPHS1*$_{FinMaj}$) mutation, but distal tubular expression was unaffected. In wildtype human conditionally immortalized podocytes, kAE1 localized to the cytoplasm and the plasma membrane; its expression was absent in *NPHS1*$_{FinMaj}$ cultured podocytes. The reintroduction of wildtype nephrin into mutant podocytes by stable expression rescued kAE1 expression and localisation.

In AE1 knockout mice, nephrin protein expression was unchanged compared with wildtype littermates but albuminuria was detected in the majority of mice studied. Scanning electron microscopy showed abnormalities in all three layers of the glomerulus, including foot process effacement and fusion, irregular glomerular basement membrane (GBM) thickening, subendothelial expansion and arcade formation.

We propose kAE1 as a novel podocyte protein that via interactions with nephrin, contributes to the structure or signaling of the SD and also via ILK connects to the GBM. This also introduces a mechanism underlying the hitherto unexplained proteinuria and glomerulosclerosis seen in patients with dRTA.

O6

The effect of exogenous $VEGF_{165}b$ on the normalised ultrafiltration coefficient in isolated intact mice glomeruli

Amit Kaura[1], Emma Wood[1], Joanne Ferguson[1], Leslie Sage[1], David O. Bates[1], Steven J. Harper[1], Andrew H. J. Salmon[1,2]

[1]Microvascular Research Laboratories, Department of Physiology, School of Veterinary Sciences, University of Bristol, Bristol, United Kingdom, [2]Academic Renal Unit, Clinical Science at North Bristol, University of Bristol, Bristol, United Kingdom

Vascular endothelial growth factor (VEGF-A) is an important regulator of glomerular function in health and disease. VEGF-A_{165} increases glomerular water permeability (normalised ultrafiltration coefficient: L_PA/V_i) (Salmon, J Physiol, 2006). The recently described VEGF-A_{165}b isoform antagonises many of the effects of VEGF-A_{165} (Bates & Harper, Future Oncol, 2005). Podocyte-specific heterozygous overexpression of VEGF-A_{165}b in mouse glomeruli reduces L_PA/V_i (Ferguson et al.). To address the mechanism underlying this effect, we assessed [1] the effect of direct application of VEGF-A_{165}b on glomerular L_PA/V_i, and [2] glomerular capillary surface area in *neph*VEGF-A_{165}b mice.

Glomeruli were isolated from wild-type mice, and incubated in either control solution (1% BSA alone), 40pM $VEGF_{165}$b or 1nM $VEGF_{165}$b for up to one hour. Glomeruli were individually mounted on an aspiration pipette, and glomerular images recorded on videotape. The rate of reduction in glomerular volume that accompanies a change in the fluid surrounding the glomerulus (from 1% BSA to 8% BSA) describes the rate of fluid efflux from the glomerulus (J_V). L_PA is calculated from the quotient of J_V and oncotic pressure difference between 1% BSA to 8% BSA. For morphometric studies, the number of intersections between the glomerular perimeter/glomerular capillary walls with an overlying lattice revealed glomerular volume/glomerular capillary surface area respectively.

VEGF-A_{165}b dose-dependently reduced L_pA/V_i ($min^{-1}mmHg^{-1}$ (mean ± S.E.M.)) (control, 1.88 ± 0.22 (n = 30); 40 pM VEGF-A_{165}b, 1.49 ± 0.17 (n = 24); 1 nM VEGF-A_{165}b, 1.19 ± 0.20 (n = 31); $p<0.05$, one-way ANOVA). Neither glomerular volume (VEGF-A_{165}b: 0.31±0.06nl; controls: 0.24±0.01nl; p=0.28) nor capillary surface area ($x10^4 \mu m^2.glom^{-1}$: VEGF-A_{165}b: 4.4±0.43; controls 4.9±0.67; p=0.57) were altered in *neph*VEGF-A_{165}b mice.

Transgenic VEGF-A_{165}b overexpression reduces L_pA/V_i via a direct paracrine effect, rather than by altering glomerular maturation. VEGF-A_{165} and VEGF-A_{165}b have opposing effects on L_PA/V_i. Altering the balance of VEGF-A_{165}:VEGF-A_{165}b in the glomerulus may have therapeutic potential for various human glomerulopathies, such as diabetic nephropathy, in which both VEGF expression and glomerular function are altered.

O7

Can Microvolt T wave alternans identify ESRD patients at high risk of sudden cardiac death ?

Rajan Patel[1], Patrick Mark[1], Henry Dargie[2], Stuart Cobbe[1], Alan Jardine[1]

[1]BHFGCRC, University of Glasgow, Glasgow, United Kingdom, [2]Department Of Cardiology, Western Infirmary, Glasgow, United Kingdom

INTRODUCTION: Premature cardiovascular events, especially sudden cardiac death, are common in end stage renal disease (ESRD) patients and significantly associated with myocardial abnormalities (collectively named uraemic cardiomyopathy). Identification of high risk patients is difficult. Microvolt T wave alternans (MTWA) is a new, non invasive method of detecting variability in ECG T wave morphology and is promising for risk stratifying heart failure patients for ventricular arrhythmias (between 55-70% have abnormal MTWA). Five percent of healthy subjects have abnormal results. We performed MTWA testing in ESRD patients to determine the prevalence of a nonnegative result.

METHODS: 154 ESRD patients (86 haemodialysis, examined 24 hours after end of last HD session; 16 peritoneal dialysis; 52 stage 5 CKD not receiving renal replacement therapy) underwent assessment including ECG, cardiac MRI and MTWA exercise testing. MTWA results were classified as "negative" or "abnormal" based on previously published reports.

RESULTS: 85 patients (53.5%) had abnormal results. This was significantly associated with past history of ischemic heart disease (11.6% negative vs 31.8% abnormal; p=0.003), cerebrovascular disease (4.3% vs 22.4%; p=0.001) and peripheral vascular disease (5.8% vs 29.4% p<0.0001). There was also a significant difference in resting ECG with ischaemic abnormalities (20.9% negative vs 43.5% abnormal; p=0.004). There was no significant difference between ejection fraction (63.8% negative vs 61.1% abnormal; p=0.28),. However, LV mass (86.9g/m^2 negative vs 100.1 g/m^2 abnormal; p=0.04), end diastolic (60.0 ml/m^2 vs 74.5ml/m^2) and end systolic (22.9ml/m^2 vs 33.2 ml/m^2; p=0.03) volumes were significantly higher in patients with abnormal MTWA results.

CONCLUSIONS: Patients with ESRD have a high prevalence of abnormal MTWA result. Despite normal LV function, this is similar to heart failure patients with normal renal function and is significantly higher than healthy subjects. Abnormal MTWA result is significantly associated with past history of macrovascular (coronary, cerebral, and peripheral) disease, and myocardial structural changes of uraemic cardiomyopathy (higher myocardial mass and LV dilation). The potential predictive role of MTWA in ESRD patients, especially for sudden cardiac death, remains to be assessed.

O8

Variability of eGFR using different measures of renal function and estimating equations in a Caucasian population

Matthew Bottomley[1], Aleh Kalachyk[2], Chetan Mevada[3], Timothy James[3], Anthony Fryer[4], Paul Harden[1]

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Several different equations exist for the calculation of estimated glomerular filtration rate and clearance, including the newer Mayo Quadratic and CKD-EPI equations, reported to predict eGFR more accurately across all stages of CKD. During a collaborative CKD prevalence study in factory workers in Belarus, we studied the effects of using different equations on the prevalence of CKD. Blood and urine samples were analysed for: serum creatinine (Jaffe & enzymatic methods), Cystatin C (Dako Petia assay) and urine albumin: creatinine ratio. eGFR was calculated using the MDRD (175- & 186- corrections), CKD-EPI & Mayo Clinic Quadratic equations (both IDMS-aligned). The 186-MDRD eGFR was also compared to the Wetzels normograms. Clearance was calculated using the Cockroft-Gault equation (creatinine) & the Grubb equation (Cystatin C). 512 participants enrolled in the study. The results for the creatinine-based eGFR equations are shown below:

ml/min/1.73m^2	**Jaffe Cr**	**Jaffe Cr**	**Jaffe Cr**	**Jaffe Cr**	**Enz Cr**	**Enz Cr**	**Enz Cr**
Method	**186-MDRD**	**175-MDRD**	**Quadratic**	**CKD-EPI**	**175-MDRD**	**Quadratic**	**CKD-EPI**
Mean	79.0	88.9	114.4	92.9	104.3	118.7	105.3
95% CI	77.8-80.2	87.3-90.5	112.9-116.0	91.6-94.1	102.0-106.7	117.1-120.3	103.9-106.7
Range	47.4-155.0	48.0-231.9	56.7-153.7	48.1-121.7	44.9-229.7	62.2-154.3	51.6-146.7
CKD Prevalence (%)	13.1	10.4	8.2	9.2	12.7	8.2	8.6
Stage 1 (%)	1.2	3.3	7.3	3.3	5.1	7.6	6.3
Stage 2 (%)	6.4	4.1	0.8	4.3	2.9	0.6	1.8
Stage 3 (%)	5.5	2.9	0.2	1.6	4.7	0	0.6
Stage 4/5 (%)	0	0	0	0	0	0	0

Cystatin C (Grubb equation) eGFR: mean (95%CI) 132 (129-135) resulting in CKD prevalence of 8.3% : Stage 1=7.1%; Stage 2= 1% and Stage 3=0.2%.

CKD prevalence varied widely, from 8.2% (Jaffe C-G) to 13.1% (Jaffe 186-MDRD). When compared to the Wetzels normograms only 3.3% had an eGFR below the 5th centile. Variability of eGFR between equations occurred despite identical serum creatinine values, creating an artefactual difference in the prevalence of CKD. It is our observation that many clinicians are unaware of the difference between equations. There is a serious risk of over estimating the prevalence of CKD in clinical practice. Our data also suggests that the current KDOQI criteria for CKD may not be appropriate for newer methods of measuring renal function and may need to be adjusted.

O9

Exercise modulates both body composition and cardiovascular function in CKD 4

Stephen John[1], George Kosmadakis[2], Paul Owen[1], John Feehally[2], Christopher McIntyre[1]

[1]School of Graduate Entry Medicine and Health, University of Nottingham, Derby, United Kingdom, [2]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom

Cross-sectional studies in dialysis patients have demonstrated muscle wasting associated with loss of function, as well as increased morbidity and mortality. The causes of muscle wasting are unclear, but the acidosis characteristic of CKD has a putative role. The utility of bicarbonate replacement in this context is unknown. Exercise has been demonstrated to improve muscle function in CKD, but its impact on the cardiovascular (CV) system is also unknown. The aim of this study was to specifically evaluate both of these core research questions relating to CV function and overall body composition.

32 predialysis patients (CKD 4) were recruited to a 6 month interventional study. 14/32 were randomised to bicarbonate supplementation (target 28mmol/l). 18/32 were randomised to exercise. The exercise programme consisted of brisk walking at a speed adjusted to correlate to a Borg Rating of Perceived Exertion Rate (RPE) of 12-14, and a heart rate range that was elicited by the target RPE. Control groups did not receive an exercise programme or oral bicarbonate. Patients were assessed at 0, 1 and 6 months. At each visit, central haemodynamics and cross-correlation time-domain baroreflex sensitivity (BRS) were measured by continuous digital pulse wave analysis (Finometer). Pulse wave velocity and analysis were assessed using applanation tonometry. Body composition was assessed utilising DEXA.

Mean age was 59.7±11.5years and 19/32 patients were male. After 1 month of exercise, fat mass decreased (-672±620g; p=0.001) and lean mass increased (563±944g; p=0.048). There were no significant effects on any measure of CV performance resulting from exercise at this time point. Bicarbonate supplementation did not result in any CV or body composition changes. Over 6 months, there were no effects on body composition. Arterial stiffness and BRS were unchanged, but whilst CV function remained stable in the exercising group, in the non-exercise group stroke volume (-11±25%; p=0.042) and cardiac output fell (-14±20%; p=0.013) and total peripheral resistance increased (28±44%; p=0.026). There were no effects from bicarbonate supplementation.

As little as one month of exercise effects body composition, but not CV function. These changes are not consistently sustained, but exercise does abrogate CKD associated CV deconditioning without effecting autonomic vasoregulation

Parallel Session

Tuesday 21 April

IgA Nephropathy and CKD

13:30 – 15:00

O10

Chronic kidney disease and association with mortality in the United Kingdom

Michael Quinn[1,2], Chris Cardwell[2], Gerard Savage[2], A. Peter Maxwell[1], Frank Kee[2], Damian Fogarty[1]

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Introduction: This study investigated the association between mortality and chronic kidney disease (CKD) in a UK population.

Methods: All creatinine results in Northern Ireland (NI) between 1st Jan 2001 - 31st Dec 2002 were obtained. All eGFR's were calculated using the 4 variable MDRD equation. Mortality follow up was provided from the Registrar Generals office through to 31st Dec 2006. Using eGFR as a time varying covariate, a Cox proportional hazards model investigated the association between CKD and mortality.

Results: 1,967,827 creatinine results from 533,798 patients were analysed. During follow up there were 59,980 deaths. Mean (SD) duration of follow up was 3.3 (2.2) yrs. The majority of subjects were female (299,835) 56%. The overall mean age within the cohort was 55(18) yrs. Adjusted hazard ratios for the association between all cause and cardiovascular mortality are reported in Table 1. Subgroup analysis of 75,345 subjects with additional detailed clinical information permitted recalculation of hazard ratios following adjustment for traditional cardiovascular risk factors and demonstrated similar results.

Table 1. Gender and Age adjusted hazard ratios (CI 95%) for all cause and cardiovascular mortality

Estimated GFR	All cause	Cardiovascular
> 60 ml/min/1.73m^2	1.00 (Ref)	1.00 (Ref)
45 - 59 ml/min/1.73m^2	1.02 (0.99-1.04)*	1.28 (1.24-1.33)
30 - 44 ml/min/1.73m^2	1.44 (1.40-1.47)	1.90 (1.83-1.98)
15 - 29 ml/min/1.73m^2	2.12 (2.05-2.20)	2.93 (2.78-3.09)
< 15 ml/min/1.73m^2	3.46 (3.24-3.70)	3.73 (3.41-4.22)

**p=0.06, all other p values <0.001*

Conclusions: This study demonstrates a strong and graded association between CKD and mortality in the tested NI population. Considering the prevalence of CKD (eGFR < 60 ml/min/1.73m^2) in NI is 3.69%; this further work clearly indicates the public health implications associated with CKD in the UK.

O11

Are age, social deprivation, ethnicity or renal diagnosis associated with the rate of eGFR decline in the year prior to starting RRT? A multi-centre study of 3,251 patients from the UK Renal Registry.

Daniel Ford[1], Margaretha Steenkamp[1], David Ansell[1], Charles Tomson[1], Yoav Ben-Shlomo[2], Damian Fogarty[3]

[1]UK Renal Registry, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom, [3]Queens University, Belfast, United Kingdom

Background: There are few studies of the factors affecting the decline in renal function in the 12 months prior to starting renal replacement therapy (RRT). We analysed the rate of decline of eGFR in association with age, social deprivation, diagnosis and ethnicity.

Methods: All incident ERF patients at 9 UK centres between 2001-2006 were included. The UK Registry extracted data electronically from renal IT systems at time points 0, 1, 2, 3, 4, 5, 6 and 12 months prior to ESRD. The 4v-MDRD eGFR was used. Rate of decline was calculated using a least-square analysis and adjusted for age, gender, ethnicity and primary renal disease.

Results: The rate of decline of eGFR (ml/min/1.73m^2/year) decreased by ~0.50 for each 10yr rise in age: 6.3 (18-35y), 5.5 (35-44y), 4.5 (45-54y), 4.2 (55-64y), 4.1 (65-74y), 3.6 (75+y). The eGFR decline in diabetes (DM, 5.3 ml/min/1.73m^2/year) and glomerulonephritis (GN, 5.8) was faster than polycystic kidney disease (PKD, 3.3), pyelonephritis (Pyelo, 3.7) and renovascular disease (RVD, 3.1) (p<0.0001). There was no difference in eGFR decline between White (4.1) and South Asian patients (3.5), but Black patients (6.4) declined faster than non-blacks (p<0.0001). There was no association between social deprivation and rate of decline.
South Asian patients (6.7 ml/min/1.73m^2) start RRT with a lower eGFR than Whites (7.1, p=0.01). There is no association between eGFR at start and either age or deprivation.

Conclusion: The rate of decline in renal function in the 12m prior to RRT varies with age, primary renal disease and ethnicity, but not with social deprivation.

Figure 1. eGFR pre-ESRD by age group

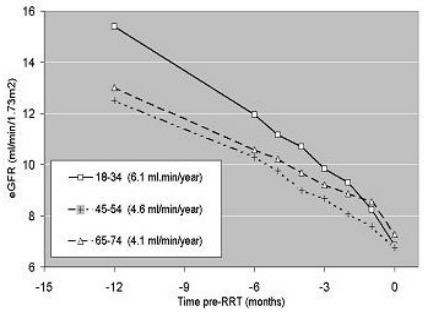
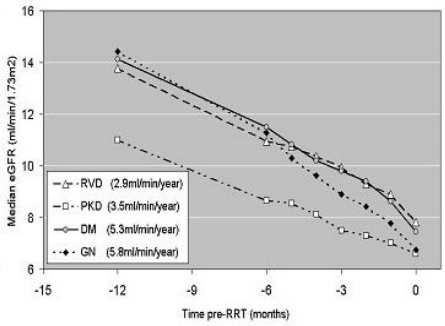


Figure 2. eGFR pre-ESRD by renal disease



O12

Aortic stiffness is independently associated with rate of decline of renal function in patients with CKD 3 and 4

Tom Chapman, Laurie Tomlinson, Martin Ford, Chakravarthi Rajkumar, Steve Holt

Brighton and Sussex Medical School, Brighton, United Kingdom

Introduction Aortic stiffness, measured by carotid-femoral pulse wave velocity (C-F PWV) is related to renal function. Pulse pressure, a surrogate marker of aortic stiffness, is an independent determinant of rate of decline of renal function. A direct relationship between aortic stiffness and rate of decline of renal function has not previously been demonstrated.

Methods 133 outpatients with CKD 3 and 4 in a prospective cohort study underwent baseline measurement of C-F PWV (Complior™) under standardised conditions. At a mean follow-up of 20.7 months, slope of reciprocal creatinine plot for each participant was calculated, using all available measurements of serum creatinine (data censured at the start of renal replacement).

Results The population had a mean age of 69.1±11.5 years, 77.4% male, 23.3% diabetic and 55.6% current or ex-smokers. Mean clinic BP was 154.7±20.9 / 82.7±11.4. Univariate correlates of slope of reciprocal creatinine plot are shown below. Mean slope of reciprocal creatinine plot was greater in diabetics ($-1.0 \times 10^{-6} \pm 4.9 \times 10^{-7}$ vs $-1.8 \times 10^{-7} \pm 2.0 \times 10^{-7}$, *P*=0.03).

	eGFR	Urine PCR	PTH	6-month mean Hb	6-month calcium phos product	C-F PWV adjusted for MBP
rho	**0.31**	**-0.18**	**-0.22**	**0.20**	**-0.21**	**-0.18**
P	**<0.001**	**0.04**	**0.01**	**0.02**	**0.01**	**<0.05**

In a multivariate model containing urine protein: creatinine ratio, diabetes, smoking, baseline CRP, systolic BP and C-F PWV adjusted for mean BP, the only independent predictor of slope of reciprocal creatinine plot was C-F PWV (ß-coefficient -0.22, P=0.01, R^2 total 0.05).

Conclusion Aortic stiffness is related to reciprocal creatinine plot, independently of other known predictors of rate decline of renal function.

O13

Determinants of reduced GFR in CKD stage 3 patients within primary care

Natasha McIntyre[1], Richard Fluck[1], Christopher McIntyre[1,2], Maarten Taal[1]

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Introduction and aims: Several studies have identified risk factors for CKD progression to identify the minority of high risk patients who require specialist referral and intervention to slow CKD progression. Many of these studies have, however, included patients with relatively advanced CKD (stage 4), already referred to Nephrology and the relevance of these risk factors to CKD stage 3 (the largest group) in Primary Care is therefore uncertain.

Methods: Three hundred patients with estimated GFR 59-30ml/min/1.73m^2 were recruited from Primary Care Practices. Detailed medical history was obtained and each participant underwent clinical assessment as well as serum biochemistry tests and urine albumin to creatinine measurements (ACR) to assess previously identified and potential novel risk factors. Urine ACR was measured on 3 consecutive early morning urine specimens. Skin autofluorescence was assessed as a measure of skin advanced glycation end-product deposition.

Results: Median (IQR) estimated GFR was 53(46-58.8)ml/min/1.73m^2 and age was 74(67-79) years. Univariate analysis revealed significant negative correlations between eGFR and age, urine albumin to creatinine ratio (ACR), uric acid; waist to hip ratio and skin autofluorescence as well as positive correlations with haemoglobin, albumin, total cholesterol, bicarbonate and diastolic blood pressure. Multivariable linear regression analysis identified higher uric acid (β=-0.355; P=<0.0001), urine ACR (β=-0.193; P=0.0002) and age (β=-0.173; P=0.001) as well as lower albumin (β =0.119; P=0.27) and haemoglobin (β=0.175; P=0.001) as independent determinants of lower GFR (R^2=0.30 for equation).

Conclusion: Risk factors for CKD progression previously identified in patients with more advanced CKD in Secondary Care are also determinants of lower GFR in patients with CKD stage 3 in Primary Care and may be useful to identify patients at higher risk of progression for specialist referral and intervention to slow progression. Uric acid, identified in several recent studies as a risk factor for CKD progression, was the strongest determinant of eGFR and warrants further study.

O14

Antihypertensive Therapy improves Arterial Stiffness and Baroreflex Sensitivity in Older People with Chronic Kidney Disease

Stephen John[1], Paul Owen[1], Jane Youde[2], Christopher McIntyre[1,3]

[1]Renal Medicine, Derby City General Hospital, Derby, United Kingdom, [2]Medicine for the Elderly, Derbyshire Royal Infirmary, Derby, United Kingdom, [3]School of Graduate Entry Medicine and Health, University of Nottingham, Derby, United Kingdom

Older patients have a propensity to falls which may be exacerbated by impaired blood pressure (BP) control secondary to impaired cardiovascular (CV) function. Doubt exists concerning the advisability of aggressive pursuit of currently mandated optimal BP targets in elderly CKD patients, especially in primary care. We aimed to investigate the CV functional and structural responses to such a multi-drug therapeutic strategy.

We recruited 50 hypertensive non-diabetic patients aged over 70 with CKD 3/4 and non-CKD controls, predominantly from primary care. Assessment was performed after antihypertensive therapy (AHT) wash out and repeated after protocol driven AHT reintroduction to target BP 130/80. Baroreflex sensitivity (BRS, composite marker of autonomic integrity) and central haemodynamics were calculated by cross-correlation time-domain analysis of continuous digital pulse wave analysis. Pulse wave velocity (PWV) and pulse wave analysis were assessed by applanation tonometry and vascular calcification (VC) was quantified by CT imaging of a standardised segment of the superficial femoral artery.

Mean age was 76±4 yrs. Mean eGFR in the CKD group (4-variable MDRD) was 42±12 ml/min. After AHT optimisation, target BP (126/69mmHg) was achieved without postural hypotension. Carotid-femoral PWV, carotid-radial PWV, rate-corrected augmentation index and pressure fell (-1.1m/s,$p<0.0001$; -0.4m/s,$p=0.004$; -3.2%,$p<0.0001$; -5.1mmHg,$p<0.0001$). Heart rate and peripheral resistance reduced (-5.1bpm,$p<0.0001$; -16%,$p=0.02$) and Buckberg index increased (17%,$p=0.001$). Cardiac output and stroke volume were unchanged. BRS increased (4.22 to 5.80ms/mmHg,$p=0.0001$). This marked improvement was seen even in patients with the most impaired renal function. Around 50% of subjects had significant VC, which did not correlate with either PWV or BRS.

Baseline arterial stiffness and BRS were abnormal, and improved with aggressive escalation of AHT to current best-practice guidelines. Fears that pursuit of an optimal hypertensive strategy in older CKD patients would lead to impairment of vasomotor control appear unfounded. Planned follow-up of this cohort will elucidate the clinical importance of these initial observations.

015

The effect of organisational factors and processes of care on between centre variation in achievement of audit measures for calcium, phosphate and PTH in UK haemodialysis centres.

Alex Hodsman, Yoav Ben-Shlomo, Anna Casula, Paul Roderick, Charlie Tomson

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Introduction: The UK Renal Registry (UKRR) collects biochemical data from dialysis centres and compares performance of each centre against audit measures in Renal Association clinical practice guidelines. This study identifies factors relating to organisational structure and processes of care that might account for between centre variation in performance against audit measures for Ca, PO_4 and PTH.

Methods: A survey on management of Ca, PO_4 and PTH was circulated to multidisciplinary teams in UK renal centres in 2008. Outcome measures were mean PO_4, Ca and PTH and the % of patients in each centre with PO_4<1.8mmol/L, adjusted Ca 2.2-2.6mmol/L and PTH 16-32pmol/L. Univariable regression analyses were undertaken to study the association between explanatory variables in the questionnaire and these outcomes. These analyses were unadjusted for case mix differences between centres but included a variable to account for clustering within centres.

Results: Organisational factors associated with a higher % achieving the audit measures were multidisciplinary quality assurance (QA) meetings with > 3 team members (vs<3) attending for Ca (OR1.7 CI 1.0-3.0), PO_4 (OR=1.4 CI 1.1-1.9) and PTH (OR1.9 CI 1.6-2.3) (all p<0.0001). Better phosphate control was associated with 2 other variables. The system of care in dialysis locations (main/satellite) was categorised in the survey as 'consultant' – one consultant responsible for long term care and monthly QA for individual patients irrespective of dialysis location, 'mixed'- one consultant responsible for monthly QA, long term care provided by>1 consultant, 'centre'-long term care and monthly QA provided by one consultant in each dialysis location. Better phosphate control was associated with 'centre' (OR 1.1 CI 1.0-1.3) vs 'consultant' (Ref) vs 'mixed' (OR 0.9 CI 0.7-1.1)(p0.025). Number of WTE nephrologists/100 HD patients (OR1.16 CI 1.0-1.3 p0.04) was also associated with better phosphate control. Number of WTE dietitians/100 HD patients was associated with better control of Ca (OR1.5 CI 1.2-1.9 p0.003) and PTH (OR1.2 CI 1.0-1.4 p0.01). Processes of care associated with better PO_4 control were use of a proforma/checklist during patient review (OR 1.23 CI 1.1-1.4 p0.002) and a possibly a prescribing guideline (OR 1.14 CI 1.0-1.3 p0.07).

Conclusions: This preliminary data from a national study has identified a number of factors associated with improved performance against audit measures for Ca, PO_4 and PTH. Case mix adjusted multivariable multilevel models are now being undertaken on these data to identify independent predictors of better outcome which can be implemented as best practice in UK dialysis centres.

Parallel Session

Tuesday 21 April

Proteinuric and Glomerular Disease

15:00 – 16:30

O16

Investigation of the mechanisms involved in interferon Beta induced increase in barrier properties of human glomerular endothelial cells and podocytes in culture - RAP-1 and IP10.

Candida Tasman, Heather Bevan, Moin Saleem, Peter Mathieson, Simon Satchell

University of Bristol, Bristol, United Kingdom

We have previously described the anti-proteinuric actions of IFNß in three distinct animal models of glomerulonephritis (JASN 2007Nov;18(11):2875-84). We hypothesised that the reduction in proteinuria was due to effects on cells of the glomerular filtration barrier and now describe an examination of the mechanism of this effect in human podocytes and glomerular endothelial cells in culture.

The ability of IFNß to block the barrier-disrupting effects of TNFα was examined using the Electric Cell-Substrate Impedance Sensor (ECIS) system. Effects of IFNß on expression of signalling intermediates and candidate effector molecules in the enhancement of barrier function were examined by focused gene array (FGA) after 4 and 24h, immunofluorescence (IF) and Western blotting after 24h. The ECIS system was used to measure the trans-endothelial electrical resistance (TEER) of a GEnC monolayer before and after treatment with IFN induced protein 10 (IP10). In further experiments an anti-IP10 antibody administered concurrently with IFNß, was used to block any autocrine effects of IP10 forming part of the response to IFN. The effect of Rap-1 knockdown using siRNA on the TEER of GEnC monolayers was also examined.

IFNß significantly ameliorated the reduction of TEER caused by TNFα treatment. There was no effect on distribution of adhesion molecules but expression of VCAM was upregulated by IFNß treatment. Gene arrays confirmed upregulation of elements of the IFNß pathway. IP10 was strongly upregulated following treatment at 4 and 24 hrs. This finding was validated by western blotting. IP10 did not, however, significantly alter the TEER of GEnC or podocytes, making it unlikely to be a contributory factor in the effect of IFNß. Most interestingly Rap1 knock-down with siRNA dramatically abrogated the TEER increase induced by IFNβ in GEnC, indicating that Rap-1 is a key intermediary in the barrier-enhancing properties of this cytokine.

These studies suggest that the direct cellular effects of IFNß may be responsible for reducing proteinuria in animal models and indicate that Rap-1 contributes to this result. These are the first data dissecting the mechanism of this powerful anti-proteinuric pathway.

O17

TRPC6 activation is functionally different between the cells of the glomerular filtration barrier

Rebecca Foster[1], Gavin Welsh[1], Simon Satchell[1], Peter Mathieson[1], Dave Bates[2], Moin Saleem[1]

[1]AOC, University of Bristol, Bristol, United Kingdom, [2]MVRL, University of Bristol, Bristol, United Kingdom

Despite its widespread expression, mutations in the cation channel TRPC6 result in a renal-specific phenotype of focal segmental glomerulosclerosis (Winn et al, 2005) (Reiser et al, 2005). To understand why the glomerulus is susceptible to these mutations we investigated normal TRPC6 activation patterns in the endothelial cells (GEnC) and podocytes (Pod) that form the glomerular filtration barrier and report a difference in the podocyte that may be explained by the presence of the podocyte-specific protein nephrin.

Cells loaded with Fura2-AM and incubated in Krebs'-ringer buffer containing 1.5mM (normal) or 200nM (minimal) Ca^{2+}, were stimulated with 200μM FFA, which specifically activates TRPC6 as described in detail previously (Foster et al, 2009), in the presence or absence of thapsigargin (TG), which depletes internal Ca^{2+} stores. Intracellular calcium ($[Ca^{2+}]_i$) was proportional to the fluorescence intensity ratio (Rnorm). The area under the curve, or Rnorm1 (normalised baseline after store-depletion), were statistically analysed. Cells were also microinjected with full length TRPC6 in a pcDNA3 vector, then imaged using confocal microscopy.

In human conditionally immortalised (ci) GEnC, TRPC6 activation was dependent on external calcium (1.5mM), yet in ciPod it was not. There were apparent differences in the localisation of microinjected TRPC6 between ciGEnC and ciPod. Depletion of internal calcium stores with thapsigarin (200nM) did not affect TRPC6 activation in ciGEnC, but inhibited TRPC6 activation in ciPod in a nephrin-dependent manner, demonstrated using nephrin deficient (ND) ciPod in conjunction with nephrin rescue experiments. Finally, activation of TRPC6 resulted in calcium store-depletion in ciPod, but had no effect on store-depletion in ciGEnC or ND ciPod.

In conclusion, in contrast to GEnC we demonstrate communication of TRPC6 with stores in podocytes. The absence of nephrin breaks this communication and enhances signalling. This highlights the potential importance of nephrin as a TRPC6 regulatory protein in health and disease.

O18

Over-expression of VEGF-A_{165}b in the kidney reduces glomerular ultrafiltration co-efficient in a gene dose dependent manner.

Joanne K. Ferguson[1], Yan Qiu[1], Chris R. Neal[1], David O. Bates[1], Andrew H.J. Salmon[1,2], Steven J. Harper[1]

[1]University of Bristol, Bristol, United Kingdom, [2]Academic Renal Unit, Bristol, United Kingdom

De-regulation of renal VEGF-A has been documented in multiple glomerular diseases, but its pathophysiological role remains unclear. Differential splicing of the VEGF-A gene forms two families of isoforms: the pro-angiogenic family (VEGF-A_{xxx}), and the anti-angiogenic families (VEGF-A_{xxx}b). To determine the effect of VEGF-A_{165}b on renal function transgenic mice overexpressing VEGF-A_{165}b under nephrin promoter (confined to podocytes) were established. In stark contrast to heterozygote *neph*VEGF-A_{164} mice that develop albuminuria shortly after birth, and die 9-12 weeks post-natally from end-stage renal failure, *neph*VEGF-A_{165}b mice, both heterozygous (HET) and homozygous (HOM), appear healthy at 18 months. They showed no physical signs of renal disease and were not proteinuric, although urinary protein:creatinine in HOM mice was slightly reduced. (WT:20.2±2.5; HET:20.7±2.8; HOM:13.7±1.14 n=10 p=0.046). Plasma creatinine levels were not suggestive of end-stage renal disease but were significantly elevated, in HOM mice (WT:2.2±0.5 n=4; HET:2.8±0.6 n=4; HOM:5.4±0.9 n=8; $p<0.05$) Glomerular L_PA/V_i was measured in each group using an oncometric technique. Glomerular L_PA/V_i was significantly reduced in the HET and HOM groups compared to age-matched littermate controls. (WT:1.95±0.16 n=8 HET: 1.41±0.10 n=19 HOMO: 0.73±0.09 n=23) The reduction in L_PA/V_i appeared to be dependent on the gene dose of VEGF-A_{165}b. These results suggest that VEGF-A_{165}b may be of therapeutic benefit in renal diseases characterised by increased glomerular permeability.

O19

Chronic Renal Insufficiency Standards Implementation Study(CRISIS): Progression of Diabetic and Non-Diabetic kidney disease and survival outcomes, results of 36 month follow-up

Richard Hoefield, Beverley Lane, Donal O'Donoghue, Philip Kalra, John New, Rachel Middleton

Salford Royal NHS Foundation Trust, Salford, United Kingdom

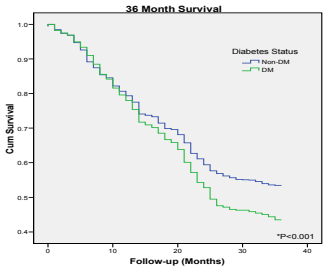
The outcomes of people with Diabetes (DM) and Chronic Kidney Disease (CKD) in large referred cohorts is not well described. CRISIS is a prospective epidemiological investigation of the progression of kidney disease and its associated co-morbidities in a prevalent population with CKD stages 3-5.The aim of this analysis was to describe survival outcomes and the natural history of progression in people with and without diabetes in a CKD population receiving nephrology care.

The cohort was divided according to presence or absence of diabetes at baseline. Survival modelling was adjusted for age, baseline eGFR and BP.

CRISIS consisted of 1516 people, with 483(31.8%) having DM (84%Type 2 DM) at baseline. People with DM were older (67.0 vs 63.8 yrs, P<0.001), had lower diastolic BP (71.5 vs 74.4 mmHg,P<0.002) and more anaemia (defined as Hb<110g/L, 24% vs 15%, P<0.001) compared to non-diabetic people. At study inception renin-angiotensin blockade (RAB 68% v 57%, P<0.001) and statin use (72% v 52%, P<0.001) were higher in the DM group. The prevalence of CVD was also greater in people with DM (57% v 42%, P<0.001).

At 36 months use of RAB (62% Non-DM vs 74% DM) and statins (58% Non-DM vs 77% DM) remained suboptimal. In both the DM and Non-DM cohorts,11% reached end stage renal disease requiring renal replacement therapy at 36 mth follow-up. Mean rate of decline of eGFR over 3 yrs was more rapid in the non-diabetic group at 1.38 mls/yr-compared to 0.97 ml/min/yr in people with DM (P<0.001). 3 year survival was significantly greater in the non-diabetic cohort (41.8 vs 53.6%, p<0.001).

This study highlights that people with diabetic kidney disease have a significantly higher risk of mortality and CVD compared to non-diabetic CKD despite slower decline of eGFR, and greater use of disease modifying agents.



O20

Measures of Obesity and Their Associations with Declining eGFR in a Non-Diabetic Patient Population.

James Burton[1], David Webb[2], Laura Gray[3], Winston Crasto[2], Bala Srinivasan[2], Melanie Davies[2], Kamlesh Khunti[3], Sue Carr[2], Kevin Harris[1], Nigel Brunskill[1]

[1]Department of Infection, Immunity and Inflammation, University of Leicester, United Kingdom, [2]Department of Cardiovascular Sciences, University of Leicester, United Kingdom, [3]Department of Health Sciences, University of Leicester, United Kingdom

Background: Obesity is a risk factor for both chronic kidney disease (CKD) and cardiovascular disease. The association between different indexes of obesity and CKD remains poorly understood. Evidence suggests that measures of central obesity such as waist circumference (WC) and waist to hip ratio (WHR) are more accurate predictors of morbidity and cardiovascular risk than body mass index (BMI). This study aimed to investigate the usefulness of BMI, WC and WHR in predicting CKD risk.

Methods: Data were drawn from a population-based screening programme. People without pre-existing diabetes aged 40-75yrs (25-75yrs in South Asians) from 20 general practices were offered a number of investigations and cardiovascular health-related assessments. 6,137 individuals were recruited and screened in a non-selected fashion and 5,818 of these agreed to have eGFR measurements (MDRD). Patients were then divided into 2 groups according to eGFR; those ≥60 (n=5,282) and those <60 (n=613).

Results: Univariate analysis confirmed the associations between increasing age, urinary albumin to creatinine ratio (ACR) and lower eGFR. There were also statistically significant associations between increasing WC and BMI but lower WHR (see table). Logistic regression analysis adjusted for age, glucose, ACR, sex and ethnicity revealed that WC and BMI were independently associated with an eGFR of <60mLs/min/1.73m^2 (P<0.001 and P<0.01) but that WHR was not (P=0.55).

Conclusions: In a random patient population without pre-existing diabetes, WC and BMI (but not WHR) are independent variables associated with declining eGFR. Given the established non-linear relationship between CKD and BMI, especially in the latter stages of disease, WC (but not WHR) may be a more useful screening tool for the detection of CKD as well as cardiovascular disease in the primary care setting.

Table: Univariate analysis of factors associated with eGFR

Variable [Mean (SD)]	All	eGFR ≥60	eGFR <60	P value
Age (years)	55.8 (10.7)	54.9 (10.5)	63.5 (8.6)	<0.0001
Fasting glucose	5.17 (0.91)	5.2 (0.9)	5.2 (0.8)	0.50
ACR	1.59 (6.66)	1.4 (4.7)	3.2 (15.3)	<0.0001
BMI (kg/m^2)	28.0 (5.0)	27.9 (5.0)	29.0 (4.9)	<0.0001
WC (cm)	93.8 (13.3)	93.7 (13.3)	94.9 (13.2)	0.04
WHR	0.89 (0.09)	0.89 (0.09)	0.88 (0.08)	0.003

O21

The use of eGFR and ACR to predict decline in Renal Function in people with Diabetes

Richard Hoefield[1], Ines Sousa[2], Peter Diggle[2], Donal O'Donoghue[1], Philip Kalra[1], John New[1], Rachel Middleton[1]

[1]Salford Royal NHS Trust, Salford, United Kingdom, [2]Combining Health Information, Computation and Statistics (CHICAS), University of Lancaster, United Kingdom

Aim: Progression of diabetic kidney disease within a single large population, with predictive modeling, has not been well described .The aim of this study was to investigate the rate of progression of chronic kidney disease (CKD) in people with diabetes according to their estimated glomerular filtration rate(eGFR) and presence of albuminuria

Methods: Data were collected on all people with diabetes living in Salford UK, where an

eGFR could be calculated using the 4 variable MDRD formula and Albumin creatinine ratio (ACR) were available. All data between 2001 and 2007 were used in the dynamic model. Patients were classified as normoalbuminuric if their first measurement of ACR was <2.5mg/mmol in men or <3.5mg/mmol in women, microalbuminuric if ACR 2.5-25mg/mmol in men and 3.5-35mg/mmol in women and macroalbuminuric if ACR >25mg/mmol in men and >35mg/mmol in women. A longitudinal mixed effect dynamic regression model was fitted to the data. The model was fitted to each of the 3 classifications of ACR allowing a different model mean for each group. This enabled predictions of population average rate of change in eGFR with time. The parameters were estimated, and inference was obtained by maximum likelihood.

Results: For the analysis of the population average progression of eGFR, ACR and drug prescribing were available in 4082 people with mean age 59.2 years, 57.2% male, 55.2% non-smokers, and 90.1% type 2 diabetes. 2832(69%) were normoalbuminuric,9 1059(26%) microalbuminuric and 191(5%) macroalbuminuric.
The regression model showed that eGFR in people with diabetes and macroalbuminuria declines at 5.5% per annum (Parameter estimate,PE: -0.055, P<0.0001) while those with microalbuminuria declined at 1.7% per annum (PE:-0.017, P<0.0001) and those without albuminuria at 0.4% per annum (PE: -0.004, P<0.0001).
In the normoalbuminuric group the duration of diabetes was associated with a lower initial eGFR at 0.2% per year(PE -0.002, P=0.0389).Similarly in the normoalbuminuric, cohort the later the first measurement of eGFR in this cohort the lower the expected eGFR by 1% per year (PE-0.010, P<0.0001).

Conclusion: The longitudinal effect of time on eGFR showed that people with diabetes and macroalbuminuria have an estimated 13.75 times more rapid decline in renal function compared to those without albuminuria. Individuals with microalbuminuria also have a significantly increased estimated rate of decline of eGFR (3.3x greater) compared to people with normoalbuminuria .

This study provides robust estimates of progression of CKD in a large diabetic population, enabling clinicians to more accurately predict decline in renal function in patients with diabetes based on ACR and eGFR measurements.

Parallel Session

Tuesday 21 April

Dialysis

17:00 – 18:30

O22

Frequent Haemodialysis Regimens are Associated with Reduction in Dialysis-Induced Myocardial Stunning

Helen Jefferies[1], Bhupinder Virk[2], Sheila Doss[2], Sumi Sun[2], John Moran[2], Brigitte Schiller[2], Christopher McIntyre[1,3]

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Recurrent haemodialysis(HD)-induced cardiac injury is associated with markedly reduced survival and development of long-term systolic dysfunction. A key determinant of this acute injury is ultrafiltration (UF) volume and therefore UF rate. This study aimed to identify differences in the occurrence and severity of myocardial stunning in stable patients receiving the current spectrum of available quotidian dialysis regimes.

Four patient groups were studied: conventional in-centre HD 3x per week (CHD3, n=12), short daily HD 5-6x per week both in centre (CSD, n=12) and at home (HSD, n=12), and nocturnal home HD (HN, n=10). The groups were matched for age and dialysis vintage. Serial two-dimensional echocardiography was performed pre-dialysis, at peak stress, and post dialysis to identify emergent dialysis induced regional wall motion abnormalities (RWMAs). Systemic haemodynamics were measured non-invasively with serial bio-impedance cardiography, and pre and post blood samples were collected for standard biochemical analyses, and biomarkers of cardiac injury and systemic inflammation.

Dialysis induced myocardial stunning was very common (11/12) in conventional thrice weekly dialysed patients. The proportion of patients exhibiting dialysis induced RWMAs progressively reduced with increasing intensity of dialysis (CHD3>CSD>HSD>HN). HN was associated with significantly less RWMAs than both in-centre modalities ($p=0.04$). More frequent dialysis (HSD and HN) was associated with significantly less RWMAS than CHD3 ($p<0.04$). The number of RWMAs in CHD3 and CSD did not differ ($p>0.05$). However, both groups were characterised by high UF volumes, which is a known critical determinant of myocardial stunning.

This study demonstrates for the first time that more frequent HD regimes are associated with less myocardial stunning compared with conventional HD. We hypothesise that this could be an important component of the improved outcomes associated with this class of therapies.

O23

The Role, Timing And Technique Of Surgery In The Management Of Encapsulating Peritoneal Sclerosis.

Angela Summers, Ravi Pararajasingham, Afshin Tavakoli, Declan de Freitas, Rosalind Williams, Helen Hurst, Louese Dunn, Paul Brenchley, Paul Taylor, Titus Augustine

Manchester Institute of Nephrology and Transplantation, Manchester, United Kingdom

Encapsulating peritoneal sclerosis (EPS) is an increasingly recognised complication of long term peritoneal dialysis (PD), associated with deposition of fibrous sheets which constrict and restrict the bowel. Previous reports have suggested surgery is associated with increased morbidity and mortality. In this study we report our single centre experience with 82 patients with advanced EPS referred for surgical management to our unit. This is the largest single centre western experience of the surgical management of this debilitating condition.

Diagnosis was based on both clinical and radiological findings. Patients presented with ascites, malnutrition, raised inflammatory markers and bowel obstruction. Between January 2000 and December 2008, there were 82 referrals of EPS: 61 local cases, 18 national referrals and 4 international referrals. Of these, 6 patients were unfit for surgery. 4 patients were declined surgery (2 due to age and co morbidity, 2 patients refused consent).

72 patients underwent surgery of whom 49 are still alive (68%). 34 patients had emergency surgery, performed within 48 hrs of referral, with a mortality rate of 56%. 38 patients underwent semi-elective surgery with preoperative nutritional support and post-operative critical care support, of whom 89% are still alive . All alive patients have returned to a normal diet without the need for naso-gastric or parenteral feeds. 3 patients have mild colic and early satiety but are on an oral diet with normal albumin. Recurrence occurred in 7 cases (10%) with 2 deaths and 4 repeat peritonectomies.

Our results show that early recognition of EPS and early referral for peritonectomy allows intense nutritional support and semi-elective surgery, which are associated with better outcomes. All patients diagnosed with EPS should have a surgical review, in the national referral centres, to allow early identification of the need for surgery facilitating improved outcomes.

O24

Decision Making About Choosing Dialysis Options Depends on Whether the Information is Presented by a Doctor or a Patient

Andrew Mooney[1], Anna Winterbottom[2], Mark Conner[2], Hilary Bekker[3]

[1]Renal Unit, St James's University Hospital, Leeds, United Kingdom, [2]Institute of Psychological Sciences, University of Leeds, Leeds, United Kingdom, [3]Institute of Health Sciences, University of Leeds, Leeds, United Kingdom

Introduction:
We have previously shown that information given to patients approaching end stage renal failure to make an informed decision about dialysis modality is frequently incomplete and difficult to comprehend (Winterbottom et al NDT 2007;22(8):2291-6). We have now studied whether there are differences in decisions made about dialysis modality according to the method employed to deliver this information

Methods:
In an on-line study, 784 participants viewed treatment information about haemodialysis (HD) and continuous cycling peritoneal dialysis (CCPD) and completed a questionnaire. A control group saw only basic information, but otherwise treatment information was varied by format (written or videotaped) and who presented the information (male or female; "patient" or "doctor"). The information was carefully controlled to ensure comparable content and comprehensibility. In addition to collection of demographic data, measures included: treatment choice, reasons for treatment choice, decisional conflict, need for affect, need for cognition, decision regret, quality of information, previous knowledge of ESRF and social comparison.

Results:
There was no preference for treatment choice for those supplied only with basic information. However, there were a number of differences in choices made among subjects who viewed written or video information presented as if by doctors or patients. There was a statistically significant effect that subjects chose the dialysis modality recommended by the patient (whether CCPD or HD). There was no significant effect of the gender of the person presenting information on the modality chosen. However, among participants, females were more satisfied with the information presented, and more likely to choose CCPD (compared to male participants). Subjects' style of information processing (need for cognition/need for affect) had no significant effect on choice of dialysis modality. There was a higher drop-out rate among subjects viewing videotaped information.

Conclusion:
Testimonials about ESRF treatment options led to biased decision making. At present it is unclear how such information might exert its influence; until these mechanisms are better understood, the use of testimonials to facilitate dialysis modality decision making should be treated cautiously.

This work was supported by ESRC and an unrestricted educational grant from Baxter.

O25

Left atrial volume predicts death in ESRD patients with LVH: a cardiac MRI study.

Joanna Powell[1], Rajan Patel[1], Alan Jardine[1], Patrick Mark[1], Nicola Johnston[2], Henry Dargie[1], Alan Jardine[1]

[1]Renal Research Group, BHFGCRC, University of Glasgow, Glasgow, United Kingdom, [2]Department of Cardiology, Western Infirmary, Glasgow, United Kingdom

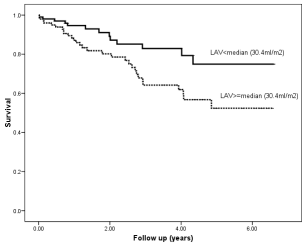
Introduction: Left ventricular hypertrophy (LVH) is common in end stage renal disease (ESRD) patients and an independent risk factor for premature cardiovascular death. In addition, elevated left atrial volume (LAV), measured by echocardiography, predicts death in ESRD patients. Cardiovascular MRI (CMR) is the "gold standard" technique to assess myocardial mass and LA volume can also reliably be measured.

Aim: We assessed the prognostic effect of elevated LA volume on a cohort of ESRD patients with LVH defined by CMR.

Methods: 201 ESRD patients (72.1% male; mean age 51.6± 11.7years) with LVH were identified by CMR (Siemens Sonata 1.5T scanner). All patients were in sinus rhythm. Left ventricular (LV) mass was measured from a stack of cine loops. LVH was defined as LV mass index (LV Mass/Body Surface Area;BSA) >84.1g/m^2 (male) or 74.6g/m^2 (female), based on published normal LV dimensions for CMR. Left atrial volume was calculated by the biplane area–length method at the end of left ventricle systole and corrected for BSA. Routine echocardiography was also performed.

Results: 54 patients died (11 following transplantation) over an 80 month follow-up; 71 patients received renal transplants. Median LAV was 30.4ml/m^2 (IQR 26.2, 58.1); LVMI and LAV were not significantly correlated (r=0.03; p=0.71). Patients were grouped into high ((≥ median) or low (< median) LAV. There was no significant difference in heart rate and mitral valve Doppler early to late atrial peak velocity ratio (E:A). Mortality was higher in patients with high LAV (36 deaths vs low LAV: 18 deaths; p=0.004). Predictors of transplant censored death by Cox regression univariate analysis were high LAV (RR 2.24, 95% CI (1.16-4.30) and LV systolic dysfunction (LVSD; 2.12; (1.13-3.97). Kaplan Meier survival analysis demonstrated poorer survival in high LAV patients (figure 1; p=0.01). Similarly, high LAV and LVSD were independent predictors of death by multivariate analysis (RR 2.12, 95% CI (1.10-4.08); RR 1.96, 95% CI (1.04-3.67) respectively).

Figure 1



Conclusions: In this pilot study using CMR to assess left atrial volume, high LAV and LVSD are independent predictors of death in ESRD patients with LVH. High LAV may be due to inadequate diastolic relaxation, mitral valve disease or fluid overload. Further study is needed to identify aetiology and effect of intervention to reduce LA dilatation during systole.

O26

CT screening for encapsulating peritoneal sclerosis (EPS) in peritoneal dialysis (PD) patients.

Catriona Goodlad[1], Ruth Tarzi[1], Wladyslaw Gedroyc[2], Adrian Lim[2], Steven Moser[2], Edwina Brown[1]

[1]Imperial College Kidney and Transplant Institute, London, United Kingdom, [2]Department of Radiology, Imperial College NHS Trust, London, United Kingdom

BACKGROUND: We have previously validated a scoring system for abdominal/pelvic CT scans in patients with EPS. We demonstrated a significant difference in scores between patients with symptomatic EPS and control PD or haemodialysis patients. However scans performed before EPS was clinically evident were near normal on CT criteria in 9 of 13 patients. The utility of CT as a screening modality in patients without abdominal symptoms is now investigated in a larger group.

METHOD: 20 patients were retrospectively identified with CT scans performed for routine screening/other indications at least 4 months before developing EPS. These "pre-diagnostic" scans and later diagnostic scans when EPS was clinically evident (bowel obstruction +/- ascites) were scored by the three radiologists who participated in the validation study. The control group was 20 PD patients with CT scans performed for various indications, none of whom have developed EPS (median follow up 2.25 years). Analysis was by non-parametric tests. The range of possible CT scores is 0-22, greater than 2.5 being considered abnormal.

RESULTS: Clinical EPS only developed after transplant or transfer to HD. Diagnostic scans scored significantly higher than pre-diagnostic or control scans (median scores 9, 2, 1; $p<0.0001$), confirming previous work. 12 patients in pre-diagnostic group were completely asymptomatic; their median CT score was 1.75, similar to the control group. Only 1 asymptomatic pre-diagnostic scan was abnormal; this patient had had normal scans 8, 10 and 14 months earlier. The other 8 patients had abdominal symptoms (7 required hospitalisation), but did not have the clinical picture of EPS; their median CT score was 4.5; ($p=0.0016$ cf control group). The time from pre-diagnostic scan to clinical EPS (median 0.82 years) and duration of PD at time of pre-diagnostic scan (median 7.1 years) did not differ significantly between the symptomatic and asymptomatic groups.

CONCLUSIONS: CT screening of asymptomatic PD patients is not indicated; EPS may occur within a year or less of a normal CT scan. Abdominal symptoms in long-term PD patients can be associated with CT scan abnormalities; stopping PD is then followed by development of the full blown EPS syndrome.

O27

High energy phosphate metabolism in diabetic ESRD, non diabetic ESRD and hypertensive patients with left ventricular hypertrophy: a phosphorus magnetic resonance spectroscopy pilot study

Joanna Powell[1], Rajan Patel[1], Patrick Mark[1], Emily McQuarrie[1], Gillian McNaught[2], Tracey Steedman[2], Henry Dargie[2], Alan G Jardine[1]

[1]Renal Research Group, BHFGCRC, University of Glasgow, Glasgow, UK, [2]Department of Cardiology, Western Infirmary, Glasgow, UK

Purpose: Premature (usually sudden) cardiovascular death in end stage renal disease (ESRD) patients is the commonest cause of death and is associated with uraemic cardiomyopathy. Diabetes mellitus is an independent predictor of mortality in this patient group. High energy phosphate (HEP) metabolism is altered in patients with diabetes, heart failure and uraemia and can be quantified using phosphorus-31 magnetic resonance spectroscopy**.** Phosphocreatinine:β ATP (PCr: β ATP) ratio represents index of metabolic activity.

Aim: We compared resting HEP metabolism in diabetic ESRD patients, non diabetic ESRD patients and hypertensive LVH patients with normal renal function. We also assessed associations of HEP levels with uraemic cardiomyopathy.

Methods: Seven diabetic ESRD (DM), 7 non diabetic ESRD (NDM) and 7 hypertensive LVH with normal renal function (LVH only) patients underwent cardiac MRI and phosphorus magnetic resonance spectroscopy of their LV (Siemens Sonata 1.5T scanner). Haemodialysis patients were assessed 24 hours after their last dialysis session. Left ventricular (LV) mass was measured from a stack of cine loops and corrected for body surface area (LV mass index: LVMI). β- ATP was corrected for blood contamination and PCr: β ATP ratios were calculated from ^{31} P-MR spectra obtained from long axis views of the left ventricle.

Results: There were no significant differences in age, sex, BMI, LVMI and ejection fraction between groups. DM patients had a lower mean PCr: β ATP ratio compared to NDM patients and hypertensive LVH patients (2.24±0.78 vs 2.43±1.88 vs. 2.88 ±2.01respectively). PCr: β ATP correlated significantly with end systolic volumes (r=0.42;p=0.04).

Conclusion: Although numbers are small, this pilot study demonstrates lower resting HEP metabolism in DM ESRD compared to NDM ESRD patients. Both have lower levels of HEP compared to hypertensive LVH patients. Abnormal HEP metabolism may be a component of uraemic cardiomyopathy and may contribute to higher risk of sudden cardiac death in this patient population.

Parallel Session

Tuesday 21 April

Young Renal Scientist Award

17:00 – 18:30

O28

$P2X_7$ deficiency protects against immune-mediated damage in experimental glomerulonephritis

Clare Turner[1,2], Simon RJ Taylor[1], John McDaid[1], Reiko Hewitt[1], Jennifer Smith[1], Matthew C Pickering[1], Darren L Whitehouse[3], H Terence Cook[1], Geoffrey Burnstock[2], Charles D Pusey[1], Robert J Unwin[2], Frederick WK Tam[1]

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Increased $P2X_7$ receptor expression has been reported in glomeruli (mesangial cells and infiltrating macrophages) in rodent models of antibody-mediated glomerulonephritis (GN). The $P2X_7$ receptor is normally expressed by immune cells and has been shown to cause release of pro-inflammatory cytokines such as IL-1β and IL-18, and cell death by apoptosis or necrosis. Previously, rodent models of nephrotoxic nephritis (NTN) have shown the importance of IL-1β in glomerular crescent formation and tubulointerstitial injury. In the present study we have used $P2X_7$-deficient mice and the selective $P2X_7$ antagonist A-438079 to examine in more detail the role of $P2X_7$ in NTN. Using a murine model of NTN we have found that $P2X_7$ knockout mice show significant renal protection compared with wild type controls, with 60% reduction in glomerular thrombosis ($P<0.01$, as indicated by PAS-positive fibrin), 52% reduction in proteinuria ($P<0.05$), 38% reduction in serum creatinine ($P<0.05$), 28% reduction in glomerular macrophage infiltration ($P=0.001$), 96% reduction in MCP-1 production ($P<0.0001$) and 24% reduction in fibrin deposition ($P<0.05$). We also assessed the potential of $P2X_7$ as a therapeutic target *in vivo* using the selective $P2X_7$ antagonist A438079 in WKY rat NTN. Two doses of antagonist were used, 100 μmol/Kg and 300 μmol/Kg, and were administered twice daily starting on the same day as the nephrotoxic serum injection and continuing for 7 days. We found that 300 μmol/Kg significantly reduced glomerular thrombosis by 96% ($P<0.01$) and proteinuria by 90% ($P<0.001$). Furthermore, glomerular macrophage infiltration (65% reduction; $P<0.001$) and MCP-1 production (50% reduction; $P<0.05$) were reduced in rats treated with 300 μmol/Kg. These results clearly demonstrate that $P2X_7$ deficiency in mice and treatment with a selective $P2X_7$ antagonist in rats protects against the inflammatory damage that occurs in GN. These results suggest a key, pro-inflammatory role for the $P2X_7$ receptor in immune mediated GN. We suggest the $P2X_7$ receptor as a potential therapeutic target in GN.

O29

Overexpression of $VEGF_{165}b$ in the kidney ameliorates diabetes induced Albuminuria.

Joanne K. Ferguson[1], Yan Qiu[1], Chris R. Neal[1], David O. Bates[1], Steven J. Harper[1], Andrew H.J. Salmon[1,2]

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VEGF-A is upregulated in the diabetic kidney and may play a role in the glomerular hyperfiltration observed in the early phase of diabetic nephropathy. Alternative splicing of the VEGF-A gene forms two families of isoforms: the pro-angiogenic family (VEGF-A_{xxx}) and the anti-angiogenic families (VEGF-A_{xxx}b). We generated transgenic mice that overexpress VEGF-A_{165}b in podocytes, under the control of the nephrin promoter.

We have previously shown that *neph*VEGF-A_{165}b mice appear healthy at 18 months but have reduced glomerular permeability to water (*neph*VEGF-A_{165}b - 1.44±0.11 n=18, controls 1.93± 0.16, n=8; t-test p=0.0169).

To determine the role of VEGF-A_{165}b in diabetic nephropathy, diabetes was induced in *neph*VEGF-A_{165}b mice (12 weeks) using streptozotocin. After 2 weeks diabetes was verified by blood glucose determination. Mice with glycaemia <20mmol/L were not included in the study. After ~6 weeks mice were placed in metabolic cages for 12 hrs, urine was collected and albumin concentration (µg.mL.12hr) measured. Diabetic (db) wildtype (WT) mice had 5.4-fold more albuminuria than sham WT mice (Sham-WT:16.4±4.1 n=5 db-WT: 88.0±35.3 n=6, $p<0.05$). $VEGF_{165}$b overexpression reduced diabetes-induced albuminuria to 2.2-fold (Sham *neph*VEGF-A_{165}b :12.5±2.9 n=5, db *neph*VEGF-A_{165}b:27.0±7.6 n=10 $p>0.05$). These results show that podocyte specific over-expression of VEGF-A_{165}b may prevent diabetic glomerular damage suggesting VEGF-A_{165}b may be of clinical benefit to patients with diabetes.

O30

A novel polycystin-2 dimerization domain essential for polycystin-1 recognition and formation of polycystin receptor-ion channel complexes

Shuang Feng[1], Aurelie Giarmachi[2], Yaoxian Xu[1], Lisa Rodat-Despoix[2], Ekaterina Bubenshchikova[3], Jizhe Hao[2], Michael Williamson[5], Tomoko Obara[3,4], Patrick Delmas[2], Albert Ong[1]

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Autosomal polycystic kidney disease (ADPKD) is caused by mutations in two genes, *PKD1* and *PKD2* which encode the proteins, polycystin-1 (PC1) and polycystin-2 (PC2) respectively. Previous work has indicated that PC2 is located in several subcellular compartments (ER, primary cilia, basolateral plasma membranes), tends to homodimerise (by N- and C-terminal domains) and can heterodimerise with PC1 (C-terminal domain) to form a G-protein regulated Ca^{2+} permeable channel. Nevertheless the molecular basis for these interactions and their regulation has remained obscure and the major site of PC2 action is debated. Here we report a previously unrecognised evolutionarily conserved sequence in the PC2 C-terminus which functions as a coiled-coil dimerisation domain. Importantly, the dimerisation of PC2 mediated by this domain is essential for binding to PC1, reconstitution of a PC1/PC2 channel at the plasma membrane and for PM-ER channel activity but not for PC2 ER channel function. Exogenous expression of dimerization-deficient human PC2 in zebrafish resulted in pronephric kidney cysts, hydrocephalus, cardiac edema and body axis curvature but had lesser effects on laterality suggesting that coiled-coil mutations preferentially abrogated PC1/PC2 function. We conclude that C-terminal dimerization of PC2 acts as a molecular signature for PC1 recognition and thus specifies the formation of a PC1/PC2 complex. Our studies also indicate that PC2 has likely distinct functions at the plasma membrane and ER.

O31

Shear stress increases NO production via eNOS phosphorylation in human glomerular endothelial cells

Heather Bevan, Haley Clarke, Simon Satchell, Peter Mathieson

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Under physiological conditions, mean glomerular shear stress is thought to be between 10 -20 dyn/cm^2, yet there is limited published data describing the effects of shear stress on glomerular endothelial cells. Here we examine the effects of shear stress on the phosphorylation of eNOS, and subsequent nitric oxide (NO) production in a unique human conditionally immortalized glomerular endothelial cell line (hciGEnCs), developed in our laboratory. hciGEnCs were exposed to either 0 or 10, 15 or 20 dyn/cm^2 of shear stress for 24 h on an orbital rotator. Protein was extracted and subjected to western blot analysis. In hciGEnCs, 24-hour exposure to 10, 15 or 20 dyn/cm^2 shear stress significantly increased the serine 1177 phosphorylation of eNOS, when compared to the static control ($p<0.05$, ANOVA), whilst time course experiments, performed over a 24-hour period at 20 dyn/cm^2, revealed that eNOS phosphorylation, at ser-1177, was rapid and sustained. Furthermore, expose to 10, 15 or 20 dyn/cm^2 of shear stress for 24 hrs, lead to a significant increase the level of total nitrate secreted into the media when compared to the static controls ($p<0.05$, ANOVA). In other microcirculations, Akt and AMPK are signaling molecules that can regulate eNOS activation and NO production, thus we next evaluate the effects of shear stress on these important signaling intermediates, as detailed above. In hciGEnCs, Akt phosphorylation, at Ser-473 was significantly increased following exposure to 10, 15 or 20 dyn/cm^2 shear stress ($p<0.05$ when compared to the static controls, ANOVA), whilst exposure to 20 dyn/cm^2 of shear reveal that this Akt phosphorylation was rapid and sustained over a 24 hour period. In contrast, AMPKα was significantly de-phosphorylated, at Thr-172, in hciGEnC exposed to 24 hour of shear stress, regardless of the degree of shear ($p<0.001$, ANOVA). A similar trend was observed with shear-induced Akt phosphorylation at ser-473. Furthermore, 20 dyn/cm^2 of shear induced a rapid but transient phosphorylation of AMPK, with a significant level of de-phosphorylation after 24 hours when compared to control.

Collectively the data discussed herein suggests that flow, and therefore shear, can be an important factor in the metabolic function glomerular endothelial cells. Furthermore, NO production may be important in modifying podocyte and/or mesangial cell behaviour in a similar manner to EnC:vSMC interactions that have been reported in other circulations.

Supported by Kidney Research UK.

O32

A role for ERK5 in a TGF-β-induced non-fibriotic outcome in renal epithelial cells

James A. Browne[1], Mysore K. Phanish[1], Deborah L. Baines[2], Mark E.C. Dockrell[1]

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Introduction: We were first to show that TGF-β1 activates the atypical MAP kinase ERK5 in proximal tubule epithelial cells (PTECs) (Browne *et al*., 08). TGF-β1 plays a key role in the development of renal fibrosis. Loss of E-cadherin and the induction of α-smooth-muscle actin (α-SMA) in response to TGF-β1 treatment are major markers of a profibrotic phenotype in PTECs. Here we examine the contribution of ERK5 to the expression of E-cadherin and α-SMA in response to TGF-β1 treatment in PTECs *in vitro*.

Methods: ERK5 siRNA was optimised and a consistent 60% knock-down of ERK5 was achieved in the transformed PTEC line, HKC-8. Cells were transfected for 24h with siRNA (100nM, ERK5 or negative control), then recovered for 24h with fresh media (5% FCS) and then deprived of serum for 24h. Following treatment for 48h with TGF-β1 (2.5ng/ml) or vehicle (0.1% BSA), cellular E-cadherin and α-SMA were assessed by western blotting.

Results: TGF-β1 induced a significant decrease in E-cadherin expression in cells transfected with negative control siRNA ($n=3$, $P<0.01$). However in ERK5 siRNA-transfected cells, TGF-β1 did not induce a significant loss of E-cadherin. Although the induction of α-SMA by TGF-β1 was not significant in cells transfected with negative control siRNA, knockout of ERK5 produced greater and significant induction of α-SMA ($n=3$, $P<0.01$).

Discussion: TGF-β1 treatment induced a fibrotic phenotype by decreasing E-cadherin expression. Previous work by our group showed that E-cadherin loss by TGF-β1 is dependent on Smad 3 (Phanish *et al*., 2006). Here, we show for the first time that ERK5 is also involved in TGF-β1-induced loss of E-cadherin. We also looked at a marker of a myofibroblastic phenotype and surprisingly ERK5 appeared to limit α-SMA induction by TGFβ1. Our results show for the first time that ERK5 appears to facilitate the early part of epithelial mesenchymal transition (EMT) but not full EMT. Hence TGF-β1 induced ERK5 may play a reparative role by limiting the profibrotic action of TGF-β1. This reparative role of ERK5 is analogous with other work from our group on BMP-7 (Veerasamy *et al*., 2008, JASN 19:144A). These results suggest a potential role of ERK5 in the repair from tubular injury and development of tubulointerstitial fibrosis.

O33

ACE inhibitors protect against progressive renal damage following podocyte injury

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Introduction: ACE inhibitors (ACEi) and receptor blockers (ARB) reduce proteinuria and preserve kidney function in proteinuric renal diseases. As proteinuria is a consequence of podocyte dysfunction, we modeled this by creating transgenic mice in which specific podocyte injury can be induced by a single injection of diphtheria toxin. This does not affect non-transgenic animals. After low doses, proteinuria is followed by progressive glomerular scarring over 6-24wks. High doses cause acute renal failure at 2-3wks.

Aim: To develop a model for testing potential renoprotective drugs using histological score as the endpoint.

Method: Groups of 16 transgenic mice and 8 wild type littermates were given ACEi captopril in drinking water or water alone 24h after one single i.p. injection of diphtheria toxin. Kidneys were examined histologically at 8 weeks.

Results: Blood pressure of ACEi treated mice was significantly reduced (84 vs 114mmHg, $p < 0.01$). Glomerular scarring was reduced almost to baseline by ACEi (toxin alone: 17%; toxin+ACEi 10%, $p<0.04$; control 7%). In this experiment creatinine and urea changed little. Urinary ACR was lowered in ACEi treated animals at all timepoints, but in toxin-treated animals did not reach baseline levels.

Conclusion: Captopril almost completely abolished the matrix accumulation and scarring seen following specific podocyte injury. This supports the hypothesis that continuing podocyte dysfunction is the key abnormality in proteinuric disease, and that the podocyte is the primary target of renoprotective drugs. It will be important to determine whether this is through preventing continuing podocyte loss, or through altered podocyte phenotype or function. The model is suitable for testing alternative hypotheses and therapies.

Parallel Session

Wednesday 22 April

Chronic Allograft Nephropathy

10:00 – 11:30

O34

An incremental increase in chronic allograft damage detected on protocol biopsies during the first year post-transplantation

A.O. Mahendran[1], M Elvey[1], N Rudarakanchana[1], P Dupont[1], A.J. Howie[2], P.S. Veitch[1]

[1]Department of Renal Transplantation, Royal Free & University College London Medical School, London, United Kingdom, [2]Department of Pathology, University College London, London, United Kingdom

INTRODUCTION: Chronic allograft nephropathy (CAN) remains the leading cause of late renal allograft failure. We conducted a 12 month prospective study to investigate the accumulation of graft damage in newly transplanted patients.

METHOD: All patients transplanted consecutively from September 2006 underwent protocol biopsies at 0 (post-perfusion), 2 and 12 months. Immunosuppression comprised Tacrolimus plus Mycophenolate mofetil with early steroid withdrawal for the majority. Specimens were anonymised and assigned an index of chronic damage (ICD)[(1,2)] by a single histopathologist . ICD is a morphometric assessment of interstitial fibrosis (IF) and tubular atrophy (TA) expressed as a percentage of cortical cross-sectional area. The trends in ICD over the 12 month period were noted for each recipient. Additional data was also compiled, including; biochemistry, donor age and cold/warm ischaemic times.

RESULTS: A total 168 biopsy specimens from 62 patients were analysed between Sept 2006 and Dec 2008. 44 patients (132 specimens) had biopsies at 0, 2 and 12 months respectively. 41% of graft were from non-heart beating deceased donors (NHBD). The mean ICD for live donor grafts were 4% (T0), 6.4% (2 mths) and 14.8% (12mths). The mean ICD for heart-beating deceased donor grafts were 5.2%, 8% and 18.8% respectively. The mean ICD for NHBD grafts was 7.1%, 11% and 21% respectively. The increase in ICD during the first year was statistically significant. There were no major biopsy complications.

CONCLUSIONS: Chronic graft damage develops as early as 2 months post-transplantation and is progressive. We saw a threefold rise in ICD during the first year post-transplantation alone. Protocol biopsies facilitate early detection of such graft damage. Measures aimed at preventing chronic allograft nephropathy must be targeted in the early post-transplant period.

REFERENCES: 1. A J Howie et al. 2001. Prognostic value of simple measurement of chronic damage in renal biopsy specimens. Nephrol Dial Transplant 16: 1163-1169. 2. A J Howie et al. 2004. Measurement of chronic damage in the donor kidney and graft survival. Transplantation 77(7); 1058-65.

O35

Prevalence of Subclinical Rejection in Routine Protocol Biopsies at Three Months Following Renal Transplantation

Sapna Shah[1], Peter Andrews[2], Jennifer Else[1], Iain MacPhee[1]

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Recent clinical trials have shown that the subclinical rejection rates in tacrolimus based immunosuppression regimens range between 0.7 and 9.5%. There are few recent published data on protocol biopsy findings in unselected patients transplanted in the UK. In our unit, renal transplant recipients receive immunosuppression regimens including tacrolimus, mycophenolate mofetil (MMF) and prednisolone with basiliximab induction. In order to inform choice of the optimal long-term immunosuppressive regimen we instituted routine protocol biopsies at three months after transplantation for all patients transplanted from May 2007 onwards. 97 patients were transplanted between May 2007 and August 2008. 24 (25%) patients did not undergo protocol biopsy because of patient refusal (n=5), co-morbidity (n=9), concomitant anticoagulation (n=3), recent indicated biopsy (n=5) or because of involvement in a clinical trial (n=2). The remaining 73 (75%) patients had a protocol biopsy with adverse events in only 3 patients who developed macroscopic haematuria. The demographic characteristics were as follows: 54 (74%) patients were male, 54 (74%) were Caucasian with a mean age of 44 years and 35 (48%) received a kidney from a living donor. All patients received tacrolimus and prednisolone and 48 (66%) patients were treated with MMF immediately after transplantation. The biopsy results showed that 49 (67%) were normal. Nine (12%) patients had borderline rejection and 7 (10%) had acute rejection (4 were classified as Banff IA and 3 as Banff IIA). Two (3%) demonstrated acute tubular necrosis and 2 (3%) had evidence of pyelonephritis. Two (3%) showed calcineurin inhibitor toxicity with a further 2 (3%) showed interstitial fibrosis and tubular atrophy (IFTA) The presence of subclinical rejection was not associated with tacrolimus blood concentrations or treatment with MMF. Our results reveal that patients comply with routine protocol biopsies, which are safe and yield useful information. We found that 22% of patients had evidence of subclinical rejection and only 6% of biopsies showed calcineurin inhibitor toxicity or IFTA at three months after transplantation. These results allow us to selectively reduce immunosuppression safely in patients with no evidence of rejection with the aim of reducing long-term toxicity. Routine protocol biopsies therefore allow timely intervention and facilitate optimization of immunosuppressive therapy.

O36

Treatment of Chronic Transplant Glomerulopathy with Rituximab

Kin Yee Shiu[1], Jack Galliford[2], Neill Duncan[2], Paul Brookes[3], Candice Roufosse[4], Terence Cook[4], David Taube[2], Anthony Dorling[1]

[1]Department of Immunology, Imperial College London, London, United Kingdom, [2]West London Renal and Transplant Centre, Imperial College Kidney and Transplant Institute, Hammersmith Hospital, London, United Kingdom, [3]Division of Immunology, Imperial College Healthcare NHS Trust, London, United Kingdom, [4]Department of Histopathology, Imperial College London, London, United Kingdom

There is no established treatment for chronic transplant glomerulopathy (TG), an important cause of allograft failure which is often a manifestation of chronic antibody-mediated rejection. TG presents with progressive allograft dysfunction, often with circulating donor specific anti—HLA antibodies (DSAb) and C4d deposition. Patients with biopsy-proven chronic TG >6 months post-transplantation and deteriorating MDRD eGFR were managed with optimised oral immunosuppression using tacrolimus and MMF. Continued deterioration was treated with 2 doses of rituximab 1g iv days 1 and 14. Patients were classified as responders if eGFRs improved or remained stable 6 months post treatment (i.e. no significant negative slope on regression analysis, and ΔeGFR<10%). Rituximab was given to 12 patients (4m, 8f; mean age 52.5±9.55yrs; mean graft age 104.7±105.6 months). 9/12 had DSAb by Luminex and 5/12 patients were C4d+ on biopsy. In the first 5 patients, 3/5 had an eGFR of <20mL/min/1.73m^2, and all these returned to dialysis by 9 months. Subsequently, rituximab was only given if the eGFR was ≥20mL/min/1.73m^2 at the time of treatment, so this analysis concerns only the 9 remaining. In all 9, eGFR was falling over the 5-6 months pre-rituximab, (median ΔeGFR of -5 (range -3 to -15), P=0.0007). eGFR remained stable in 6/9 (66%) at analysis 6 months later. This preliminary data demonstrates that in TG refractory to standard immunosuppression, rituximab can be used to stabilise allograft function in 2/3rds of patients. The long-term efficacy and safety of this treatment needs to be determined in a randomised controlled trial, which is ongoing but encouragingly, one of the treated patients continues to have stable graft function at 2 years.

O37

Strong predictive value of post transplant proteinuria and its evolution within the first year after renal transplantation on renal graft outcomes.

Aravind Cherukuri, Matthew Welberry Smith, Niaz Ahmad, Chas Newstead, Andrew Lewington, Richard Baker

St James's University Hospital NHS, Leeds, United Kingdom

The significance of very early proteinuria as an independent predictor of long term renal allograft outcomes remains unclear. We analyse proteinuria measured at three months post-transplantation using urinary Protein Creatinine Index (PCI), with other potential factors to establish its independent effect on long term death censored graft survival.

477 consecutive renal transplants performed and followed up in a single centre (1988-03) with a mean follow-up of 120 months were analysed. Patients were divided into 4 groups based on the median third month PCI (group-1=PCI<150, group-2=150-500, group-3=500-1000, group-4 >1000). Univariate and Multivariate Cox-Regression Analyses were performed to study the independent effect of proteinuria on the death censored graft survival. Proteinuria at 3 months strongly predicted death censored graft survival (group-2 HR 7.0, 95%CI=1.6-28.5, p=0.009, group-3 HR 12, 95%CI=3-53, p=0.001, group-4 HR 15, 95%CI 3.3-70, p<0.001). Clearly, group-3 and group-4 have very poor long term graft survival when compared to group-1. (Figure-1). We followed group-2 patients with a repeat PCI performed at 1 year and divided them into two sub-groups based on further deterioration (PCI<500 at 12/12, PCI>500 at 12/12). At 1 year (figure-2) the subgroup with PCI>500 had poor graft survival (RR=3.3, 95%CI=1.6-7, p=0.001).

In conclusion, our study clearly establishes proteinuria measured by PCI as early as 3 months as a simple marker for risk stratification for long-term death censored graft survival. Especially minimal degree of proteinuria (PCI 150-500) affected graft outcomes. When followed up, patients with deteriorating PCI within this group are shown to be possibly responsible for the bad outcomes in this group. This group represents a potential opportunity for intervention.

Figure-1:

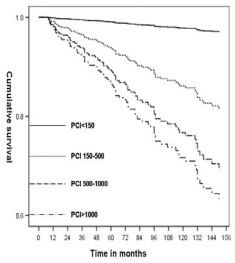
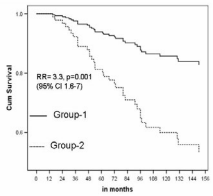


Figure-2:



O38

Renal allograft failure: examination of the mechanism and consequence of TGFβ activation

Sarah Jenkinson, Marcin Pekalski, Elizabeth Poyner, Helen Robertson, Simi Ali, John Kirby

University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom

Introduction: Inactive TGFβ is stored in normal renal tissues in the form of a large latent complex (LLC) which is bound to heparan sulphate proteoglycans in the matrix. This complex can be activated locally by the αVβ6 integrin which may be induced on epithelial cells. However, the consequences of such activation are complex; TGFβ can induce polarisation of T cells towards proinflammatory (Th17) or immunoregulatory phenotypes and can also induce graft fibrosis through induction of epithelial to mesenchymal transition (EMT) leading to non-cytolytic loss of renal tubules.

Aim: To examine the potential for activation of LLC TGFβ by activated renal tubules and to define downstream consequences for allograft pathology

Methods: The potential to activate LLC TGFβ was assessed using αVβ6 integrin transfectants and a sensitive TGFβ reporter cell line. The potential of TGFβ to induce Th17 and regulatory (FOXP3+, CD103+) human T cells was assessed *in vitro*. Immuno-cytochemistry was used to examine renal rejection biopsies for expression of the αVβ6 integrin, Th17 and FOXP3+ T cells and tubules undergoing EMT (which express S100A4).

Results: Epithelial cells expressing the αVβ6 integrin presented active TGFβ which could be released from the matrix with heparin; this activation of TGFβ could be inhibited by specific blockade of the RGD recognition site of the αVβ6 integrin. Many tubules in allograft renal tissue expressed high levels of the αVβ6 integrin; this integrin was not seen in normal renal tissue. Activated T cells upregulated FOXP3 and CD103 in the presence of TGFβ; further supplementation of the culture with IL1β and IL-23 induced the Th17 phenotype. The IL-17 produced by these cells stimulated tubular cells to release rejection-associated chemokines. In biopsy tissue, Th17 cells were localised within areas of acute inflammation whilst FOXP3+ cells were predominantly observed in areas of chronic lymphocytic infiltration and tubule loss associated with the presence of S100A4-expressing cells.

Conclusions: After transplantation, **r**enal tubules can express the αVβ6 integrin allowing the activation of TGFβ which remains bound to the tubules. Depending on the availability of proinflammatory cytokines this TGFβ can induce either Th17 or regulatory T cells. If T cell-mediated cytolysis is limited, TGFβ can also induce EMT leading to allograft failure.

O39

Donor natural killer cells determine long-term human kidney transplant outcomes through HLA-C sub-group dependent recipient dendritic-cell maturation

Rajesh Hanvesakul[1], David Briggs[1], Chandrashekhar Kubal[1], Jason Moore[1], Alison Whitelegg[1,2], Desley Neil[1,2], Nicholas Inston[1,2], Simon Ball[1,2], Paul Moss[1,2], Paul Cockwell[1,2]

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Introduction: Natural killer (NK) cells have a critical role in the maturation of the immune response. We hypothesised that NK cells are a major determinant of long-term kidney transplant outcome through interactions between NK-cell killer immunoglobulin receptors (KIR) and their ligand HLA-C. HLA-C has two subgroups, HLA-C1 and HLA-C2: based on KIR specificity, HLA-C2 is a more potent inhibitor of NK cell activation than HLA-C1.

Methods & Results: (i) In 760 kidney transplant recipients, those with HLA-C2 genotype had better 10-year graft survival than those with HLA-C1 genotype (66% & 44% respectively; p=0.002, HR=1.51, 95%CI=1.16-1.97). Donor HLA-C genotype did not influence long-term graft survival. (ii) Isolated NK cells (by CD56 staining) were present in a peri-tubular distribution in kidneys (n=5) donated for transplantation (pre-perfusion). (iii) In an allogeneic (indirect) NK-Dendritic Cell (DC) in-vitro co-culture system, the possession of HLA-C2 by DC was associated with anti-inflammatory cytokine production (IL-1ra/IL-6), diminished DC maturation (CD86, HLA-DR), and absent CCR7 expression. In contrast, possession of HLA-C1 by DC was associated with pro-inflammatory cytokine synthesis (TNF-α, IL-12p40/p70), enhanced DC maturation and CCR7 expression. These responses were IL-15 dependent.

Conclusion: These data indicate that donor derived NK cells differentially interact in situ with recipient DC through KIR/HLA-C interactions in the presence of IL-15 (which is present in the kidney early after transplantation). HLA-C2 recipients sustain less priming for indirect allorecognition than HLA-C1 recipients and have better long-term outcomes. As the NK(KIR)/DC(HLA-C) synapse is not inhibited by current immunosuppressive protocols, it represents a potent new therapeutic target in human kidney transplantation.

Parallel Session

Wednesday 22 April

Paediatric Adult Interface

10:00 – 11:30

O40

Safety of laparoscopic procurement in 306 paediatric live donor recipients: an analysis of UK Transplant data

Vassilis Hadjianastassiou[1], Rachel Johnson[2], Nizam Mamode[1]

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Laparoscopic donor nephrectomy is now the most common form of procurement for living donor paediatric recipients in the UK. However, following a previous OPTN/UNOS analysis showing higher acute rejection (AR) and delayed graft function (DGF) after LDN, doubts about safety persist. The aim of this study was to compare outcomes including graft and patient survival, AR and DGF, in paediatric recipients of living donor kidneys procured laparoscopically (LDN) and by open surgery (ODN), using data submitted to UK Transplant. The UK Transplant national database was interrogated from November 2000 to October 2007, and patients with missing data were included in this analysis, which thus represents a complete capture of all paediatric recipients. Categorical variables were compared with Pearson's chi-square tests, continuous variables with 2-tailed independent T-tests, and time to event (survival) comparisons using the log rank test. A Cox proportional hazards model was used to adjust survival for confounding variables.

306 consecutive recipients, with a mean age of 10.7 (SE 0.3) years were studied. 119 had LDN kidneys and in 9 nephrectomy type was unknown. There was no significant difference in DGF between the groups (5/119 LDN v 7/178 ODN p=0.241), or in the incidence of acute rejection censored at 2 years post-transplant (19/72 LDN v 13/49 ODN p=0.99) but mean (S.E.) cold ischaemia time was significantly different (2.7(0.1) LDN v 2.1(1.3) ODN p<0.001). Unadjusted graft survival (GS) was significantly better in the LDN group, although no difference was seen in patient survival (PS).

	2 yr GS	Log rank P value	2 yr PS	Log rank P value
ODN	93.2%	0.02	97.6%	0.10
LDN	99.1%		100.0%	

The significant influence of the type of nephrectomy on graft survival censored at 2 years remained after adjusting for year of transplantation and cold ischaemic time, but this influence disappeared after adjusting for acute rejection in the first 2 years post-transplant.

We conclude, contrary to previous reports, that LDN offers better medium-term graft survival for paediatric recipients when compared with ODN and that it should be the method of choice for procurement.

O41

The Haemodynamic Response to Haemodialysis In Children

Daljit Hothi[1], Lesley Rees[1], Christopher McIntyre[2]

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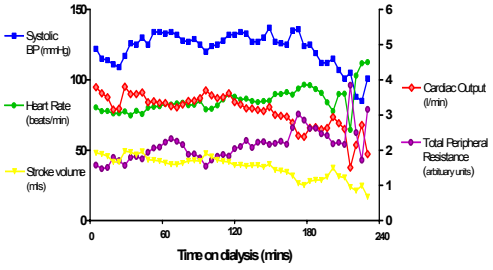
Purpose of Study: Placing children on haemodialysis (HD) places a high demand on the cardiovascular system, effecting both objective and subjective tolerability. The aim of the study was to determine the haemodynamic response to this stress in this previously inadequately studied patient group.

Method: We included 8 chronic HD patients (11-17 years) dialysis dependent for 4-130 mths. Non-invasive, continuous haemodynamic monitoring was undertaken using a Finometer (TNO instruments Amsterdam) through pulse-wave analysis at the digital artery for the duration of the dialysis session. Patients were dialysed for 4hrs 3 times/wk, using high flux polysulfone or triacetate cellulose membranes against a constant dialysate temperature of 37.0°C. Dialysate contained sodium 140 mmol/l, calcium 1.75mmol/l and bicarbonate 34mmol/l. The net ultrafiltration volume ranged from 5-61mls/kg.

Results:



The combined group trend, as illustrated in the graph, showed a falling cardiac output (CO) and stroke volume (SV) and rising heart rate (HR) with time on dialysis. As the systolic blood pressure (SBP) fell in the latter half of dialysis the total peripheral resistance (TPR) increased. This pattern was however not homogeneous to all subjects. Characteristically there was severe CV functional perturbation in the last hour of HD.

Conclusion: The hemodynamic response to hemodialysis and ultrafiltration is different and individual to each child. Knowledge of their specific adaptive responses may allow us to target interventions in supporting their circulation during dialysis.

O42

Monitoring of Tacrolimus using fingerprick blood compared with venous blood sampling

Sheila Ramjug[1], James Fildes[1], Anna Baynes[1], Nizar Yonan[1], Brian Keevil[2]

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Introduction

Monitoring of Tacrolimus levels of transplant recipients is an essential part of their post-transplant care. Routinely venous bloods are taken at clinic visits to ascertain levels. However not infrequently many patients return to clinic solely for a Tacrolimus level. Consequently, as already demonstrated with Cyclosporin, the question has been raised as to whether it would be possible to measure Tacrolimus levels from fingerprick blood samples. This would allow patients to take the samples themselves and in the future post them to the laboratory. This is currently being performed with Cyclosporin levels and since this application there has been a 10-15% fall in outpatient visits and a happier transplant population who are no longer making clinic visits simply for drug monitoring.

Methods

Blood samples n=60, were obtained from adult heart and lung transplant patients. At the time of venous blood sampling a fingerprick sample was also acquired. Fingerprick samples were analysed using liquid chromatography mass spectrometry micro assay (LC-MS/MS) a process developed by our biochemistry department in order to deal with such small blood samples – 10uL.

Results

Between batch imprecision (CV%) for the last 12 months (n=270) at a concentration of 3.5, 6.9, 13.9ug/L was 8.0%, 5.4% and 5.2% respectively. Passing and Bablock regression analysis between fingerprick and venous blood showed fingerprick Tacrolimus = 1.01 (venous blood Tacrolimus) -0.07. Bland Altman analysis showed good agreement with a bias of 0.1ug/L and 95% limits of agreement from -1.1 to 1.1 ug/L.

Conclusion

Therefore this LC-MS/MS methodology developed by our biochemistry department has shown conclusively that there is the potential to allow patients to collect fingerprick blood samples at home and send them to the laboratory using the postal service, thus avoiding unnecessary clinic visits whilst maintaining a high standard of post-transplant care.

O43

Haemodialysis induced myocardial stunning is common in children and associated with dialysis induced hypotension

Daljit Hothi, Lesley Rees, Jan Marek, Christopher McIntyre

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Purpose of Study: In adults sequential haemodialysis (HD) induced cardiac injury leads to heart failure with an attendant increased mortality. Intradialytic hypotension and higher ultrafiltration (UF) volumes appear to be major drivers of this process, but the relevance of conventional epicardial coronary artery disease (CAD) remains unclear. Uraemic children share the full gamut of CKD related CV abnormalities as adults, but without significant classical atheromatous CAD. Therefore we investigated children on HD for the onset of cardiac injury.

Method: We included all single centre chronic HD patients (n=12, aged between 2-17 years). Patients with overt cardiac disease were excluded. Patients were dialysed for 4hrs using high flux polysulfone membranes against a dialysate temperature of 37.0°C. Through serial echocardiography (pre-dialysis, 240m and 15mins after dialysis) we measured LV regional wall motion. Significant stunning was defined as a 20% reduction in wall motion (RRWM) in more than 2 segments, hyperkinesis as > 20% and >50% increase in shortening fraction (SF).

Results: All 12 patients developed RRWM in 1-5 segments during dialysis and 11/12 showed partial recovery after dialysis. 11/12 patients developed 20% hyperkinesis in 2-4 segments during dialysis and 9/12 developed 50% hyperkinesis in 1-5 segments. This resulted in left ventricle ejection fraction being maintained over HD. The mean segmental $\%SF_{[total]}$ and mean segmental $\%SF_{[RRWM]}$ was significantly lower at baseline compared with the end of dialysis {(2.19 to 1.77, $p<0.05$) and (2.72 to 1.37, $p<0.05$) respectively}. Intradialytic BP change was significantly associated with mean segmental $\%SF_{[RRWM]}$ ($p<0.05$).

Conclusion: Paediatric HD patients receiving conventional HD suffer from HD induced myocardial stunning. As in adults, this reflects the degree of HD induced haemodynamic instability. These data, in combination with previous studies of myocardial blood flow during HD (in adults), suggest that the characteristic cardiovascular phenotype in HD patients predisposes to significant demand ischaemia in the absence of conventional epicardial CAD.

O44

Pre emptive coronary angiography and intervention improves cardiac survival in transplant patients and those awaiting transplantation.

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West London Renal and Transplant Centre, London, United Kingdom

Renal transplantation improves quality of life and prolongs survival in patients with End Stage Renal Disease [ESRD]. Recent interest has focused on wait listing patients without pre-treating coronary artery disease [CAD] in order to expedite transplantation.

Our practice is to aggressively manage CAD prior to transplantation irrespective of cardiac symptoms. Between Jan 2006 and Jan 2008, 431 patients [m=282 f=149 age=56.96 ± 9.62 years] underwent coronary angiography as part of their pre-transplant assessment. 384/431 [89.1%] patients were wait listed and 132/384 [34.4%] patients were transplanted during the follow up period, 20.78 ± 6.66 months. The mean time from cardiac referral to coronary angiography and intervention if necessary was 4.87± 2.71 months.

Survival in patients not wait listed was poor, 83.6% and 65.3% respectively at 1 and 3 years compared with 98.7% and 94.0% at 1 and 3 years in the wait listed patients [Logrank $p<0.001$].

127/431 [29.5%] of patients were offered coronary intervention. Survival in patients [n=8] who declined coronary revascularisation and were therefore not wait listed for transplantation was also predictably poor with a 75.0% 1 yr and 12.5% 3 yr patient survival [5 deaths, 4/5 due to cardiac causes]. Patients who underwent coronary intervention followed by transplantation [n=30] had a 100.0% and 90.0% cardiac event free survival at 1 yr and 3yrs respectively, comparable to those patients in whom intervention was not indicated. Cardiac event free survival in those patients who underwent intervention but remained on dialysis awaiting deceased donor transplantation was similar, 90.0% and 86.2% at 1 and 3 yrs respectively [Logrank $p=0.07$].

Our data suggest that pre emptive coronary angiography and intervention on flow limiting coronary artery lesions, not only improves survival in patients subsequently transplanted but also in those patients waiting on dialysis.

O45

Patients awaiting a renal transplant have a severe functional impairment of their left ventricle when assessed with cardiopulmonary exercise testing

Joanna McKinnell[1], Robert Higgins[1], Chris Imray[2], Duncan Watson[3], Pritwith Banerjee[4], David Parr[5], Daniel Zehnder[1,6]

[1]Department of Nephrology, [2]Vascular Surgery, [3]Critical Care, [4]Cardiology, [5]Respiratory, University Hospitals of Coventry and Warwickshire, Coventry, UK, , [6]Warwick Medical School, University of Warwick, Coventry, UK

The ability to adapt to increased oxygen demand predicts the risk of early death and also postoperative outcome. It is mainly influenced by cardiac left ventricular function. Chronic kidney disease (CKD) patients are profoundly affected by impaired cardiac function. Tests designed to identify myocardial ischemia alone will fail to detect cardiac failure and are inadequate as a screening test for the assessment of postoperative cardiac risk in patients undergoing non-cardiac major surgery. At present there are no methods to predict the risk after renal transplant. We present data of a functional cardiopulmonary test for the assessment of our CKD patients awaiting a renal transplant.

Aerobic capacity as a measure for left ventricular function was assessed by cardiopulmonary exercise testing (CPET). This value has been shown to be a predictive for mortality after other types of surgery and at altitude in healthy people. The anaerobic threshold (AT) expressed as the most repeatable and relevant value of oxygen consumption index to body mass (ml/min/kg) was compared to known predictors of survival in CKD patients including age and diabetes as well as traditional pre-transplant cardiac assessment tools.

Over 12 months CPET results were obtained on 110 patients (1 technical failure, 1 failure to reach AT, 1 failure due to poor mobility). The age range was 25-74 years (median 54.7) with an AT range between 5.6-30.8 ml/min/kg (mean 12.0); maximal oxygen uptake (peak VO_2) 6.6-34.6 ml/min/kg (mean 16.1), on average 55.9% of the predicted values. AT was correlated with age ($p<0.0001$). Male gender (88%) predicted a higher AT (13.4 vs. 10.5 ml/min/kg; $p=0.003$) and diabetic patients had a significantly lower AT (9.5 vs. 12.3 ml/min/kg; $p=0.02$). Echocardiographical evidence (n=77) of left ventricular hypertrophy (LVH) resulted in a lower AT ($p=0.02$).

When an AT <11 ml/min/kg was used as a threshold, a cut off shown by other groups to identify various patient populations at high risk of premature death and significant peri-operative mortality, 48% of patients on the transplant waiting list were in this category. They were older ($p=0.02$), had higher BMI ($p=0.008$), more had diabetes and evidence for LVH and diastolic dysfunction. CKD and dialysis duration, lung function and haemoglobin levels were not different in the two groups. In these cohorts evidence of coronary artery disease had no impact on the AT values.

To our knowledge this is the first study investigating the 'normal' range of cardiopulmonary functional capacity of CKD patients, by quantifying the AT with CPET. Almost half of the patients had a low AT putting them potentially at increased risk of premature cardiovascular death and peri-operative mortality. However, the threshold observed in non-renal patients may not apply. The usefulness of CPET as a predictive tool for CKD patients, replacing classical methods, is under investigation.

Parallel Session

Wednesday 22 April

Long Term Outcomes

14:00 – 15:30

O46

Long-term safety of Belatacept: 5 year results of a Phase II study

Peter Friend[1], Ferdinand Mühlbacher[2], Bernard Charpentier[3], Christian Larsen[4], Mamta Agarwal[5], Flavio Vincenti[6]

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Belatacept is the first drug in its class, a T-cell co-stimulation blocker which inhibits CD28 mediated T-cell activation and provides selective immunosuppression. An interim report of an open-label long-term extension (LTE) of the Phase 2 trial is presented.

The Phase 2 trial design and results have been described previously. For the LTE, Belatacept arms were dosed as either 4-weekly or 8-weekly maintenance infusions of 5mg/kg; control patients received cyclosporine (CsA), dosed to target C_0 levels (150-300 ng/ml). All patients continued to receive MMF and steroids per protocol. Results for outcomes and serious adverse events (SAE) are presented as incidence rates per 100 patient-years of drug exposure. No formal comparisons or statistical testing were applied.

128 of 218 original patients elected to participate in the LTE and remained on their assigned treatment; 102 received Belatacept, 26 received CsA. Among LTE patients enrolled, 92 (72%) patients remain (76/102, 75% Belatacept; 16/26, 62% CsA). Median follow-up from original randomisation was 60 months (range 15 to 78 m). Results for SAE categories, acute rejection (AR), and death/graft loss are shown below.

At up to five years, Belatacept remains safe and associated with low rates of acute rejection, death and graft loss as part of a long-term, CNI-free immunosuppression regimen in renal transplant. Belatacept is also being evaluated in Phase 3 trials as CNI-free immunosuppression in renal transplantation – results of these studies are awaited.

	Bela Rate/100 pt-yr (95% CI)	CsA Rate/100 pt-yr(95% CI)
Infections	4.0 (2.3-6.5)	7.1 (2.8- 14.6)
Neoplasms	3.0 (1.5-5.2)	3.0 (0.6-8.9)
Cardiovascular	0.5 (0.1-1.8)	3.0 (0.6-8.9)
Treated AR	3.0 (1.5-5.4)	3.2 (0.7-9.3)
Death or Graft Loss	1.0 (0.3-2.6)	2.0 (0.2-7.3)

O47

Long-term results of renal transplants from non-heart-beating donors: a case-matched comparison with heart-beating donors

Adam Barlow[1,2], Matthew Metcalfe[2], Yasha Johari[1,2], Rosemary Elwell[2], Peter Veitch[2], Michael Nicholson[1,2]

[1]University of Leicester, Leicester, United Kingdom, [2]Leicester General Hospital, Leicester, United Kingdom

Background:

The function and survival of renal transplants from non-heart-beating donors (NHBD) has been shown to be comparable to those from heart-beating donors (HBD) up to 10 years post-transplantation. However, there is little data on outcome after 10 years.

Methods:

112 predominantly uncontrolled NHBD renal transplants performed in Leicester between April 1992 and January 2002 were matched for factors known to influence graft survival with 164 HBD renal transplants performed over the same time period. Graft function and survival were assessed.

Results:

There was no significant difference between the groups for factors known to influence graft survival, other than warm ischaemic time (P<0.0001). Delayed graft function was significantly higher in the NHBD group (NHBD vs. HBD, 81% vs. 22%, P<0.0001). Primary non-function rates were similar in the two groups (NHBD vs. HBD, 5.4% vs. 1.8%, P=0.16). Overall serum creatinine was significantly higher in the NHBD (P<0.0001). 1, 3, 5, 10 and 15-year crude survival were 83.9%, 81%, 67.3%, 49.2% and 25% respectively for NHBD kidneys and 88.3%, 86.7%, 75.4%, 56.9% and 42.7% respectively for HBD kidneys (P=0.09). Median crude allograft survival was 114 months for NHBD kidneys and 157 months for HBD kidneys. 1, 3, 5, 10 and 15-year refined survival, accounting for recipient mortality, were 87.9%, 79.3%, 75%, 60.9% and 36.7% respectively for NHBD kidneys and 91.8%, 89.1%, 86.3%, 69.9% and 57.4% respectively for HBD kidneys (P=0.05).

Conclusion:

In conclusion, this study demonstrates comparable allograft survival for NHBD and HBD kidneys followed for up to 15 years, despite higher rates of DGF and higher serum creatinine levels in the NHBD group. These findings further support the use of NHBD kidneys, particularly those from Maastricht category II uncontrolled donors, which made up the majority of this series.

O48

Calcineurin Inhibitor Free Immunosuppression Improves Kidney Graft Function but at the Expense of an Increase in Acute Rejection. A Meta-analysis of RCTs

Neil Russell[1,2], Andrew Bradley[1], Peter Morris[2]

[1]Department of Surgery, University of Cambridge, Cambridge, United Kingdom, [2]Centre for Evidence in Transplantation, Royal College of Surgeons of England, London, United Kingdom

Introduction: The nephrotoxicity of calcineurin inhibitors (CNI) can result in decreased kidney graft function and may ultimately impact on long term graft survival. This has lead to the introduction of new immunosuppression protocols that reduce exposure to CNIs. Such protocols include the withdrawal of the CNI at a designated time point after transplantation.

Methods: Detailed literature searches of the Medline, Embase and Cochrane databases were performed. RCTs that met the inclusion criteria were identified. The primary outcome of the meta-analysis was renal graft function. Secondary outcomes were acute rejection rates, patient and graft survival, BP, lipid profile and incidence of post transplant diabetes. Confidence intervals (CI) were set at 95%.

Results: A total of 29 articles reporting on 16 trials including 2037 patients met the inclusion criteria. Creatinine was significantly improved with CNI withdrawal at 6 months (4 trials, 844 patients (pt), WMD -13.0µmol/l, CI -21.2 to -4.8), and at 12 months (7 trials, 1403 pt, WMD -11.8, CI -18.6 to -5.1). GFR was also improved with CNI withdrawal at 6 months (3 trials, 417 pt, WMD 6.1 ml/min, CI 4.2 to 9.7) and at 12 months (7 trials, 1201 pt, WMD 5.4, CI 3.5 to 7.4). Acute rejection was increased in the CNI withdrawal protocols at 12 months (11 trials, 1600 pt, RR 1.53, CI 1.3 to 1.9), and at 2 years (3 trials, 674 pt, RR 1.9, CI 1.4 to 2.7). There was no significant difference seen in graft or patient survival with the longest follow up being 5 years. No difference was seen in blood pressure or diabetes with withdrawal of CNI but both cholesterol (8 trials, 1117 pt, WMD 0.5mmol/l, CI 0.3 to 0.6) and lipids (6 trials, 1017 pt, WMD 0.3mmol/l, CI 0.2 to 0.5) were increased.

Conclusion: Withdrawing CNIs results in better kidney graft function but an increased acute rejection.

Parallel Session

Wednesday 22 April

Transplant Immunology / Basic Science

14:00 – 15:30

O49

NKT cells participate in the alloimmune response and can promote allograft survival or rejection depending on the type of transplant

John-Paul Jukes, Zhenlin Zhao, Kathryn Wood, Nick Jones

University of Oxford, Oxford, United Kingdom

NKT cells have been found to be either pro-inflammatory or pro-tolerogenic in a number of models of autoimmune disease and malignancy, however their role in transplantation remains unclear. To investigate NKT cell responses in transplantation we have employed a model of skin transplantation using MHC mismatched BALB/c donors and C57BL/6 (B6) recipient mice. Using an αGalCer-loaded CD1d tetramer to detect NKT cells, we found that NKT cells homed specifically to the lymph nodes draining the skin graft by 10 days post transplantation (median survival time (MST) of skin allografts was 16 days). Furthermore, NKT cells were detectable in skin allografts by 3 days post transplant, increasing by 3 fold by day 10. We also examined NKT cell responses to either syngeneic or allogeneic cardiac grafts in B6 mice. Following transplantation, NKT cells significantly increased in number ($6.7x10^5$ compared to naïve $2.7x10^5$) and were found to have up-regulated the activation marker CD69 in the spleen of both syngeneic and allogeneic heart recipients (increase of 23% and 24%, respectively compared to naïve NKT cells). By 5 days post transplantation splenic NKT cell numbers had significantly decreased however, at this time NKT cells were found to have infiltrated allogeneic but not syngeneic heart allografts.

We next examined the impact of NKT cell responses on the induction of prolonged allograft survival. We found that administration of anti-CD154, -CD4 and -CD8 monoclonal antibodies (mAbs) resulted in prolonged BALB/c skin graft survival (from 16 days in untreated mice to 38 days in mAb treated B6 mice). Interestingly, in B6 NKT knockout recipients skin allograft survival was further extended (MST=53 days, p=<0.0001 WT vs NKT KO). In clear contrast, administration of anti-CD154 mAb prolonged BALB/c heart allograft survival in B6 mice (from 9 days to 60 days) whereas NKT knockout recipients treated with anti-CD154 mAb rejected grafts more rapidly (MST=41 days, p=0.01 WT vs NKT KO).

In conclusion, these results suggest that NKT cells participate in the immune response to allografts where they are detrimental to skin allograft survival but promote the survival of heart allografts. We are currently investigating the mechanism by which NKT cells contribute to allograft rejection and tolerance in these models.

O50

The induction and function of S100A4 during inflammation in liver transplants.

Helen Robertson, Karolina Rygiel, Alastair Burt, John Kirby

Newcastle University, Newcastle upon Tyne, United Kingdom

Background: Damage to bile ducts is characteristic of ductopenic allograft rejection; this may be a result of immune-mediated cytolysis of bile duct epithelium (BEC). However, recent studies suggest that BEC can undergo transition to become myofibroblasts by epithelial to mesenchymal transition (EMT) after stimulation by factors such as TGFβ. EMT results in loss of epithelial markers and acquisition of fibroblast markers, including S100A4. S100A4 can modify cell motility and its induction occurs sufficiently early to visualise BEC *in situ* during the initial phases of EMT. This study was designed to define a role for S100A4 during induction of the EMT phenotype and to identify an association between S100A4 in BEC and intraepithelial T cells in liver tissue undergoing rejection. **Methods:** Primary BEC were cultured with a range of stimuli including $TGF\beta_1$ and TGFβ-presenting T cells (MOLT16). Phenotypic changes were detected by immunofluorescence. 3-dimensional (3-D) structures produced by a chloangiocyte line (H69) were incubated with either TGF-β1 or MOLT16. Chemokines produced by H69 cells were detected in media using chemokine array. Phenotyping of portal tract infiltrate was undertaken in liver transplant biopsy tissue and BEC expressing S100A4 identified. TGFβ distribution and activity in tissue sections was assessed. Day 0 transplant biopsies served as control tissue. **Results:** Resting BEC expressed cytokeratin-7 (CK-7) but did not express S100A4. $TGF\beta_1$ and MOLT16 both caused BEC to undergo phenotypic change to produce cells with a fibroblastic morphology, loss of CK-7 and increased expression of S100A4. 3-D branching structures of H69 cells produced chemokines including IL-8, GRO, MCP-1, MIP-1β and RANTES that attracted T cells which adhered to the cell surface and infiltrated the epithelium. Accumulations of CD4+ T cells, including FOXP3+ T cells, were found in the portal tract infiltrate but the bile duct infiltrate was predominantly CD8+. Many cells expressing both CK-7 and S100A4 were present in infiltrated bile ducts but S100A4 was absent from normal bile ducts. **Conclusions:** Inflamed bile duct epithelium has the potential to undergo EMT as a result of induced expression of the motility associated protein S100A4. The phenotypic plasticity of BEC could explain the apparent reversibility of bile duct loss after cellular rejection in liver transplants.

O51

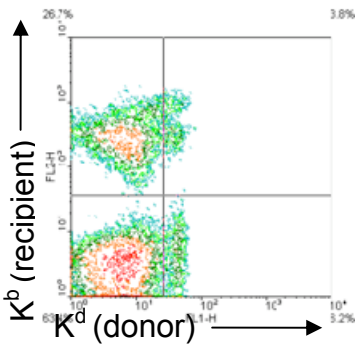
Intercellular MHC transfer in vivo during immune response and at rest

Mehmet Fidanboylu, Kathryn Brown, Steven Sacks, Wilson Wong

King's College London, London, United Kingdom

Introduction Transfer of intact surface molecules (trogocytosis) between cells of the immune system has been demonstrated under artificial conditions such as solid organ transplantation. When intact donor MHC molecules are transferred to the surface of recipient antigen present cells (APC), they will be recognised by T cells via the direct antigen presentation pathway, despite being presented by recipient APC. These recipient APC also express self MHC molecules that can present donor derived peptides, recognised via the indirect pathway. Thus, this "semi-direct" antigen presentation pathway could link allospecific T cells of these 2 distinct pathways. However, it is not yet known if trogocytosis occurs under normal physiological conditions, and if so, if it is a process that is regulated or even 'up-regulated' during conditions of immune stress such as infection. Using irradiation bone marrow chimera in mice, we studied trogocytosis at rest and following stimulation of the immune system via TLR-2 receptor signalling.

Methods DBA/2(H-2^d) to BL/6 (H-2^b) bone marrow chimera was generated by injecting 20x10^6 donor bone marrow cells into BL/6 recipients pre-conditioned with 5.5Gy of total body irradiation. Peripheral blood was analysed using FACS.



Results Donor K^d positive cells could be detected in peripheral blood of recipients at all time points studied, ranging from 0.4 to 39.9% of all MHC class I positive cells. Cells that were positive for both donor K^d and recipient K^b molecules could also be detected at all time points (figure). Of cells that were positive for donor K^d molecules, between 18.9 and 99.4% (mean = 59.8 ± 8.01%) also express recipient K^b molecules, indicating that intercellular MHC transfer has taken place. Injection of the TLR-2 agonist, Pam_3CSK_4 did not significantly alter the level of MHC transfer observed.

Conclusions and implications Our data suggest that trogocytosis of MHC class I does occur in this model of near normal 'physiological' conditions at rest. This may have important implications for many aspects of immunology including organ transplantation.

Parallel Session

Wednesday 22 April

Marginal Donors

15:35 – 16:35

O52

Pancreas Transplantation using Expanded Criteria Donors

Anand Sivaprakash Rathnasamy Muthusamy[1], Nancy Suh[1], Shirley Lockhart[1], April Stanley[1], David Mitchell[1], Jens Brockmann[1,2], Anil Vaidya[1], Sanjay Sinha[1], Peter Friend[1,2]

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

Introduction: The disparity between the availability and demand for donor pancreases has increased in recent years. In an effort to increase the donor pool, we have expanded our acceptable donor criteria to include older (age >45 yrs) and non-heart-beating donors (NHBD). Results from expanded criteria donors (ECD) have been compared with those from standard criteria donor grafts (SCD) (heart-beating donors; age <45 yrs).

Methods: From April '04 to September '08, 238 pancreas grafts were transplanted from 161 SCD (133 SPK, 22 PAK and 6 PTA) and 77 ECD (49 SPK, 15 PAK and 13 PTA). The ECD group included 25 NHBD. All grafts were implanted intraperitoneally with enteric exocrine and systemic venous drainage. Median follow up was 20 months (range 3-56) for SCD and 12 months (range 3-49) for ECD. Outcome measures include the incidence of delayed graft function (DGF) of pancreas & kidney, graft & patient survival.

Results: SCD recipients were significantly younger (42.34±6.88) than ECD recipients (45.6±8.28) (P=0.0015), due to an effort to match the donor age in SCD (29.46±9.89) & ECD (45.97.1±12.88). ECD had body-mass index similar to SCD (23.63±3.60 vs. 24.37±3.62), and were predominantly female in comparison with SCD. Mean cold ischemia time was similar in both groups (11h30min vs. 11h24min). Average hospital stay (18.1±11.6 vs. 19.2±14.39 days), re-admissions rate (37.2 vs. 37.6%), rejection incidence (18.3 vs. 14.3%) and re-operations (22.9% vs. 24.6%) were similar. ECD grafts had a higher incidence of DGF of both kidney (26.5% vs. 12.7%, P<0.05) and pancreas (10.3% vs. 0.6%, P=0.0006). Overall pancreas (87% vs. 83%), kidney (93% vs. 92%) and patient survival (96% vs. 95%) were similar.

Conclusions: ECD offers a large potential pool of pancreas grafts which can provide similar early patient and graft outcomes compared to SCD, despite a higher incidence of DGF for both kidney and pancreas. These donors provide a valuable source of pancreases for transplantation.

O53

Impact of donor age in pancreas transplantation. A UK single centre experience.

Bence Forgacs, Sarah Heap, Maria Mitu-Pretorian, Abbas Ghazanfar, Deep Malde, Sanjay Mehra, Tunde Campbell, Hany Riad, Neil Parrott, Ravi Pararajasingam, Titus Augustine, Afshin Tavakoli

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Background: The shortage of cadaveric donors for pancreas transplantation has prompted the use of organs from donors previously regarded as suboptimal.

Objective: The aim of our study was to compare the outcome and complications in pancreas transplant recipients transplanted with organs from different donor age groups.

Material and method: 166 pancreas transplants were performed in our unit between 2001 to December 2008. 128 simultaneous pancreas kidney (SPK), 30 pancreas after kidney (PAK) and 8 pancreas transplantation alone (PTA). Clinical data was collected prospectively into an electronic database (Microsoft Excel). Patients were grouped according the donor age and analysed. Group I (n=25): donor age< 18, Group II (n=116): donor age 18-45 and Group III: (n=25) donor age >45 years old. Clinical outcomes including early and long term surgical morbidity (e.g. bleed, thrombosis, infections, etc), graft, patient survival and hospital stay were compared between all groups.

Results: The one year patient survival rate in Group I was 100%, 89% in Group II and 88% in Group III. The one year pancreas graft survival rate was 84%, 76% and 68% respectively.

Major surgical complications	**Group I**	**Group II**	**Group III**
Graft thrombosis (%)	8	15	20
Bleed/Haematoma (%)	12	12	20
Wound infection (%)	0	21	16
Radiological collection drainage (%)	0	15	16
Major fistula (%)	8	11	8
Peritonitis/Intraabd. Abscess (%)	4	22	24

The median HDU/ITU stay was shorter in group I (3.5days) and II (2.5days) compare to group III (5.5 days), the median hospital stay was similar (18, 15.5 and 17.5 days respectively).

Summary: Both patient and graft survival rate was higher in the group receiving transplant from paediatric donors. Similarly the rate of major surgical complication tended to be lower. Recipients with organs received from younger donor have shorter HDU/ITU stays.

O54

Kidneys declined by other centres do not have inferior outcomes

Nagappan Kumar[1], Susanna Piloi[2], Rachel Johnson[2], Rommel Ravanan[1]

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Aims: Recipient transplant teams may turn down potential donor kidneys offered by UKT for individual patients. A number of donor, recipient and logistical issues are recorded by UKT as reasons for refusal of donor organs. Knowledge of the number of prior refusals by previous centres may trigger/promote concerns regarding organ viability in subsequent centres offered the same kidney. The aim of this study was to see if the number of times a kidney was refused and the reasons behind such refusals had an impact on transplant outcome.

Methods: Adult, first kidney only, deceased donor transplants carried out in the UK between 01 January 2000 and 31 December 2004 [n = 4000] were followed up to 31 December 2007 or death or graft failure whichever was earliest. Kaplan-Meier survival analysis and Cox proportional hazards regression were used to investigate whether the number of refusals [categorised as none, 1-4 refusals or >4 refusals] and reason for refusal [categorised as none, donor, organ or recipient reason] influenced subsequent outcome. Donor and organ factors accounted for were age, history of hypertension, serum creatinine at retrieval and organ damage.

Results: Univariate analysis suggested that number of declines [p = 0.04] and reason for refusal [p = 0.01] influenced subsequent graft and patient survival. However, after adjustment for relevant donor and recipient variables, number of refusals was no longer a significant factor [p >0.5] and amongst reasons for refusal only donor reasons had a significant association [p = 0.02] with outcome. Even the least well performing groups [>4 refusals or organs refused for donor reasons] achieved >75% five year patient & graft survival.

Conclusion: We conclude that knowledge of the number of times a donor kidney offer has been turned down by other centres is a poor predictor of post transplant outcome after accounting for key donor factors. Despite prior refusals, such kidneys can be expected to achieve acceptable 5 year outcomes. Based on this information UKT, in conjunction with transplanting units, should reassess if the current “opt out policy” for donor offers by transplant centres is appropriate and, if not, how it should be altered.

		Number analysed	Patient survival HR[CI]	p-value	Graft survival HR[CI]	p-value
Number of refusals	0	2565	1.00		1.00	
	1-4	1237	1.08[0.8-1.3]	0.5	1.07[0.8-1.2]	0.5
	>4	198	1.04[0.6-1.6]	0.9	1.02[0.7-1.4]	0.9
Reason for refusal	None	2944	1.00		1.00	
	Donor	399	1.24[0.9-1.6]	0.2	1.33[1.05-1.6]	0.02*
	Organ	135	0.95[0.5-1.5]	0.8	0.92[0.6-1.3]	0.7
	Recipient	522	1.07[0.7-1.4]	0.7	0.91[0.7-1.1]	0.5

Parallel Session

Wednesday 22 April

Transplant Immunology / Basic Science

15:35 – 16:35

O55

Effect of the Indirect Alloimmune Response on Endothelial Dysfunction

Y. Xu, B. Hariri, A. Chester, A. McCormack, M.L. Rose

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Background Endothelial dysfunction is an early marker for the development of cardiac allograft vasculopathy (CAV) in cardiac transplant patients. The causes of endothelial dysfunction are not known. Here we have investigated whether the indirect immune response mediates endothelial dysfunction. Utilizing a single MHC class I-disparate rat model of alloantibody mediated CAV, we have assessed the function of the micro and macro-vasculature of cardiac allografts and syngrafts at various times after transplantation. **Methods** PVG.RT1^{u} rat hearts were transplanted into thymectomised CD8 T-cell depleted allogeneic (PVG.R8) or syngeneic (PVG.RT1^{u}) recipients. Hearts were removed at 2, 4 and 8 weeks post-transplantation to assess endothelial function using langendorff preparations and immunohistochemistry. Aortic rings of control PVG R8 rats were exposed to anti-class I antibody, and the effect on endothelial relaxation was investigated. **Results** All allografts showed luminal occlusion 4 weeks (29±6%) and 8 weeks (58±2%) post-transplantation and myocardial infiltration by monocytes. Capillary C4d deposition on the microvasculature was positive in all allografts, but there was no difference in numbers of CD31 positive endothelial cells between syngeneic and allogeneic hearts. At 4 weeks post-transplantation, basal coronary flow of the allograft was 54% lower compared to the syngraft ($p<0.01$). Serotonin (10^{-6}M) and SNP (10^{-6}M) did not evoke a marked increase in coronary flow in the allograft heart (4.4% *vs* 43.8% and 16.1% *vs* 61.2% in the syngraft control, respectively, $p<0.01$). Similar basal flow was obtained in allogeneic and syngeneic hearts after 2 weeks transplantation (5.0ml/min vs 5.5ml/min), probably reflecting lack of luminal occlusion at this time. In contrast, in allografts, the 5-HT stimulated coronary flow was significantly less than syngrafts (21.9% *vs* 47.1%, $p<0.05$); whilst SNP stimulated flow showed a tendency to decrease (41.2% *vs* 60.6%), suggesting endothelial function is adversely affected at 2 weeks. The ability of aortic rings from normal PVG R8 rats to relax in response to acetylcholine was significantly inhibited ($p<0.01$) in a dose-dependent manner by exposing to anti-class I antibody *in vitro* for 24h. **Conclusion** Our data suggested that the indirect pathway and alloantibody mediate vascular dysfunction within 2 weeks of transplantation; studies are in progress to investigate whether alloantibody affects pathways of NOS production.

O56

Therapy with non-glycosaminoglycan-binding mutant CCL7: a novel strategy to prevent allograft inflammation

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Chemokines form stable concentration gradients by interaction with glycosaminoglycan (GAGs); these gradients support vectorial lymphocyte recruitment from recipient blood to graft tissues during allograft rejection. A non-GAG-binding mutant CCL7 was developed which retained its affinity for chemokine receptors. This mutant induced leukocyte migration in diffusion gradients but did not stimulate trans-endothelial migration ($p=0.005$). Unlike wild-type CCL7, the mutant chemokine persisted in the circulation of BALB/c mice for more than 6 hours after intravenous administration and prevented leukocyte infiltration of BALB/c skin isografts ($p<0.05$). Treatment with mutant CCL7 marginally increased the survival of C57BL/6 to BALB/c skin allografts but these grafts showed fewer infiltrating CD3+ cells than control tissue ($p<0.05$). Importantly, mutant CCL7 promoted long-term (>40 day) graft survival following HY antigen mismatched C57BL/6 skin transplantation; control grafts were rejected by day 24. Unlike wild-type CCL7, the mutant chemokine reduced CCR2 expression by circulating leukocytes for 6 hours ($p<0.5n$). Chronic stimulation with CCL7 also blocked the normal increase in affinity of α4β1 integrins for VCAM-1 following transient chemokine stimulation. These data suggest that mutant CCL7 persists in the circulation and reduces the capacity of circulating immune cells to respond to GAG-bound chemokine at sites of developing inflammation. Although this anti-inflammatory activity was sufficient to prevent the rejection of HY mismatched skin grafts, full MHC-mismatched skin allografts were rejected almost normally.

O57

31 Phosphorus Magnetic Resonance Spectroscopy for dynamic assessment of ATP levels in pancreas preserved by the two-layer method

Aditya Agrawal, Alan Bainbridge, Martin Press, Steve Powis, Barry Fuller, Brian Davidson

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Background: Cold preservation injury influences islet graft function. Reliable tools to predict pancreas viability before processing for islets are lacking.

Objective: To assess the effect of different preservation conditions on the bioenergetic profile of pancreas by developing a model that is also clinically relevant and will allow non-invasive dynamic assessment of mitochondrial function prior to islet isolation.

Methods: 31-phosphorus spectra were collected from rat pancreas stored in five randomly assigned preservation groups: cold Marshall's, static Two-Layer method (TLM) and continuous TLM immediately after harvest, and static TLM and continuous TLM after 30 min warm ischaemia. Signal amplitudes were measured for phospho-mono-esters (PME), inorganic phosphate (Pi) and α-, β- and γ - nucleotide triphosphate (ATP) and [γ-ATP]/[Pi] and [β-ATP]/[Pi] were computed.

Results: The group-mean rates of increase of [γ-ATP]/[Pi] and of [β-ATP]/[Pi], derived from the linear regressions to the data from individual experiments, were significantly different between the preservation groups in both studies. In the *immediate cold preservation study,* [γ-ATP]/[Pi] and [β-ATP]/[Pi] increased in the continuous TLM group (rate of increase 0.043 (0.033) and 0.029 (0.029) respectively) and decreased in the static TLM (rate of decrease 0.023 (0.016) and 0.015 (0.026), $p<0.001$ and <0.05 respectively)and in Marshall's group (rate of decrease 0.049 (0.025) and 0.036 (0.019) respectively, $p<0.001$ for both) with respect to continuous TLM. The rate of decrease in the latter two groups was not significantly different. In the *warm ischemia study*, [γ-ATP]/[Pi] and [β-ATP]/[Pi] increased in the continuous TLM group (rate = 0.008 (0.009) and 0.007 (0.008) respectively) and decreased in the static TLM group (rate = 0.018 (0.008) and 0.014 (0.004) respectively, $p<0.001$ for both).

Conclusions: 31 Phosphorus MRS is an effective tool for non-invasive assessment of pancreas viability. Continuous TLM preserves cellular bioenergetics and is superior to non-PFC based solutions for pancreas preservation.

Parallel Session

Wednesday 22 April

Kidney Transplantation – Clinical 1

17:00 – 18:30

O58

A Fast and Safe Living-Donor "Finger-Assisted" Nephrectomy Technique: Results of 359 Cases

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Introduction:

"Finger assisted" is a modification of the mini-open donor nephrectomy technique that allows retrieval of the kidney via a small incision anteriorly to the 11th rib, without rib resection and by using the ETS-FLEX endoscopic articulating linear vascular cutter for dividing the ureter and the renal vessels. This technique, combines the advantages of the standard open and laparoscopic donor nephrectomy techniques.

Aim:

To analyse the intra-operative and post-operative outcomes, using the finger assisted technique at a single Centre.

Methods:

359 consecutive live donor nephrectomies performed in our Centre between October 2000 and November 2008 using the finger assisted mini-open live donor nephrectomy technique, were included in this study. Patient demographics, intra-operative parameters and post-operative outcomes were prospectively recorded. Median follow-up was 19 months (range, 2-97 months).

Results:

Mean donor age was 44.2±12.3 years (range, 21-75 years), with a mean body mass index of 28.2±5.3 (range, 17.1-44.9). Right-sided donor nephrectomies were performed on 23 patients (6%) and 41 kidneys (11%) were found to have multiple renal vessels. Median incision length was 6.8cm (range, 3.5-15cm). Average operative time was 117 minutes (range, 50-265 minutes), with a median blood loss of 109mL (range, 20-500mL) and an average warm ischaemia time of 4.5minutes (range, 1.5-10 minutes). Four patients (1%) required peri-operative blood transfusions. There were no other intra-operative complications, no patients required re-exploration and there were no donor deaths. Thirteen patients (4%) developed minor post-operative complications, including two incisional hernias, but no patients developed chronic wound pain.

Conclusions:

This prospective series demonstrates that the finger assisted modification to the mini-open donor nephrectomy technique allows a fast and safe nephrectomy via a smaller incision with very few and not serious post-operative complications.

O59

Medium-term follow up of renal transplant recipients from a randomised controlled trial of laparoscopic versus open live donor nephrectomy

Monika Kaushik, Rosemary Elwell, Atul Bagul, Peter Veitch, Michael Nicholson

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Background

Laparoscopic live donor nephrectomy continues to gain in popularity but there are still some concerns that this technique reduces morbidity in the donor at the expense of increased morbidity in the recipient. The aim of this study was to evaluate recipient outcome at a median follow up of 6 years following a randomised controlled trial of laparoscopic versus short incision open donor nephrectomy.

Methods

Eighty-four live kidney donors were randomised in a 2:1 ratio to laparoscopic (LDN n=56) or short incision open donor nephrectomy without rib resection (ODN n=28). The two groups of transplant recipients were followed up for between 4 and 8 years and outcome data recorded prospectively. Particular attention was paid to rates of ureteric complications and renal function parameters.

Results

LDN operation time was longer (168±30 vs 145±27 min; P=0.0042) and LDN kidneys suffered longer first warm ischaemic times (3.8±1.1 vs 2.2±1.1 minutes; P<0.0001). There were no episodes of arterial or venous thrombosis but one kidney in each group suffered delayed graft function. At a median follow-up of 74 months, one ureteric stenosis requiring re-operation had occurred in each group (NS) and there were no differences in renal function or allograft survival between the ODN and LDN groups (Table).

	LDN (n=56)	ODN (n=28)	P Value
Creatinine – year 1	129±40	125±35	0.692
Creatinine – year 3	168±176	156±162	0.761
Creatinine – year 5	141±72	168±165	0.468

Conclusions

Laparoscopic nephrectomy does not lead to an increase in ureteric complications. Despite subjecting the donated kidney to a prolonged pneumoperitoneum and longer first warm ischaemic time, laparoscopic donor nephrectomy does not compromise long-term recipient renal function.

O60

Preoperative decline in titres and lack of antibody rebound in ABO incompatible transplantation with anti-CD20 therapy

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ABO incompatible transplantation (ABOi) is increasingly common, yet uncertainty exists over the most appropriate Ab removal regime. Little is known about the ability of anti-CD20 therapy to reduce Ab levels, prior to other treatments. Antibody rebound may be uncommon after anti-CD20 therapy.

20 patients underwent ABOi, with a mean follow-up of 317 days. Starting titres ranged from neat to 1 in 512. All were given rituximab, 375mg/m^2, 1 month prior to transplantation. Immediately prior to transplantation antibody removal was accomplished by blood group specific immunoabsorption or double filtration plasmapheresis. 11 patients were given ivIgG 0.5g/kg the evening prior to surgery, and immunosuppression consisted of Basiliximab, Tacrolimus, MMF and Prednisolone. The first 6 patients underwent routine post-operative Ab removal; subsequently this was abandoned.

Graft and patient survival was 100% and 7 patients developed acute rejection. Mean serum creatinine at follow-up was 122um/l. Following anti-CD20 therapy, Ab titres showed a significant reduction in 8 patients with a fall of 2 or more dilutions in 7. There was no difference in age (53 yrs v 49 yrs p=0.24) or rejection rate (4 v 3, p=0.22) in those who did or did not show a reduction.

At follow-up, all patients had antibody titres within 2 dilutions of the post-operative value, and all remained at 1 in 8 or lower, irrespective of any post-operative antibody removal. No rejection episodes were accompanied by a rise in titre.

We conclude that anti-CD20 therapy alone may reduce ABO titres, and that postoperative rebound is uncommon following its use. Routine post-operative immunoabsorption, and monitoring of titres may no longer be necessary. Good short and medium term results are achievable after ABO incompatible transplantation using anti-CD20 therapy, Tacrolimus and MMF

O61

The utility and cost of the British Transplant Society guidance on screening HLA antibodies in the first year after renal transplantation

James Fotheringham, William McKane

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Background: Published BTS guidance advocates intensive HLA antibody screening at 1, 2, 3, 6, 9 and 12 months and when rejection is clinically likely. Although antibodies detected in the first year are associated with acute rejection, the clinical utility of an intensive screening programme is unproven. Methods: All transplants performed in 2006-2007 were reviewed in a centre that aims to achieve the above regime. Demographic data, rejection episodes, 12 month eGFR and urine protein:creatinine ratio (PCR) were obtained. The number and result of antibody tests was recorded. Cost was estimated using the NHSBT tariff for antibody screening/identification. All antibody testing was with Luminex beads (screening, identification and where necessary single antigen). Results: 103 transplants were analysed with 4 early graft failures excluded. 38% Female, 68% deceased donor, 38% presensitized, mean A+B mismatch 1.88 (0 – 4, SD 1.25), mean DR mismatch 0.5 (0 – 2, SD 0.59). 478 tests were performed (median 4, range 1-11), with 31 patients (30%) having 6 tests or more. New specificities were identified in 23 (22.3%) patients, 8 of which were Donor Specific (DS, 7.7% the total group). More DS patients had acute rejection than the Non-DS or presensitized patients (4/8 vs 5/41, p=0.028) and 75% of rejection in DS patients was humoral. However, clinical markers of rejection, usually graft dysfunction, were evident prior to the DS antibody being detected by screening. In 35% of cases the new specificity was transient. Four of the patients with transient new DS were completely stable. At 1 year, proteinuria was significantly greater in patients with new specificities (49.2 vs 18.3 mg/mmol, p=0.012) however eGFR was equivalent (51.0 vs 50.1 ml/min/1.73 m^2, p=0.85). 3 graft failures occurred prior to 12 months post transplant (1 DS, 1 Non-DS, 1 no antibodies, p=NS). Cost of the screening was approximately £700/patient although this does not include non-laboratory costs and single antigen bead testing. Conclusions: Knowledge of HLA antibodies may aid clinical decision-making but this study does not provide evidence that intensive and costly screening will improve outcomes. Rationalization of the schedule may be justified such that clinical factors are used to determine the frequency of testing. Even in the first year, an association between HLA antibodies and proteinuria can be demonstrated.

O62

Socioeconomic status, ethnicity and access to deceased donor kidney transplantation in England and Wales

Udaya Udayaraj[1,5], Yoav Ben-Shlomo[2], Paul Roderick[3], Anna Casula[1], Christopher Dudley[4], David Ansell[1], Charles Tomson[4,1], Rachel Johnson[6], Dave Collett[6], Fergus Caskey[6]

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Background: The association between socioeconomic status (SES) and its contribution to the ethnic differences in access to deceased donor (DD) kidney transplantation in England and Wales (E&W) is not known. **Methods:** Patients aged 18-70 years (n= 11299) starting RRT (1997- 2004) in centres linked to the UK Renal Registry were considered. Patients with malignancies and those who subsequently received a living kidney donor transplant were excluded. Townsend index was used as proxy for individual level SES with patients divided into population quintiles (Townsend quintile (TQ) 5 most deprived). Association between SES and access to DD kidney transplant waiting list (TWL) and access to DD kidney transplant once waitlisted were studied separately in White patients (n=9602) using multivariable Cox regression models controlling for patient age, gender, cause of renal failure, year of RRT start), blood group, HLA matchability score, % panel reactive antibody, centre. Association between ethnicity (White, Black, South Asians) and access to DD TWL and DD transplant once waitlisted was examined controlling for above factors and Townsend index. **Results:** In fully adjusted models, patients living in the most deprived areas had reduced access to DD TWL: Hazard ratio (HR) for TQ 5 is 0.53 (95 %CI 0.59, 0.66, trend p < 0.0001). SES gradients were more pronounced for those aged > 50 years (interaction test p =0.009). Sensitivity analyses including only those who survived three years or more from RRT start yielded similar results suggesting comorbidity does not fully explain reduced access to TWL. Once waitlisted, patients living in more deprived areas had equal access to DD transplant compared to those in more affluent areas: HR for TQ 5 is 0.92 (95%CI 0.78, 1.08, p-value for trend =0.2). Compared to Whites, Blacks (HR 0.95, 95%CI 0.79, 1.14) and South Asians (HR 1.10, 95%CI 0.97, 1.24) had equal access to DD TWL once controlled for SES and centre. Amongst those aged > 50 years (interaction test p=0.004) and in centres who list more patients (interaction test p=0.03), Blacks had greater access to TWL compared to Whites. Once waitlisted, access to DD transplant was lower for Blacks (HR 0.66, 95%CI 0.49, 0.87) and Asians (HR 0.74, 95%CI 0.65, 0.85) in the fully adjusted models. **Conclusions:** Socially deprived patients had poor access to TWL but once waitlisted they had equal access to DD transplant. These differences could be due to patient and/or health care related barriers that may be amenable to intervention. Blacks and South Asians had equal access to TWL after controlling for SES but relatively reduced access to DD transplant once waitlisted. Residual confounding from HLA tissue type differences could explain the reduced access to DD transplant for non-Whites.

O63

Outcomes of live donor kidney transplantation in IndoAsian patients in the West Midlands: overseas and local transplantation

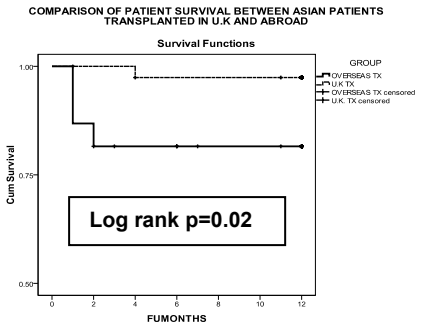
Nithya Krishnan, Paul Cockwell, Indy Dasgupta

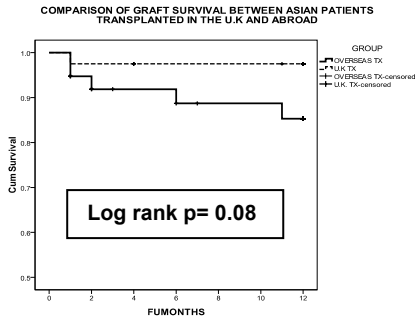
University Hospitals Coventry & Warwickshire NHS Trust, Coventry, United Kingdom, University Hospitals Birmingham, Birmingham, United Kingdom, Heart of England NHS Foundation Trust, Birmingham, United Kingdom

Indo Asian (IA) patients with ESRF often travel abroad for commercial kidney transplantation. Here we compare outcomes of West Midlands IA patients receiving overseas transplants with local live donor transplants from 1996 to 2006.

Forty adults from 6 renal units were transplanted; 3 were transplanted twice and 2 were lost to follow up. Results for 38 patients (41 transplant episodes, 39 live-unrelated, 2 deceased) were analysed. Median follow up was 33.6 months (range 0-106) and median recipient age was 51.5 years (28-87). Forty patients were transplanted locally. They all received first grafts from live donors; 26 were from blood relatives. The median recipient age was 40 years (16-61). In the overseas group 12% of grafts (n=5; death censored) failed within 12 months and 18% of patients (n=7) died within 3 months of transplantation. Composite one year graft and patient survival was 68.5%. In the local group composite graft and patient survival was 95% (one graft loss (death censored) and one death). Kaplan Meier Survival curves are shown in figs 1 & 2. There was a significant difference in patient survival (p= 0.02). In the overseas group 39% had major infections, the majority Hep B (n=4) or Hep C (n=5), compared with 15% (all CMV) in the local group (p= 0.02).

In conclusion, IA patients who choose to travel overseas for kidney transplantation have poor clinical outcomes and should be counselled accordingly.





Parallel Session

Wednesday 22 April

Renal Science Abstracts

17:00 – 18:30

O64

An activating mutation of HIF2α results in autosomal dominant erythrocytosis and pulmonary arterial hypertension

Daniel Gale, Sarah Harten, Nicholas Talbot, Federico Formenti, Edward Tuddenham, Peter Robbins, Patrick Maxwell

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Erythropoietin (EPO) production by the kidney is regulated by the oxygen-labile transcription factor Hypoxia Inducible Factor (HIF)-α, which exists in at least three forms, the relative contributions of which are poorly understood.

We have identified a family in which there is autosomal dominant inheritance of erythrocytosis with elevated EPO levels. Affected individuals developed significant pulmonary arterial (PA) hypertension in their sixth decade and additional clinical features include headache and reduced plasma volume. A genome-wide study demonstrated linkage to HIF2α and resequencing disclosed heterozygosity for a G to A substitution at base 2097 from the transcription start site, predicting a Glycine (Gly) to Arginine (Arg) change at residue 537 of this protein. All affected and no unaffected members of the pedigree were heterozygous and the mutation was absent in 88 unrelated UK individuals. Transfection of plasmids containing HIF2αArg537 into hepatoma cells resulted in greater activation of a HIF responsive reporter gene compared to wild type HIF2α in the presence of oxygen, but a similar degree of activation when under hypoxia. One younger affected individual exhibited mildly elevated resting PA pressure with a markedly abnormally increase in response to brief experimental hypoxic exposure.

These findings suggest that HIF2α plays an important role in regulating both erythropoietin expression and pulmonary arterial tone in humans. This may have implications for therapies which aim to increase HIF stability for the treatment of renal anaemia. Moreover, HIF2α may provide a target for new therapies for pulmonary hypertension. Notably, aspects of the phenotype in this family are features of high altitude exposure and it is possible that variation in HIF2α may explain differing susceptibility to the effects of high altitude observed in individuals and populations.

O65

Changes in Ca^{2+} transients and phasic contractions induced by uropathogenic E.coli (UPEC) in smooth muscle of the rat ureter.

Rachel Floyd[1], Ali Bakran[2], Craig Winstanley[3], Susan Wray[1], Theodor Burdyga[1]

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Urinary tract infection was the cause of 61% of all admissions for infection in a recent audit in our transplant unit, leading to long-term deterioration of function in a significant minority of patients. UTI, therefore, remains a constant and important clinical as well as economic problem. Ascending urinary tract infections cause abnormal ureteric function and maybe a factor in the development of UTI post-transplantation, especially since the ureter is denervated but little is known about the mechanisms causing this effect. Our preliminary studies have shown that prolonged intraluminal exposure of rat ureter to UPEC caused changes in ureteric smooth muscle contractility however the underlying mechanisms causing this effect were unclear. In the present study changes in phasic contractions and Ca^{2+} transients evoked by electrical field stimulation of Indo-1 loaded rat ureters during exposure to UPEC were investigated. Exposure of ureters to pathogenic UPEC J96 caused a time-dependent decrease in amplitude and duration of the Ca^{2+} transient and phasic contractions. Non-pathogenic TG2 under identical conditions had little or no effect. Inhibition of K^+ channels by TEA (5mM) significantly but not completely reversed the inhibitory effects of J96 on Ca^{2+} transients and force. J96 also decreased Ca^{2+} transients and force induced by sustained high-K^+ depolarisation. Our data indicate that a decrease in the amplitude of the phasic contractions induced by prolonged exposure to J96 in rat ureter smooth muscle is associated with a decrease in the amplitude and duration of the Ca^{2+} transient. The data suggest that this modulation of the Ca^{2+} transient and force in rat ureter smooth muscle induced by intraluminal J96 exposure is likely associated with an upregulation of the activity of potassium channels and downregulation of the activity of L-type calcium channels.

O66

Gene expression profiling in ureteric obstruction implicates unsuspected molecules in congenital obstructive uropathy

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Fetal urinary flow impairment, accompanied by renal dysplasia (poor differentiation) and hypoplasia (too few nephrons), is implicated in 20% of children needing dialysis and kidney transplantation. To model the disorder, we surgically induced unilateral ureteric obstruction in wild-type 48-hour old neonatal mice; in this species, 90% of nephrons form in the first postnatal week. Obstructed and sham-operated kidneys were harvested at one and 12 days after surgery and were analysed by histology and for gene expression for which we designed and used a SuperArray RT Profiler PCR Array System plate, allowing simultaneous quantitative PCR of 80 genes implicated in nephrogenesis and renal epithelial differentiation with a panel of five housekeeping genes. Experimental groups were compared with paired t-tests (with Bonferroni correction, significant if $p<0.0005$). After just one day of ureteric obstruction, kidneys were hydronephrotic, with widespread dilatation of tubules and small cysts in the nephrogenic zone. At this stage, there was a significant upregulation of smooth muscle actin and downregulation of both Ift88/Polaris and Invs. The latter two transcripts encode proteins implicated in primary ciliary function and maintenance of planar cell polarity. Furthermore, mutation of Ift88 causes polycystic kidneys in mice whereas mutation of the human homologue of Invs causes nephronophthisis, a disease associated with renal cysts and fibrosis. At 12 days, kidney histology is dominated by intense fibrosis and loss of normal tubules. We found further upregulation of smooth muscle actin and downregulation of aquaporin-2 and γ-glutamyl transferase: markers of collecting ducts and proximal tubules, respectively. Transcripts for two growth factors were deregulated: epidermal growth factor (15-fold downregulated) and leukaemia inhibitory factor (8-fold upregulated). Additionally, Prox1, a transcription factor implicated in renal hypoplasia caused by maternal low protein diet, was downregulated. Thus, gene expression profiling in this mouse model implicates several nephrogenic and epithelial differentiation molecules hitherto unsuspected in the biology of congenital obstructive nephropathy.

O67

Measurement of glomerular water permeability in mice

Deborah Edison, Kirsty Hart, Dave Bates, Steve Harper, Andy Salmon

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Different rat species have physiologically important differences in glomerular water permeability. Mouse glomerular water permeability has not been measured before. Transgenic manipulation of native glomerular proteins has proven a robust method for examining glomerular pathophysiology *in vivo*, but transgenic mice are often generated on different background mouse strains. Before measuring glomerular permeability coefficients in transgenic mice, we considered it important to [1] measure mouse glomerular permeability coefficients, [2] assess differences in glomerular permeability between mouse strains, and [3] assess differences in glomerular permeability between mice and rats.

C57Bl6 mice (aim 1), DBA2/J mice (aim 2), and Wistar rats (aim 3), were assessed. Glomeruli were isolated via a standard sieving technique, and incubated in control solution (1% BSA alone) for up to 200mins. Glomeruli were individually mounted on an aspiration pipette, and glomerular images recorded on videotape. Fluid surrounding the glomerulus was exchanged from 1% BSA to 8% BSA (oncotic pressure difference 29.2mmHg). The initial (<0.1s) rate of reduction in glomerular volume that accompanies this fluid exchange describes the rate of fluid efflux from the glomerulus (J_V). The ultrafiltration coefficient, L_PA, is the quotient of J_V and applied oncotic pressure difference (Salmon, J Physiol, 2006).

C57Bl6 mouse L_PA values (nl.min^{-1}.mmHg^{-1}; mean±s.e.m. (n)) were 1.01±0.19 (12). As with rat L_PA values, there was no significant change in L_PA for >3 hours post-mortem, and there was a significant relation between L_PA and glomerular volume (V_i). There was no significant difference between L_PA values for C57Bl6 (1.01±0.19 (12)) and DBA2/J mice (0.92±0.14 (14), p>0.6). L_PA values were similar for mice and rats (rats: 0.82±0.06 (41)), despite a 2.7-fold difference in V_i (mouse: 0.35±0.03nl; rat: 0.94±0.04nl). When this volume difference was accounted for (L_PA/V_i: min^{-1}.mmHg^{-1}), mouse L_PA/V_i values (2.89±0.27 (26)) were significantly higher than Wistar rat L_PA/V_i (0.85±0.05 (41)) (p<0.05).

Mouse glomerular water permeability coefficients are not different between strains, but are significantly different from values in rats when differences in glomerular volume are accommodated. This implies a fundamental difference in the permeability of the glomerular filtration barrier of rats and mice.

O68

Hepatic upregulation of 11 β-HSD1 and associated excessive gluconeogenesis: A likely mechanism of insulin resistance in uraemia.

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The mechanism of uraemia induced insulin resistance (IR) is poorly understood. We proposed the hypothesis that IR in uraemia can partly be explained by excessive gluconeogenesis due to increased hepatic synthesis of glucocorticoids through 11 β-HSD1.

Rats were subjected to 5/6 nephrectomy to mimic chronic renal disease. Rats (N=4-8) were divided into 4 groups (1) 5/6 nephrectomy (2) 5/6 nephrectomy plus and non selective inhibitor of 11 β HSDI carbenoxolone (CX) (3) Sham operated (4) Sham operated plus CX. Livers were harvested and snap frozen in liquid nitrogen. Plasma insulin levels were measured using a specific ELISA kit (Crystal Chem. Inc, IL, USA). To assess gluconeogenesis, activity of phosphoenolpyruvate carboxykinase (PEPCK; gene code *PCK1*), the rate limiting enzyme of gluconeogenesis, was assayed using luminescence methodology based on the conversion of oxaloacetate to phosphoenolpyruvate. *PCK1*, *PGC-1α* (PPAR gamma coactivator 1 alpha; a coactivator of *PCK1* gene expression and inducible by glucocorticoids) and *11βHSD1* mRNA levels were measured using qRT-PCR. Statistical comparisons were determined by ANOVA.

Plasma urea (3.4 ± 0.5 fold; $p<0.05$) and creatinine (2.5 ± 0.2; $p<0.05$) levels were raised in uremic rats. Plasma insulin levels were raised in uraemia (116 ± 5.5 pg/ml; $p<0.01$) compared to sham operated controls (18.1 ± 5.5 pg/ml), whilst plasma glucose levels were similar. In parallel, uraemia increased mRNA levels for *11βHSD1* (2.9 ± 0.9 fold; $p<0.01$) *PCK1* (1.8 ± 0.2 fold; $p<0.01$), *PGC1 alpha* (7.6 ± 2.5 fold; $p<0.01$) as well as PEPCK activity (30 ± 3.5%; $p<0.01$). Administration of CX to uremic rats lowered plasma levels of insulin ($p<0.01$) and also reversed changes in activity of PEPCK ($p<0.05$) to basal levels.

These results suggest that uraemia can cause insulin resistance and hyperinsulinaemia through abnormally elevated gluconeogenesis, potentially occurring as a result of increased 11βHSD1 mediated glucocorticoid synthesis. This data opens the possibility of novel therapeutic strategies for treatment of chronic kidney disease.

O69

Distinct but essential roles for diacylglycerol kinase and phosphatidylinositol-3-kinase in the release of primary granules from ANCA stimulated neutrophils

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In systemic vasculitis, proteases that are released following ANCA (anti-neutrophil cytoplasmic antibody) activation and degranulation of neutrophils, represent the major cause of vascular and glomerular injury. We previously demonstrated that diacylglycerol kinase (DGK), through the production of monounsaturated phospatidic acid (PA), promotes ANCA-induced neutrophil adhesion. As adhesion and degranulation are often coupled, we investigated a role for DGK and also phosphatidylinositol-3-kinase (PI3K) in ANCA induced neutrophil degranulation.

Neutrophils isolated from healthy donors were incubated with the DGK specific inhibitor R59022 (18μM) or the PI3K specific inhibitors wortmannin (10nM) or LY294002 (3μM) prior to priming with TNF-α in the presence of cytochalasin B. Cells were treated with ANCA (200μg/ml) and supernatants analysed for the presence of myeloperoxidase (MPO) and serine proteases using specific substrates. ANCA significantly induced the release of both MPO and serine proteases above that of control IgG treated cells ($p<0.01$). The release of both enzymes from ANCA treated cells was reduced significantly in the presence of R59022 and either wortmannin or LY294002 ($p<0.01$). Degranulating cells exhibited increased forward scatter (size) and decreased side scatter (granularity) along with a significant increase in the surface expression of CD63, which was not observed in either DGK or PI3K inhibited cells. Addition of PA restored primary granule release in DGK but not PI3K inhibited neutrophils, whereas fluorescence microscopy revealed that both wortmannin and LY294002, but not R59022, inhibited translocation of granules from the cytosol, thus indicating different mechanisms of action for the two enzymes. Addition of the PI3Kγ specific inhibitor AS-604850 (4μM) inhibited MPO and serine protease release from ANCA activated neutrophils, suggesting a preferential role for this isoform.

In conclusion, ANCA may activate both DGK (PA dependent) and PI3K (PA independent) to promote neutrophil primary granule release. DGK represents an intriguing target for small molecule inhibitor therapies, since these could uncouple ANCA induced adhesion and degranulation from other functions, potentially reducing microvascular injury during vasculitic glomerulonephritis.

Parallel Session

Wednesday 22 April

BTS / BASL Symposium

09:30 – 18:30

O70

Cardiopulmonary exercise testing predicts early postoperative survival following liver transplantation

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Cardiopulmonary exercise testing (CPX) has been used to predict postoperative mortality. This study aimed to assess its use as a preoperative predictor of 90 day survival in a consecutive group of patients undergoing liver transplantation.

Methods

We performed preoperative submaximal CPX tests on patients being assessed for liver transplantation from April 2006 to Jan 2008. CPX results were interpreted by two trained personnel to determine a measure of cardiorespiratory reserve (anaerobic threshold - AT) using standard criteria. The values derived from the CPX test did not influence surgical decision or any aspect of peri-operative patient care. Prospective data collection included patient demographics, MELD and UKELD score, disease type and survival data at 90 days. All were collected by a researcher without a priori knowledge of CPX results. Student's t-test was used for quantitative group differences. Receiver Operator Curve (ROC) analysis was used to determine optimum AT level for 90 day survival.

Results

Fifty two submaximal CPX tests were performed. 4 patients had indeterminate tests due to inadequate effort and they were excluded from analysis. 25 of the tested patients underwent OLTx. AT (mean) in the patients deemed not to require transplantation was 11.2 (2.7) ml/min/kg compared with 10.9 (2.7) ml/min/kg in patients who underwent transplantation ($p>0.05$). 90 day survival in the transplanted group was 21/25 (84%). Age, BMI, MELD, UKELD and time on waiting list were not statistically different between the survivors and non-survivors. AT in survivors was 12.1 (2.2) ml/min/kg compared with 7.9 (1.5) ml/min/kg in the non-survivors ($p=0.003$). ROC curve analysis demonstrated an AT value of 9.6 ml/min/kg with 100% positive predictive value for survival (Sens 87%; Spec 100%: AUC 0.95 (CI 0.74 -0.99) ;$p=0.0001$).

Conclusion

Our results show that in an unselected group of patients undergoing liver transplantation, a measure of cardiopulmonary reserve (AT), rather than standard scores of liver dysfunction, can predict those at risk of increased 90-day mortality rates. This implicates cardiopulmonary reserve, rather than liver dysfunction severity, as being a major factor in early liver transplantation survival.

O71

Liver Transplantation from Non-Heartbeating Donors: An Analysis Using Matched Pairs

James Pine, Amer Aldouri, Alistair Young, Mervyn Davies, Giles Toogood, Stephen Pollard, Peter Lodge, Raj Prasad

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Introduction: Grafts from non-heart-beating donors (NHB) are used to increase organs available for liver transplantation. There are concerns as the warm ischaemia may impair graft function. We compared our NHB recipients with a case-matched group of heart-beating (HB) recipients.

Method: Between January 2002 and April 2008 39 NHB grafts were transplanted. These were matched with 39 HB recipients based on identified variables that had significant impact on mortality. These were used to individually match NHB and HB patients with similar predictive mortality. We compared patient/graft survival, primary non-function (PNF) and rates of complications.

Results: 6.1% of total liver transplantations were NHB grafts. PNF occurred twice in the NHB group. The incidence of non-anastomotic biliary strictures (NABS) (20.5% v 0%, p=0.005) and hepatic artery stenosis (HAS) (12.8% v 0%, p=0.027) in the NHB group was higher. 1-yr (79.5% v 97.4%, p=0.029) and 5-yr (74.4% v 92.3%, p=<0.0001) graft survival was lower in the NHB group. 5-yr patient survival was also lower (76.9% v 94.9%, p=<0.0001).

Discussion: Our study is the first to use case-matched patients and compare groups with similar predictive mortality. There was higher incidence of NABS and HAS in the NHB group. The NABS are likely a result of warm ischaemia. The HAS may be due to ischaemia or arterial injury during retrieval. The NHB group had significantly poorer outcomes but NHB grafts remain a valuable resource. With careful donor/recipient selection, minimisation of ischaemia and good post-operative care acceptable results can be achieved.

O72

Relationship between cardiorespiratory reserve, the donor risk index and outcome following liver transplantation

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Following Liver Transplantation (LT), it is recognised that donor variables often influences 90 day mortality. At our institution, we have demonstrated that recipients with an adequate cardiorespiratory reserve (anaerobic threshold AT >= 9.6ml/min/kg) have improved survival. The aim of this study was to assess the relationship between the donor risk index (DRI), the preoperative cardiorespiratory reserve and their influence on 90 day survival in a small cohort study.

Methods

Between April 2006 to Dec 2008, 52 potential LT recipients underwent preoperative submaximal cardiopulmonary exercise tests (CPEx) prior to listing for elective LT.

Low cardiorespiratory reserve was defined by an AT <9.6 ml/min/kg. Prospective data collection included patient demographics, MELD and UKELD score, disease type, donor variables including calculation DRI and survival data at 90 days. Student's t-test was used for quantitative group differences. The values derived from the CPEx test did not influence surgical decision or any aspect of peri-operative patient care

Results

90 day survival was 21 out of 25 (84%) in patients who underwent elective liver transplantation. Six patients had low preoperative cardiorespiratory reserve. All 4 patient deaths occurred in this group, despite preoperative MELD, UKELD and DRI being comparable with the patient group(n=19) with high/normal cardiorespiratory reserve. In the low cardiorespiratory reserve group(n=6), both mean donor age and donor risk index were greater in the 4 non-surviving patients compared with the two survivors (DRI 1.51 vs 1.23; donor age 52.3 vs 20.0 respectively).

Conclusion

In this small study, we found that the donor liver quality, as defined by the donor risk index, did not influence 90 day survival in those patients with an adequate cardiopulmonary reserve. However, in those patients with low cardiorespiratory reserve, the quality of the donor organ may have more impact upon survival. These findings may have an effect on future donor organ allocation but need to be qualified in a larger multi-centred study.

O73

Single centre experience in conversion of calcineurin inhibitor to sirolimus-based immunosuppression following liver transplantation

Simon Harper, William Gelson, Ines Harper, Graham Alexander, Paul Gibbs

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Objective The use of sirolimus remains limited in liver transplantation in comparison with renal transplantation. The potential advantage of the low nephrotoxicity of sirolimus balances against significant side effects. The aim of this study is to report extensive experience in conversion of CNI to sirolimus-based immunosuppression in liver transplantation.

Methods A retrospective review of 148 patients converted from CNI to sirolimus following liver transplantation was undertaken using patient records.

Results Ninety-four patients were male and 54 female and the median age was 61 years old. The most common indications for transplantation were hepatitis C virus (HCV) (33%) and alcoholic liver disease (23%). The most common indications for sirolimus use were renal impairment (52%), HCV (32%) and CNI intolerance (9%). One hundred and eleven (75%) patients remained on sirolimus after median follow up of 1006 days (range 30 – 2759). The mean (+/- S.D.) GFR of patients just prior to conversion was 59 +/- 29 ml/min increasing to 69 +/- 36, 70 +/- 37 and 72 +/- 39 ml/min at 6 months, 3 years post-conversion and follow up respectively ($p<0.05$). No significant change in liver function tests, haematological parameters, HbA1C or mean arterial pressure was observed following conversion. Biopsy proven acute rejection occurred in 4 patients following conversion. A total of 112 side effects attributed to sirolimus occurred in 101 (68%) patients and included peripheral oedema (21%), mouth ulceration (15%) and pneumonitis (5%). Sirolimus was withdrawn in 20 patients (14%) due to drug intolerance after a median treatment period of 345 days (range 10 – 2097). Mean serum LDL was 4.4 +/-1.1 mmol/L pre-conversion, increasing to 5.5 +/- 1.3 at 6 months and levelling at 4.9 +/- 0.8 at 5 years ($p<0.05$). Mean serum triglyceride levels followed a similar pattern. Statins were commenced in 83 (51%) patients. The percentage of patients with detectable proteinuria pre-conversion, 1 month, 6 months and 5 years post-conversion was 45%, 68%, 72%, 58% respectively. Proteinuria was not associated with deterioration in renal function. Pre and post-conversion biopsies were available in 33 patients with HCV over a median follow up of 708 days. Fifteen (45%) patients had documented improvement in terms of liver fibrosis, 13 (39%) were unchanged and 5 (16%) had deteriorated.

Conclusions This study demonstrates that in liver transplantation, conversion from calcineurin inhibitor to sirolimus-based immunosuppression results in a significant improvement in renal function unaffected by an increased incidence of proteinuria. Sirolimus-related side effects are common but can usually be managed conservatively. Sirolimus may offer additional benefits in attenuating graft fibrosis in HCV patients.

O74

Initial experience of microdialysis as a method of monitoring inflammatory, ischaemic and immunological events following liver transplantation.

Irum Amin, Andrew Butler, Paul Gibbs

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Introduction: Microdialysis offers a new approach to monitoring acute events within a solid organ transplant in the immediate post-operative period and may allow earlier identification of adverse events such as acute rejection and ischaemic insults. In this study we have investigated the feasibility of utilising this technique in liver transplantation.

Methods: During 2008, 11 patients undergoing liver transplantation (including the recipient of the right lobe of a split liver) were monitored for the first post-operative week with intra-hepatic and subcutaneous 100kDa microdialysis catheters. Markers of liver function such as lactate, pyruvate, glucose and glycerol were measured between 1 and 3 hourly over the first 7 post-operative days and correlated with clinical events. Cytokine production was monitored daily and the pattern of expression of intra-hepatic cytokines identified.

Results: The technique was successful in all but 1 patient in whom the intra-hepatic catheter failed after 2 days. No complications attributable by the microdialysis catheter were seen. Both catheters were removed without problems on the 7th post-operative day.

Although the study has so far included a small number of patients a significant rise in the lactate/pyruvate ratio was seen in patients with ischaemic damage to the liver. It has also confirmed the findings of the only other published microdialysis study in liver transplantation that an adverse clinical event such as rejection can be identified earlier using this technique. The cytokines IL-2, IL-6, IL-8 and IL-12 were identified within the liver within a few days of transplantation.

Conclusion: Our initial experience with microdialysis would suggest that this maybe a useful tool for more accurate monitoring of the liver post-transplant and may in time be able to be used to monitor graft perfusion especially in the context of inotrope usage and possibly allow the earlier diagnosis of events such as acute rejection.

O75

Effect of donor hepatectomy time during multi-organ retrieval on early graft function following adult cadaveric liver transplantation

Mettu Reddy, Syed Raza, James Pine, Rajendra Prasad, Niaz Ahmed

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Introduction
Time taken to recover the graft liver after aortic cross-clamp depends on both donor and surgeon factors. We aimed to investigate the effect of duration of donor hepatectomy (tHep) on the early outcomes after adult heart-beating donor whole liver transplantation (LT).

Methods
LT carried out in a single LT unit in the UK were analysed. To standardize retrieval protocol and cold ischaemia times, livers retrieved by our recovery team alone were included in the study. tHep and pertinent donor and recipient data was collected from a prospectively maintained database. Post-transplant data in the form of primary non-function (PNF), hepatic artery thrombosis (HAT), initial poor function (IPF), graft loss within one month and deranged liver function tests (LFT) at 6 months (serum bilirubin >20 μmol/l and serum alkaline phosphatase >500U) were collected. IPF was defines as prothrombin time>16sec and ALT level>2000 U between post-transplant days 2-7. The effect of tHep on the incidence of above end-points was analysed.

Results
Data was available for 348 grafts transplanted between Feb 2000 and April 2006. The median hepatectomy time was 38 minutes (Inter-Quartile Range: 30-49 min). There were 7 patients with PNF, 21 with IPF, 6 HAT and 13 early re-transplants. Six month LFTs were available for 285 patients alive with the original graft liver. Fourteen patients had deranged LFT. There was no significant difference in the tHep in patients with or without PNF, IPF, hepatic artery thrombosis or early re-transplant. tHep was longer in patients with deranged LFT as compared to patients with normal LFT (52 vs 40 minutes, Mann Whitney U, p=0.042). Patients with prolonged tHep (>50 minutes) had a higher risk of deranged LFT at 6 months (7/70 vs. 7/215; Fisher's exact test, p=0.023).

Conclusions
Prolonged tHep is associated with an increased risk of abnormal liver function tests at 6 months post-transplant. This may be a mark of re-warming injury sustained by the graft during a complicated recovery procedure.

Parallel Session

Thursday 23 April

Stem Cells

09:00 – 10:30

O76

Immunogenicity of tissues differentiated from epiblast stem cells for use in regenerative medicine

Minadora Brimpari, Gabrielle Brons, Ludovic Vallier, Roger Pedersen, Andrew Bradley, Eleanor Bolton

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The potential for embryonic stem cells (ESC) to differentiate into tissues originating from all three germ layers raises the prospect that they may be used for developing tissues for transplantation. While ESC are relatively non-immunogenic since they express little MHC I and no MHC II, their in vivo counterpart develops into immunogenic tissues. Mouse epiblast stem cells (EpiSC), unlike mouse ESC, are equivalent to human ESC and may better model, in vitro, human embryonic development. We investigated whether EpiSC induced to differentiate into 3 developmentally distinct germ layers were able to express increased MHC-I and II.

EpiSC were derived from post-implantation mouse embryos and grown in chemically defined medium with specific growth factors. Differentiation was assessed by FACS, immunostaining and Q-PCR for expression of developmentally specific genes. EpiSC were activated with IFN-g for 0-48h and MHC gene expression was assessed.

EpiSCs were shown to differentiate into mesendoderm, neurectoderm and extra-embryonic tissues, confirmed by expression of lineage-specific genes including Brachyury, Sox2 and CDX2. Differentiated EpiSCs expressed low levels of MHC-I and beta2m which was upregulated with 50ng IFN-g for 48h. They did not express MHC-II even when stimulated with IFN-g. We then studied two genes that regulate MHC-II gene expression, RFX 5 and CIITA. Only mesendoderm-, and not neurectoderm- or extraembryonic tissue-differentiated cells transiently expressed moderate levels of CIITA and persistently high levels of RFX5 when cultured with IFN-g. Costimulatory molecule (CD80 & CD86) expression was not detected.

The capacity for MHC I upregulation in inflammatory conditions may protect embryonic and EpiSC-derived tissues from NK-mediated killing. Only mes-endodermal-differentiated EpiSC, from which lineage leukocytes, APC and endothelial cells subsequently develop, have the capacity to express MHC II but this is silenced downstream of MHC regulatory gene expression, possibly as a survival mechanism.

O77

'In Vitro Infectious Tolerance' - Naturally Occurring $Foxp3^+CD4^+$ Cells Facilitate Ex Vivo Generation of Alloreactive Adaptive Treg

Ross Francis, Gang Feng, Kathryn Wood, Andrew Bushell

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Background and aims: Naturally-occurring $Foxp3^+CD4^+$ regulatory T cells (Treg) play a crucial role in the control of self-directed immune responses. Similar populations of Treg have also been shown to suppress alloimmune responses, offering the potential to prevent transplant rejection without the requirement for indefinite global immunosuppression.

We have developed an in vitro culture system that generates graft-protective Treg from naïve total $CD4^+$ T cells. $CD4^+$ T cells are conditioned for 14 days in the presence of allogeneic bone marrow-derived dendritic cells (BMDCs) and interferon-γ (IFN-γ). The resultant conditioned T cell population (Tcon) are enriched for $Foxp3^+$ cells and prevent skin allograft rejection by a defined $CD4^+$ effector population after adoptive transfer into lymphopenic mice. The aim of this study was to determine key mechanistic factors in this process.

Methods: $Foxp3^+$ and $Foxp3^-$ cells were flow-sorted from genetically labelled mice (CBA, $H2^k$ or CBK, $H2^k+K^b$) and combined at a 1:9 ratio to mimic the frequency of naturally occurring Treg in total $CD4^+$ cells. After conditioning in the presence of allogeneic BMDCs ($H2^b$) and IFN-γ for 14 days, the resulting cell population was analysed by FACS to determine the relative contribution of input $Foxp3^+$ and $Foxp3^-$ cells to the resulting $Foxp3^+$ population.

Results: $Foxp3^+$ cells present after conditioning were derived from both input $Foxp3^+$ and $Foxp3^-$ cells. In the absence of naturally occurring Treg, less than 1% of input Foxp3- cells were converted to a regulatory phenotype. However, strikingly, when $Foxp3^-$ cells were conditioned in the presence of a trace population of naturally occurring Treg, 43% of $Foxp3^-$ precursors became $Foxp3^+$.

Discussion: These data indicate that the IFN-γ conditioning protocol generates $Foxp3^+$ Treg both by expansion of alloreactive naturally occurring Treg, and conversion of non-regulatory precursors. The data suggest that conversion of $Foxp3^-$ cells is not a direct effect of IFN-γ, and is critically dependent on the presence of naturally occurring Treg in a process akin to in vivo infectious tolerance. Further experiments to identify the key factors in this conversion are in progress and should help optimise this protocol for potential evaluation in the human setting.

O78

Dendritic cell modification by CTLA4-KDEL results in inhibition of the indirect pathway of allorecognition and long term corneal graft survival.

Adnan Khan, Hongmei Fu, Jeni Harper, Myra McClure, Frank Larkin, Andrew George

Imperial College London, London, United Kingdom, Moorfields Eye Hospital, London, United Kingdom

The transduction of dendritic cells with the gene encoding CTLA4-KDEL results in inhibition of cell surface expression of the co-stimulatory molecules CD80/86. Exposure of allogeneic T cells to CTLA4-KDEL expressing dendritic cells induces alloantigen specific hyporesponsiveness, anergy and regulation. This is seen in both major antigen mismatch combinations (in which allorecognition is primarily by the direct pathway) and in transgenic models (CBK to CBA) in which $CD4^+$ allorecognition is by the indirect pathway alone. Administration of CTLA4-KDEL expressing dendritic cells *in vivo* results in allospecific T cell hyporesponsiveness, anergy and the induction of regulatory cells that are capable of mediating linked suppression to third party alloantigens.

In corneal transplantation the rejection of the allogeneic cornea is primarily by the indirect pathway. We therefore determined if administration of modified dendritic cells prior to grafting could result in prolongation of corneal graft survival. When CTLA4-KDEL expressing dendritic cells of donor strain were injected intravenously into mice prior to allografting there was a moderate, but significant prolongation of graft survival, with an increase in median survival from 10 days (control transduced dendritic cells) to 18 days. However, when CTLA4-KDEL dendritic cells from F1 animals (donor x recipient) were used there was greatly prolonged graft survival with the majority of corneas surviving >100 days.

These data show that a single administration of CTLA4-KDEL transduced dendritic cells can result in specific and effective suppression of indirect allogeneic responses, in the absence of any other intervention. This is of importance not only for prevention of corneal graft rejection, but also for prevention of immune-mediated chronic rejection in other organs.

Parallel Session

Thursday 23 April

Ischaemia Reperfusion Injury

11:00 – 12:30

O79

Renal Hemeoxygenase deficiency in aged mice: a novel correctable cause of acute kidney injury.

David Ferenbach, Jennifer McKay, Noemie Nkejabega, Matthew Beesley, Spike Clay, Lorna Marson, David Kluth, Jeremy Hughes

Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom

Introduction: We hypothesized that defective induction of endogenous tissue protective responses such as the anti-inflammatory enzyme hemeoxygenase-1 (HO-1) might underlie the association of increased age with susceptibility to renal ischaemia reperfusion injury (IRI). We therefore examined HO-1 expression in young and old mice before and after renal IRI, and the therapeutic efficacy of the HO-1 inducer Hemearginate (HA).

Methods: Young (8-12 wk) and old (52-60 wk) FVB/N mice were used. Selected animals received HA (30mg/kg wt) or vehicle 24h pre IRI. Following right nephrectomy, IRI was induced by left renal pedicle clamping (20 mins). Blood and tissue was collected 24 hrs post IRI and stained for F4/80 (Mϕ), GR1 (PMN), CD3 (T cells), B220 (B cells) and HO-1 prior to quantification by computer image analysis. Acute tubular necrosis (ATN) was determined by counting the percentage of necrotic tubules in the outer medulla.

Results: There was no baseline difference in serum creatinine (Cr) or urinary protein:Cr ratio. Baseline kidneys of old mice showed no leukocyte influx, capillary loss or scarring compared to young mice. Old mice exhibited comparable baseline HO-1 expression but reduced cortical and medullary HO-1 upregulation following IRI (Cortex- 11.5±4.8 vs 25±7.5% staining; old vs young; $p<0.05$: Medulla- 0.8±0.3 vs 6.5±1.3% staining; old vs young; $p<0.05$). Old mice exhibited worse renal function (Cr 120±35 vs 38±6 μmol/L; old vs young; $p<0.01$) and ATN (75±1.2 vs 55±0.4 %ATN; old vs young; $p<0.01$). HA pretreatment of old mice induced HO-1 (cortex 0.81±0.29 vs 44±6.1% staining $p<0.001$, medulla 0.14±0.08 vs 2.52±0.83% staining $p<0.05$; control old vs old+HA). HA treatment resulted in functional (Cr 129±32 vs 50±6 μmol, old vs old+HA $p=0.02$) and structural protection (58±13 vs 21±7% ATN old vs old+HA $p<0.05$). No difference in F4/80+, CD3+ or B220+ cell infiltration was evident between groups whilst old mice exhibited increased PMN infiltration (23±7 vs 7±6 GR1+ PMN/hpf; old vs young; $p<0.05$), which was entirely abolished by HA therapy (32.3±6.9 vs 1.7±0.7 GR1+ PMN/hpf old vs old+HA; $p<0.005$).

Conclusion Reduced HO-1 upregulation following renal IRI increases structural and functional injury in old mice and represents a therapeutic target in the aged population.

O80

Effects of silencing caspase - 3 gene on apoptosis and cell viability in porcine proximal tubular cells subjected to transplant related injury

Bin Yang, Joshua Elias, Michael Nicholson

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Background: Proximal tubular cells (PTCs) are most vulnerable to ischaemia reperfusion injury (IRI) in renal transplantation. Caspase-3 (C3) is crucial in apoptotic cascades and up-regulated by IRI due to various pathogenic processes such as oxidative damage.

Methods: The effect of silencing C3 gene by naked small interfering RNAs (siRNAs) on apoptosis (*in situ* end labelling of fragmented DNAs) and cell viability (trypan blue staining) in porcine PTCs (LLC-PK1) treated by an oxidiser, hydrogen peroxide (H_2O_2), was investigated in this study. The LLC-PK1 cells were transfected with C3 siRNAs 6 h prior to H_2O_2 stimulation, then maintained up to 24-96 h. The level of C3 activity, protein and mRNA was detected by enzyme assay, western blotting and quantitative RT-PCR.

Results: In LLC-PK1 cells, C3 activity was significantly increased by transfection reagent (TR, 140 ± 3% vs. 100 ± 13%), decreased by 3-day transfection of 2 and 20 nM C3 siRNAs (114 ± 13% and 49 ± 10%). C3 activity was dose- and time-dependently increased by H_2O_2, with a maximised effect at 100 μM, 24 h. In contrast to H_2O_2 treated cells (100 ± 51%), C3 activity was further increased by TR (252 ± 46%); reduced by C3 siRNAs at both dosages (113 ± 39% and 110 ± 13%). The active C3 protein (39 ± 12% vs. 100 ± 19%) and its precursor (72.3 ± 8.3% vs. 100.0 ± 7.79%) were also decreased at 96 h, $p<0.05$. The expression of C3 mRNA was significantly reduced by 20 nM siRNAs up to 50% at 24 h. More importantly, the number of apoptotic cells (per high power field) was significantly increased by TR (2.5 ± 0.3 vs. 0.4 ± 0.2); reduced by siRNAs at both dosages (0.5 ± 0.3 and 1.3 ± 0.6). Apoptotic cells were greatly induced by 100 μM H_2O_2 (11.8 ± 2.0), further increased by TR (15.6 ± 2.0), but significantly decreased by 3-day C3 siRNAs transfection at 2 and 20 nM (3.0 ± 0.9 and 4.8 ± 3.9). In addition, cell viability was unchanged by TR alone or siRNA in normal cells (93 ± 1%), decreased by H_2O_2 (85 ± 3%), but improved by 20 nM siRNAs (81 ± 4% vs. 89 ± 3% TR only).

Conclusions: Silencing C3 gene by naked siRNAs significantly decreased C3 activity and its protein expression, subsequently reduced apoptosis and improved cell viability in LLC-PK1 cells with or without transplant-related injury. Therefore, C3 siRNAs could be used as an intervention to ameliorate IRI in transplantation.

O81

Farnesoid X Receptor Agonist (GW4064) Protects the Kidney from Ischemic Acute Kidney Injury

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Background

Farnesoid X Receptor (FXRα) is a member of the nuclear receptor superfamily of ligand-activated transcription factors that is highly expressed in liver, intestine, adrenal gland and kidneys. FXR plays an important role in maintaining bile acid, lipid and glucose homeostasis by activating target genes in the liver and intestine. In contrast, no functional role for FXR in the renal proximal tubular cells has yet been identified.

Aim

(1) To determine whether functional FXR is present in the kidney proximal tubular cells

(2) Whether it contribute to the survival or death of proximal tubular cells in a mouse model of ischemic acute renal failure.

Results

FXR (mRNA and protein) was detected in the human proximal tubular cell line (HK-2 cells) and in the mouse (C57/BL6) kidneys. At concentrations that had no direct effect on viability, the FXR agonist, GW4064, induced expression of mRNA for the FXR target genes, small heterodimer partner (SHP) and bile salt excretory pump (BSEP) but not the intestinal bile acid binding protein (IBABP) in a dose-dependent manner, in HK-2 cells. In mice (n=8) renal ischemia reperfusion injury (I/R) caused by bilateral renal pedicle clamping for 30 minutes, GW4064, administered 12 hour and an hour before clamping, ameliorated acute kidney injury at 24 h reperfusion (serum creatinine, 132μmol/L ± 32 to 68μmol/L ± 40; I/R+V versus I/R+GW4064, $p < 0.01$, respectively; and serum urea, 48μmol/L ± 8 to 27μmol/L ± 12; I/R+V versus I/R+GW4064, $p < 0.01$, respectively; V- vehicle).

Conclusion

Our findings show for the first time that functional FXR is expressed in renal proximal tubular cells and is a promising pharmacologic target for acute kidney injury.

Further experiments are being conducted to elucidate the mechanism and further explore its precise role ischemic renal I/R.

Parallel Session

Thursday 23 April

Diabetes & Transplantation

11:00 – 12:30

O82

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

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

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Purpose: To review the early experience of pancreas transplantation from NHBD in the UK and to correlate donor, recipient and graft characteristics with early outcome.

Methods: Data were obtained from the National Transplant Database. From July 2005 to September 2008, 6 centres performed 61 transplants (31 SPK, 17 PAK, 13 PTA) from Maastricht category 3 and 4 NHBD. Pancreases were retrieved if donor asystole occurred within 60 minutes of treatment withdrawal. There was no pre-mortem cannulation or pharmacologic intervention. 'No-touch' time varied between 5-10 minutes. In situ perfusion with University of UW solution was carried out via the common iliac artery in most cases. The liver was also retrieved in 82% and kidneys in all donors.

Results: Mean (±SD) donor age was 28.64±11.83 yrs; BMI 23.3±6.09 kg/m^2. Predominant causes of donor death were trauma (34%), CVA (27%), hypoxia (29%). 18 recipients had >30% allosensitisation. Median time on the waiting list was 106 days (0-1448). Median HLA mismatch was 4. Mean recipient age was 41.96±7.89 yrs. All grafts except one were implanted intraperitoneally, with caval (93%) or portal (7%) venous drainage and enteric (89%) or bladder (11%) exocrine drainage. Median cold ischemia time was 832.5min (316-1320). All centres used antibody induction with depleting (54%) or non-depleting (46%) antibodies and maintenance with tacrolimus (80%) or cyclosporine (20%) and mycophenolate with (49%) or without (51%) maintenance steroids. Median follow up was 75 days (1-1158). Delayed graft function occurred in 19% of kidneys, and in 8% of pancreases. Overall patient survival was 95%; uncensored graft survival was 77% (SPK 87%, PTA 77% and PAK 59%). Grafts were lost to thrombosis (13%), anastomotic leak (3.2%), death with functioning graft (5%) and rejection (1.6%). Univariate analysis of risk factors for early pancreas loss included donor BMI >27kg/m^2 (p=0.01), PAK vs.SPK (p=0.03). HLA-DR mismatched grafts (p=0.1) and sensitised recipients (p=0.08) tended to poorer outcome. Donor or recipient age, sex, graft number, donor perfusion technique, waiting time, cold ischemia time, implantation technique, vascular reconstruction, maintenance immunosuppression did not appear to influence the outcome.

Conclusion: Nearly all early pancreas losses are due to thrombosis. These results suggest better pancreas survival in SPK compared to PAK. Higher donor BMI is associated with increased risk of early graft loss. The role of histocompatibility and allosensitisation needs further investigation.

O83

Campath induction and steroid avoidance in pancreas transplantation – a single centre experience in 231 patients

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Purpose: To study the impact of Campath induction in pancreas transplantation, with particular reference to steroid avoidance.

Methods: Campath (alemtuzumab) is a humanised anti-CD52 T & B-cell depleting antibody, clinically effective in many immune-mediated disorders. From August 2004 to November 2008, 234 pancreas transplants were performed in 231 patients receiving Campath induction (175 simultaneous pancreas kidney (SPK), 37 pancreas after kidney (PAK) and 37 pancreas transplant alone (PTA)). 25 transplants (2 SPK, 12 PAK, 12 PTA) were from donors after cardiac death. 30 mg of Campath was given either IV (n=193) or subcutaneously (n=41) on day 0 & 1 with tacrolimus (trough level 8-12ng/ml) and mycophenolate mofetil for maintenance immunosuppression. Methyl prednisolone was given IV before reperfusion of the grafts. No steroids were used in the maintenance regimen. Patient and graft survival, rejection rate and adverse events were recorded.

Results: The median length of follow-up was 18 months (range 0-53 months) in 140 males and 94 females with a median age of 43 (range 25-67). Overall patient survival was 97%. 96 % of SPK patients are currently off dialysis and 88% of all pancreas recipients have a functioning pancreas graft. 17% received treatment for rejection. 4 patients (8%) developed BK viruria, but still have functioning renal grafts. Viral infections included CMV (5.9%), varicella zoster (1.7%), herpes simplex (1.3%) and parvovirus (0.4%). 24% of patients required re-operation. 12.3% developed neutropenia and 1.7% received granulocyte-colony stimulating factor. 89.4% have received no steroids post-transplant and 7 patients (3%) are currently on steroids. 3 patients (2 SPK & 1 PAK) developed post-transplant lymphoproliferative disorder and have responded to immunosuppression reduction and have functional grafts.

Conclusions: Campath is safe and enables pancreas transplantation with acceptable rejection rates and without the need for steroid maintenance in 89% of cases.

O84

Cardiovascular Disease following Simultaneous Kidney Pancreas Transplant in Diabetes

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Background: Patients with diabetes and end-stage renal disease experience high rates of cardiovascular disease (CVD). For diabetic patients following simultaneous kidney pancreas (SPK) transplant in the UK, the frequency and determinants of CVD are not well described. Using data from the UK National Transplant Database, we assessed risk factors for CVD, and tested the association between CVD and graft failure.

Methods: Data were obtained on 729 deceased donor SPK transplants performed between 1 January 2001 and 31 October 2008 at the 8 designated pancreas transplant centres in the UK. We defined CVD as the occurrence of a myocardial infarction, cerebrovascular accident or lower extremity amputation (LEA) within three-months of transplant. We assessed donor and recipient factors measured prior to transplant for fatal or non-fatal CVD following transplant using logistic regression, and between incident CVD and pancreatic graft survival at 90 days using proportional hazards modelling.

Results: During the three months post-transplant, 72 of 729 individuals (10%) experienced a CVD event. LEA was the most common, and of all events, over 90% occurred within the first week. Of 72 cases, 5 died. In univariate analyses, patients with incident CVD were more likely to be older, heavier, unemployed and have type 2 (vs type 1) diabetes, and to have received organs from older, heavier, and shorter donors (all $p \leq 0.1$). Smoking or relative hyperglycaemia in the recipient did not increase risk. In multivariate analysis (n=432), increasing recipient age (odds ratio, OR, 1.89, 95% confidence interval (CI) 1.23 – 2.88 for each 10 years, $p = 0.004$) and increasing body mass index (BMI) (OR 1.09, CI, 1.01 – 1.16, per each 10 kg/m^2, $p = 0.02$) were both associated with CVD independent of sex and type of diabetes. Relative to those who did not develop CVD, individuals with CVD were approximately 3 years older and had a BMI 2 kg/m^2 greater. At 3 months, 52 of 548 patients with available data had graft failure. In a time-dependent proportional hazards model controlling for year of transplant, cold ischaemia time, and donor age, incident CVD increased the risk of graft failure (hazard ratio 3.4, CI 1.5 – 7.3, $p = 0.002$).

Conclusions: In the UK, the risk of CVD following SPK transplant remains high affecting one-tenth of individuals within three months. Of factors tested, only recipient age and adiposity increased the risk of CVD, which, in turn, markedly increased the risk of graft failure at 3 months.

Parallel Session

Thursday 23 April

Renal Fibrosis

11:00 – 12:30

O85

Reversible Unilateral Ureteric Obstruction is Characterised by Profound Loss of Myofibroblasts and Alteration in Matrix Constituents

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Introduction and Aims: Fibrotic scarring generated by glomerular and interstitial myofibroblasts is a key determinant of the progression of CKD. This study examined myofibroblasts, extracellular matrix deposition, matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) in reversible unilateral ureteric obstruction.

Methods: Male FVB/N mice (6-8 wks) underwent unilateral ureteric obstruction (UUO) for 7 days (d7UUO). UUO was reversed in some groups and kidneys removed after a further 7 (d7/14) or 14 (d7/21) days. Control d7 sham and normal mice were included. Tissues were immunostained for F4/80 (macrophage marker), α-smooth muscle actin (SMA, myofibroblast marker) and collagen III and analysed by computer image analysis. Real time PCR (RT-PCR) was used to determine the expression of TGFβ, MMP-2, -9, -12 and -13, TIMP-1 and TIMP-2. Each group consisted of at least 7 mice.

Results: At d7UUO obstructed kidneys exhibited prominent macrophage infiltration (8.41$\pm$1.81% area), interstitial SMA+ myofibroblasts (16.13$\pm$1.74% area) and collagen III deposition (17.78$\pm$1.07% area). Following reversal of UUO, there was a profound loss of myofibroblasts at d7/14 which returned to normal levels over time (d7UUO=16.13$\pm$1.74% area, d7/14=5.14$\pm$1.41, d7/21=2.21$\pm$0.56). This coincided with a 2.6-fold reduction in TGFβ expression at d7/14. Collagen III expression was reduced in the cortex at d7/21 (d7UUO=17.99$\pm$1.63% area, d7/21=7.17$\pm$1.57) but remained unchanged in the medulla. Macrophage infiltration was unchanged following UUO reversal. No clear change in pattern was evident in MMP/TIMP expression.

Conclusion: Reversal of UUO results in a rapid and profound loss of myofibroblasts. There is also partial resolution of collagen deposition that is limited to the renal cortex. The mechanisms underlying myofibroblast loss is unclear but may include active killing or reduced support from mitogens or survival factors. The persistent macrophage infiltrate suggests involvement in the reparative features evident following UUO reversal. Further studies will dissect the mechanisms underlying these novel findings.

O86

Translational Regulation of Transforming Growth Factor-β_1 mRNA by its 5′-Untranslated Region

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Transforming Growth Factor-β_1 (TGF-β_1) is the principle stimulus for renal fibrosis in chronic kidney disease. TGF-β_1 synthesis is controlled post-transcriptionally, in part by Y Box-1 Protein (YB-1) binding to the TGF-β_1 5′-Untranslated Region (5′-UTR). The aim of the current study is to provide further mechanistic insight into this process.

A reporter vector containing the TGF-β_1 5′-UTR showed significant reduction in luciferase expression compared to control. No significant changes in amount of vector-derived mRNA were detected by RT-qPCR, suggesting that transcription and mRNA stability are unaffected by the 5′-UTR. Deletion analysis confirmed that the major inhibitory element resides in nucleotides +1 to +167. *In silico* analysis of the RNA secondary structure was performed by Vienna RNAfold software. Calculations revealed a region centred around nucleotide +90 which is predisposed to formation of stable secondary structure due to its high GC content and self-complementarity. A stem loop structure spanning nucleotides +77 to +106 was predicted in the majority of the ensemble of structures. Circular dichroism spectroscopy of nucleotides +75 to +113 confirmed the presence of a stable stem loop structure. Site directed mutagenesis showed that mutations predicted to interfere with the formation of the stem loop structure or a putative YB-1 binding site reversed the translation-inhibitory effect. Preliminary data suggests that mutations leading to enhanced protein synthesis are due to loss of protein binding to this region.

In summary, we have defined the TGF-β_1 5′-UTR sequence responsible for post-transcriptional regulation of TGF-β_1 synthesis and have linked binding of YB-1 and other unidentified regulatory proteins to this mechanistically. Future work will focus on fine mapping of the RNA structure, identification of other regulatory factors and manipulation of RNA-protein interactions, aiming for complete mechanistic insight into the regulation of TGF beta synthesis.

O87

Regulation of TGFβ1-induced post-transcriptional splicing of Fibronectin

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Fibronectin (Fn) is an important extracellular matrix (ECM) protein with both physiological and pathological roles. One of the aspects of Fn which allows multiple functions is post-transcriptional RNA splicing resulting in the expression of multiple forms. The EDA+ Fn variant is associated with fibrotic disease suggesting it as the "pathological" form. Previously, we have identified p38 MAP kinase as a regulator of TGFβ1-induced transcription of Fn in proximal tubule epithelial cells (PTEC) this work examines regulation of EDA+Fn production by RNA splicing.

Primary human PTEC and transformed human PTEC (HKC8) were used. TGFβ1-induced Fn deposition was assessed by immunocytochemistry using antibodies to total and EDA+ Fn. Fn mRNA was investigated by RT-PCR using a single primer pair producing two products for EDA+ and EDA-. EDA+ and EDA- Fn protein expression was determined by Western blotting. SRp40 knock-down was achieved by RNA interference. Cells were treated with TGFβ1, 2.5 ng/ml, SB202190, 2.5 μM and LY294002, 10 μM.

TGFβ1 induced marked deposition of EDA+ Fn which was inhibited by p38 MAP kinase blockade, however mRNA analysis indicated that the proportion of EDA+ to EDA- Fn was not altered. Selective knock-down of the splicing factor SRp40 inhibited TGFβ1-induced EDA+ Fn without significantly altering EDA- Fn expression. SRp40 expression and cellular distribution was not altered by TGFβ1, indicative of regulation by phosphorylation in the nucleus. PI 3kinase-mediated activation of Akt has previously been shown to regulate phosphorylation of SRp40. LY 294002 inhibited TGFβ1-induced PI 3 kinase activity and reduced EDA+ Fn expression.

The regulation of the different splice variants of Fn may be a key consideration in both the diagnosis and treatment of renal fibrosis. We have presented the first evidence for the regulation of Fn RNA splicing by SRp40, a member of the SR protein family of splicing factors in adult human epithelial cells. We further propose that regulation of TGFβ1-induced SRp40 activity may be by PI 3 kinase activation. Targeting post-transcriptional events may provide a novel selective therapeutic strategy for the treatment of fibrosis.

O88

Genetic Variation in Dimethylarginine Dimethylaminohydrolase 1 (DDAH1) is Associated with Rate of Decline in Renal Function in Chronic Kidney Disease (CKD)

Ben Caplin, Herpreet Gill, Richard Hoefield, Dorothea Nitsch, Jill Norman, Rachel Middleton, James Leiper, David Wheeler

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Observational studies suggest high plasma asymmetric dimethylarginine (ADMA) is associated with poor renal outcome in CKD patients. To evaluate a potential causal role of ADMA in progression of CKD, we investigated whether variation in genes encoding the ADMA-degrading enzymes, *DDAH1* and *DDAH2*, modulated decline in estimated glomerular filtration rate (eGFR) in two CKD cohorts (varied aetiologies, LACKABO and CRISIS).

Single nucleotide polymorphisms (SNPs) in *DDAH1* and *DDAH2* were genotyped by PCR. eGFR was calculated using the MDRD formula at baseline and follow-up visits (until dialysis commenced). Urinary protein (UP) was determined by protein:creatinine ratio or 24 hour collection and plasma ADMA quantified by HPLC (LACKABO only). Variables predicting eGFR over time were estimated using a multivariate multilevel model with random slope and intercept. To avoid confounding by racial group, and as numbers of non-white subjects were low, genotype effects were examined in white only subgroups.

In LACKABO (n=268, 73% male, 71% white, mean baseline eGFR 40.8mL/min, mean follow-up 566 days) and CRISIS (n=922, 85% male, 96% white, mean baseline eGFR 33.6mL/min, mean follow-up 1082 days) UP associated with decline in eGFR. Genotype was not associated with baseline eGFR. However, each G allele at SNP rs17384213 (*DDAH1*c.303+45805C>T, reverse strand) was associated with a steeper decline in eGFR independent of UP (Table). This association also held when including all racial groups. There was no consistent relationship with other loci in *DDAH1* or *DDAH2*. Higher ADMA levels were not associated with faster decline in eGFR or with the G allele at rs17384213.

Table: Effect of Genotype at rs17384213 on eGFR

	LACKABO cohort mean (95% CI)	**CRISIS cohort** mean (95% CI)
Baseline eGFR, *mL/min/1.73m^2/G allele*	1.59 (-2.68 to 5.84)	0.34 (-2.07 to 2.76)
Change in eGFR over time, *mL/min/1.73m^2/G allele/year*	-1.18* (-2.34 to -0.02)	-0.78** (-0.97 to -0.59)

*P<0.05; **P<0.01

In CKD patients, the G allele at rs17384213 associates with steeper decline in eGFR but not with higher plasma ADMA (the impact on tissue ADMA and in other groups is unknown). These data imply a role for DDAH1 in progression of renal dysfunction in patients with CKD.

O89

Experimental Glomerulosclerosis is associated with an Up-Regulation of the LIM Protein, Hic-5, which controls Extracellular Matrix regulation of Mesangial Cell Apoptosis

Nick Hornigold, Tim Johnson, Rosamunde Banks, Andrew Mooney

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Glomerulosclerosis is the final common pathway through which all glomerular diseases lead to renal failure. It is characterised by progressive loss of functional glomerular cells through apoptosis associated with deposition of abnormal extracellular matrix (ECM). In an in vitro model of mesangial cell apoptosis, we have previously demonstrated that mesangial cells are more susceptible to apoptosis if subcultured on ECM expressed in sclerosed glomeruli (Collagen I), compared to cells subcultured on constituents of normal glomerular ECM (Collagen IV), and that this susceptibility was mediated by the LIM protein, Hic-5 (Renal Association Meeting 2007). Cells subcultured on Collagen IV downregulated Hic-5 and were less susceptible than cells subcultured on Collagen I; siRNA knock down of Hic-5 restored resistance to pro-apoptotic triggers in such cells.

We have now studied Hic-5 expression in vivo, using subtotally-nephrectomised rats. 6 rats underwent 5/6ths nephrectomy by standard procedures and 6 animals underwent sham operation. Rats were fed on normal chow with free access to drinking water and no other intervention, and 3 operated and 3 control animals were sacrificed at days 90 and 120. Immunohistochemical staining for Hic-5 was performed and glomerular staining scored by a blinded observer on a 0-5+ scale. In rats subjected to sham operation, Hic-5 expression (assessed by immunohistochemistry), was confined to the distal tubules, with undetectable levels of expression in glomeruli (staining score 0.1+/- 0.3 [mean +/- S.D.]). However, in rats subjected to subtotal nephrectomy, glomerular expression of Hic-5 increased significantly at days 90 and 120 in mesangial areas in all glomeruli in a segmental pattern (staining score 3.05+/- 1.05). The timing of peak expression of Hic-5 coincides with the time of maximal glomerular cell apoptosis in this model.

These in vivo data support the hypothesis that Hic-5 is pivotal in the regulation of mesangial cell susceptibility to apoptosis.

This work was supported by KRUK, and The Yorkshire Kidney Research Fund.

O90

Tissue retention of gadolinium after a single injection of Omniscan in the rat following sub-total nephrectomy

John Haylor, Anne Dencausse, Melissa Vickers, Jean-Marc Idee, David Slater, Sameh Morcos

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Patients with reduced renal function may develop nephrogenic systemic fibrosis (NSF) following MRI diagnostic tests. Contrast agents, containing the paramagnetic ion gadolinium (GD) to enhance the MR image, are thought to be responsible. MRI contrast agents contain the GD ion in combination with either linear or macrocyclic chelates which are rapidly excreted from the body by glomerular filtration. The retention of the contrast agent in patients with reduced renal function may enhance the dissociation of the GD chelate, increasing the availability and therefore toxicity of the GD ion. In vivo animal studies investigating the association between NSF and MRI contrast agents are currently limited to the use of multiple GD injections, of up to 20 daily doses, in rats with normal kidney function.

Male Wistar Han rats were subjected to sub-total nephrectomy (SNx) by an excision technique under isoflurane anaesthesia. The glomerular filtration rate (GFR) was assessed from the 24-hour creatinine clearance. After some 3 months, animals with either 20% of normal GFR or 40% of normal GFR, received a single intravenous injection of Omniscan 2.5 mmol/kg (GE Healthcare, USA) (n=4 per group). The retention of GD was measured, by inductively coupled plasma mass spectrometry (ICP-MS), from tissue obtained 4 weeks following Omniscan administration.

Serum GD was below the level of detection in all animals studied. Both the bone and liver GD content showed a positive correlation with the serum creatinine. Rats with a lower GFR (20% vs. 40% of normal) showed an increase in the tissue retention of GD; a 3-fold increase in the skin (49.5 ± 14.1 vs. 16.9 ± 4 nmol/g, $p<0.05$); a 10-fold increase in the liver (221 ± 56 vs. 20 ± 15 nmol/g, $p<0.01$) and a 25% increase in bone (109 ± 14 vs. 75 ± 9 nmol/g, $p<0.05$). Rats with 20% normal GFR showed increased cellularity in skin samples taken from the dorsal surface but no external damage to the skin surface was observed.

The tissue retention of gadolinium, in skin, liver and bone can be demonstrated following a single intravenous injection of Omniscan in rats with a low GFR associated with an increased in skin cellularity.

Parallel Session

Thursday 23 April

Medawar Medal

14:30 – 16:30

O91

Randomised controlled trial of Alemtuzumab and low dose Tacrolimus monotherapy with Daclizumab, Tacrolimus and Mycophenolate Mofetil in Renal Transplantation

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We have previously shown that the cheap and simple combination of Alemtuzumab induction with low dose Tacrolimus and a steroid sparing regime is safe and effective. We have now completed a randomised controlled trial [RCT] of this regime compared with Daclizumab induction, conventional dose Tac and Mycophenolate Mofetil [MMF] in renal transplantation.

Recruitment into this trial [ClinicalTrials.gov: NCT00246129] finished 12 months ago and mean [±1SD] follow up is 21.6±8.78 months.

82 patients [54m, 28f; mean age 47.3±13.36 years] received Alemtuzumab, low dose Tac [0.1mg/kg; target level 5-8 ng/mL] and 41 patients [27m, 14f; mean age 47.0+10.64 years] received Daclizumab, Tac [0.15mg/kg; target level 8-12 ng/mL] and MMF [target level: 1.5-3.0 mg/L]. Both groups received our steroid sparing regime [prednisolone 60mg daily day 1-3; 30mg daily day 4-7 and then stopped]

In the event of rejection, steroids and MMF were added to the Tac monotherapy group.

One year patient and graft survival is similar in both groups [Alemtuzumab 100% and 97.6%; Daclizumab 97.5% and 97.6% respectively]

The incidence of biopsy proven allograft rejection at 1 year is lower in the Alemtuzumab group, 9% vs 18% in the Daclizumab group, but not statistically significant [p=0.13].

Allograft function [MDRD eGFR, mL/min/1.73m2] is similar at 6 and 12 months [Alemtuzumab 53.7+3.63, 56.8±4.01vs Daclizumab 49.5±4.78, 50.7±5.80, p>0.05; mean±95%CI].

73.2% of the Alemtuzumab group remained on Tac monotherapy at 1 year.

Infection rates [positive bacterial and viral isolates, expressed as incidence/100 patient months] are similar in both groups.

This RCT shows that our simple regime of Alemtuzumab induction and low dose Tacrolimus monotherapy provides excellent patient and allograft survival with a low rate of rejection, infection and good function equivalent to a conventional Daclizumab, Tacrolimus and MMF protocol.

O92

Allospecific B cells can receive effective help from CD4 T cells that recognise an unrelated antigen.

Thomas Conlon, Kourosh Saeb-Parsy, Siva Sivaganesh, Reza Motallebzadeh, Chris Callaghan, Eleanor Bolton, Andrew Bradley, Gavin Pettigrew

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Alloantibody responses often incorporate additional specificities against non-donor MHC antigens; how such 'bystander' activation occurs is poorly understood. In theory, antibody specificity is restricted by the requirement for T cell help delivered through 'cognate' recognition of processed target antigen that is presented following BCR internalization. Here we examine whether CD4 T cells that recognise additional mismatched alloAg can provide help for anti-MHC class I alloantibody responses.

B6 ($H2^b$) mice challenged with BALB/c ($H2^d$) hearts produced strong anti-K^d IgG alloantibody responses. T cell deficient B6 (TCR KO) allograft recipients reconstituted with 10^7 monoclonal TCR Tg CD4 T cells specific for self-restricted K^d peptide (which provide cognate help through recognition of processed allopeptide on K^d-specific B cells) mounted a 3-fold greater anti-K^d response. Surprisingly, TCR KO female mice reconstituted with Mar CD4 T cells (specific for self restricted H-Y peptide) developed anti-K^d IgG alloantibody following male, but not female, BALB/c heart transplantation, that was one third of the wildtype response. Further confirmation that T cell recognition of additional graft alloantigens can provide help for anti-class I alloantibody responses was provided by the development of anti-K^d responses in TCR KO allograft recipients reconstituted with TEa CD4 T cells (that recognise self-restricted donor I-E MHC II peptide). Finally, female TCR KO mice reconstituted with Mar T cells and challenged with male B6 APC (that provoked strong Mar responses) did not develop alloantibody to female BALB/c hearts. Thus although helper T cells can recognise a different antigen from allospecific B cells, both antigens need to be expressed on the graft for effective humoral immunity. We hypothesise that as alloantigen-specific B cells internalise target alloantigen, neighbouring donor proteins are also captured, processed and presented to helper T cells.

Our results challenge the tenet of 'linked' antigen recognition between the BCR and helper TCR as a critical requirement for T-dependent antibody responses and provide a mechanism to explain how alloantibody specificities can diversify after transplantation.

O93

Early renal transplant protocol biopsies directly influence patient management.

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INTRODUCTION: In this prospective observational study, we explored whether early protocol biopsies directly influenced patient management and subsequent graft function.

METHOD: A protocol biopsy programme was instituted for patients transplanted consecutively from September 2006. All recipients received baseline immunosuppression; a calcineurin inhibitor and mycophenolate mofetil with early steroid weaning for the majority. Those patients with combined kidney-pancreas transplants or early graft loss were excluded. Protocol biopsies were performed at 2/3 and 12 months post-transplantation. Specimens were analysed for adequacy and conventional histology. An index of chronic damage (morphometric assessment of tubular atrophy and interstitial fibrosis - ICD) was also assigned. ICD values at implantation and 2/3 months were compared. Biopsy results were reviewed at a weekly multi-disciplinary meeting. An independent observer recorded whether a change in patient management was instituted as a direct result of the biopsy findings.

RESULTS: 154 patients were transplanted between Sep 2006 and July 2008. 35.2% received a live donor graft. 142/154 patients (92.2%) underwent biopsy at a median 2 months post-transplantation. There were no major complications as a result of protocol biopsy. In 32 patients (23.2%) protocol biopsy findings directly altered patient management. 7 patients were treated for subclinical rejection, 5 for hitherto undiagnosed viral infection in the graft and 21 had evidence of CNI toxicity. Early protocol biopsy findings instituted a management change which was shown to improve graft function in patients with subclinical rejection ($p= 0.011$).In 110 patients, negative biopsy findings did not directly alter management but engendered confidence in allowing further CNI dose reductions. This may be important for long term graft survival since we noted that the ICD increased significantly between implantation and biopsy ($p = 0.112$) suggesting that chronic allograft nephropathy develops early post-transplantation.

CONCLUSIONS: Early protocol biopsies are safe and directly influence patient management in >20% of cases. Chronic graft damage can develop as early as 2 months post-transplantation.

O94

Acquisition of intact alloantigen by recipient DCs provokes cytotoxic CD8 T cell and alloantibody responses

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Introduction: The ability of DCs to retain and re-present unprocessed antigen raises the possibility of a novel pathway of allorecognition, whereby recipient DCs present intact alloantigen to direct pathway T cells. Teleologically, however, this pathway is advantageous over conventional pathways only if intact and processed alloAg are presented by the same DC, as this provides a mechanism for the delivery of help from indirect pathway CD4 T cells to direct-pathway cytotoxic CD8 T cells through interaction on a single cell.

Methods: Day 7 BMDCs from B6 (H-2b) and BALB/c (H-2d) mice were co-cultured overnight. Acquisition of MHC class I alloAg and presentation of processed MHC class II alloAg on B6 DCs was assessed using allotypic and idiotypic mAbs (anti-Dd and anti-I-Ab/I-E peptide). Following mixing, B6 DCs were sorted and injected into naive B6 mice. Cytotoxic CD8 T cell, alloantibody and indirect pathway CD4 T cell responses (division of I-E-peptide-specific TEa cells) were assayed 10 days later. DC presentation of intact alloantigen after transplantation was assessed by transfer of B6 splenic DCs, purified 5 days after BALB/c (H-2d) heart grafting.

Results: As expected B6 BMDCs acquire and present processed alloAg after co-culture with BALB/c DCs (mean 16.1% of cells). Smaller numbers of B6 DC expressed intact Kd alloantigen on their surface (mean 4.4%), with, importantly, 2.3% of DCs presenting both intact and processed alloantigen. Increased staining was not a consequence of non-specific antibody binding following DC activation, because isotype-control Ab binding did not change upon mixing. B6 DCs, sorted after co-culture, provoked strong alloantibody, cytotoxic and indirect-pathway CD4 T cell responses upon injection into naive B6 recipients. This was not due to contamination with BALB/c DCs, because the population of B6 DCs that expressed Kd alloAg provoked strong cytotoxic CD8 T cell responses, whereas only minimal responses were generated by B6 DCs with no detectable surface Kd. B6 DC that lacked MHC II acquired similar levels of intact Kd, but provoked only minimal CD8 T cell responses; thus highlighting that effective cytotoxic alloimmunity requires presentation of both processed and intact alloantigen by the same recipient DC. Finally, splenic DCs purified from heart-grafted recipients induced indirect-pathway CD4 T cell responses and weak, but detectable, cytotoxic CD8 T cell responses.

Conclusions: Our results demonstrate that DCs present simultaneously intact and processed alloantigen for indirect pathway CD4 and direct-pathway CD8 T cell responses. This may be particularly important for the generation of anti-graft cytotoxicity late after transplantation, when donor DCs are no longer present.

O95

Steroid withdrawal following renal transplantation increases the risk of acute rejection but improves cardiovascular risk factors: a meta-analysis

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Introduction: The morbidity related to long-term steroid therapy has led to interest in withdrawal of steroids from immunosuppressant regimens following renal transplantation. A number of recent trials have provided greater longer term information regarding the risks and benefits of steroid avoidance or withdrawal.

Methods: A detailed literature search was performed using Ovid Medline and Embase, the Cochrane Library and the Transplant Library from the Centre for Evidence in Transplantation. All trials comparing a maintenance steroid group with either complete avoidance or withdrawal of steroids were included in the review. All studies were assessed for methodological quality. Meta-analysis of extracted data was performed using the statistical software R. All data are reported as summary effect (relative risk (RR) or weighted mean difference (WMD)) and 95% confidence intervals (CI).

Results: A total of 117 publications from 34 studies met the inclusion criteria; these included a total of 5,472 patients. Only 14 (41%) of the studies were rated as good quality. Steroid avoidance/withdrawal (SAW) regimens significantly increased the risk of acute rejection over maintenance steroids (RR 1.56, CI 1.31-1.87, P<0.0001). This effect was independent of time of withdrawal of steroids and concomitant immunosuppression. No significant differences in corticosteroid resistant acute rejection, patient survival or graft survival were observed. Serum creatinine was increased and creatinine clearance reduced with SAW (serum creatinine WMD 4.42 µmol/L, CI 1.70-6.16, *P*=0.0006, clearance WMD -3.36 ml/min, CI -4.96 - -1.76, *P*<0.0001). Cardiovascular risk factors including incidence of hypertension (RR 0.91, CI 0.85-0.97, *P*=0.003), new onset diabetes (RR 0.53, CI 0.41-0.70, *P*<0.0001) and hypercholesterolemia (RR 0.76, CI 0.66-0.87, *P*<0.0001) were reduced significantly by SAW.

Conclusion: Despite an increase in the risk of acute rejection with steroid avoidance or withdrawal protocols, there is only a small effect on graft function with no measurable impact on graft or patient survival during the duration of the included studies. However there are significant benefits in cardiovascular risk profiles following steroid avoidance or withdrawal which may lead to a longer-term reduction in cardiovascular morbidity and mortality.

O96

Ex vivo Generated Treg Ameliorate Transplant Arteriosclerosis by Inhibiting Effector Cell Priming and Graft Infiltration

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Background and aims: The ability to generate regulatory T cells (Treg) capable of suppressing immune responses to alloantigens offers the possibility of preventing transplant rejection without the requirement for indefinite global immunosuppression. We have developed an in vitro culture system that generates graft-protective Treg from naïve $CD4^+$ T cells. CBA ($H2^k$) $CD4^+$ T cells are conditioned for 14 days in the presence of allogeneic B6 ($H2^b$) bone marrow-derived dendritic cells (BMDCs) and interferon-γ (IFN-γ). Following this protocol, the conditioned T cell population (Tcon) are enriched for $Foxp3^+$ cells and prevent skin graft rejection by $CD4^+$ effector T cells following adoptive transfer into lymphopenic mice. The aim of this research was to ask whether Tcon also control the development of transplant arteriosclerosis using a relevant mouse model of vasculopathy.

Methods: T and B cell deficient CBA.$rag^{-/-}$ mice were reconstituted with 1×10^5 naïve CBA $CD25^-CD4^+$ effector T cells (Teff) with or without 4×10^5 Tcon on day −1. The following day, a B6.$CD31^{-/-}$ aortic interposition graft was performed. $CD31^{-/-}$ grafts were used so that the degree of endothelial repopulation could be assessed histologically as a marker of graft damage. On day 30, the animals were sacrificed and the spleen and graft harvested for histological, functional and phenotypic analysis.

Results: Mice that received Tcon and Teff had significantly reduced arteriosclerotic lesions compared to mice that received Teff alone (intimal expansion 11.7±13.1% vs. 29.7±14.5%; p=0.04). Significantly, in mice reconstituted with Teff alone the donor $CD31^{-/-}$ endothelium was entirely replaced by $CD31^{+/+}$ recipient endothelial cells reflecting an active immune response against the graft. However, co-transfer of Tcon completely prevented this endothelial repopulation.

To investigate the mechanisms by which Tcon attenuated transplant arteriosclerosis, we analysed graft-infiltrating cells by histology and splenic T cells by FACS and IFN-γ ELISpot. Strikingly, the frequency of primed donor-reactive IFN-γ-secreting $CD4^+$ cells was reduced from 170±16 per 1×10^5 in mice that received Teff alone to 48±15 per 1×10^5 in mice that also received Tcon. This correlated with $CD4^+$ T cell infiltration into grafts, which was markedly reduced in the presence of Tcon.

Discussion: These data indicate that the mechanisms by which ex vivo generated Treg control transplant-associated vasculopathy include a reduction in both effector cell priming and infiltration into the graft. These data emphasise the potential of ex vivo generated Treg to control not only acute allograft rejection but also vascular changes associated with chronic allograft dysfunction.

O97

Indirect allorecognition of HLA 'public' T-cell epitopes is associated with chronic allograft dysfunction.

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We recently reported human $CD4^+$ T lymphocyte responses to peptide epitopes derived from sequences of class I HLA that exhibit little polymorphism, some that are identical to self and many of which bind promiscuously to MHC class II ('public T cell epitopes' PTE). This contrasts with other studies in which there is an assumption that epitopes arise from highly polymorphic sequences. If responses to PTE's are representative of indirect alloimmune responses in general, then they may allow the development of a standardised assay of cellular immunity in renal transplantation despite the polymorphism of HLA. This could be developed as a biomarker that may for example be applied in chronic allograft dysfunction (CAD).

We undertook a cross-sectional analysis of the immune response to a restricted set of HLA class 1, α-3 domain derived PTE's. This was assessed by PBMC γ-interferon production using ELISPOT in 110 renal transplant recipients under long term follow-up at our centre. The relationship between these responses and two indicators of (CAD): late transplant biopsy (LTB) for clinical indication after the 1^{st} post-transplant year and deteriorating renal function in the previous 3 years (DRF) was assessed. 30 patients underwent LTB and an intersecting group of 30 defined as having DRF. In both groups, 22 patients made a response in the ELISPOT (ER) that was above a normal range defined in healthy controls. This was significantly higher than in patients in whom there was no LTB or DRF (22/30 vs 32/80, 73.3% vs 40%; p=0.002 in both). In multivariate analysis ER was the variable most strongly associated with LTB and the only variable associated with DRF. Of the 54/110 transplant recipients with an ER, 22/54 had undergone LTB compared to 8/56 non-responders. Identical results were observed for DRF. The combination of ER and/or anti-HLA antibody was present in 65/110 and absent in 45/110. The likelihood of LTB or DRF was low amongst non responders in ELISPOT (ER vs non-ER: 41.6% vs 6.7% for LTB $p<10^{-3}$; 40% vs 8.9% for DRF $p<10^{-3}$).

These data suggest that responses to this set of peptides are significantly associated with a diagnosis of CAD in a population unselected for HLA type. Although necessarily limited by the retrospective nature of the analysis, the strength of these associations and the potential for such an assay to be generalised to large populations, suggest that this is a viable biomarker of 'chronic rejection' amenable to further investigation in longitudinal studies.

O98

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

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Introduction Ischaemia reperfusion injury (IRI) is an important cause of delayed graft function, an adverse indicator of renal allograft survival. Endothelial cells are highly susceptible to IRI. Strategies that promote their survival are likely to be beneficial by maintaining organ perfusion. Hemeoxygenase-1 (HO-1) is reported to improve outcomes in animal models of transplantation. We investigated the utility of the novel Hemeoxygenase-1 (HO-1) inducer Hemearginate (HA) in models of IRI and experimental murine renal transplantation (Tx) **Methods** *In Vitro* Murine cardiac endothelial cells (MCEC's) were pre-treated with HA, and exposed to conditions of hypoxia + hypercarbia (HCR) (0.5% O2, 11.5% CO2) for 24h followed by 24h recovery. Cells were then fixed, stained and counts of viable cells per high-powered field (hpf) were obtained. *In Vivo* IRI was induced by 20min clamping of the left renal pedicle with right nephrectomy in male FVB/n mice. PBS treated animals were compared with those given 30mg/kg iv HA. Renal function was determined by serum Creatinine (SCr). Acute tubular necrosis (ATN) was determined by quantifying necrotic tubules in the outer medulla on H&E stained sections. Preliminary studies looked at the effect of donor mouse HA pre-treatment in a model of renal transplantation. **Results** *In Vitro* HCR caused increased MCEC death compared to normoxic cells (9.2±5.9 vs. 30.1±3.9 viable cells/hpf, $p<0.05$). HA pre-treatment provided marked protection from HCR compared to untreated cells (22.7±3.5 vs. 9.2±5.9 viable/hpf, $p<0.05$). Thus HA treatment improved MCEC survival from 30% to 75% in HCR injury. A specific inhibitor of HO-1 (Zinc Protoporphyrin) reversed this protection. *In Vivo* HO-1 induction by HA was validated by western blot. In renal IRI, HA therapy offered significant structural (69.6 ±10.2 vs 36.5±3.5 %ATN control vs HA; $p<0.05$) and functional protection (sCr 132±44.4 vs 78±24.3µmol/l control vs HA; $p<0.05$). HA therapy induced relative preservation of the microvascul-ature (%medulla CD31+ve 8.7±1.3 vs 13.1±2.0 $p=0.096$). Initial results in HA treated isografts showed encouraging protection of both CD31+ microvasculature and medullary tubular integrity compared to vehicle treated controls. **Conclusion** Our data show that HO-1 upregulation protects renal structure and function post IRI. HO-1 Induction by HA is a novel and feasible intervention for this key component of post-transplant injury.

Parallel Session

Thursday 23 April

Immunological Renal Disease

14:30 – 16:30

O99

Cryoglobulinaemic glomerulonephritis is induced by connective tissue growth factor (CTGF) over-expression in lymphoid cells

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Cryoglobulins are immunoglobulins which show reversible precipitation at low temperature. In mixed essential cryoglobulinaemia (MEC), there is a predilection for their precipitation in the kidney and development of a mesangiocapillary glomerulonephritis. In certain countries hepatitis C is a frequent association with MEC, however, the factors stimulating cryoglobulin production remain poorly understood.

To date the only spontaneous animal model of cryoglobulinaemia is a transgenic mouse expressing thymic stromal lymphopoietin, a cytokine promoting B cell differentiation and proliferation.

We have discovered a new mouse model of cryoglobulinaemia in which CTGF is overexpressed in the kidney and lymphoid compartments under the influence of the renin (REN1) promotor. Importantly, CTGF overexpression using a collagen(COL1) promoter, which did not result in lymphoid cell expression, did not induce cryoglobulinaemia.

CTGF-Tg mice were normal until 7 months of age when they began to develop signs of cryoglobulinaemic glomerulonephritis, which increased in severity with increasing age. Both IgM and C3 deposits were found in the glomeruli as well as typical EM appearance of cryoglobulinaemia. By 12 months 75 % of CTGF-Tg mice had some evidence of circulating cryoglobulins, proteinuria and renal impairment. The cryoprecipate varied in different mice with some predominantly expressing K light chains and others λ light chains. By contrast to human disease we found no evidence for C3 or C4 consumption. CTGF was overexpressed in the lymphoid compartment as was its activated phosphor-TRKA receptor. In vitro, B cell lines were found to overexpress CTGF.

To investigate whether haematopoetic cells were the main instigators of disease we generated CTGF-Tg chimeric mice, in which bone marrow from CTGF-Tg mice were transplanted into irradiated WT recipients(n=5). The animals were left for 12 months at which point 60% developed circulating cryoglobulins and 100% had developed evidence of cryoglobulin deposition in the kidney. We are currently investigating the overexpression of CTGF in patients with cryoglobulinaemia, which should inform us as to whether overproduction of CTGF underlies human MEC and allow us to develop new therapies.

O100

The defunctioning polymorphism in *FCGR2B,* rs1050501, is associated with protection against bacterial infection and malaria but susceptibility to SLE.

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Polygenic autoimmune diseases, such as systemic lupus erythematosus (SLE), are a significant cause of morbidity and mortality worldwide. In recent years, functionally important genetic polymorphisms conferring susceptibility to SLE have been identified, but the evolutionary pressures driving their retention in the gene pool remain elusive.

rs1050501, single nucleotide polymorphism (SNP) in the inhibitory receptor FcγRIIb, causes an isoleucine to threonine substitution in the transmembrane domain which abrogates receptor function. This SNP has been associated with SLE in Asian populations. We have demonstrated that homozygosity for the threonine form of the receptor ($Fc\gamma RIIb^{T232}$) is also associated with an increased susceptibility to SLE in a UK Caucasian population (OR 2.4, p = 0.014).

The frequency of $Fc\gamma RIIb^{T232}$, the minor allele, is 0.1 in Caucasians, but almost three times higher in Asians and Africans, populations from areas where malaria is endemic. We genotyped 684 Kenyan children with severe malaria and 998 ethnically matched controls. Homozygosity for $Fc\gamma RIIb^{T232}$ was associated with protection against malaria, OR 0.50, $p = 1.0x10^{-3}$. We have also shown that, i*n vitro*, this lupus-associated FcγRIIb polymorphism enhances phagocytosis of *Plasmodium falciparum*-infected erythrocytes. These results suggest that FcγRIIb has an important role in controlling the immune response to falciparum malaria.

Previous *in vivo* studies have shown that FcγRIIb protects against bacterial infection with *Streptococcus pneumonia,* and *in vitro*, macrophages from individuals homozygous for $Fc\gamma RIIb^{T232}$ phagocytose opsonised *S. pneumonia* more efficiently than those from $Fc\gamma RIIb^{I232}$ donors. We genotyped 809 Kenyan children with blood culture positive bacterial infection, and found $Fc\gamma RIIb^{T232}$ homozygosity was associated with protection, OR 0.66, p = 0.031.

Hence rs1050501, a defunctioning polymorphism of FcγRIIb, may be maintained in the population because it protects against bacterial and malarial infection, thereby contributing to the increased incidence of SLE in people of Asian and African origin.

O101

The role of neutrophil serine proteases in glomerular endothelial cell dysfunction during glomerulonephritis.

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Endothelium lining the vasculature may be a target for injury by neutrophils during inflammatory glomerulonephritis. Serine proteases (SP) released during the degranulation of neutrophils, are particularly implicated and potentially amenable to therapeutic inhibition. Prolonged exposure to high concentrations of SP is known to induce endothelial cell (EC) apoptosis. Less appreciated are the pro-inflammatory properties of SP.

At low concentrations (1-2µg/ml), proteinase 3 (PR3) or human neutrophil elastase (HNE) did not alter EC mitochondrial activity, monolayer integrity, cell attachment or induce apoptosis of Human umbilical vein EC (HUVEC) or glomerular EC (GEnC; a transformed cell line developed by SCS) detected by MTT or crystal violet assays, DAPI staining, FACS and western blotting for cleavage of caspase-3. Neutrophil adhesion to PR3/HNE-treated EC was assessed under static or flow conditions. At concentrations, at which EC injury was not detectable, pre-treatment of HUVEC or GEC with either protease (1µg/ml for 2hr) increased static neutrophil adhesion (PR3 $p<0.001$; HNE $p<0.05$). Under flow conditions, PR3 (not HNE) enhanced neutrophil capture by HUVEC ($p<0.05$). Classic adhesion molecules (ICAM-1, VCAM-1 & E-Selectin, detected by ELISA or FACS) and VAP-1 (detected by FACS & western blotting) were not induced by protease treatment, suggesting enhanced release of IL-8 was promoting neutrophil adhesion. Endothelial activation was confirmed by vWF release determined by ELISA on supernatants from SP-treated HUVEC (PR3 $p<0.05$; HNE $p<0.01$) and GEnC (HNE $p<0.01$). The effects of PR3/HNE on vWf release were inhibited by the presence of human alpha1-proteinase inhibitor (Prolastin, a gift from Talecris) at molar excess concentrations.

In conclusion, EC from different vascular beds can be activated by non-cytotoxic levels of SP, supporting cytokine release, adhesion of neutrophils and release of vWf. Inhibition of SP activity by Prolastin suggests the involvement of protease dependent pathways. PR3 was less damaging to cell monolayers than HNE, and PR3 could induce neutrophil adhesion even under flow conditions, potentially relevant to pathogenesis of neutrophil-dependent EC injury during diseases such as vasculitis. Thus, SP may represent viable targets for therapy with physiological or small molecule inhibitors.

O102

Genetic susceptibility to experimental autoimmune glomerulonephritis: role of QTL on chromosome 13 confirmed in congenic rats

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In experimental autoimmune glomerulonephritis (EAG), a model of Goodpasture's disease, WKY rats immunized with the recombinant NC1 domain of the α3 chain of type IV collagen (α3(IV)NC1) develop circulating and deposited anti-GBM antibodies, and focal necrotising glomerulonephritis with crescent formation. By contrast, LEW rats are resistant to the development of EAG. A genome-wide linkage analysis of backcross animals revealed a major quantitative trait locus (QTL) on chromosome 13 (LOD=3.9) linked to the severity of glomerulonephritis. In this study we investigated the susceptibility of congenic rat strains to the induction of EAG. Reciprocal congenic rats were created by transferring the chromosome 13 QTL region from WKY rats to LEW (LEW/WKY13 congenic) and the same region from LEW rats to WKY (WKY/LEW13 congenic). Groups of WKY (n=6), LEW (n=5) and reciprocal congenic (n=7) rats were immunised with recombinant α3(IV)NC1 and assessed for the development of EAG. WKY/LEW13 congenic rats showed a marked reduction in albuminuria, severity of glomerular abnormalities, and number of glomerular macrophages, when compared to WKY controls. No reduction in the level of circulating or deposited antibody was observed. By contrast, LEW/WKY13 congenic rats were resistant to the development of EAG, as were LEW controls. Macrophage activation was assessed by incubating bone marrow derived macrophages (BMDM) with fluorescently labeled immune complexes (Fc Oxyburst). WKY/LEW13 congenic rats showed a significantly lower percentage of activated BMDM, when compared to WKY controls. The results from this study demonstrate a reduction in the severity of EAG, and in Fc receptor mediated macrophage activation, in WKY/LEW13 congenic rats. These results confirm the importance of the chromosome 13 QTL and should lead to insights into the genetic susceptibility to EAG, which may be applicable to human glomerulonephritis.

O103

Anti-plasminogen Antibodies in UK ANCA Vasculitis Patients Compromise Fibrinolysis

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Antibodies recognising plasminogen, a key component of the fibrinolytic system have recently been reported in one cohort of ANCA systemic vasculitis (ASV) patients and are associated with venous thromboembolism. In theory, such antibodies might also promote glomerular thrombosis and exacerbate renal injury. We investigated the prevalence and functional activity of anti-plasminogen antibodies in a UK ASV patient cohort. IgG was purified from the plasma exchange fluid of 74 ASV patients and screened by ELISA. 18/74 (24.3%) were positive for anti-plasminogen antibodies (7/29 MPO- and 11/45 PR3-ANCA) compared to 0/50 healthy donor control IgG (based on the mean + 2 SD of controls, $P<0.05$). In contrast, only 5/74 ASV patients bound to plasmin. Evidence of specificity for the interactions between IgG and plasminogen were demonstrated using competitive inhibition assays. IgG was pre-incubated for 2 hrs with increasing concentrations of soluble plasminogen prior to the plasminogen ELISA. Soluble plasminogen significantly inhibited IgG binding by 60%. This is comparable to the level of inhibition achieved when using a highly specific commercially available anti-plasminogen antibody (70.1%). In contrast, soluble plasminogen denatured with beta-mercaptoethanol prior to incubation with IgG only inhibited IgG/plasminogen interactions by 12%. Furthermore, IgG reactivity to plasminogen was abolished following plasminogen denaturation. Using an *in vitro* fibrinolysis assay 16/74 (21.6%; $P<0.05$) ASV-IgG and only 1/50 control IgG retarded clot lysis when added to plasminogen prior to combining with tissue plasminogen activator (t-PA). Importantly, 11 of 18 (68.7%) anti-plasminogen positive patients retarded fibrinolysis versus only 5/56 (8.9%) of antibody negative patients ($P=0.0001$ Fishers' exact test). Antibodies against t-PA were identified in 1/5 ASV-IgG that retarded fibrinolysis in the absence of anti-plasminogen antibodies. In total, anti-t-PA antibodies were identified in 13/74 (17.5%, $P<0.01$) ASV-IgG compared to 1/50 control IgG. In conclusion, ASV patients from this UK cohort demonstrate anti-plasminogen reactivity by ELISA. Moreover, IgG from some patients mediated functional inhibition of fibrinolysis. Perturbation of fibrinolysis may be prevalent in ASV patients and further investigation into this phenomenon and its clinical correlations is warranted.

O104

Randomised Trial of Rituximab versus Cyclophosphamide for ANCA Associated Renal Vasculitis: RITUXVAS

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Cyclophosphamide (CYC) based induction regimens for ANCA associated renal vasculitis (AAVr) are effective in 90%, but mortality and adverse event rates remain high. Rituximab (RTX) has a superior safety profile and has led to remission rates >80% in refractory vasculitis. We compared a RTX based regimen with a standard intravenous CYC regimen as induction therapy for new AAVr.

Eligibility required a new diagnosis of AAVr and ANCA positivity. 44 patients were randomised; 33 to RTX 4x375mg/m^2 & 2x15mg/kg IV CYC; and 11 to IV CYC 6-10x15mg/kg. Both groups received the same IV and oral prednisolone regimen. Minimum follow-up was 12 months.

At entry: median age was 68 years, Wegener's granulomatosis 50%, microscopic polyangiitis 50%; CRP 28; BVAS 18; PR3-ANCA 58%, MPO-ANCA 42%, GFR 18ml/min, 18% required dialysis.

Primary end points at 12 months: (1) Sustained remission: 25/33 (76%) RTX vs 9/11 (82%) CYC (p=0.67 for risk difference). (2) Severe adverse events: 45% RTX (40 events, 15 patients) vs 36% CYC (16 events, 4 patients) (p=0.60 for difference). 8 patients died (6/33 (18%) RTX, 2/11 (18%) CYC). 7 within 12 months.

Secondary end-points: Remission (BVAS 0x2) occurred in 27/33 (82%) RTX and 10/11 (91%) CYC (no significant difference in time to remission). Median GFR at 0 & 12 months was; RTX 25 & 51 ml/min vs CYC 15 & 33 ml/min (p=0.42 for difference). 5/8 RTX & 1/1 CYC recovered from dialysis dependence at entry and one from each group became dialysis dependent during follow-up. 89% RTX & 81% CYC became ANCA negative by 6 months.

Conclusions: There is no evidence that a rituximab based regimen is less effective than IV cyclophosphamide for remission induction in AAVr. Severe adverse event rates were similar in both groups and consistent with previous reports in this patient population.

GFR and BVAS

Median & IQ range

	0 months	3	6	12
RTX GFR	**25 (12-55)**	**48 (34-60)**	**49 (33-62)**	**51 (38-57)**
CYC GFR	**15 (11-41)**	**31 (23-51)**	**35 (25-59)**	**33 (24-59)**
RTX BVAS	**19 (14-24)**	**0 (0-0)**	**0 (0-0)**	**0 (0-0)**
CYC BVAS	**18 (12-24)**	**0 (0-0)**	**0 (0-0)**	**0 (0-0)**

Parallel Session

Thursday 23 April

Donation Pathway

14:30 – 16:30

O105

The effect of a "required referral" policy in an acute trust setting on the donor referral rate.

Dawn Lee, Susan Duncalf, Jane Monks, Lee Alexander, Greg Bleakley

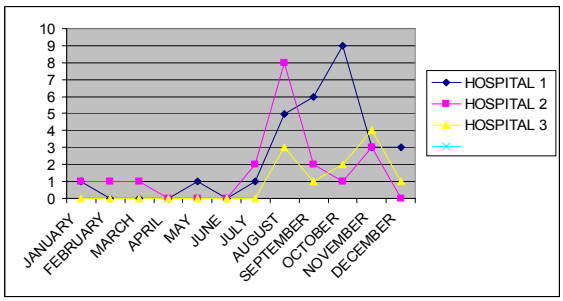
Manchester Royal Infirmary, Manchester, United Kingdom

INTRODUCTION Following the endorsement of the Organ Taskforce Recommendations, (2008) the Northwest Regional Donor Co-ordinators seized the opportunity to challenge the way donors are identified in this region.

METHOD The Potential Donor Audit clearly identified missed/potential donors in the Critical Care areas. In line with recommendations 4, 5 and 6 a generic, simple and easy to understand hospital policy was developed with a working title of "Required Referral." The policy clearly states when and how to refer patients, allowing early involvement of the transplant co-ordinator resulting in expert approaches to families, vital staff support and excellent donor management.

A large hospital trust was identified (encompassing 4 hospital sites) and with Trust Board backing agreed to pilot the policy for 6 months. (From 1st July 2008) An extensive teaching program was undertaken prior to the pilot launch with 100% of all ICU clinical staff trained. (100% = 170 staff)

OUTCOME A prospective six month audit revealed impressive results:



100% referral has been achieved in these hospitals and the results have generated local and national media interest.

SUMMARY The pilot policy converted to a trust wide policy on 1st January 2009 and successfully encompasses recommendations 4, 5 and 6. It is easily adapted to suit individual trusts/clinical areas and the majority of Northwest regional trusts are now in the process of adopting and implementing the policy. The aim is to have the policy in place in all of the Northwest regions ICU's and ED's by the end of 2009.

O106

Abstract Withdrawn

O107

Psychosocial impact of kidney transplantation: A qualitative study of quality of life outcomes for transplant recipients and their partners.

Susan Darwent[2], Jane Smith[1], Abdul Hammad[1], Helen Poole[2]

[1]Liverpool John Moores University Hospital, Liverpool, United Kingdom, [2]Royal Liverpool University Hospital, Liverpool, United Kingdom

Transplantation is the treatment of choice in end-stage renal disease (ESRD) and research indicates that transplanted patients have better quality of life (QOL) than those on either peritoneal or haemodialysis. Quantitative QOL measures tend to focus on four areas: physical health, functional ability, social support and psychological well-being however these may miss issues important to those undergoing treatment.

Orr *et al*. (2007) used focus groups to explore the experience of living with a transplanted kidney, in order to gain a deeper understanding of QOL from the recipients' perspective. Other studies have used qualitative methodology to explore the impact of chronic illness on patients and their spouses (Eklund *et al.,* 2004; Erikson & Svedlund, 2005). The current study extends these qualitative explorations into the experiences of the transplanted patient, their partner and the interaction between them. Eight kidney recipients, who attend a unit in the north of England, and their partners, were interviewed individually using a semi structured interview format.

The transcripts were analysed using Interpretative Phenomenological Analysis, following the system suggested by Smith (2003). Five super-ordinate themes emerged, which were 'Changing identity', 'Coping', 'Appraisal', 'Relationship balance' and 'Confident futures'. The results illustrated the dynamic relationship which exists between partners in their attempts to cope with the series of crises that chronic illness brings. From the partners' perspective, four overarching themes were apparent: 'Partners as a resource'; 'Proximity of death'; 'Adjustments imposed' and 'Protective factors'. Contemporaneously with the progression of the chronic illness, major life decisions were made: for example, three partners gave up work, while others adapted their roles. Various psychological and social coping strategies were employed to enable partners to continue to support their spouses. Together these had attendant effects on partners own QOL, both negatively e.g. social isolation, depression, and positively e.g. a belief that their relationship had become stronger. Several participants commented that the interview gave them their first opportunity to review and appraise the illness journey and to see how far they had come in surmounting the impact of renal disease and its treatment.

Recommendations for clinical practice include facilitating realistic expectations of transplantation. Despite being given information, some recipients seemed to feel that transplantation was the only mode of treatment rather than a choice. Issues to be addressed include managing uncertainty about symptoms, graft outcome and life expectancy and the potential for relationship and sexual difficulties. Acknowledging these factors and provision of support for partners as part of a total care package together with ensuring access to information and to senior staff may be indicated.

O108

Maximising donation from the Emergency Departments: A 'back to basics' approach.

Paula Aubrey[1,2], Scot Lister[1], Sara Arber[2]

[1]NHS Blood and Transplant, London, United Kingdom, [2]University of Surrey, Guildford, United Kingdom

Given the critical shortage of donor organs in the UK, it is vital to examine novel ways to increase donors. The two major barriers to transplantation are lack of deceased donors and relative refusal rate, which stands on average at 39% across the UK. The majority of organ donors are referred from the intensive care unit (ICU) and despite numerous initiatives to increase numbers of potential donor referrals from ICU the number of organ donors has remained static.

A 'back to basics' organ donation education programme directed at medical and nursing staff, has dramatically increased solid organ donor referrals from the Emergency Departments (ED) within this region. These referrals have resulted in the lives of many patients being saved.

The ED education programme was shaped by findings of a retrospective audit of deaths undertaken in Emergency Departments that identified a significant missed potential of solid organ donors. The ED education programme, run by Donor Transplant Coordinators, has involved assessing the educational needs of ED nursing and medical staff, and developing instructive programmes aimed at helping key clinicians to identify potential donors.

The results of this ED education programme have dramatically increased the number of organ donors. In 2003, this region reported that there was only one donor and 3 solid organ transplants from Emergency Departments, in 2007-08 there were 6 donors and 17 solid organs transplants and since April 2008 to the current date there have been 16 donors and 49 solid organ transplants.

This successful initiative has led to the development of ED donation programmes in other regions and should be introduced in all regions across the UK.

Up until now, the UK has missed a large number of potential organ donors by neglecting deaths in Emergency Departments. It is therefore timely to redress this imbalance and consider the ways that which the pioneering work carried out in this Region can be replicated throughout the UK.

Parallel Session

Thursday 23 April

Kidney Transplantation – Clinical 2

17:00 – 18:30

O109

Renal allograft rejection after Alemtuzumab induction and Tacrolimus monotherapy

Jack Galliford, Kakit Chan, Michelle Willicombe, Tom Cairns, Candice Roufosse, Anthony Dorling, Anthony Warrens, Terry Cook, Adam McLean, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

There are few data detailing the incidence, nature, timing and outcome of acute rejection [AR] in patients treated with Alemtuzumab and Tacrolimus [Tac] monotherapy.

In this study, we report our experience of renal allograft rejection in 320 patients [196m, 126f], mean age 46.9±12.8 yrs, 191 live donors, 129 deceased donors] receiving Alemtuzumab induction [30mg iv immediately post operatively], medium dose Tac [0.1mg/kg/day, target level 5-8 ng/ml] and 7 days of oral steroids. Allograft rejection [AR] was diagnosed by biopsy and designated to be cellular [ACR], cellular with a vascular component [ACR+V] or antibody mediated [AMR]. ACR was treated with iv methyl prednisone, 0.5g x 3, the introduction of oral steroids and Mycophenolate Mofetil. AMR and ACR+V was similarly managed with the addition of plasma exchange and ivIg [2g/kg].

Rejection free survival at 6, 12, 24 and 36 months were 90.74%, 86.84%, 82.33% and 77.12%.

47/320 [14.7%] patients experienced AR and there was no difference in % patient survival [100 vs 99.47, 97.06 vs 98.25 and 97.06 vs 97.15; logrank p=0.9427] or % allograft survival [97.92 vs 95.99, 95.04 vs 94.81 and 85.53 vs 93.76; logrank p=0.7188] at 12, 24 and 36 months when compared with those that did not. However allograft function [MDRD eGFR, ml/min/1.73m^2] after AR, is significantly inferior at 6, 12 and 24 months [48.0±2.55 vs 54.5±2.6; p=0.029, 45.7±5.5 vs 56.8±2.4; p=0.0001, 41.7±16.7 vs 55.0±3.1; p=0.009].

There were 8 cases of AMR, 7 of ACR+V and 32 ACR. The mean time to AMR was 30.1 days and significantly shorter than ACR and ACR+V [127.7 days and 350.2 days respectively; p=0.07].

AR was significantly more common in less well matched transplants [3.6±1.4 vs 3.1±1.6 HLA mismatches, p=0.03], and in patients with pre-existing class I, class II and both classes of HLA antibodies [10 vs 29; p=0.039, 7 vs 12; p=0.0049 and 6 vs 9; p=0.0046].

This study shows that in patients receiving Alemtuzumab induction, AR is relatively uncommon, is associated with pre-existing HLA antibodies, increased HLA mismatching, but rarely associated with allograft loss.

O110

The Maximum Tolerated Dose Of Mycophenolic Acid (MPA) Is Higher With Enteric-Coated Mycophenolate Sodium (EC-MPS) Compared To Mycophenolate Mofetil (MMF) In Kidney Transplant Recipients: Results Of A Randomized, Multicenter Trial

Magdi Shehata[1], Sunil Bhandari[2], G Venkat-Raman[3], Richard Moore[4], Richard D'Souza[5]

[1]Nottingham University Hospitals, Nottingham, United Kingdom, [2]Hull And East Yorkshire Hospitals NHS Trust and Hull York Medical School, Hull, United Kingdom, [3]Queen Alexandra Hospital, Portsmouth, United Kingdom, [4]Cardiff Royal Infirmary, University Hospital of Wales, Cardiff, United Kingdom, [5]Royal Devon & Exeter Hospital, Exeter, United Kingdom

Introduction: No randomized trial has assessed if conversion from MMF to EC-MPS permits an increase in tolerated MPA dose, with the potential for improved long-term outcomes.

Methods: In a randomized, multicenter, open-label trial at 19 UK centers, kidney transplant patients with gastrointestinal (GI) complications, or who had required MMF dose reduction due to GI events, either remained on MMF or switched to an equimolar dose of EC-MPS. EC-MPS 1440mg was considered bioequivalent to MMF 2000mg. At week 2, MPA dose in both groups was adjusted to achieve the highest tolerated dose. Patients were followed to 12 weeks post-randomization.

Results: The ITT population comprised 68 EC-MPS patients and 61 MMF patients. Baseline mean MMF dose (EC-MPS 1283±461mg/day, MMF 1279± 485mg/day) and concomitant immunosuppression were similar between groups. The primary efficacy endpoint, proportion of patients maintained at 12 weeks on an EC-MPS dose ≥180mg/day or MMF dose ≥250mg/day higher than at randomization, was greater in the EC-MPS arm (32/68, 47.1%) vs. the MMF arm (10/61, 16.4%; p<0.001). At week 12, 50.0% (34/68) of EC-MPS patients were receiving the maximum recommended dose vs. 26.2% (16/61) of MMF patients (p=0.007). 16/36 EC-MPS patients (44.4%) with a low baseline dose (1000mg/day MMF) were receiving the equivalent of MMF >1000mg/day at week 12 vs. 6/31 MMF patients (18.4%). The decrease (i.e. improvement) in Gastrointestinal Symptom Rating Scale total score from baseline to week 12 was -0.49 in the EC-MPS arm vs. -0.22 in the MMF cohort (n.s.).

Conclusions: Kidney transplant patients receiving reduced doses of MMF due to GI side effects can tolerate a significant increase in MPA dose after conversion to EC-MPS without compromising quality of life.

O111

Renal function with enteric-coated mycophenolate sodium in combination with reduced and standard tacrolimus levels: Results of a 6-month study in de novo renal transplant recipients

Argiris Asderakis[1], Laurence Chan[2]

[1]Cardiff Transplant Unit, University Hospital Wales, Cardiff, CF14 4XW, United Kingdom, [2]Transplant Centre, University of Colorado, and on behalf of the ERL2409 Study Group, Aurora, Colorado, United States

This study investigated the safety and efficacy of *myfortic*® (enteric-coated mycophenolate sodium, EC-MPS) used in combination with different tacrolimus (tac) exposures in order to preserve renal function.

Methods: In a 6-month, multicentre, randomised trial, de novo renal transplant patients (n=292) were randomised (1:1) to one of two treatment regimens, all receiving basiliximab, EC-MPS 720 mg bid and steroids: *Group A* was treated with low-dose tac (target troughs of 5-9 ng/mL, first 3 months, 3-6 ng/mL in subsequent 3 months), and *Group B* with standard-dose tac (10-15 ng/mL, then 8-12 ng/mL). Primary endpoint was calculated GFR at 6 months (Nankivell formula). Secondary efficacy endpoint was incidence of treatment failure (biopsy proven acute rejection [BPAR], graft loss or death).

Results: *Group A* and *B* were comparable at baseline as was the mean daily dose of EC-MPS (1296 and 1325 mg, respectively). In the ITT population, no significant difference in mean GFR was observed between treatments (63.6 vs. 61.0 mL/min). However, there was a poor differentiation between the groups with regards to tac levels, with 68% of patients not complying with the prespecified range. There were 158 patients who consistently adhered to one of the two tac ranges and analysis on this population showed that GFR was higher in patients with reduced tac levels than in those exposed to standard tac concentrations (69.9 vs. 63.2 mL/min, p=0.038). Treatment failure was observed in 14.6% and 11.3% of patients in *Group A* and *B*, respectively, with a BPAR rate of 11% and 10%, respectively (ITT population). The overall safety profile was comparable between ITT and sub-analysis groups.

Conclusions: This 6-month study showed that EC-MPS with reduced tac exposure is equally efficacious and safe as a regimen with standard tac exposure. In patients where tac levels were consistently adhered to, better renal function could be observed with reduced tac levels, with no loss of efficacy. This post-hoc analysis though should be interpreted with caution.

O112

Rejection in HLA antibody incompatible transplantation; early glomerular infiltration.

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

[1]University Hospital, Coventry, United Kingdom, [2]NHS BT, Biringham, United Kingdom, [3]Warwick Medical School, Coventry, United Kingdom

Background: The histological appearances of antibody-mediated rejection are described in the Banff 07 classification of renal allograft pathology. The aim of this study was to compare the classification with the findings in our programme.

Methods: Renal biopsies from patients with donor specific antibodies (DSA) to HLA were scored by Banff 07, and were stained for CD45, and a subset also for CD20, CD68 and CD3. Numbers of positively stained glomerular cells, and total cortical cells per high power field (hpf) were counted. Glomerular neutrophil cell counts were made on H+E stained sections

Results: 36 patients had 72 renal biopsies; 29 patients had pre-transplant plasmapheresis to remove DSA. 29 biopsies were performed 30 minutes after graft reperfusion. The mean number of CD45+ cells per glomerulus was higher than in control antibody compatible grafts ($p<0.04$). The number of glomerular cells was associated with the DSA level ($p<0.01$), and 8/9 patients with greater than 5 CD45+ cells per glomerulus had rejection or oliguria, compared to 11/20 with less than 5 CD45+ per glomerulus ($p<0.01$).

In the first 10 days post-transplant, although peritubular capillary (PTC) leucocyte margination grade 3 and C4d deposition were specific for rejection, their sensitivities were low. PTC C4d staining was not seen in the first 5 days after transplant, even in the presence of rejection, but was present in the majority of biopsies with rejection after the first 5 days. In biopsies with leucocyte subset staining, the glomerular cells were 1% CD20+, 66.6% CD68+, and 32.4% CD3+ the interstitial cells were 1.8% CD20+, 50.2% CD68+, and 48% CD3+.Glomerular PMN were counted in biopsies with mean glomerular CD45 + > 5cell/glom, and showed that PMN made up a mean of 52% of CD45+ cells on day 0 biopsies, and 48% of CD45+ cells on later biopsies.

Conclusions: Glomerular margination of lympho-histiocytic (CD45 +) cells occurred early after transplantation and was associated with DSA level and early graft dysfunction. PTC margination grade 3 was always associated with rejection, but PTC grades 1 and 2 were not specific for serious rejection. A significant proportion of the leucocytes in glomeruli and renal interstitium were CD3+. C4d was not seen in PTC for the first few days after transplantation, even in the presence of cellular margination, and this requires further investigation.

O113

Predicting Risk of Non-melanoma Skin Cancer in Renal Transplant Recipients

Sarah Milborrow[1], Jane Dalley[1], John Lear[2], Ven Samarasinghe[2], Sheila Russel[2], Tony Fryer[1]

[1]Institute for Science and Technology in Medicine, Keele University, Stoke on Trent, Staffordshire, United Kingdom, [2]Department of Dermatology, Manchester Royal Infirmary, Manchester, United Kingdom

The risk of non-melanoma skin cancer (NMSC) in renal transplant recipients (RTR) is markedly increased compared to non-immunosuppressed subjects. The American Society of Transplantation recommended annual dermatological screening for RTR. However, in temperate climates, this approach may not be cost effective. This study used demographic (age at transplantation, gender, duration of immunosuppression, smoking history, etc), and ultraviolet radiation (cumulative sun exposure, sunbathing score, frequency of sun burning during childhood, skin type, eye/hair colour, etc) data from 698 RTR recruited from the Manchester Royal Infirmary and Salford Hospital to develop a predictive index (PI) identifying patients at risk of NMSC. Stepwise Cox's regression models, used to identify variables associated with time from transplantation to development of the first NMSC, selected age at transplantation, smoking history, frequency of childhood sun burning and eye colour as significant variables. These were used to generate the following equation:

PI score = Age_at_tranplant>45*4)+(Blue_or_hazel_eyes*2)+(Ever_smoker*1)+ (Frequent_childhood_sunburning*2)

This gave a range of scores between 0-8. Inspection of Kaplan-Meier plots identified three risk groups: low (scores 0-1), moderate (scores 2-4) and high (score $\geq$5). Compared with the low risk group, moderate and high risk groups demonstrated significantly reduced time to first NMSC (both $p<0.001$, hazard ratios; 3.3, 13.5). The proportion tumour-free for the three groups at 10 and 20 years post transplantation were 98.0%, 94.7%, 71.0% and 90.1%, 67.2%, 44.8%. This study shows that this approach can be used to identify patients at high risk of NMSC and could inform surveillance strategies for NMSC.

O114

Lymphopenia induced by Alemtuzumab is not associated with an increased risk of infection after renal transplantation

Rawya Charif, Kakit Chan, Anisha Tanna, Nicky Kumar, Jack Galliford, Adam McLean, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

Although Alemtuzumab causes profound and long lasting lymphopenia which may result in a higher incidence of infection, there are no specific reports describing the incidence, nature and severity of infection following the use of this agent in renal transplantation.

340 patients [204m, 136f, mean age: 46.9± 12.87 yrs], average follow up 19.8 ± 14.03 months, received Alemtuzumab induction [30mgs] and Tacrolimus monotherapy [0.1mg/kg/day, target trough level 5-8ng/ml] with no maintenance steroids or mycophenolate mofetil. All patients received 3 months Valganciclovir and 6 months Co-trimoxazole prophylaxis. Patients deemed high risk for tuberculosis [TB] also received Isoniazid and Pyridoxine.

Positive urine, blood, bronchiolar lavage and drain fluid cultures constituted significant episodes of bacterial infection. CMV PCR positivity [> 1000 copies/ml] and BK viral nephropathy [diagnosed by allograft biopsy] were considered significant markers of viral infection.

Results are expressed as episodes of infection per 100 patient years [pt yrs] as previously described by Snyder et al. [KI; Nov 2008].

All patients became lymphopenic post Alemtuzumab [$< 1 \times 10^9$/L] and only 50% patients had normal lymphocyte counts one year post transplantation.

Cumulative patient and censored allograft survival is 97.2% and 94.8% at 4 years. Although 5 patients [0.015%] died [3 cardiac, 1 cancer, 1 encapsulating sclerosing peritonitis], there were no infection associated deaths.

There were 273 episodes of infection [76.7/100 pt yrs]. Urinary tract infection was the most common cause of infection [38.8/100 patient years] followed by bacteraemia [12.65/100 pt yrs] and surgical site infections [8.7/100 pt yrs]. There were 4 cases of CMV, 4 cases of BK viral nephropathy [1.1/100 pt yrs], 2 cases of parvovirus B19 and 2 cases of non-invasive mucocutaneous fungal infection [0.6/100 pt yrs].

There was no TB or PTLD.

This study shows that although Alemtuzumab causes profound and long lasting lymphopenia after transplantation, the rate of infection is low and comparable to published data.

Parallel Session

Friday 24 April

Basic Science

09:30 – 11:00

O115

Inhibitory Fc receptors in acute and chronic allograft rejection

CJ Callaghan[1], TS Win[1], S Sivaganesh[1], EM Bolton[1], JA Bradley[1], RJ Brownlie[2], KG Smith[2], GJ Pettigrew[1]

[1]Dept of Surgery, University of Cambridge, Cambridge, United Kingdom, [2]Dept of Medicine, University of Cambridge, Cambridge, United Kingdom

INTRODUCTION: The inhibitory Fc receptor, FcγRIIb, is a key regulator of innate and adaptive immunity. Expressed on myeloid cells and B cells, its ligation inhibits their activation; FcγRIIb$^{-/-}$ mice are thus prone to autoimmunity. FcγRIIb is also likely to regulate allograft rejection, but its role in transplantation has not yet been studied.

METHODS: Acute and chronic cardiac allograft rejection was investigated using the BALB/c (H-2^{d}) to Bl/6 (H-2^{b}) and bm12 to Bl/6 (MHC class II-mismatched) models and survival compared in WT Bl/6, FcγRIIb$^{-/-}$ Bl/6, and transgenic Bl/6 recipients bearing increased FcγRIIb on their macrophages (MPTG). We have previously shown that bm12 heart graft rejection is characterised by progressive allograft vasculopathy, with endothelial complement deposition and the development of donor CD4 T cell-dependent anti-nuclear autoantibody (quantified by staining HEp-2 cells). In the acute model, alloantibody was assayed using ELISA and cytotoxic CD8 T cell responses by IFNγ ELISPOT.

RESULTS: WT Bl/6 mice rejected bm12 hearts slowly (MST=95d, n=13). Whereas rejection kinetics in non-transgenic FcγRIIb$^{-/-}$ littermate controls were similar to WT mice, rejection in FcγRIIb$^{-/-}$ recipients occurred rapidly (MST=28d, n=8) and was associated with severe vascular obliteration and markedly augmented autoantibody responses. There was however no difference in autoantibody responses or in bm12 graft survival between MPTG and non-TG littermate controls, suggesting that the accelerated rejection in FcγRIIb$^{-/-}$ mice is due to aggressive humoral immunity from loss of inhibitory signalling in B cells. In the acute model, FcγRIIb$^{-/-}$ recipient mice rejected BALB/c heart grafts at the same tempo (MST=7d, n=6), and with similar alloAb and cytotoxic CD8 T cell responses, as WT recipients.

CONCLUSIONS: Inhibitory FcγRIIb modulates chronic but not acute rejection and, in particular, influences chronic autoantibody, but not acute alloantibody responses. Polymorphisms in FcγRIIb gene expression exist in humans and are thus likely to influence allograft survival.

O116

Antibody Combination Therapy Extends Heart Allograft Survival in Presensitised Murine Recipients.

Hina Shariff, Yakup Tanriver, Kathryn Brown, Nizam Mamode, Stipo Jurcevic

King's College London, London, United Kingdom

Memory T cells play a critical role in heart transplant rejection however, current treatments that are effective in controlling naïve T cell alloresponses have limited effects on memory T cells. We used a novel antibody combination therapy comprising anti-CD154, -CD70, -CD8 (days 0 and 4) post-transplantation and Rapamycin (days 0-4) in a pre-sensitised fully MHC mismatched heterotopic heart transplant model in mice. Graft survival in the treated group (MST = 78 days, n=8) was significantly prolonged compared to untreated controls (MST=8, n=9). Furthermore an additional "rescue therapy" comprising the same antibodies administered on days 30, 60 and 90 post-transplantation resulted in indefinite graft survival. This correlated with a reduction in the number of graft-infiltrating $CD4^+$ and $CD8^+$ T cells than in the absence of rescue therapy, low levels of allospecific IgG and fewer IFN-γ secreting cells. Levels of splenic $CD4^+CD25^+Foxp3^+$ T regulatory cells (Treg) in both control and treated mice were similar at day 10 (mean=19.3%), however, there was a moderate decline in treated group by day 20 (15.1%) and 30 (11.5%) post transplantation. Interestingly, a slight increase in the number of Treg cells at day 60 was noted in the absence of rescue therapy (17.5%), which coincided with allograft rejection. In contrast, the levels of splenic Treg cells remained low (13.1%) in the group that received rescue therapy. We conclude that treatment alone extends heart allograft survival in pre-sensitised recipients and when combined with rescue therapy leads to indefinite graft survival. Therefore, graft survival does not correlate with the presence of $CD4^+CD25^+Foxp3^+$ cells and their role in controlling the pre-sensitised alloresponse remains unclear.

O117

The Role of LTβR Signalling in the Formation of Tertiary Lymphoid Organs within Cardiac Allografts.

Reza Motallebzadeh[1], Sylvia Rehakova[1], Thet Su Win[1], Chris Callaghan[1], Siva Sivaganesh[1], Eleanor Bolton[1], Nancy Ruddle[2], Andrew Bradely[1], Gavin Pettigrew[1]

[1]Cambridge University, Cambridge, UK, [2]Yale University, New Haven, United States

Introduction: Tertiary lymphoid organs (TLOs) are found at sites of chronic inflammation and in explanted solid organ transplants. The present study aims to characterise TLOs in a model of chronic allograft vasculopathy, and to determine whether LTβR, a receptor which is involved in the development of lymphoid organs and the associated vasculature of lymph nodes, also participates in this process.

Methodology: Bm12 heart allografts were excised from B6 recipients at day 20(n=5), 40(n=5) and 100(n=3). Serial frozen sections, 100μm apart, were stained with H&E and lymphoid aggregates characterised by immunohistochemical staining of adjacent sections. Presence of TLOs was confirmed by: discrete aggregates of B220+ B cells, CD4+ T cells, and PNAd/MadCAM-1-expressing high endothelial venules (HEVs). Lymphatic vessel (LV) density was assessed by immunofluorescence staining with anti-LYVE-1 mAb. Blockade of LTβR was achieved with weekly intraperitoneal injection of 100μg LTβR-Ig fusion protein. Control animals received a non-specific IgG-protein complex. We have previously reported that bm12 heart allografts in B6 recipients provoke antinuclear autoantibody; autoantibody responses in treated and control recipients were compared by quantifying binding to nuclear antigen expressing HEp-2 cells.

Results: Aggregates of B cells and CD4 T cells were present in 12/13 grafts; these were associated with HEVs and thus fulfilled criteria for TLO. The number of TLOs within grafts increased with time (from 1[1-2] at d20 to 4[2.5-4.5] at d100). LVs were present in each heart, but were not evenly distributed. Small numbers of LVs also stained for HEV markers suggesting derivation from a common progenitor vessel. LV density was less in syngeneic hearts, and notably neither lymphoid aggregates nor HEVs were present. Compared to control-treated animals, LTβR-Ig treatment abrogated formation of HEVs (0.4 vs 2.1 per field, p=0.04) and inhibited LV proliferation (LV density = 1427 vs 2952 μm2, p=0.02), although lymphoid aggregates were of equivalent quantity and size. Nevertheless in both groups, bm12 allografts developed similar vasculopathy and provoked comparable autoantibody responses.

Conclusions: TLOs consistently feature within chronically rejecting heart allografts. Despite inhibiting HEV formation, aggregates still developed when LTβR was blocked, suggesting that their accumulation is governed by additional factors, e.g. LTβ3 and/or TNFβ3 signalling via TNF receptors.

O118

Evaluation of the XM-ONE® Assay and the Role of Endothelial Cell Antibodies in Recipients of Living Donor Renal Transplants.

Jeanette Procter[1], Michelle Ray[1], Juliet Agudelo[1], Anand Muthusamy[1], Peter Friend[1,2], Kathryn Wood[2], Susan Fuggle[1,2]

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

Despite improvements in immunosuppression, HLA antibody detection and crossmatch techniques, rejection episodes occur, even in HLA-matched siblings. We are investigating a potential role for anti-endothelial cell antibodies (AECA) detected with the XM-ONE® assay (Absorber AB) and have tested 22 living donor renal transplants performed since April 2008.

Patients were screened for HLA and MIC antibodies using Luminex technology. Allogeneic and autologous crossmatches were performed pre-transplant on peripheral blood mononuclear cells (PBMC) by complement-dependant cytotoxicity (CDC) and flow cytometry (FC) and by FC on endothelial cell precursor cells isolated from peripheral blood using XM-ONE®.

While all patients had negative CDC and FC pre-transplant crossmatches against donor PBMC, 6/22 (27%) recipients were donor AECA IgM+ of which 3/6 were also donor AECA IgG+. There was no association between AECA and pre-transplant sensitising events (83% AECA+ patients; 50% AECA- ($p=0.3$)) or the presence of HLA and MIC antibodies (50% AECA+ patients; 19% AECA- ($p=0.3$)).

Patients received Basiliximab induction, Tacrolimus, Prednisolone and Azathioprine (low risk) or Mycophenolate (high risk). 50% AECA+ patients and 56% AECA-patients received the low risk regimen. To date one patient in each group has experienced biopsy proven rejection, both within 2 weeks of transplant. AECA+ patients were significantly better HLA-DR matched than AECA- patients (0:1:2 DR mismatches; 83%:17%:0% vs 25%:69%:6% $p=0.02$). However preliminary analysis of follow-up shows that there was an increase between 1 and 3 month creatinine levels in the well matched AECA+ patients ($n=3$; 127±22 and 152±34; $p=0.04$) but not in the AECA- patients ($n=11$; 140±46 and 129±39).

The XM-ONE® crossmatch is easily performed alongside standard CDC and FC PBMC crossmatches. These preliminary results are consistent with recent data showing a correlation between AECA and increasing creatinine levels (Breimer et al, Transplantation 2009). Further investigation into the significance and role of AECA is warranted.

O119

Atorvastatin directly inhibits active caspase-3 and subsequently protects against renal ischaemia reperfusion injury in rats

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Background: Beneficial effects on ischaemia reperfusion injury (IRI) in the kidney have been reported for statins administered prior to the ischaemic insult. However, the mechanism for this protective effect is unknown.

Methods: Male rats underwent a right nephrectomy. The left renal hilus was clamped (45 min) followed by reperfusion for 4 hours. Atorvastatin (AT) 10 mg/kg was administered intravenously after clamping but prior to reperfusion. Histological injury, inflammation, apoptosis and oxidative damage were assessed. Caspase-3 activity was measured in renal homogenates and purified enzyme. Caspase-3 activation was also examined by western blotting. Involvement of nitric oxide was assessed using antibodies to S-nitrosocysteine as well.

Results: AT decreased tubulointerstitial damage (2.89 ± 0.06 vs. 2.14 ± 0.18, $p<0.01$), ED1+ cellular infiltration (5.4 ± 1.2 vs. 1.4 ± 0.4 cells / high power field (HPF)), tubular apoptosis (2.3 ± 0.2 vs. 1.2 ± 0.2 cells / HPF), interstitial apoptosis (1.9 ± 0.4 vs. 0.7 ± 0.3 cells / HPF) and tubular necrosis (4.3 ± 1.2 vs. 1.2 ± 0.5 cells / HPF). IRI was associated with an increase in caspase-3 activity due to cleavage of its low molecular weight (MW, 12 & 17 kD) active subunits. Caspase-3 activity was reduced following IRI in animals treated with AT. However, there was no evidence of any reduction in its low MW active subunits. Protein S-nitrosylation, including a 12 kD band, was increased following IRI but not further affected by AT. Caspase-3 activity in the tissue homogenate of IR kidneys containing 20 µg protein and 5 ng recombinant human caspase-3 was dose dependently inhibited by AT, reaching a statistically significant difference at 1000 and 4000 µM respectively. Thus AT has a direct selective inhibitory effect on the caspase-3 enzyme itself. Serum cholesterol and triglyceride remain unchanged.

Conclusions: These studies in the rat suggest that acute administration of AT can improve reperfusion injury tolerance following an acute ischaemic insult through a direct inhibitory effect on caspase-3. This effect is independent of any reduction in serum cholesterol. Although the long-term impact on renal function requires further investigation, the acute administration of AT to the donor organ immediately prior to reperfusion could provide a potential strategy to reduce reperfusion injury after renal transplantation.

O120

Administration of 3-Hydroxykynurenine leads to prolongation of corneal allograft survival.

Sarah Zaher[1,2], Conrad Germain[1], Hongmei Fu[1], Frank Larkin[2,1], Andrew George[1]

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Indoleamine 2,3-dioxygenase (IDO) has been shown to prolong corneal graft survival. IDO modulates the immune response by depletion of the essential amino acid tryptophan and by the production of kynurenines which act directly on T cells. We have therefore investigated the role of the kynurenines in corneal graft rejection.

In order to assess the effect of kynurenines on T cell responses, the molecules were added into both mixed lymphocyte reactions and anti-CD3/CD28 bead stimulation of T cells. In both human and mouse 3-Hydroxykynurenine (3-HK) and 3-Hydroxyanthranilic acid (3-HAA), but not L-Kynurenine or Quinolinic acid, inhibited T cell proliferation. This was accompanied by significant cell T cell death. There is no evidence of induction of regulatory T cells as shown in the mouse by failure to induce FoxP3 expression. Neither 3-HK nor 3-HAA has a major effect on dendritic cell function, nor do they affect apoptosis or the activation status of corneal endothelial cells.

In order to determine if these agents can prolong graft survival we carried out corneal allografts in a murine model. Administration of 3-HK on a daily basis to BALB/c mice receiving a C3H corneal graft resulted in considerable prolongation of graft survival (MST of controls = 12 days, of treated = 19 days). This was seen when the 3-HK was given between day 1-7, 7-14 or 1-14. Chronic administration of 3-HK resulted in no significant alteration in CD4, CD8 or FoxP3 positive splenic T cells.

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

Plenary Session

Friday 24 April

Best Abstracts

14:15 – 15:30

O121

Ten-year experience of virtual cross-matching for renal transplantation

Vasilis Kosmoliaptsis, Davide Prezzi, Mark J Salji, Menna R Clatworthy, Christopher J Watson, J Andrew Bradley, Craig J Taylor

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Introduction: Undertaking a pre-transplant donor lymphocyte cross-match before renal transplantation is considered mandatory to eliminate the risk of hyperacute rejection. Because the cross-match procedure may increase cold ischaemia time and adversely affect graft outcome, we started a policy of performing a virtual cross-match and proceeding to transplantation when a negative result was predicted with sufficient confidence. We report our ten year experience of this strategy.

Methods: We were the first centre (1997) to introduce the policy of proceeding to transplantation on the basis of a virtual cross-match alone. The decision to undertake transplantation in the absence of a donor lymphocyte cross-match result was taken for non-sensitised recipients when a history of priming events for alloantigen could be excluded with confidence. In sensitised patients awaiting first transplant we only proceeded to transplantation when antibody specificities could be precisely defined and were not directed against mismatched donor HLA-specificities. A prospective, cross-audited, computerised database was analysed to assess the safety and clinical efficacy of this policy for the period 1997-2008.

Results: During the study period, 677 cadaveric renal transplants were undertaken, of which 282 (42%) were performed on the basis of a predicted negative lymphocyte cross-match. Most (96%) of the virtual cross-match transplants involved non-sensitised recipients (IgG panel reactive antibody ≤15%). In all cases where a virtual cross-match was performed, a negative donor HLA-specific antibody cross-match was confirmed after transplantation, and there were no cases of hyperacute rejection. Donor kidneys in the virtual crossmatch group had a mean cold ischaemia time of 14 hrs (range 5-32 hrs) compared to 16.5 hrs (range 5-40 hrs) in the prospective cross-matched group ($p<0.0001$). There was no significant difference in the incidence of delayed graft function, acute rejection episodes and graft survival between the two groups.

Conclusion: A virtual cross match policy can be applied safely in selected recipients and effectively reduces cold ischaemia time, although there is no apparent clinical benefit in terms of immediate function rate and transplant outcome.

O122

Is virtual crossmatching for sensitised renal transplant recipients, based on HLA-specific antibody screening using single antigen beads, safe?

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Background: Our routine practice for deceased donor kidney transplantation is to perform a virtual crossmatch (XM) in selected (non-sensitised) patients and proceed to transplant when confident (approximately 50% of cases) that the XM will be negative. To extend our virtual XM policy we have examined whether donor specific HLA antibodies, as detected by single antigen beads (SAB), enables prediction of the XM result in sensitised patients.

Methods: T cell Flow cytometric crossmatch (FCXM) results and corresponding serum HLA class I-specific antibody screening results were obtained for all potential donor-recipient pairs considered for kidney transplantation in our centre over a 2 year period (n=160). The relationship between SAB antibody binding levels for each donor HLA-A, -B and –C mismatch (as well as the sum and product of antibody levels to all donor class I mismatches) and the T cell FCXM result was determined.

Results: SAB identified donor specific HLA class I antibodies in 53 (33%) of 160 sera. 52 (33%) of the sera gave a positive FCXM result, of which 16 (31%) would not have been predicted positive by a virtual XM using SAB. The best correlation between virtual XM using SAB and the FCXM result was achieved using the sum of antibody levels to all mismatched donor HLA-class specificities (Spearman's $r = 0.68$, $P < 0.0001$), compared to using the single highest donor specific antibody level alone ($r = 0.66$, $P < 0.0001$). When the individual HLA class I loci were considered, HLA-A and B both correlated with the FCXM result ($r = 0.45$, $p = 0.0094$ and $r = 0.52$ $p = 0.0002$, respectively), whereas there was no correlation between donor specific antibodies to HLA-C mismatches and FCXM ($r = 0.31$, $p = 0.07$). Conclusion: Measurement of donor specific antibodies by SAB, even when all donor specific antibodies are considered, fails to predict a positive XM result in around 10% of unselected cases and cannot, therefore, be used in isolation when formulating a virtual XM policy.

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O123

Tacrolimus preserves renal function better than cyclosporine at 10 years – long term results of a randomised controlled trial

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Introduction: Calcineurin inhibitors (CNI) are known to be nephrotoxic. However, trials on newer CNI sparing regimens do not differentiate between tacrolimus (tac) and cyclosporine (cyc). We analysed the long term results of a single centre randomised controlled trial comparing tac and cyc and report the data on actual follow up at 10 years.

Materials and Methods: Renal transplant patients at the Cardiff Transplant unit were randomised to tacrolimus (0.2mg/kg/day) or cyclosporin (8 mg/kg/day) as part of a trial between 1996 and 2000. All patients received azathioprine and corticosteroids. Corticosteroids were withdrawn at 3 months if high dose steroid pulse therapy for acute rejection had not been required. The trial ended in 2001 but patients were followed up until 31 October 2008 or death. The demographic data, previous transplants, HLA match, preoperative diabetes, cold ischemic time, anastomosis time were noted. Estimated GFR (eGFR) was measured using the Cockraft-Gould formula. On an intention to treat basis the graft and patient survival were analysed using the Kaplan Meier method and log rank analysis for comparison. Continuous variables were compared using the Student t-test and categorical variables using the Mann Whitney U test.

Results: There were 150 patients (76 in the cyc group and 74 in the tac group). There was no difference in the recipient age, sex, previous transplant, HLA match, preoperative diabetes, cold ischemic time and anastomosis time between the two groups. The median follow up was 9.6 years (0.1-12). There were significantly more rejections in the cyc group than the tac group (0.8 vs 0.4 rejection/patient, P=0.004). The eGFR at 1 year was cyc (57ml/min) vs tac (64ml/min) (P=0.06). The 10 year graft and patient survival was 55% vs 67% and 69% vs 78% for the cyc and the tac groups respectively (P=NS). At 10 years 39% of cyc group and 61% tac group were free of any rejections. The eGFR at the completion of follow up was 33 ml/min for cyc group vs 43 ml/min for the tac group (P=0.018). There was significant correlation between the eGFR at 1 year and 10 years of follow up (P=0.01).

Conclusion: We conclude that Tacrolimus provides significantly better long term renal function compared to cyclosporin. This has to be taken into account in any future trials on CNI sparing regimen.

O124

Indirect Pathway CD4 T cells Provide Help for Generating Cytotoxic Effector Responses Through Recognition of Processed Alloantigen on the Surface of Allospecific CD8 T Cells

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University of Cambridge, Cambridge, United Kingdom

Indirect allorecognition makes a progressively greater contribution to allograft rejection late after transplantation, but it is not clear how indirect pathway CD4 T cells that recognise processed alloantigen presented by recipient APCs provide 'unlinked' help for direct pathway cytotoxic CD8 T cells recognising allogeneic MHC class I on donor cells.

Female Mar (B6 RAG1$^{-/-}$) recipients, whose monoclonal CD4 T cells recognise self-restricted male H-Y peptide, rejected male BALB/c (H-2^{d}) heart grafts acutely (MST 12 d, n=6), but only if reconstituted with 10^6 effector female B6 CD8 T cells. Female BALB/c grafts survived >50 days, confirming rejection was mediated by CD8 T cells and dependent on help from Mar CD4 T cells recognising H-Y alloantigen indirectly. Surprisingly, although the epitopes for Mar CD4 and CD8 T cell recognition are on different APCs (recipient vs donor), CD8-reconstituted Mar recipients that were additionally challenged with male B6 APC (that induced strong Mar CD4 T cell activation) mounted minimal cytotoxic T cell responses and did not reject female BALB/c grafts, demonstrating that effective help is generated only when H-Y and MHC I alloantigens are co-expressed on graft cells.

We hypothesised that the requirement for co-expression reflected acquisition of H-Y antigen from graft cells by allospecific CD8 T cells, with subsequent processing and presentation in the context of MHC II for Mar CD4 T cell recognition, as analogous to the provision of cognate T cell help to B cells. In support, MHC II I-Aβ gene expression was detected in naive and activated (but not MHC II$^{-/-}$) CD8 T cells and flow cytometric analysis revealed surface MHC II expression, but only on activated CD8 T cells. Furthermore, reconstitution of Mar recipients with MHC II$^{-/-}$ CD8 T cells delayed rejection of male BALB/c grafts (MST 21 d, n=6). In contrast, male B6 x BALB/c F1 grafts (which enable 'linked' help via direct allorecognition of both Mar CD4 and CD8 T cell epitopes on donor APCs) were rejected at similar tempo (MST 8 d, n=4), indicating that MHC II expression on CD8 T cells is only required for indirect CD4 T cell help.

During indirect allorecognition, help to allospecific CD8 T cells is potentiated through TCR-mediated internalisation of alloantigen and presentation of processed allopeptide on surface MHC II for recognition by indirect pathway CD4 T cells.

O125

Comparing risk factors and incidence of cancer in kidney-pancreas and kidney transplant recipients reported by UNOS between 1988 and 2006

Alireza Hamidian Jahromi, Ian MacPhee, Mohamed Morsy, Jiri Fronek, Nicos Kessaris

Renal Transplant Unit, St. George's Hospital, London, United Kingdom

Kidney-Pancreas (KP) transplantation is the treatment of choice in type-1 diabetic patients with end-stage renal failure as it confers distinct advantages with respect to mortality and quality of life. However, KP transplantation is not without disadvantages, as recipients are at increased risk of infections and cancer. The aim of this study was to identify risk factors and incidence of cancer in KP transplant recipients and compare it with risk factors and incidence of cancer in renal transplant recipients.

METHODS: United Network for Organ Sharing (UNOS*) data, as of February 25, 2008, were used. The data included 14152 KP transplant recipients (M= 8446, F= 5706) and 234145 renal transplant recipients (M=140320, F=93825) transplanted between 1988-2006. Relative Risk(RR) or Odds Ratio(OR) for cancer were calculated for each risk factor.

RESULTS: In total, 691(4.9%) KP recipients (M=404, F=287) and 12120 (5.2%) renal recipients (M=8087, F=4043) developed cancer during the study period. Female KP recipients and male renal recipients had higher risk of developing cancer (OR=1.05, OR=1.36 respectively) compared to their opposite sex recipients. Of the reported cases, skin cancers were the most common types of post-transplantation cancer constituted 37.1% and 34.1% of all tumours in the KP and renal transplant recipients. The incidence of cancer in the KP recipients increased between 1988-1991, stayed high between 1991-1997, but has been declining since. The incidence of cancer in the renal recipients increased between 1988 and 1994, but has also been declining continuously since. In KP recipients 159 patients (23%) had cancer within 3 years and 335 (48.5%) within 6 years post-transplantation but in renal transplant recipients cancer was diagnosed in 4079 patients (33.7%) who were up to 3 years post-transplantation, and in 4650 recipients (38.4%) who were 6 or more years post-transplantation. Age $\geq$ 65 years (OR=1.77, 1.96), white ethnicity (OR=3.05, 2.98) and previous history of cancer (RR=1.74, 3.38) were associated with increased risk of cancer in the recipients. (Figures in the parenthesis show the RR or OR for KP and renal transplant recipients respectively.) While different immunosupression regimens using Ciclosporin (RR=2.11, 1.45), Muromonab (RR=1.87, 1.23), Steroid (RR=1.35, 1.73) and Azathioprine (RR=2.3, 1.63) were associated with increased risk of cancer, other regimens using Tacrolimus (RR=0.45, 0.63), Sirolimus (RR= 0.71, 0.66) and Mycophenolate mofetil (RR= 0.55, 0.77) were associated with a reduction in the risk of cancer. Incompatible donor-recipient ABO match had a RR of 1.41 and 0.89 in the KP and renal transplant recipients. Use of ATG was associated with an increased risk of cancer in KP recipients (RR= 1.62) and a decreased risk of cancer in renal transplant recipients (RR= 0.64).

CONCLUSION: Age$\geq$65 years, white ethnicity, gender, Ciclosporin, Azathioprine and steroids as well as history of pre-transplant malignancy were considered as main risk factors for cancer in the KP and renal transplant recipients. [*This work was supported by Health Resources and Services Administration contract 234-2005-370011C.]

O126

Autoantibody contributes to the development of allograft vasculopathy, but only in concert with conventional alloimmune responses.

Ines Harper[1], Koroush Saeb-Parsy[1], Thet Su Win[1], Martin Goddard[2], Eleanor Bolton[1], Andrew Bradley[1], Gavin Pettigrew[1]

[1]Department of Surgery, University of Cambridge, Cambridge, United Kingdom, [2]Papworth Hospital, Cambridge, United Kingdom

Introduction: The development of autoimmunity is increasingly associated with poor outcomes after transplantation. An effector role for autoantibody in graft damage has been suggested, but it is unclear whether this is independent of, or whether it complements, conventional *allo*immune responses. Here we investigate synergy between humoral autoimmunity and alloimmunity in the development of allograft vasculopathy (AV).

Methods: We have previously demonstrated that rejection of MHC II-disparate bm12 heart grafts is characterised by progressive AV, with complement endothelial deposition and the development of anti-nuclear auto-, but not allo-, antibody. Autoantibody responses are contingent upon help from donor CD4 T cells that are passengers within the graft. Thus the effector role of autoantibody can be examined independently from that of conventional alloimmunity, by reconstituting T cell-deficient TCR KO B6 recipients of bm12 heart or aortic allografts with bm12 or B6 or both bm12 and B6 CD4 T cells.

Results: Injecting B6 mice with 10^6 bm12 CD4 T cells 2 weeks prior to bm12 heart grafting primed for autoantibody and resulted in severe AV and rapid rejection (MST 35 days vs. WT MST 95). In contrast, isografts in autoantibody-primed recipients survived indefinitely, without developing AV and with no complement deposition, suggesting that autoantibody only contributes to rejection by exacerbating existing alloimmune-mediated damage.

Potential synergy was further examined by aortic allograft transplantation. Bm12 aortic grafts did not develop AV (day 40) in B6 recipients and did not provoke autoantibody; thus, unlike heart grafts, aortic grafts do not contain significant numbers of CD4 T cells. In contrast, priming for autoantibody, by injection of 10^6 bm12 CD4 T cells at transplantation, resulted in severe AV. The essential role of recipient CD4 T cell responses in alloantibody-mediated vasculopathy was confirmed by the demonstration that TCR KO recipients only developed significant aortic AV when reconstituted with both B6 and bm12 CD4 T cells, whereas grafts remained disease free when reconstituted with either population alone.

Conclusions: Autoantibody only affects AV in concert with conventional alloimmune responses, presumably because autoantibody binding is dependent on an initiating insult that translocates autoantigen to the endothelial cell surface.

Renal Association

Poster Sessions

Tuesday 21 April

11:30 – 12:30

Acute Kidney 1

Moderated by Dr David Goldsmith

P01

Statin therapy, falls, rhabdomyolysis and acute kidney injury- a rising life threatening recipe?

Syed Shahreer Anisul Huq, Kottarathil Abraham Abraham, Christopher Federick Wong

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Introduction Acute kidney injury remains an important prognostic factor in hospitalised patients. In June 2008, we encountered three patients with acute kidney injury secondary to rhabdomyolysis, all within a week. They were admitted following falls or found collapsed and were on 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins).

Methodology We report a novel observation that the use of statin therapy increases the risk of rhabdomyolysis in patients with falls or prolonged immobility. A review of the literature on 'Acute kidney injury, rhabdomyolysis, falls and statin' was made.

Result, Case Series All our cases were independent, elderly (aged 64, 66 and 75 years old), on statins and had type 2 diabetes mellitus**,** among other co morbidities. All our three cases presented with a history of fall or prolonged immobility. One patient had known chronic kidney disease stage 3 and she was on a high dose of statin. Their peak creatine kinase were 150,300, 19,849 and 19,068 IU/L respectively. They were all critically ill and were managed in the intensive therapy unit. Two of the patients had required continuous venovenous haemofiltration. Their 6 months follow-up clinic serum creatinine were 242, 174 and 155µmol/L.

Discussion Our hypothesis is that statins increase the susceptibility of [these] patients presenting with falls or prolonged immobility to the development of rhabdomyolysis and acute kidney injury. The risk of rhabdomyolysis with statins increases with serum concentration of the medication and this depends on the glomerular filtration rate. The risk of rhabdomyolysis with different statins is variable. Intervening early with forced alkaline diuresis and renal replacement therapy may improve outcome. With increasing dosages of statin required to achieve recommended target cholesterol levels, falls are associated with a greater risk of rhabdomyolysis and acute kidney injury. When prescribing statin therapy, one needs to assess the risk of falls and immobility as when prescribing warfarin therapy.

Conclusion Our cases highlighted a novel observation and the need for a high index of suspicion in patients on statin therapy presenting with falls or prolonged immobility to the development of rhabdomyolysis and acute kidney injury.

P02

Prevention of contrast induced nephropathy following fistulagram and fistulaplasty in non-dialysis patients with advanced chronic kidney disease

MOBIN MOHTESHAMZADEH, MATTHEW GIBSON, LEO BAILEY, JULIA SMITH, LINDSEY BARKER, EMMA VAUX, RAMESH NAIK

Royal Berkshire NHS Foundation Trust, Reading, Berkshire, United Kingdom

Introduction: Patients with advanced chronic kidney disease (CKD) are often exposed to contrast media, either as part of their work up for transplantation or to image their veins and arterio-venous fistulae (AVF). Much of the work done on contrast induced nephropathy (CIN) is in the setting of coronary angiograms in patients with mild to moderate CKD. There is some evidence that even small volumes of contrast (10-100ml) may be associated with CIN. To precipitate the need for dialysis in a patient an AVF that is not yet mature, obviously will impact on morbidity and mortality. Our current practice is to admit patients for intravenous saline before, during and after the procedure, as well as to give N-acetylcysteine the day before and on the day of the procedure. Patients are also told to omit some of their medication on the day of the procedure (ACEi, ARB, NSAID and diuretics). The patient is allowed home the next day but a repeat creatinine (eGFR) is requested after 48hours.

Methods: We reviewed data on patients with advanced CKD who had received contrast during their fistulagram or fistulaplasty over a 4 month period. We collected baseline, post contrast and 1 month data.

Results: We identified 18 patients with a median creatinine of 486 (eGFR 10) and range of 371-696 (eGFR 7-15). There was no significant rise in creatinine post contrast, median 489 (eGFR 10) and range 376-638 (eGFR 8-14). At 1 month 5 (28%) patients had electively started dialysis via their AVF. The remaining 13 patients had a median creatinine of 495 (eGFR 11) and range of 375-572 (eGFR 6-15).

Conclusions: Patients with advanced CKD are prone to acute kidney injury, with the consequent need for dialysis. A simple pathway, as described above allowed the avoidance of the need for immediate dialysis and time for the access to develop following fistulaplasty and a timely start of dialysis using an AVF. The need for an overnight stay is a drain on limited hospital resources and not always convenient to patients. We are currently in the process of reviewing our pathway to one which can be used as a day-case.

P03

The incidence and outcomes of patients requiring renal replacement therapy on the Intensive Care Unit

Simon Lines, Arvind Cherukuri, Mark Bellamy, Andrew Lewington

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We have analysed the incidence and outcomes of the largest series of patients in the UK requiring renal replacement therapy (RRT) on the Intensive Care Unit (ICU). There were 5582 admissions to the ICU over a six-year period between 2002-2008. The incidence of RRT was 16.5% (n=921), which is significantly higher than has been previously reported.

	AKI	Dialysis patients	Transplant Patients
n	**821** (89.1%)	**87** (9.5%)	**13** (1.4%)
Age (yrs)*	**61** (47-73)	**62** (46-69)	**52** (44-65)
APACHE II score*	**29** (24-36)	**30** (24-36)	**36** (28-43)
Length of hospital stay (days)*	**18** (7-38)	**20** (10-32)	**16** (6-25)
Length of ICU stay (days)*	**6** (3-12)	**3** (2-9)	**4** (2-6)
Medical / Surgical diagnosis (%)	**55** / **45**	**48** / **52**	**69** / **31**
ICU mortality	**448** (55%)	**34** (39%)	**6** (46%)
Hospital mortality	**544** (66%)	**44** (51%)	**8** (62%)
*expressed as Median (Interquartile range)			

The ICU mortality rate of the 821 patients who had acute kidney injury (AKI) was 55%. Of the survivors 95 (25%) patients were transferred to the renal unit for continued management. Only 6.5% of the hospital survivors remained RRT dependent (including 7 patients who were inter-hospital ICU transfers). Baseline creatinines were available for 423 (52%) patients and the presence of CKD (eGFR<60) did not predispose to an increased mortality rate (p=ns). Follow-up of the hospital survivors demonstrated that there was a non-significant increase in the mean creatinine from 111μmol/L to 127μmol/L (p=ns) at the time of hospital discharge. At 12 months the mean serum creatinine of the survivors was 134 μmol/L, representing a significant increase from the baseline values (p<0.001). Five (38%) transplant patients survived with one transferred to another ICU still RRT dependant. The remaining 4 transplant patients regained independent renal function with one becoming dialysis dependant 3 months after leaving ICU. The ICU mortality for the dialysis patients was 51% rising to 59% six months following discharge from hospital.

P04

Mortality secondary to Acute Kidney Injury (AKI) after cardiac surgery- an analysis based on AKIN (Acute Kidney Injury Network) criteria and staging.

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Mortality associated with AKI averages between 15-30% depending on the definition of AKI and the post-operative period studied.

In this study of 2232 patients who had cardiac surgery in a single centre from January 2005 to December 2007, we comprehensively studied the independent effect of various stages of AKI based on the AKIN criteria (stage-1 absolute rise of Creatinine of>26.4mmol/L or 1.5-2 times rise from the baseline, stage-2 2-3 times rise from the baseline, stage-3 >3 times rise from the baseline including RRT) on hospital mortality.

Mortality is analysed between the groups with and without AKI using chi-square test. Univariate and multivariate logistic regression is used to study the relative risk of mortality with each stage of AKI. Potential confounders like age, gender, day-0 e-GFR, diabetes, NYHA class and EURO score have been adjusted for in the multivariate logistic regression model to study the independent effect of AKI.

In this population, 250 patients (14%) developed AKI. 166 patients were in stage-1, 44 in stage-2 and 40 in stage-3 AKI. The overall hospital mortality rate for our study population is 2.6% (n=58/2232). The summary of the analysis of mortality is shown in table-1. From the table we can clearly see that mortality rate dramatically increases from 1.2% without AKI to 14% with AKI. Even though this is secondary to the significant mortality seen in patients with stage-2 and stage-3 AKI, it is important to note that even milder forms (stage-1) significantly effect mortality (RR=4). It is therefore crucial to be able to identify risk factors even for such smaller increments in creatinine to be able to plan appropriate therapeutic strategies to address this problem.

Table-1:

	Mortality% (n)	**Mortality-RR**	**95% CI**	**p-value**
Univariate				
AKI-no	1.2% (23/1982)	1		
AKI-yes (overall)	14% (35/250)	13.9	8-24	<0.001
AKIN-1	6% (10/166)	5.5	2.6-11.7	<0.001
AKIN-2	23% (10/44)	25.0	11.1-56.7	<0.001
AKIN-3	37.5% (15/40)	51	24-109	<0.001
Multivariate				
AKI-yes (overall)		9.5	4.9-18.2	<0.001
AKIN-1		4	1.7-9.6	0.001
AKIN-2		21	8.5-51.2	<0.001
AKIN-3		28	11.1-71	<0.001

P05

Does Remote Ischemic Preconditioning Prevent Acute Kidney Injury In Patients Undergoing Elective Cardiac Surgery?

Vinod Venugopal[1], Derek J Hausenloy[1], Andrew Ludman[1], Chris M Laing[2], Derek M Yellon[1]

[1]The Hatter Cardiovascular Institute, UCL, London, United Kingdom, [2]UCL Centre for Nephrology, Royal Free Hampstead NHS Trust, London, United Kingdom

BACKGROUND: Remote ischemic preconditioning (RIPC) is a phenomenon whereby brief episodes of ischemia /reperfusion of one organ protect another organ from a subsequent episode of lethal ischemia/reperfusion. We have recently reported that RIPC using transient arm ischemia reduces myocardial injury during cardiac surgery. Acute kidney injury following cardiac surgery is an important determinant clinical outcome. We hypothesised that the potential cardioprotective benefits of RIPC may extend to reducing the acute kidney injury encountered during cardiac surgery.

METHODS: We recruited 114 consecutive patients (21% female; 32% diabetic) undergoing elective coronary artery bypass graft (CABG) surgery between February 2006 and February 2008, who were randomized to either RIPC or control. RIPC was induced by 3 cycles of upper limb ischemia/reperfusion using a blood-pressure cuff applied to the upper arm and inflated to 200mmHg for 5 minutes with an intervening 5 minutes deflation. Control comprised a deflated cuff placed on the upper arm for 30 minutes. Patients with a pre-operative baseline creatinine >130mmol/L were excluded as were patients with recent (<4 weeks) myocardial infarction. The primary endpoint studied was the summary measure of serum cardiac troponin T released over 72 hours. In addition, we measured serum creatinine at baseline and daily for the first three days post-operatively. Renal impairment was defined according to the Acute Kidney Injury (AKI) criteria.

RESULTS: RIPC resulted in a reduction in absolute cTnT release over 72 hours from 30.2±22.7µg/ml in the control group (n= 57) to 22.9±12.1µg/ml in the RIPC group (n=57) (mean±SD). The mean baseline creatinine was 82±14 mmol/L in controls and 83±18 mmol/L in RIPC. 8 patients in the control group (12.3%) and 7 (14%) in RIPC developed AKI stage 1. In addition in the RIPC group, 2 (3.5%) patients developed AKI stage 2 and 1 developed AKI stage 3 necessitating haemodialysis. Overall, there was no significant difference in the incidence of acute kidney injury between the two groups.

CONSLUSIONS: RIPC induced by transient limb ischemia reduces myocardial injury during elective CABG surgery but appears to have no effect on acute kidney injury over the first three days.

P06

Gentamicin associated Acute Kidney Injury: Associations and Outcomes

Nicholas Selby, Susan Shaw, Richard Fluck, Nicholas Woodier, Nitin Kolhe

Derby Hospitals, Derby, United Kingdom

Background: The incidence of gentamicin associated acute kidney injury (AKI) as defined by the RIFLE criteria is unknown. We performed a retrospective observational study to examine this and the predictive value of RIFLE stage on patient outcome with once daily dosing. In addition, we analysed quality of gentamicin prescribing and monitoring in day to day practice.

Methods: Data on all patients treated with gentamicin in our acute trust between 1st Oct and 1st Nov 2007 were collected (n=228). In addition to demographic details, data were collected regarding indication for gentamicin use, gentamicin dosing, gentamicin assay results, the presence of additional renal insults and baseline and peak serum creatinine results. Gentamicin prescriptions were compared with dosing schedules and local guidelines issued by the microbiology department.

Results: Gentamicin prescribing was not done well with 92 (42.2%) patients either prescribed the wrong dose or in whom body weight was not recorded. AKI occurred in 51 (24.4%) patients; 37 (17.7%) 'Risk', 9 (4.3%) 'Injury', 5 (2.4%) 'Failure'. Mortality rate increased with each RIFLE stage ($p<0.0001$, figure 1). On multivariate analysis, independent predictors of gentamicin associated AKI were number of gentamicin levels >2mg/l (OR 1.845, 95% CI 1.22 to 2.79) and higher baseline serum creatinine (OR 1.014, 95% CI 1.001 to 1.028). The mean gentamicin trough level was significantly higher in the AKI group (2.3 ± 1.7mg/l versus 1.4 ± 1.7mg/l, $p=0.0017$).

Conclusions: This study shows that gentamicin associated AKI remains a common and potentially serious clinical problem with the risk of mortality positively correlated with RIFLE class. In addition, gentamicin may not always be correctly prescribed in day to day practice, which may further impact on efficacy and toxicity of treatment.

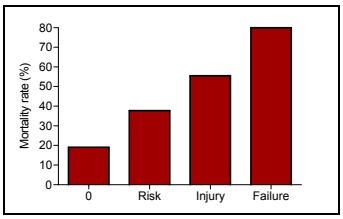


Figure 1: association between RIFLE class and mortality

Poster Sessions

Wednesday 22 April

13:00 – 14:00

Acute Kidney 2

Moderated by Dr Sunil Bhandari

P07

Acute Kidney Injury in English hospitals: HES analysis.

K Abraham. E Thompson, M Pearson

Only some patients with renal disease have access to renal teams. Also, systematic data on the scale of acute kidney injury [AKI] remains sparse. Hospital Episode Statistics [HES] were analysed to identify the burden of AKI in a sample of English hospitals.

All inpatient episodes in 06/07 were analysed for four renal "hubs" and their "spoke" hospital trusts. The significant numbers of renal ICD10 codes detected in the first seven positions were analysed. Hospitals were classified as transplanting renal unit [1], renal unit without transplantation [2], hospital with visiting renal input [3], hospital with renal input at request only [4]. Mean values were calculated for each category.

AKI is associated with high mortality. Most AKI patients are managed by non renal teams, but visiting consultations are not recorded in HES. Many spoke hospitals have no renal physicians and appear to have a higher mortality. Despite coding issues, if this higher mortality is confirmed on the national dataset, trusts may have to develop a renal service.

Hospital Trust	No.	% renal	Mean %	% RRT	Mean %	% Died	Mean %
Aintree 2	291	27.5	15.4	7.6	3.8	28.2	26.8
Southport 3	129	0.0	4.7	3.9	1.3	31.8	32.1
Walton 4	0	NA	0.0	NA	1.5	NA	28.7
N Bristol 1	420	31.9	12.6	16.4	10.3	21.9	28.3
UH Bristol 3	136	0.7	4.7	2.9	1.3	26.5	32.1
Weston 4	136	0.0	0.0	1.5	1.5	28.7	28.7
Bath 3	314	17.2	4.7	1.0	1.3	23.6	32.1
Leicester 1	663	0.3	12.6	6.5	10.3	32.3	28.3
Lincolnshire 2	324	4.9	15.4	0.0	3.8	33.3	26.8
Northampton 2	153	10.5	15.4	2.0	3.8	23.5	26.8
Peterborough 2	176	39.8	15.4	1.1	3.8	22.7	26.8
Bolton 3	205	0.0	4.7	1.5	1.3	40.5	32.1
Pennine 3	351	2.3	4.7	0.6	1.3	39.3	32.1
Salford 2	267	1.9	15.4	7.1	3.8	22.1	26.8
Trafford 3	58	0.0	4.7	0.0	1.3	32.8	32.1
Wrightington 3	158	0.0	4.7	0.6	1.3	27.2	32.1

P08

Effect of iso-osmolar contrast on Renal Function in Patients undergoing Femoral Arteriography: A Single Center Study.

Ying Kuan[1], Lukasz Chrobak[1], Helen Murray[2], Ken McCune[2], Zola Mzimba[2], Paul Bateson[2], Deidre Campbell[3]

[1]Renal Unit, Altnagelvin Hospital, Londonderry, BT47 6SB, Northern Ireland, United Kingdom, [2]Vascular Surgery Unit, Altnagelvin Hospital, Londonderry, BT47 6S, Northern Ireland, United Kingdom, [3]Department of Radiology, Altnagelvin Hospital, Londonderry, BT47 6S, Northern Ireland, United Kingdom

Introduction

Acute Kidney Injury (AKI) associated with contrasts is regarded as a major source of morbidity among patients undergoing vascular investigations. However, relatively few studies have looked specifically at patients undergoing investigations for peripheral vascular disease. Patients with vascular disease are at high risk for both chronic kidney disease (CKD) and AKI. This study retrospectively analyses the outcome in a cohort of patients who underwent femoral arteriography, and are exposed to low volume of iso-osmolar contrasts. It also quantifies the loss of renal function that occurred, focusing especially on patients with CKD.

Method

Data (age, gender, presence or absence of diabetes and renal function measurements using both creatinine and estimated GFR using the four variable MDRD equation) were retrospectively collected from patients attending Altnagelvin Hospital, Londonderry, Northern Ireland between January 2004 in October 2006 and obtained prior to, and after intervention. All patients were given between 100-150mls of isosmolar contrast agent (iodixanol,Visipaque). None received prophylactic acetylcysteine.

Results

118 patients were included in the study. They were aged 70.0 $\pm$ 11.7 years. 29 patients were female, 35 patients have diabetes and 54 have CKD or worse (eGFR<60mls/min). The eGFR of the population was 63.8 $\pm$ 20.2 years. Patients who have CKD III-V experience a statistically significant decline in eGFR after the procedure (from 46.5 $\pm$ 10.6 to 44.3 $\pm$ 13.1 mls/min/1.73m^2), whereas those with better renal function did not. In all, 32 patients in the group with CKD experience a decline in renal function averaging 6.6 $\pm$ 5.6 mls/min/1.73m^2. No patient required renal replacement therapy as a consequence of this investigation. Multiple logistic regression suggest that diabetes is a significant independent risk factor for this, whereas age and gender are not.

Conclusion

This study suggest that investigation of peripheral vascular disease using low dose iso-osmolar contrasts can result in deterioration of renal function, especially in those with pre-existing CKD. The presence of diabetes further increases this risk. Whilst this is clinically inconsequential in the majority of patients, a transient decline of nearly 7 mls/min/1.73m^2 may occur. This is an especially important consideration in those with significant CKD.

P09

The acute kidney injury network classification predicts hospital stay, renal recovery and mortality in hospitalised patients: a prospective study

Muhammad Shahed Ahmed[1], V Selvaratnam[2], R Lim[2], A James[2], K A Abraham[2], C F Wong[2]

[1]Royal Liverpool University Hospital, Liverpool, Merseyside, United Kingdom, [2]Aintree University Hospital, Liverpool, Merseyside, United Kingdom

Introduction: Many hospitalised patients have acute kidney injury (AKI) which is associated with severe consequences. The aim of the study was to determine weather the acute kidney injury network classification[1] predicts hospital stay, renal recovery and mortality.

Materials & Methods: Hospitalized patients who were referred to nephrology service over six months were studied. Statistical analysis was performed on their demography, stage of AKI and outcome of AKI in terms of renal recovery, length of stay and mortality.

Results: Among the 238 patients who were referred, 166 had AKI. In AKI group, the median age is 74 (range 24- 95), M: F ratio 81: 85 and 32 % were diabetics. The overall all cause mortality of AKI group on 18 months follow up was 58% as opposed to 29% in non-AKI group (n=72), p value 0.0001. In AKI group, 43% (n=71) had stage 1 AKI, 18% (n=30) had stage 2 AKI and 39% (n=65) had stage 3 AKI. Ten percents needed acute intermittent haemodialysis. The median duration of hospital stay was 21 (range 3-187) days. The all cause mortality during admission and at the end of 18 months follow-up were (25%, 49%) in Stage 1, (43%, 67%) in stage 2 and (37%, 63%) in stage 3 AKI. The main cause of mortality in the AKI group was infection (43%). Full renal recovery on admission in AKI stage1 was 74% compare to 41 % of stage 3 AKI (p value 0.002). In addition, 32 % of AKI stage 3 had no recovery of renal function compare to 11 % of stage 1 AKI (p value 0.019).

Conclusion: The Acute Kidney Injury Network staging of AKI predicts prolonged hospital stay, renal recovery and mortality. Even a small increment of serum creatinine ≥ 26.4 µmol/l in 48 hrs alone predicts clinical outcomes and therefore, mandates early identification and appropriate treatment measures.

Reference: 1. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. R L Mehta, J A Kellum, S V Shah et al. *Critical Care* 2007, 11**:**R3

P10

An analysis of potential pre-operative risk factors for the development of Acute Kidney Injury (AKI) after cardiac surgery.

Aravind Cherukuri, Gary Campbell, Seerapani Gopaluni, Salman Saajid, Syed Ahmed, Simon Lines, Kalyanachakravarthy Javanigula, Philip Kay, Andrew Lewington

St James's University Hospital NHS, Leeds, UK, Leeds General Infirmary, Leeds, UK

Acute Kidney Injury Network (AKIN) proposed new diagnostic criteria for AKI, defined as an absolute rise in serum Creatinine of >26.4mmol/L or an increase of ≥1.5 times from the baseline within 48hrs. Although several studies analysed risk factors for AKI after cardiac surgery, none analysed AKI as defined by the AKIN. It is important to identify factors that effect these minor changes in Creatinine as they are associated with adverse outcomes in various settings.

We report the results of the first study analysing AKI in accordance to AKIN criteria. Various pre-operative variables from the data of 2232 patients undergoing cardiac surgery in a single centre between Jan 2005 and Dec 2007 are analysed using univariate and multivariate logistic regression to identify risk factors that predict AKI, as defined by AKIN.

All significant results are summarized in table-1. 11.2% (n=250) of our patients had AKI. Gender, MI within 30 days, hyperlipidemia, smoking status, COPD, CVA, BMI and the extent of coronary disease are not significant. From the results, we demonstrate the independent effect of age, NYHA class, diabetes, CCF requiring diuretics, previous cardiac surgery, day-0 e-GFR, pre-op cardiogenic shock and combined surgery on AKI. From this analysis we hope to develop the first risk prediction score for AKI as defined by AKIN and this could be used to risk stratify patients before surgery to assess the risk of post-operative AKI.

Table-1:

Age>65yrs	2.1	1.2-2.6	<0.001	1.5	1.1-2	0.01
NYHA>2	2.1	1.6-2.7	<0.001	1.5	1.1-2	0.009
Diabetes Mellitus	1.7	1.3-3.3	<0.001	1.6	1.1-2.1	0.006
Hypertension	1.5	1.1-2.0	0.007	1.4	0.98-1.9	0.07
CCF requiring diuretics	2.3	1.7-3.1	<0.001	1.2	0.8-1.7	Ns
Previous Cardiac surgery	2.7	1.7-4.5	<0.001	2.8	1.6-4.9	<0.001
Day-0 e GFR<60	6.1	3.6-10.4	<0.001	5.0	2.8-8.7	<0.001
Peripheral Vascular disease	1.5	1.1-2.1	0.01	1.3	0.9-1.9	Ns
LV-Ejection Fraction <0.3	2.5	1.7-3.6	<0.001	1.4	0.9-2.2	0.09
Pre-op shock	5.3	2.7-10.4	<0.001	2.7	1.2-6.2	0.02
Pre-operative ventilator support	5.3	1.5-19	0.01	1.8	0.3-9	Ns
Combined surgery	2.0	1.5-2.8	<0.001	1.8	1.3-2.4	0.001

P11

The incidence of acute kidney injury in patients who died following surgery; a report from the Scottish Audit of Surgical Mortality.

Andrew Lewington[1], Paul Roderick[2], John Feehally[3]

[1]St James's University Hospital, Leeds, United Kingdom, [2]Southampton University, Southampton, United Kingdom, [3]Leicester General Hospital, Leicester, United Kingdom

The 2007 Scottish Audit of Surgical Mortality (SASM) proforma contained a section to capture data on patients who developed acute kidney injury (AKI). Acute kidney injury was defined using the RIFLE staging system. Relevant data was available for 804 of the 1106 cases (72.7%).

- incidence of post-operative AKI was 33.2%.
- mean age was 73.4 years
- 150 patients were male and 117 patients female
- coexisting cardiovascular disease was present in 200 (74.9%) patients
- coexisting renal disease was present in 89 (33%) patients
- coexisting diabetes mellitus was present in 30 (11.2%) patients
- admission to intensive care unit (ICU) was required in 158 (60%) patients
- sepsis and haemodynamic imbalance were contributory factors in at least 169 (63.2%) and 156(58.4 %) patients respectively, with both being contributory in 104 (39%) patients
- nephrotoxic drugs were identified to be contributory in 16 (6%) patients
- AKI was felt to be avoidable in only 4 (2%) of patients

Of 1106 patients, 93 (8.4%) patients developed AKI and required renal replacement therapy

- mean age was 67.6 years
- 59 patients were male and 34 patients female
- coexisting cardiovascular disease was present in 67 (72%) patients
- coexisting renal disease was present in 39 (42%) patients
- coexisting diabetes mellitus was present in 11 (11.8%) patients
- admission to ICU was required in 84 (92%) patients
- hypotension and sepsis was felt to be contributory in 65(70%) and 59 (63%) cases respectively; both being noted in 44 cases
- there were only three cases [3.2%] in which nephrotoxic drugs were identified as a contributory factor
- AKI resulting in RRT was reported as unavoidable in 69 cases [74%] and possibly avoidable in 17 cases [19%]

Post-operative AKI is a multifactorial entity, and more critical analysis of 'avoidability' will require a detailed review of clinical case records. AKI was considered possibly avoidable in one fifth of patients who developed AKI requiring RRT; whereas it was judged definitely or probably avoidable in only 2% of all cases with AKI. Such a discrepancy requires closer analysis.

P12

'Early' Acute Kidney Injury in Northern Ireland Intensive Care Units.

Emma Borthwick[1,4], S Harris[2], C Welch[3], AP Maxwell[1], DF McAuley[4], P Glover[4], DA Harrison[3], K Rowan[3]

[1]Regional Nephrology Unit, Belfast City Hospital, Belfast, United Kingdom, [2]Centre for Anaesthesia, University College, London, United Kingdom, [3]Intensive Care National Audit and Research Centre, London, United Kingdom, [4]Regional Intensive Care Unit, Royal Victoria Hospital, Belfast, United Kingdom

Introduction: There are limited data about the epidemiology of acute kidney injury (AKI) in critically ill patients in Northern Ireland. The aim of this study was to examine AKI within 24 hours of ICU admission ('early' AKI) and its relation to outcomes (ICU mortality and acute hospital mortality).

Methods This was a secondary analysis of prospectively collected data in the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme (CMP) Version 2.0 and 3.0. The Case Mix Programme Database was interrogated and data extracted from 22,313 admissions to eight ICUs from 1999-2007. The presence of AKI was assessed within the first 24 hours after admission (early AKI) and classified according to the RIFLE criteria. Trends over time were described for the RIFLE categories and outcomes of admissions in each category were summarised. Where available, information on the use of renal replacement therapy (RRT) during the ICU stay was analysed.

Results Trends in 'early' AKI changed little over time: 35.5% of patients sustained AKI ('Risk' 13.5%, 'Injury' 11.1%, 'Failure' 9.8%, 'End-stage' 1.2%) and 9% of patients received RRT. Outcomes are shown in Table 1.

Table 1: Outcomes

	No AKI (n=14385)	**Risk** (n=3020)	**Injury** (n=2446)	**Failure** (n=2183)	**End-stage** (n=259)
ICU mortality, n (%)	1,350 (9.4)	563 (18.6)	834 (33.8)	909 (41.6)	48 (18.5)
Hospital mortality, n (%)	2,258 (16.8)	900 (31.9)	1,092 (47.2)	1,137 (55.9)	82 (32.7)

Conclusions For the first time we have established the incidence of early AKI using the RIFLE criteria in Northern Ireland ICUs. This data will inform development of renal services within ICUs in NI. The incidence of severe AKI is high relative to the rest of the UK[1] though lower than published data from the US[2]. Mortality increases with severity of renal injury.

References [1]Kolhe et al, Crit Care,2008,12(Suppl1)S2,[2]Hoste et al, Crit Care 2006,10:R73.

Poster Sessions

Tuesday 21 April

11:30 – 12:30

CKD & Bone Disease 1

Moderator Dr Daniel Zehnder

P13

Oral Paricalcitol is safe and effective for the treatment of secondary hyperparathyroidism in haemodialysis patients

Yasir Abdelrahim, Yasir Banaga, Kieran Hannan

Department of Medicine,Cavan General Hospital, HSE Dublin North-East, Cavan, Ireland

Introduction: Secondary hyperparathyroidism (SHPT) affects the majority of the haemodialysis (HD) population with recent evidence linking SHPT to increased cardiovascular risk. Dietary advice, phosphate binders and Vitamin D supplements are the mainstay of the treatment of SHPT.

Aim: The study was designed to assess the efficacy of oral Paricalcitol (PCT) in reducing Parathyroid Hormone (PTH) in HD patients with SHPT.

Methods: Twenty two HD patients in a single centre were commenced on oral PCT for the treatment of SHPT. Doses used was between 3-14 mcg/week. PTH, serum Calcium (Ca) and phosphate (PO4) were measured at the beginning of the study and bimonthly thereafter for a total of ten months. Dietary measures and phosphate binder use, both calcium and non-calcium based, were consistent with Renal Association guidelines.

Results: The mean PTH level before PCT treatment was 490±157ng/L. It declined to 349±140ng/L (P=0.0031) after two months of treatment. The reduction in PTH level remained statistically significant thereafter with mean PTH level of 281±161ng/L (P<0.0001) at ten months. The average reduction of PTH at the end of the study period is 47% while 15 patients (68%) achieved the target PTH level of <300ng/L. Although an associated statistically significant rise in serum Ca level was noted throughout the study, the mean serum Ca was only raised by 0.1mmol/L at ten months (P=0.0076) (range 0.06-0.14 mmol/L). Phosphate levels remained unchanged.

Conclusion: Oral PCT is safe and effective in reducing PTH levels. This effect was most marked in the first two months of treatment. A small rise in serum Ca levels, which was not clinically significant, was observed. PCT was well tolerated by all the participants.

P14

Lanthanum Carbonate in Dialysis population - A real time experience

Durga Kanigicherla, E Bailey, R A Coward, L R Solomon

Royal Preston Hospital, Lancashire, United Kingdom

High plasma phosphate (PO4) concentrations are associated with increased morbidity and mortality in patients with end stage renal failure. Lanthanum Carbonate has been shown to control serum phosphate in dialysis patients in clinical trials. We assessed its effectiveness in day-to-day practice in our dialysis population.

65 patients were on Lanthanum Carbonate; constituting 11% of those on PD and 13% on HD. Follow up was for up to 15 months (3 – 15 months). Lanthanum Carbonate was mainly used as a second line agent when other PO4 binders (including Sevelamer) failed to achieve adequate PO4 control (65% of patients). In others, it was used because of hypercalcaemia or intolerance / poor compliance to other PO4 binders.

The biochemical variables were as follows:

	Before Lanth	**After Lanth**	**P value**
Mean PO4 mmol/L	**2.27 ± 0.42**	**1.71 ± 0.46**	**< 0.01**
Mean Ca mmol/L	**2.34 ± 0.19**	**2.33 ± 0.34**	**NS**
Mean PTH pg/mL	**486**	**513**	**NS**

Serum PO4 level at serial follow-up (in %) were as follows:

PO4 (mmol/L)	**<1.8**	**1.8 – 2.2**	**> 2.0**
Pre Lanthanum	**9**	**36**	**55**
3 months	**43**	**22**	**35**
6 months	**42**	**24**	**34**
12 months	**70**	**22**	**8**

Conclusion: Lanthanum Carbonate leads to a sustained improvement in PO4 control in routine clinical practice in the dialysis population. This included challenging patients, in whom other PO4 binders could not achieve target PO4 levels.

P15

Role of Tc-99m MIBI Single photon emission / computed tomography scanning (MIBI) in management of hyperparathyroidism in chronic kidney disease

Muhammad Imran, Radhakrishnan Jayan, Jeevinesh Naidu, Hameed Anijeet

Royal Liverpool University Hospital NHS trust, Liverpool, United Kingdom

Introduction: Chronic kidney disease (CKD) is the most common cause of secondary hyperparathyroidism (SHPT). According to Renal Association guidelines, Parathyroid hormone (PTH) should be to kept between 2 to 4 fold normal (i.e <28 pmol/L; as our lab's normal value of PTH is 1.1 - 6.9 pmol/L). Tc-99m MIBI Single photon emission computed tomography scanning (MIBI) is commonly used to define the anatomical location of the hyperplastic glands (HGs). We reviewed our data to evaluate the role of MIBI scan to determine anatomical location of HGs and its clinical significance in CKD patients.

Methods: We reviewed clinical data of CKD patients who had MIBI scans since April 2006 in our centre (n=69,mean age 56, 33 male; transplant n=22, dialysis n=37,CKD n=10).Main indications to perform the scan were, raised PTH >28 pmol/L and unresponsiveness to conventional treatment (n=54) and raised Calcium >2.6 mmol/L (n=39).

Results: Total 72 HGs were identified on MIBI scan. 55% patients (n=38) had unilateral, 23% (n=16) bilateral or multiple and 22% (n=15) had no HGs found. The commonest anatomical location was inferior lobes (68%, n=49). 4% glands were located at ectopic sites. 29% (n=20) patients needed cinacalcet and 36% (n=24) needed parathyroidectomy for refractory SHPT in addition to conventional treatment. Mean PTH in all groups before scan was 66 ± 47 pmol/L) and after intervention was 32 ± 35 pmol/L. Mean Calcium was 2.63 ± 0.22 mmol/l and 2.49 ± 0.24 mmol/L after intervention. Mean inorganic Phosphate was 1.31 ± 0.58 mmol/L before scan and 1.25 ± 0.55 mmol/L after intervention. Patients in cinacalcet group had mean PTH 98 ± 57pmol/L before scan and 50 ± 56 pmol/L after addition of the drug. A significant fall was noted in PTH in patients managed with cinacalcet (p=0.001) and parathyroidectomy (p=<0.0001). In patients with PTH >28pmol/L, MIBI scan was 85% sensitive and 33% specific in identifying HGs (positive and negative predictive values 82% and 38% respectively).

Conclusions: Our study showed that MIBI scan has high sensitivity (85%) in locating HGs in CKD patients with PTH >28 pmol/L. It also confirmed previously known fact that inferior glands are more likely to be found on MIBI scan. It can assist in the medical and surgical management of patients with SHPT.

P16

Differences in bone mineral biochemistry by ethnic group in the year prior to RRT: an observational study of 2,515 patients from the UK Renal Registry

Daniel Ford[1], Margaretha Steenkamp[1], David Ansell[1], Charles Tomson[1], Yoav Ben-Shlomo[2], Damian Fogarty[3]

[1]UK Renal Registry, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom, [3]Queens University, Belfast, United Kingdom

Introduction and aims

It is recognised that there are differences in phosphate, calcium and parathyroid hormone between different ethnic groups in patients receiving dialysis therapy. However, there is little published in the period prior to the start of renal replacement therapy (RRT). This study examines whether there are differences in bone mineral biochemistry between ethnic groups.

Methods

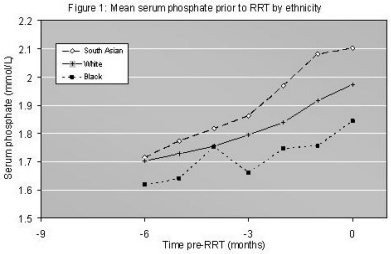
All patients commencing RRT in 7 UK renal centres between 2001 and 2006 were considered for analysis. The UK Renal Registry extracted biochemical data electronically from renal IT systems at pre-defined time-points during the year prior to RRT. Late referrals (patients presenting within 3 months of RRT) were excluded. Mean serum phosphate, corrected calcium (cCa) and parathyroid hormone (PTH) were calculated for Black, White and South Asian patients using a multi-level model. Groups were compared using the Tukey-Kramer method after adjustment for age, gender and renal disease.

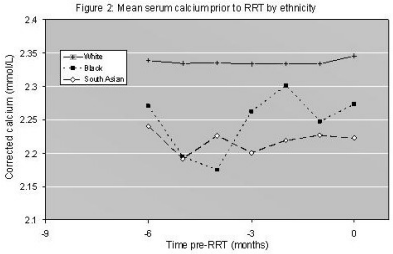
Results

2,515 patients with complete biochemical and ethnicity data were studied. Mean serum phosphate rises from 1.70 mmol/l at 6 months pre-RRT to 1.97 immediately pre-RRT. Black patients (1.69 mmol/l) had a significantly lower adjusted mean serum phosphate in the 6 months pre-RRT than both Whites (1.83, p=0.006) and South Asians (1.88, p=0.003) (Figure 1). White patients had a significantly higher cCa (2.33 mmol/l) than both Blacks (2.24, p=0.0002) and South Asians (2.21, p<0.0001) (Figure 2). White patients (19.4 pmol/l) had a lower PTH than Blacks (29.6, p=0.003) and South Asians (30.4, p<0.0001).

Conclusion

There are ethnic differences in phosphate, calcium and PTH in patients with CKD in the pre-RRT period. These pre-RRT differences are comparable with those previously described by ourselves and others in dialysis patients.





P17

Endogenous sulphuric acid production rate is a strong predictor of myofibrillar protein degradation in patients with CKD stage 4-5

Emma L. Clapp[1], George Kosmadakis[2], Izabella Pawluczyk[2], Joao L. Viana[1], Alice C. Smith[2], John Feehally[2], Anne-Marie Seymour[3], Virginia Lee[4], Alan Bevington[2]

[1]School of Sport & Exercise Sciences, Loughborough University, Loughborough, United Kingdom, [2]Renal Laboratory, Dept of Infection, Immunity & Inflammation, University of Leicester, Leicester, United Kingdom, [3]Dept of Biological Sciences, University of Hull, Hull, United Kingdom, [4]Dept of Chemical Pathology, Royal Infirmary, Leicester, United Kingdom

Myofibrillar protein degradation (MPD), leading to cachexia, is a frequent problem in CKD and is strongly associated with morbidity and mortality. An important stimulus for MPD is uraemic metabolic acidosis. In CKD Stage 4-5 this arises from impaired ability to excrete sulphuric acid (H_2SO_4) derived from catabolism of dietary sulphur amino acids. Study aims To measure the rate of H_2SO_4 production in patients with CKD4-5, and determine whether patients with higher H_2SO_4 production show correspondingly elevated rates of MPD.

Fifteen CKD4-5 patients (9M, 6F) median age 62 (range 38-83 years), underwent a diet free from animal protein for 72h, followed by a 24h urine collection on the same diet. Ten healthy control subjects (5M, 5F) median age 42 (range 31-53) underwent the same diet and urine collection. MPD was assessed from urinary excretion of 3-methylhistidine (3MH). H_2SO_4 production was assessed from urinary excretion of sulphate.

Daily sulphate output varied widely in the patient group (median 33.1, range 8.9-53.3 mmol/24h) and was only marginally higher than in the control group (median 24.5, range 15.0-39.4, P=0.036). MPD in the patients also varied widely (median 0.42, range 0.17-1.31 mmol of 3MH/24h), but did not differ significantly from the control group (median 0.36, range 0.20-0.65, P=0.31, NS). However, in the patients a strong positive correlation occurred between sulphate output and 3MH excretion (Spearman Rank Correlation Coefficient, Rs=0.80, P=0.00031).

Conclusions H_2SO_4 production rates are 3-5 times higher in some patients than others, and correlate strongly with MPD, suggesting that rapid endogenous acid production may be a significant risk factor for cachexia in CKD. Therapy aimed at diverting sulphur catabolism away from H_2SO_4 towards non-acidic end-products (e.g. taurine) should therefore be investigated in high-risk acid-generating patients.

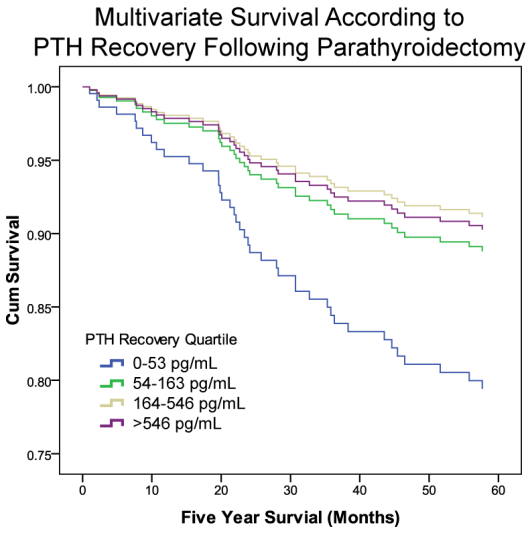
P18

The Impact on Survival of the Recovery of Intact PTH Levels Following Parathyroidectomy in a Single Centre Stage V Chronic Kidney Disease Population

James Fotheringham[1], Barney Harrison[2], Mark Hill[1], Martin Wilkie[1]

[1]Sheffield Kidney Institute, Sheffield, South Yorkshire, United Kingdom, [2]Department of General Surgery, Royal Hallamshire Hospital, Sheffield, South Yorkshire, United Kingdom

Background: Surgical parathyroidectomy is established as a therapy for refractory secondary renal hyperparathyroidism (SHPT). The impact of recovering intact PTH levels post parathyroidectomy on outcome is poorly understood. Methods: Patients who underwent surgical parathyroidectomy for SHPT in one renal unit between 1990 and 2007 were identified from waiting lists and coding on informatics systems. Duration of dialysis prior to surgery, age at surgery, diabetes and date of death were recorded. Biochemical values were extracted from laboratory systems. Results: 252 Patients with adequate follow-up were identified. 65,505 calcium, 60,442 phosphate and 5,155 PTH results were available for analysis. Population statistics: median age 50.7 yrs (19.6 - 82.1), median duration on dialysis 6.0 yrs (-5.9 - 33.7), 13.5% diabetic. PTH recovery, as measured by the maximum PTH in the follow-up period, varied amongst the group. In contrast to those who remained on dialysis, the 27% patients who were transplanted were less likely to recover PTH to levels recommended (2 - 4 times normal range). Survival was not influenced by the duration of dialysis or diabetes, with PTH recovery being evenly distributed across these variables. However being in the lower quartile for PTH recovery (0 - 53 pg/mL) incurred a worse 5 year survival than recovering to higher PTH levels (see graph). Conclusions: Survival in renal patients following surgical parathyroidectomy for SHPT is influenced by intact PTH recovery which has potential implications for the preferred surgical technique.



Poster Session

Thursday 23 April

13:30 – 14:30

Glomerulonephritis 1

Moderator Dr Cath Sterling

P19

23 years of lupus quiescence: an extinct volcano?

J A McCaughan, W Marshall, J S Smyth, N Leonard

Ulster Hospital, Dundonald, Belfast, United Kingdom

A 46-year-old haemodialysis patient presented with hypoxia, pyrexia and hypotension. Following a diagnosis of lupus nephritis in 1985, she had been on longterm renal replacement therapy. There had been no evidence of active disease since 1985 and all immunosuppressive therapy was stopped in August 2007 (Fig 1).

Chest X-ray demonstrated perihilar air space shadowing (Fig. 2) but there was no clinical response following 72 hours of empirical antibiotic treatment for hospital acquired pneumonia and inflammatory markers continued to rise. High resolution CT chest revealed peribronchovascular nodular change, septal thickening and ground glass changes (Fig. 3) and bronchoscopy was subsequently performed. Bronchoalveolar lavage was culture negative.

Over the next 48 hours, she developed peritonism and arthralgia. dsDNA titres were markedly elevated and complement was low. The unifying diagnosis was of lupus activation with pneumonitis and there was dramatic clinical response to steroid therapy.

Lupus nephritis relapse after 24 years [1.] has been reported but relapse after such a long period of quiescence has not previously been described in a haemodialysis patient. This case reinforces the statement made by Moroni et al that 'there is no such thing as 'burnt-out lupus', any more than there are extinct volcanoes: the possibility of further eruption is always present.'.

1. Gabriella M, Greloni GC & Ponticelli C. Late recurrence of lupus nephritis after longterm clinical remission. Nephrol Dial Transplant (2001) 16; 849-852.

P20

Drug-Induced Lupus secondary to cysteamine therapy and Antiphospholipid Syndrome in a Paediatric Renal Allograft recipient.

Leah Krischock[1], Catherine Horsfield[2], Susan PA Rigden[1]

[1]Evelina Children's Hospital, London, United Kingdom, [2]St Thomas' Hospital, London, United Kingdom

Drug-induced lupus (DIL) has been described in association with a wide variety of drugs. There are no specific diagnostic criteria for DIL. Laboratory findings include an elevated ESR and positive antinuclear antibodies. Anti-histone antibodies are positive in more than 90% of cases. Symptom improvement occurs after discontinuation of the suspected agent.

A 14 year old girl was found to have laboratory findings consistent with DIL during work-up for a live related renal transplantation, for treatment of end-stage renal failure secondary to nephropathic cystinosis.(ESR 134, +ve ANA, IgG titre 320 [NR 0-1], IgM titre 40 [NR 0-1], +ve anti-histone antibodies, C3 0.62g/l [NR 0.75-1.65], C4 0.04g/l [NR 0.11-0.43] and high titres of anti-cardiolipin antibodies [IgA 22.1, IgG 74.4, IgM 268.0 -normal ranges 0.0-5.0, 0.0-7.0 and 0.0-7.0 respectively). Cysteamine was considered the most likely causative medication.

Antihistone antibodies disappeared after stopping cysteamine, confirming the diagnosis. The transplant course was complicated by severe thrombosis, with histological findings in the native nephrectomy consistent with Antiphospholipid Syndrome(APLS). Management was further complicated by the need to restart cysteamine post-transplantation, generally not recommended in DIL, to manage the underlying metabolic disorder of cystinosis.

Our patient fulfils the criteria for DIL. Serological evidence of DIL developed after years of cysteamine treatment and improved on cessation. Hypocomplementaemia, although not typical, has been reported in DIL and the structural similarities of cysteamine and penicillamine provide further evidence for a causative role for cysteamine. APLS is less common in DIL. Anticardiolipin Abs have remained positive in our patient after stopping cysteamine. Immunosuppression started after transplantation may ameliorate the reappearance of DIL, but following reintroduction of cysteamine, complement levels are again falling, raising difficult questions about the future management of DIL in a renal transplant recipient with cystinosis.

P21

A novel case of nephrotic syndrome secondary to membranous glomerulonephritis in association with Kimura's disease in a Caucasian; a treatment dilemma!

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Department of Nephrology, University Hospital Aintree, Liverpool, United Kingdom

Introduction: Nephrotic syndrome in association with Kimura's disease has been reported mainly in Orientals. Kimura's disease is an angiolymphoid proliferative disorder of unknown aetiology. Treatment of nephrotic syndrome in association with Kimura's disease remains uncertain.

Methodology: We report a novel case of nephrotic syndrome secondary to membranous glomerulonephritis in association with Kimura's disease in a Caucasian male. A review of the current literature for treatment of the nephrotic syndrome in association with Kimura's disease was made.

Results: Case report. A 48 year Caucasian male presented in December 2005 with a spontaneous major pulmonary embolism and was commenced on lifelong warfarin. In July 2007 he developed a deep vein thrombosis in the left lower limb. An incidental finding of left groin lymph node enlargement was found on doppler of the lower limb and was confirmed on computerised tomography to have bilateral inguinal lymphadenopathy. He underwent an excision right inguinal lymph node biopsy in February 2008 and histology was consistent with Kimura lymphadenopathy. In April 2008, he was found to have nephrotic syndrome with oedema, proteinuria of 12.72g/day (9.22g/L) with hypoalbuminaemia of 18g/dl, hypercholesterolemia of 7.3mmol/L. He had eosinophilia of 1.6 $x10^9$/L. He had normal renal function with serum creatinine of 81µmol/L with eGFR > 90ml/min. His renal ultrasound showed normal sized kidneys and renal immunology was normal except for a raised IgE at 606ku/L, and low Antithrombin 3 and Protein C levels. He underwent a renal biopsy in July 2008 and histology demonstrated membranous glomerulonephritis. He was commenced on prednisolone 60mg/day. His antihypertensive regimen was maximised and included irbesartan 300mg/day, ramipril 10mg/day and furosemide 40mg/day. In November 2008, he had partial remission with his nephrotic range proteinuria improving to 5.73g/day (2.45g/L) and albumin increasing to 26g/L after 3 months of steroid therapy. His renal function remains stable with a serum creatinine of 88µmol/L. There are a few case series and case reports of nephrotic syndrome in association with Kimura's disease, almost exclusively in Orientals.

Discussion: Literature review regarding nephrotic syndrome in association with Kimura's disease is presented here.

Conclusion: We report a novel case of nephrotic syndrome secondary to membranous glomerulonephritis in association with Kimura's disease in a Caucasian male. The treatment of these patients remains uncertain. Our case would support lymph node biopsy for diagnosis and we suggest conservative surgical excision and the use of steroid therapy in inducing remission of their nephrotic syndrome.

P22

Renal survival in nephritic focal segmental glomerulosclerosis is dependent on remission but not on relapse

Tanya Pankhurst[1], Alexander Howie[2], Dwomoa Adu[1]

[1]Department of Nephrology, Queen Elizabeth Hospital, Birmingham, United Kingdom, [2]Department of Pathology, University College London, London, United Kingdom

Previous studies suggest that long term renal outcome in nephrotic FSGS is dependent on remission and relapse of nephrotic syndrome. We studied 107 patients presenting consecutively to our centre with primary FSGS and nephrotic syndrome. Eighty-four patients (79%) had early classical FSGS, 23 (22%) had late classical FSGS. Median age was 48 years (range 16-92) and 60% were men. The median glomerular filtration rate (MDRD equation) was 62ml/min (range 0-223) at presentation.

The patients were treated with steroid and in some cases further immunosuppression.

At the mean follow up (69 months) overall renal survival was 83%. When analysed for remission, 51% had achieved complete remission (proteinuria <0.5g/24hours); 22% had achieved partial remission (proteinuria <3g/24hours) and 24% were still nephrotic. Renal survival was dependent on remission (p=<0.001) fig 1. Of those who achieved full remission 41% subsequently relapsed. This did not influence renal survival.

The long term outcome of FSGS appears to have improved. Achieving remission improves renal survival and relapse does not worsen it.

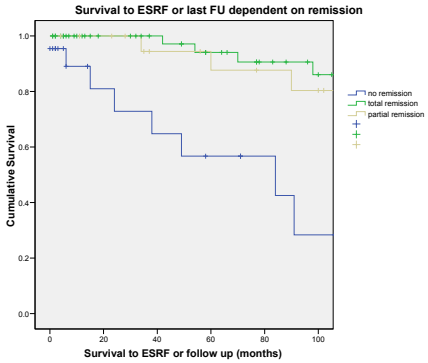


Figure 1: Survival to ESRF is dependent on remission from nephrotic syndrome in FSGS

P23

Treatment of Persistent Granulomatous Lesions in ANCA-associated Vasculitis with Rituximab

Scott R Henderson[1], Philip W Ind[1,3], Alan D Salama[2]

[1]Imperial College Healthcare NHS Trust, London, United Kingdom, [2]Renal Section, Division of Medicine, Imperial College, London, United Kingdom, [3]National Heart & Lung Institute, Imperial College, London, United Kingdom

Introduction - Treatment of granulomatous lesions in ANCA-associated vasculitis (AAV) with Rituximab (RTX) remains controversial. While treatment of vasculitic symptoms and glomerulonephritis with Rituximab has been successful, resolution of granulomatous lesions is still problematic with reports suggesting lack of resolution. The role of Rituximab in persistent granulomatous lesions, despite conventional immunosuppression, has therefore been reviewed.

Methods - Patients with Wegener's Granulomatosis (WG) and predominant granulomatous lesions (n=5) were retrospectively evaluated. Systemic manifestations, disease activity, previous immunosuppression, absolute B cell number and serological inflammatory markers were recorded pre- and post-RTX infusion, after 6 months, during relapse and at the study end point. Imaging at each time point allowed correlation with degree of pulmonary involvement.

Results - Five patients were evaluated (3 male, 2 female) with a mean age 34 (range 22–52) years. ENT and pulmonary involvement was present in all patients. Manifestations included chronic sinusitis, rhinitis, nasal granulomas with bony destruction or septal perforation, subglottic stenosis and pulmonary nodules with or without cavitation. RTX was associated with radiological improvement in pulmonary manifestations in all patients at 6 months accompanied by absolute B cell depletion (<5 cells/uL). Relapse was observed in 3 patients at a mean of 14 (range 8–17) months after initial RTX accompanied by significant B cell re-population (average 93 cells/uL). Repeated RTX was associated with new radiological improvement and further absolute B cell depletion (<5 cells/uL). A fivefold greater absolute B cell number at induction was observed in relapsing patients compared to those achieving remission with single-dose RTX. Direct correlation with autoantibody titres and degree of pulmonary or ENT involvement was not identified.

Conclusion - Monoclonal anti-CD20 antibody therapy may be used to successfully treat granulomatous lesions in AAV. However, our findings recognise that disease remission is directly related to sustained absolute B cell depletion (<5 cells/uL) which may therefore be used to direct further therapy.

P24

Interstitial nephritis; 9 years experience from a single UK renal centre

Muhammad Naeem Raza, Mohammed Hadid, Coralie Bingham

Royal Devon & Exeter Hospital, Exeter, United Kingdom

Background: Interstitial Nephritis (IN) has been reported as a significant cause of reversible acute renal failure in 6-25% cases. In the majority this is drug induced, mostly related with use of antibiotics and NSAIDS. Use of steroids remains debatable and most of the evidence comes from small studies.

Aim and objective: To find the incidence of IN, implicated drugs apart from antibiotics and NSAID's and trends in the use of steroids .

Methods: Patients with a histological diagnosis of IN were identified from consecutive renal biopsies performed between Nov 1999 and June 2008 and their records reviewed.

Results: Out of a total 1037 native kidney biopsies, 49(4.7%) had IN as the main diagnosis. Out of those,8(16%) cases were from the first 3 years, 15(31%) from the next 3 years and majority 26(54%) from the last 3 years(2006-2008). Median age of our cohort was 71 years (18-92), 31(63%) males and 18(37%) females.

Histological details include, acute IN with eosinophils in 31 cases, acute and chronic IN in 6, acute IN with DM in 3, acute IN with vasculitis in 1, TINU in 3 and acute granulomatous interstitial nephritis in 3 cases.

Antibiotics remain the most commonly implicated drugs, exclusively in 10(20%) and in combination for 20(41%) cases. Commonest antibiotic was amoxicillin followed by flucloxacillin. Proton Pump inhibitors (PPI's) were the second commonest group responsible, exclusively implicated in 7(14%) cases and in combination with antibiotics for 13(26%). 90% of PPI's related cases were from the last 30 months. Other major categories included statins and NSAID's 5(15%) each.

Median Creatinine (Cr) at presentation was 519 mmol/L (107-1286) with eGFR of 11mls/m (4-26). Twelve (24%) patients required dialysis at presentation or during the course, 7 (58%) were treated with steroids of which 3(43%) improved compared with 5(42%) not given steroids of which 3(60%) improved.

In a total, thirty six (73%) patients were treated with steroids for median duration of 5 months, 24 (67%) of those treated showed >50% improvement in serum Cr compared with 7(54%) not treated with steroids. Overall in total 31(55%) patients showed >50% improvement in their serum Cr with median Cr of 206 mmol/L(82-759) and eGFR of 39 mls/m(8-75) >6M after presentation.

Conclusion: Incidence of IN was higher in the last three years compared to the first 6 years in our unit, however overall seems less compared to previously reported studies. Apart from antibiotics and NSAIDS, PPI's and statins were other major drug categories implicated in a significant proportion of cases. Steroids were used as a treatment in the majority of cases.

Poster Session

Tuesday 21 April

11:30 – 12:30

CKD 1

Moderator Dr Phil Kalra

P25

The Use of Evidence-Based Renal Care Pathways to Inform the Commissioning of Evidence-Based Care for Chronic Kidney Disease

Emma Stanton[1,2], Will Perks[2], Teresa Morris[2], Henriette Coetzer[1]

[1]Department of Health, London, United Kingdom, [2]Bupa Health Dialog, London, United Kingdom

Initial Problem

"If the levels of transplant are increasing and the rates of dialysis remain constant why are the levels of emergency dialysis starts increasing?"

Methodology

Care pathways were used to

-map current volumes in all Nephrology Outpatients in Hillingdon PCT (volumetrics)

-map best practice for Chronic Kidney Disease from systematic review of literature

-develop and disseminate guidelines to be used in Primary Care to improve detection and management of Chronic Kidney Disease

Findings

- Significant increase in Nephrology Outpatient total number of attendances from 2984 in 06/07 to 4168 in 08/09. No increase in volumes of renal transplants (15 in 06/07, 11 in 07/08 and 12 in 08/09).

- Hillingdon PCT population is 13.6% Asian who are at greater risk of diabetes and subsequently developing Chronic Kidney Disease.

- In 07/08, 1484 patients were seen in Nephrology Outpatients. "Crash landers" represented only 29 patients during the year and over half of these were known to Outpatient clinics. Very low numbers of patients on peritoneal dialysis (5) and home dialysis (2).

Conclusion

Care pathways are an effective way of challenging initial assumptions that the levels of transplants and emergency dialysis are increasing.

Illustrations of the evidence for treating Chronic Kidney Disease in the form of pathways can be used to inform commissioners about specific recommendations to improve quality of renal care.

Recommendations

Collaborative working can be used to develop pathways to be used as local guidelines. These are due to be sent to all GPs in Hillingdon PCT.

P26

Chronic Kidney Disease in English hospitals: Analysis of HES.

K Abraham, E Thompson, M Pearson

A gap exists between patients with identified renal dysfunction and those covered by renal teams. GFR estimation has contributed to this awareness. Hospital Episode Statistics [HES] were used as one part of the solution to detect and monitor renal patients in their pathway.

All inpatient episodes in 06/07 were analysed for four renal "hubs" and their "spoke" hospital trusts. The significant numbers of renal ICD10 codes detected in the first seven positions were analysed. Hospitals were classified as transplanting renal unit [1], renal unit without transplantation [2], hospital with visiting renal input [3], hospital with renal input at request only [4]. Mean values were calculated for each category.

Even in hospitals with renal teams on site, many cases of CKD are managed by other specialists. Patients are more likely to receive dialysis in renal centres and mortality in type 3 and 4 hospitals is higher. This project suggests that there are significant differences in hospital CKD care, verging on a post code lottery. If the hypothesis that specialists provide better care is accepted, these findings provide an incentive to improve care significantly.

Hospital Trust	No.	% Renal	Mean %	% RRT	Mean %	% Died	Mean %
Aintree 2	647	58.9	21.8	44.4	27.8	4.6	7.0
Southport 3	171	0.0	4.6	4.1	8.2	9.4	8.4
Walton 4	0	NA	0.0	NA	0.0	NA	7.2
N Bristol 1	1282	53.7	29.9	38.5	34.9	4.1	7.0
UH Bristol 3	269	4.1	4.6	3.0	8.2	4.8	8.4
Weston 4	153	0.0	0.0	0.0	0.0	7.2	7.2
Bath 3	398	16.8	4.6	3.3	8.2	6.3	8.4
Leicester 1	1140	2.0	29.9	29.6	34.9	10.0	7.0
Lincolnshire 2	499	8.2	21.8	2.8	27.8	9.6	7.0
Northampton 2	246	19.9	21.8	5.7	27.8	11.4	7.0
Peterborough 2	307	32.9	21.8	7.2	27.8	12.1	7.0
Bolton 3	193	0.0	4.6	3.1	8.2	11.4	8.4
Pennine 3	726	2.6	4.6	18.7	8.2	7.4	8.4
Salford 2	1080	3.1	21.8	40.3	27.8	4.8	7.0
Trafford 3	114	0.0	4.6	0.0	8.2	20.2	8.4
Wrightington 3	228	0.0	4.6	0.9	8.2	10.1	8.4

P27

Introduction of Referral Guidelines is Associated with a 50% Reduction in Dialysis "Crash Landers" – A Single Centre Audit

Helen Ford, Lizzi Lindley, Andrew Mooney

Renal Unit, St James's University Hospital, Leeds, United Kingdom

It is known that an appropriate duration of specialized pre-dialysis follow up is associated with a better outcome for long term dialysis patients with end stage renal failure (ESRF). Over the past 8 years there have been several guidelines published aimed at improving the identification of patients with chronic kidney disease and reducing the number of late presenting patients (Renal Association Standards, 2000; National Service Framework, 2005; Quality Outcome Framework and eGFR Reporting, 2006). A previous audit in our unit (Leeds Teaching Hospitals), prior to these publications, showed 37% of ESRF patients starting dialysis in a 12 month period had less than 90 days of pre-dialysis follow up. We have re-audited this data in the light of these guidelines.

The unit's electronic database was used to identify all patients who had started haemodialysis (n=127) in the period between October 2007 and September 2008. Among other data, dates of first contact with renal services and date of first dialysis were identified. Further data was then collected from the data base and review of patient notes, including demographic data, primary renal disease, modality of first dialysis and desired modality of dialysis.

The audit demonstrated that percentage of patients who had less than 90 days of specialised renal follow up has dropped by 41% (compared to 2000), to 15.75% during the period October 2007-September 2008. In addition the majority of patients who started long term dialysis within 90 days of presentation to specialist renal services had rapidly progressive acute renal failure and only a small those who were known to renal services for less than 90 days (n=20) minority could have potentially been referred earlier. All patients presenting less than 90 days from the start of renal replacement therapy initially had haemodialysis catheters, and none started on peritoneal dialysis. We conclude that recent guidelines and eGFR reporting have been associated with a large reduction in the "crash lander" rate, and also that it is unlikely that further refinement of these guidelines will reduce this amount further.

P28

Impact of Routine Estimated GFR (eGFR) Reporting to General Practice (GP) on Referral Rates to Renal Services.

Joanne Shields, Robert Mullan, Ronan Cunningham, Camille Harron

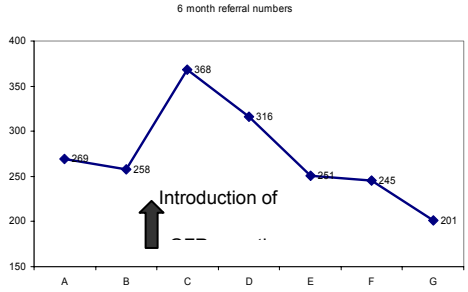
Antrim Area Hospital Renal Unit, Antrim, United Kingdom

Introduction: In May 2005, routine eGFR reporting was introduced for GPs in the Northern Board area of Northern Ireland (population 430,500). We aimed to assess how this influenced referral patterns to specialist nephrology services.

Methods: Referral numbers were collated on a six-monthly basis for three time points: the year before the introduction of eGFR reporting (May 2004-April 2005, A+B), the year following eGFR reporting (May 2005-April 2006, C+D) and for 18 months from May 2007-Oct 2008, E, F & G. Detailed analysis of demographic factors and clinical information given was made for 60% of referrals six months pre- and post-eGFR reporting.

Results: Annual referral numbers increased from 527 to 684 with a 42% increase in the 6 month period following eGFR introduction. Referrals for chronic kidney disease (CKD) accounted for the increased rate. The proportion of females referred increased from 47% to 53%, with the age at referral increasing from 67 to 70 years. The average creatinine at referral was lower following eGFR reporting. The majority of referrals were for patients with Stage 3 CKD. Following local and national CKD education programmes for GPs and the introduction of Quality and Outcome Framework (QOF) points, the annual referral rate was re-examined. Referral rates have returned to the level pre-introduction of eGFR reporting.

Conclusion: Introduction of eGFR reporting to GPs increased referral rates but this increased rate has not been sustained three years later.



P29

Comparison of Chronic Kidney Disease in Gloucestershire United Kingdom, to NEOERICA (New Opportunities for Early Renal Intervention by Computerised Assessment) estimates

Angharad Marks, Anthony Williams, Allan Rose

Gloucester Royal Hospital, Gloucester, United Kingdom

Introduction **-** Estimates of Chronic Kidney Disease (CKD) prevalence vary from 3.8% to 15.6%. Recent estimates of CKD prevalence in the UK (based upon NEOERICA study) have been published. We sought to examine the CKD prevalence in Gloucestershire (Glos), a rural county.

Methods **-** All serum creatinine measurements performed in Glos from 01.06.07 to 31.05.08 were collected, with age, sex and unique identifiers. eGFR was calculated using the abbreviated MDRD equation. CKD was defined if the last eGFR in the year was less than 60ml/min/1.73m^2. A group with two eGFRs more than 3 months apart, less than 60ml/min/1.73m^2 (current CKD definition in the UK) were also available, data up to 31.8.08.

Results **-** The total population of Glos (mid 2006 estimate from 2001 census) is 578,631, (220,080 female (F) and 234,800 male (M), age > 18 yrs). 476,093 valid samples were obtained from 185,013 individuals, (41% of the adult population) ranging from 11.1% of M, 18-24 yrs to 84.2% of M >85 yrs. Overall the point prevalence of CKD was 8.0% (M=6.6%, F=9.3%). The estimate from NEOERICA for this population is 9.8% (M=7.1%, F=12.3%). Analysis of those age bands >65yrs, shows observed/expected prevalence ratios of 0.70 - 1.12, and more than 69% of this population had a test result. The CKD O/E prevalence of female age bands 18 - 54 yrs was 0.27 - 0.72, but much lower population testing (23-36%). The CKD O/E prevalence of M age 18-24 yrs, and M age 25-34 yrs was 6.2 and 1.15, despite only 11% and 15% of these populations having a result. 78799 adults had a repeat creatinine after 3 months, 19550 had both an original and subsequent eGFR less than 60ml/min/1.73m^2, prevalence M=3.66%, F= 4.9%. Amongst the starting population 325 were dialysis and transplant patients, and 50 commenced RRT during the year.

Conclusion - In Glos the point prevalence of CKD in the older age groups, where a large proportion of the population was tested, is similar to that predicted. In the younger groups the expected female preponderance is not apparent, and the female rates are more similar to younger males. This may be explained by the low sampling rate of F age 18-24 yrs however does not explain the very high prevalence in M, age 18-24 yrs where only 11% were sampled. This pattern held amongst those who had follow up eGFR after 3 months.

P30

Chronic Kidney Disease (CKD) in Surrey in 2008: cross-sectional analysis and targets for Quality Improvement (QI)

Hugh Gallagher[1,4], Simon de Lusignan[1], Jeremy Van Vlymen[1], Tom Chan[1], Nicola Thomas[2,5], Michael Nation[2], Jo Moore[2], Neerja Jain[2], Kevin Harris[3]

[1]St George's University, London, UK, [2]Kidney Research UK, Peterborough, United Kingdom, [3]University Hospitals, Leicester, UK, [4]SW Thames Renal Unit, St Helier Hospital, Surrey, UK, [5]City University, London, UK

CKD is an important challenge for public health and target for primary care. We present cross-sectional baseline data analysis of 135,733 individuals drawn from 14 representative Surrey practices, drawn from a larger sample participating in a national QI initiative.

Crude and adjusted prevalence, using standardised creatinine measurements, of stages 3-5 CKD were 6.3 and 5.8% respectively, lower than previously reported. This compares with a locality QOF median prevalence of only 2.4%. Females accounted for 71% cases of stage 3a CKD, but 65, 56 and 50% of stage 3b, 4 and 5 disease respectively.

The crude prevalences of diabetes (3.3%), hypertension (HT, 22.3%) and ischaemic heart disease (3.0%) were lower in Surrey compared with the UK average, although these conditions were over-represented in those with CKD. HT was more common co-morbidity in stage 3b (71.3%) as compared with stage 3a (51.3%) CKD.

Renal anaemia was more prevalent than in previous UK samples. Over 5% with stage 3-5 CKD were anaemic (NICE definition, Hb < 11 g/dl); this compares with 3% of the population with eGFR > 60 ml/min/1.73m^2 (OR 1.78, 95% CI 1.59-1.99). The proportion with Hb < 11g/dL in stages 3a, 3b, 4 and 5 CKD was 3.5, 12.0, 22.7 and 37%.

Quantitative proteinuria recording was poor. Measurements of TPCR and ACR were available in only 90 and 126 non-diabetic patients respectively. However there were 4.345 other proteinuria tests recorded (largely reagent strip tests), and these were far more likely to be performed in people with stage 3-5 CKD than without (odds ratio 3.88, 95% CI 3.59-4.20). BP was higher in those with CKD (136 mmHg) than without (127 mmHg). Mean systolic BP progressively rose with declining eGFR. The mean systolic BP in those with CKD with and without a positive proteinuria test (including dipsticks) was identical.

In conclusion this population exhibits important differences from earlier UK samples, which may be related in part to demographic differences. There is scope to improve management. CKD remains under-reported, and efforts should be further directed to targeting of high risk individuals identified by quantitative proteinuria testing.

P31

Improving Access to Nephrology Outpatients through Introduction of CKD Guidelines

Richard W Corbett, Joanne Holland, Michael K Almond

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Introduction: The introduction of UK Chronic Kidney Disease guidelines in 2006 has the potential to improve care but may have led to an increase in the number of patients referred and seen in general nephrology outpatients. The Pan-Thames Renal Audit Group (PTRAG), of which Southend is one of the thirteen contributing centres, demonstrated in a prospective audit in 2006 a high number of potentially dischargeable patients in Southend who continued to be seen in secondary care. Follow-up of those patients discharged to primary care has previously been demonstrated to be good.

Methods: The guidelines clearly identify those patients those patients who should continue to receive continuing hospital-based nephrology care. Initially in 2006, as part of the PTRAG audit all patients attending general nephrology out-patients were audited excluding all dialysis, transplant and low-clearance clinic patients. Following the introduction of CKD guidelines, the identical fortnight in May was re-audited in 2008 against the same criteria.

Results: Over a two week period (2006 v 2008), similar numbers of patients were seen (44 v 37). There was no significant difference in median age (59 v 68 years $p = 0.16$) or systolic blood pressure (129 v 130 mmHg $p = 0.12$). However, median serum creatinine between the two groups had increased significantly (145 v 206 µmol/l $p = 0.009$), reflected in a greater proportion of patients with CKD 4 or 5 being seen (27% v 63%). Furthermore the ratio of potentially dischargeable patients who were actually discharged, had improved significantly (6/16 v 8/12 $p = 0.006$).

Conclusion: The adoption of an active discharge program based on CKD guidelines has led to increasing number of patients being appropriately discharged to primary care. By reducing the inappropriate work load within a general nephrology clinic there are up to one-third more appointments available for those requiring continuing specialist care as well as increased new-patient capacity.

P32

Blood Pressure and Proteinuria in the CKD Population: How Attained Levels Associate with Risk of Starting RRT

Peter Thomson[1], Christopher Deighan[1], Catherine Stirling[1], Amaraj Raja[2], Gordon Prescott[2], Keith Simpson[1]

[1]Renal Unit, Glasgow Royal Infirmary, Glasgow, [2]University of Aberdeen, Aberdeen

Introduction

In this study the association between systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg) and urinary protein to creatinine ratio (PCR, mg/mmol) on risk of starting renal replacement therapy (RRT) in a CKD population was examined over a 20-year period.

Methods

A retrospective analysis of data recorded on the electronic patient record (EPR) of the Glasgow Royal Infirmary Renal Unit was performed. The EPR contains routine clinical and laboratory data prospectively recorded for all patients seen by the renal services in this hospital from 31/07/1984 onwards. All patients registered on the EPR between 31/07/1984 and 11/01/2005 was examined. All patients with a creatinine clearance (CrCl) of <50mL/min (derived by Cockcroft & Gault formula) and progressive renal dysfunction were identified. Initial data and data averaged over the predialysis follow-up period were obtained for a range of variables including SBP, DBP and PCR. Univariate and multivariate analysis were performed with regard to the outcome of commencement on renal replacement therapy (RRT) for established renal failure (ERF).

Results

1739 patients fulfilled our inclusion criteria with mean follow-up of 57.6 months. 549/1739 (31.6%) patients started RRT for ERF. Univariate analysis demonstrated a significant association ($p<0.05$) between shorter time to commencing RRT and primary renal diagnosis, increased age, higher calcium phosphate product, urate, total cholesterol, body mass index, eosinophil count, ferritin, HbA1C, cholesterol to HDL ratio, average SBP, initial and average DBP, initial and average urinary PCR and lower initial CrCl, haemoglobin, serum HDL and serum albumin.

Multivariate Cox regression analysis demonstrated an independent incremental rise in risk of requiring RRT with each 10mmHg stepwise increase in initial and average SBP from 120mmHg upwards (HR increasing to 8.96 with SBP >170mmHg, $p<0.001$) and each 100unit stepwise increase in average PCR from >100 upwards (HR up to 11.8 with PCR >500, $p<0.001$). Age, primary renal diagnosis, albumin, BMI, CrCl and haemoglobin were also independently associated with outcome. On multivariate analysis averaged DBP was not associated with time to commencement of RRT.

Conclusion

Increasing SBP and urinary PCR as measured in routine clinical practice have a particularly strong independent association with shorter time to commencing RRT.

Poster Session

Wednesday 22 April

13:00 – 14:00

CKD & Bone Disease

Moderator Dr David Wheeler

P33

A dietitian led, protocol based management of phosphate binders in HD patients results in better outcomes

Pramod Nagaraja, Anne Williams, Rommel Ravanan

University Hospital of Wales, Cardiff, United Kingdom

Background: Achieving RA targets for serum phosphate, corrected calcium levels and calcium-phosphate product requires a close working relationship between the patient, dietitian, renal nurses and doctors. Other than ensuring dialysis adequacy, the patient – dietitian relationship is critical as appropriate dietary and phosphate binders advice is likely to result in better outcomes. Therefore, we introduced a dietitian led, protocol driven management to improve achievement of renal bone disease biochemical targets in haemodialysis patients.

Methods: A phosphate management protocol was drawn up which authorized an appropriately trained renal dietician supervising a 12 station [48 patients] dialysis unit to recommend initiation and adjustment of phosphate binder dosage to the patients' GP. Statistical process control (SPC) charts were used to analyze outcomes over 12 months before and 6 months after introduction of the new protocol. Data on pill burden and cost per patient was also evaluated.

Results: Introduction of the protocol caused significant changes in key biochemical values as evidenced by identifying "special cause variation" on the SPC charts. The protocol based management resulted in significantly improved mean phosphate levels and percentage of patients achieving phosphate targets without causing hypercalcaemia. These improvements were achieved despite a reduction in the average number of phosphate binder pills/ patient as well as average cost.

Conclusion: Dietitian led, protocol driven management of phosphate binders in haemodialysis patients is safe & can result in improved outcomes without increasing pill burden or cost.

P34

Outcomes of a Large Series of Parathyroidectomies Performed in a Single Centre.

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Introduction: Secondary Hyperparathyroidism (SHPT) is an important complications of renal failure and its management remains a challenge. Total parathyroidectomy (PTX) is widely used but questions regarding long term outcomes remain unanswered. Low paratharmone (PTH) levels and adynamic bone disease following (PTX) are considered significant risk factors for fractures.

Methods: Between 2000 to 2007, 131 total parathyroidectomies were performed without re-implantation at a single centre by a single operator. Clinical information and biochemistry data were obtained along with fracture data. Calcium, phosphate and PTH were recorded pre-operatively and at 1, 6 and 12 months after PTX.

Results: Mean age at the time of PTX was 47 years. Time on RRT before PTX varied from 20 to 100 months with an average of 65 months. Mean follow up period is 3.5±2.06yrs. The PTH fell significantly from a median of 995pg/ml pre surgery to 7.9pg/ml at 1 month and remained low at 6.0pg/ml at 6 months and 33.0pg/ml at 12 months. The average calcium level pre-operative was 2.6mmol/L (SD 0.24mmol/L) which dropped to 2.28mmol/L(SD 0.38mmol/L) at 1 month and 2.36mmol/L(SD 0.3mmol/L) at 12 months. There was no significant fall in phosphate levels after surgery. Six patients who had recurrence of SHPT underwent repeat PTX and one patient required 2 repeat operations. Only four patients had fractures following PTX equating to 7.77 fractures per 1000 patient years. All the four patients who had the fractures had recurrence of SHPT and the 63% of patients with PTH suppressed below 70pg/ml at 12 months had no fractures. There were no cases of laryngeal nerve palsy and no significant surgical complications. There were no deaths in the first year following surgery and 19 deaths thereafter.

Conclusions: In our centre PTX plays an important role in the management of severe SHPT. It can be a safe and effective treatment resulting in significant suppression of PTH, a fall in the mean serum calcium and no increased risk of fractures over 1-7 years following surgery.

P35

Impact of a Novel Dietician-led Phosphate Control Initiative in a Haemodialysis Satellite Unit

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Background: Haemodialysis patients with chronically elevated serum phosphate (PO_4) levels are at increased risk of vascular calcification, an important non-traditional risk factor for cardiovascular disease. In many patients, non-adherence to dietary restrictions and PO_4 binder therapy contributes significantly to poor phosphate control. Traditionally the dietician's role has been confined to providing dietary advice since dieticians are not recognised as supplementary prescribers. Our unit has piloted a trial of dietician-led prescribing under a patient group direction, guided by a pre-defined unit protocol.

Aim: To assess the efficacy and safety of a dietician-led phosphate control initiative in a satellite haemodialysis unit.

Methods: This was a 6-month prospective non-randomised observational study. 112 haemodialysis patients were studied. Group A (n=56) received usual care with their binder prescription adjusted by their physician. Group B (n=56) had their phosphate-binders adjusted according to a pre-defined protocol as part of a dietician-led monthly ward round. All patients gave written consent for participation in this pilot study. Data was collected on serum Ca^{+2}, PO_4 and PTH levels. Adherence to treatment was also assessed and binder use recorded. Any serious adverse events attributable to binder medications were also documented.

Results: In the dietician-led arm, mean serum phosphate at the beginning of the study was 1.64mmol/L falling to 1.44mmol/L at 6 months. Mean serum phosphate in the control group at the start of the study was 1.73mmol/l falling to a mean of 1.48mmol/l (A vs B, p=NS at 6 mo; Student t test). Mean Ca^{+2} x PO_4 levels were 3.98 in the intervention group falling to 3.39 at 6 months and 3.92 falling to 3.54 in the control. The proportions in each group achieving Renal Association / KDOQI targets for calcium, phosphate, Ca^{+2} x PO_4 were similar (A vs B, p=NS; Student t test). No serious adverse events were encountered.

Our results suggest that dietician-led management of serum phosphate using protocol-based prescribing is a safe and effective approach with outcomes comparable to conventional physician-led prescribing.

P36

The effect of case mix differences on variation in serum phosphate concentrations between UK dialysis centres.

Alex Hodsman[1], Yoav Ben-Shlomo[2], Julie Gilg[1], Paul Roderick[3], Charlie Tomson[1]

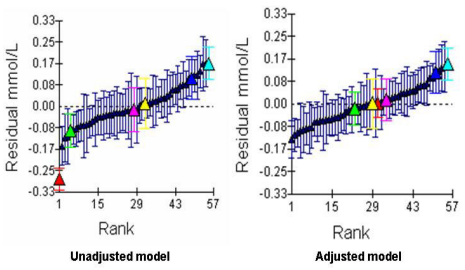
[1]UK Renal Registry, Bristol, United Kingdom, [2]Dept of Social Medicine, University of Bristol, Bristol, United Kingdom, [3]Dept of Public Health, University of Southampton, Southampton, United Kingdom

Introduction: The UK Renal Registry compares performance of dialysis centres against biochemical audit measures specified in Renal Association clinical practice guidelines. Several factors are proposed to account for the between centre variation observed in performance. This study shows novel methodology for case mix adjustment and the effect on variation in PO_4 observed between UK dialysis centres.

Methods: PO_4 values for the prevalent 2006 HD cohort were used. A random effects multilevel model (using MLWin) was used to account for centre clustering. Variance partition coefficients (VPCs) were calculated pre and post case mix adjustment. These determine the % of the total variation attributable to patient and to centre level effects. Unadjusted centre level residuals were calculated. These are differences between the centre mean and the overall mean with adjustment for centre size. The effect of case mix factors including age, gender, ethnicity, socioeconomic status, transplant waiting list status (a marker of co-morbidity) and pre dialysis creatinine (a marker of nutritional status) on mean PO_4 for a centre were analysed.

Results: Mean PO_4 for the cohort was 1.63mmol/L. The unadjusted and adjusted centre level residuals (+/-1.96SDs) are shown in the figure. There is significant between centre variation which is reduced after adjustment for case mix. Factors with a significant effect on between centre variation were age ($p<0.0001$), gender ($p=0.02$), ethnicity ($p<0.001$), transplant waiting list status ($p<0.0001$) and predialysis serum creatinine ($p<0.0001$). Centre ranking is also affected by case mix adjustment (shown by the highlighted centres). The VPCs calculated show that 1/3 of between centre variation can be explained by the patient differences in case mix analysed.

Conclusions: Several case mix factors routinely collected by the UK Registry have a significant effect on between centre variation in mean PO_4 (accounting for 1/3).The remaining variation may be due to differences in processes of care but may also represent unmeasured case mix differences.



P37

Fibroblast Growth Factor -23 (FGF-23) – an important role in Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) ?

David Goldsmith, Padmini Manghat, Ignac Fogelmann, Anthony Wierzbicki, Ellie Asgari, Geeta Hampson

Kings Healthcare Partners, London, United Kingdom

CKD-MBD is an important clinical problem. FGF-23 is markedly elevated in CKD, although the driving stimuli for, and role of, the increase in FGF-23 are unclear. The aim of this study was to assess the predictors of circulating FGF-23 levels in CKD stages 1-4 and also the relationship between FGF-23 levels and bone metabolism. We studied 145 ambulant patients (85 M and 60 F) (age mean [SD] 53 [14] years). 41 patients had CKD 1,2 (eGFR >60 ml/min; mean [SD] 78 [14]), 59 patients had CKD 3 (eGFR 30-59 ml/min; mean [SD] 45 [8]) and 45 patients had CKD 4 (eGFR <30 ml/min; mean [SD] 21[4]). Bone Mineral Density (BMD) and Bone Mineral Content (BMC) were measured at the lumbar spine (LS), femoral neck (FN), forearm (FA) and total hip (TH) by DXA. Serum PTH, FGF-23, 25 (OH) vitamin D, Bone Alkaline Phosphatase (BAP), Tartrate- Resistant Acid Phosphatase (TRAP), high sensitivity CRP (hs-CRP) were determined. Univariate analyses and multiple linear regression models were used. In the whole population, univariate analysis showed significant relationship between FGF-23 and CaxP ($r = 0.31$, $p = 0.0002$), hs-CRP($r= 0.21$, $p<0.02$), Serum phosphate ($r = 0.34$, $p<0.0001$), fractional excretion of phosphate ($r = 0.29$, $p = 0.0005$), eGFR ($r = -0.40$, $p<0.0001$) and haemoglobin ($r = -0.35$, $p<0.0001$). There was no significant correlation between PTH and FGF-23 ($r = 0.15$, $p=0.08$). Following correction for confounders in a multivariate model, age ($p <0.05$), eGFR ($p = 0.001$), CaxP ($p< 0.0001$) and hs-CRP($p< 0.0001$) remained significant independent predictors of FGF- 23 and explained 45% of the variance in the circulating levels. Patients with CKD 3 and 4 had significantly higher FGF-23 ($p< 0.002$), PTH ($p< 0.0001$), BAP ($p< 0.05$) and TRAP($p< 0.005$) compared to CKD 1 and 2.Univariate analysis between FGF-23 and bone metabolism showed significant negative association with BMD ($r = -0.28$, $p<0.005$) and BMC ($r = -0.24$, $p=0.008$) of the hip. No correlation was found between FGF-23 and the bone turnover markers. Significant correlations were observed between PTH and BAP ($r = 0.45$, $p<0.0001$) and TRAP($r = 0.37$, $p<0.0001$).Multivariate analysis showed that FGF- 23 ($p< 0.05$) and TRAP ($p=0.057$) were associated with hip BMC.

In summary, circulating FGF-23 levels were associated with inflammation, and also bone density – both of these associations suggest an important role for FGF-23 in CKD-MBD.

Poster Session

Thursday 23 April

13:30 – 14:30

CKD & Conservative Management

Moderator Dr Jeremy Levy

P38

Attitudes towards advance care planning, co-morbidity and symptom burden and expectations for the future in dialysis patients not suitable for renal transplantation.

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Background

For patients commencing dialysis, where transplantation is not feasible, dialysis remains palliative. Little is known about how these patients fare in terms of expectations, symptom burden when they start renal replacement therapy (RRT) and their views on advance care planning (ACP). Facilitating ACP is an important aspect in caring for patients with chronic disease and has been shown to improve end of care life. We carried out a qualitative interview study with patients who started chronic RRT in whom there was no prospect of renal transplantation.

Methods

All patients who started RRT and were not suitable for transplantation were included in the study which is ongoing. We collected demographic information, co-morbidity data using the Charlson Index, functional capacity using the Karnofsky Index, and devised tools for symptom assessment, QOL, support network and advance planning readiness.

Results

Over a 3 month period, we collected data on 21 patients. Male to female ratio 6:1. The average age was 68 years (range 57 to 86 years). The average Charlson Index was 3.2 indicating most patients were in the medium risk category. The average Karnofsky index at the time of starting RRT was 97.5. In the qualitative questions about quality of life and symptom burden patients often seemed to down play their symptoms and overestimate their functional status. The commonest symptom was tiredness, and overall the level of anxiety in these patients was low and the level of hope for the future high. Only a very small proportion had made any end of life plans, none had discussed their wishes with any member of the medical or nursing team. The majority of patients felt that they would not want to be resuscitated and would rather have palliative care than active management at the end of their life. All of the patients said that it has been very useful for them to discuss these issues and in follow up a significant proportion had discussed end of life issues with their families.

Conclusion

Older patients who start RRT often have a poor understanding of, and unrealistic expectations of RRT. They tend to over estimate their functional status and often under report symptoms because they feel that they should be stoical. The majority of patients seem prepared to go along with whatever plan is suggested to them by the doctor. End of life planning is uncommon and while patients valued the opportunity to discuss this they all admitted that they would never have brought he issue up with medical staff or their relatives. This study should help to encourage openness between staff and patients, aid communication and address issues that were formerly thought to be taboo.

P39

Quantifying the role of palliative medicine in end stage renal disease: use of at risk register

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Introduction: There is an increasing recognition of the need for good palliation of symptoms for those patients with non-malignant diseases . The Gold Standard Frameworks(GSF) Committee devised Prognostic Indicator Guidance(PIG) in November 2007 to aid identification of adult patients with advanced disease, in the last months or year of life, who are in need of supportive or palliative care.

Objectives: To use the GSF Prognostic Indicator Guidance to formulate a list of patients predicted to die within 1 year with ESRDand to analyse the data to establish the specificity and sensitivity of this register.Method .The surprise question suggested by the PIG from the GSF was used. “Would you be surprised if this patient were to die in the next 12 months? An at-risk register was then formed between 1st Feb ‘07 and 31st July ‘08 . Patients were characterised by their demographic details, dialysis vintage and modality as well as co-morbidities. Mortality rates were calculated and compared to those of patients not on the register, but were part of the dialysis-programme or followed up in the low-clearance clinics.Results 28(48%) out of 58 patients on the list died (32%). In comparison to the patients who died but not on the list (8%). These two group of patients did not have significant difference in their demographic details, dialysis vintage, dialysis-modality or co-morbidities . Identification of patients with chronic kidney disease and reduced life expectancy by this method appears to have a high sensitivity (67%) and specificity (78%). In particular the negative predictive value for mortality for those on the register appears to be very high (88.%), indicating the very low mortality among those not on the register.

Conclusions: Patients with chronic kidney disease and a reduced life expectancy can be adequately identified by a multidisciplinary team using the surprise trigger question with a relatively high sensitivity and specificity independent of traditional risk factors .The identification of these patients allows appropriate end of life care planning to begin in keeping with patients wishes and within published guidelines.

P40

Cognitive function in elderly dialysis patients: data from BOLDE (Broadening Options in Long-term Dialysis in the Elderly)

Lina Johansson[1], Edwina Brown[2], Tom Sensky[1], Nigel Beckett[1], Ken Farrington[3], Hugh Gallagher[4], Maria Da Silva-Gane[3], Mary Hickson[2]

[1]Imperial College London, London, United Kingdom, [2]Imperial College Kidney and Transplant Institute, London, United Kingdom, [3]Lister Hospital, Stevenage, United Kingdom, [4]St Helier Hospital, Carshalton, United Kingdom

The aims of part 1 of BOLDE are to determine the impact of dialysis modality on patient well-being in older PD and HD patients. Cognitive impairment (CI) has been shown to be more common in dialysis patients. We therefore measured CI and determined its relationship with dialysis duration, dialysis modality, education and depression.

HD patients were matched to PD patients ≥65 years by sex, age, ethnicity, length of time on dialysis and Index of Deprivation. Cognitive function was measured by Mini-Mental State Examination (MMSE) and Trail Making Test B (TMT-B) a measure of executive function. Other tests included HADS (Hospital Anxiety and Depression Score).

Data on 104 patients (52 matched pairs) have been analysed. Median age is 72 years (range 65-89); median dialysis duration 1.8 years (range 0.25-8.4 years). Mean MMSE is 27.6±2.25; 6 (2PD and 4HD) patients had a score <24. Mean TMT-B is 167.3±95.7 sec (range 68-604); normative value corrected for age and level of education would be 105.4 sec. TMT-B was not completed by 15 patients (11 HD and 4 PD); reasons included visual problems (5HD) and cognitive problems or refused (5HD, 1PD). Results in 48% patients completing TMT-B were outside the normal range.

Relationship between time on dialysis and MMSE score was assessed using multiple hierarchical regression analysis, with stepwise entry of age, gender, HD v PD, years of education, and depression scores in the first step, followed by entry of duration of dialysis in the second step. Dialysis duration made a significant independent contribution to MMSE scores (beta=-0.231, p=0.012), with significant contributions also from education (beta=0.308, p=0.001) and depression (beta=-0.219, p=0.018), the overall model accounting for 18% of the variance in MMSE scores. The analysis was repeated for TMT-B times; dialysis duration again made a significant contribution (beta=0.285, p=0.006), with education also contributing significantly (beta=-0.267, p=0.009), the overall model contributing 11% of the variance in TMT-B scores. These results confirm that CI is common in older dialysis patients with impairment of executive function in almost 50%. CI is not related to age, gender or dialysis modality. Dialysis duration, education and depression appear to have a significant relationship to measures of cognitive function.

P41

The relationship between measured and nurse-predicted quality of life in patients on renal replacement therapy.

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[1]Royal Liverpool University Hospital, Liverpool, United Kingdom, [2]University of Liverpool, Liverpool, United Kingdom

Introduction: Health-related quality of life (QoL) is important and is diminished in patients with end-stage renal failure. It is not routinely measured in clinical practice and it remains unclear to what extent health-care workers understand the QoL of their patients. We have therefore compared QoL measurements from dialysis patients with estimates of QoL from their primary nurses.

Methods: A cross-section of 110 pairs of patients and their primary nurses (83 haemodialysis patients (HD) and 27 peritoneal dialysis patients (PD)) were prospectively studied at the Royal Liverpool University Hospital in 2008. QoL was measured and estimated using the validated 36 item Short Form Health Survey (SF-36).

Results: The mean age of this population was 58.3±1.5y (20-82y). The measured QoL (physical component score 40.3±1.9, mental component score 44.3±1.6, total score 43.4±1.8) was significantly lower than that estimated by the nurses (physical component score 55.6±2.2, mental component score 58.7±2.1, total score 57.9±2.1) ($p<0.0005$). The greatest over-estimates of QoL were in the following domains: 'physical role limitations' (101%), 'general health perceptions' (65%) and 'mental health' (69%) ($p<0.0005$ for difference between measured and estimated QoL). Measured QoL was also significantly lower than that of a healthy age and sex matched historical control population (physical component score 71, mental component score 75, total score 75) ($p<0.0005$).

The differences in measured and estimated QoL were similar in both HD and PD sub-groups. Measured QoL did not correlate with haemoglobin or albumin concentration and did not differ between the following sub-groups: HD and PD, diabetics and non-diabetics, HD patients with a functioning fistula or graft and those without.

Conclusions: Patients on dialysis have a significantly reduced QoL compared with a healthy control population. Their QoL is consistently over-estimated by approximately 35% by their primary nurses. This would suggest that formal measurement of QoL should be performed routinely to improve our insight into this important clinical outcome.

P42

Do changes in renal function help predict illness trajectories in patients with advanced CKD on conservative pathways?

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[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom, [2]The Leicestershire Hospice, Leicester, United Kingdom

Background: A number of illness trajectories in the "end of life" period have emerged from different chronic disease populations. There is little evidence to suggest that these patterns apply in patients with advanced chronic kidney disease (CKD) who choose conservative therapy. Nephrologists need more evidence about survival times and better ways of identifying illness trajectories in these patients to permit effective recognition of the "end of life" period. We analysed changes in renal function over time to see if this could predict illness trajectory and help inform discussions regarding "end of life" care.

Methods: All current patients coded on the Nephrology (PROTON) database as "Advanced CKD for conservative therapy" on 1st February 2008 were identified. The list was checked with clinicians and members of the multi-professional team to minimise missed cases. Patient demographics and information related to eGFR at first nephrology review, eGFR at decision for conservative treatment and most recent eGFR were retrospectively collected. The length of time patients were known to renal services before and after the decision for conservative treatment was also calculated.

Results: 59 patients (25 male, 34 female) fulfilled the criteria for inclusion. Mean age was 81 and 25% were from an ethnic minority. The underlying renal disease was unknown in 54% and hypertension and diabetes contributed to a further 35% of cases. 61% were known by nephrologists for at least 1 year before they chose conservative therapy. The mean number of days between 1st contact and the decision for conservative treatment was 996. The mean change in eGFR of the cohort over that period was -1.96mls/min/1.73^2. The mean number of days between choosing a conservative treatment and the audit date was 391. The mean change in eGFR of the cohort over that period of time was +0.05mls/min/1.73^2. When plotting the individuals' changes in eGFR, it was clear that many were on a declining trajectory of renal function but seemed to stabilise or even improve after choosing supportive care. This is also shown by mean eGFR values at the three time points:-

First eGFR in mls/min/1.73^2	**Decision eGFR** in mls/min/1.73^2	**Latest eGFR** in mls/min/1.73^2
22.6 (SD 8.3)	**17.2** (SD 5.6)	**17.3** (SD 5.9)

Conclusion: The majority of patients who choose conservative therapy are well known to nephrology services. However, rates of decline in renal function do not seem to be a reliable way of distinguishing illness trajectories in patients who choose conservative therapy. Further work is needed to determine better ways to identify patients with the steepest decline in health which might include closer assessment of co-morbid conditions. This is essential as an accurate prediction of the illness trajectory permits patients to make rationale and timely decisions regarding their "end of life" care and preferred place of death.

P43

Depression and illness perceptions soon after dialysis initiation: differences between planned and unplanned starters.

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[1]Renal Unit, Lister Hospital, Stevenage, United Kingdom, [2]The Centre for Lifespan and Chronic Illness Research University of Hertfordshire, Hatfield, United Kingdom, [3]Renal Unit, Royal Free Hospital, London, United Kingdom, [4]Renal Unit, Addenbrooke's Hospital, Cambridge, United Kingdom

Introduction: The prevalence of depression at dialysis initiation is not fully appreciated. How individuals perceive their illness (illness representation) has been shown to influence psychological distress. This study investigated depression and illness representations in initiating dialysis patients, exploring differences between those with a planned and unplanned entry. Planned starters were defined as patients with known CKD who saw a nephrologist at least once within 3 months predialysis. Failed planned, crash-landers or later referrals were defined as unplanned, having never seen a nephrologist preadmission or no contact within the last 3 months.

Design: This is a cross sectional analysis of baseline data taken from an ongoing longitudinal, multi-centre study of a minimum of 150 incident dialysis patients. Depressive symptoms (Beck Depression Inventory, BDI) and illness perceptions (Revised Illness Perception Questionnaire) were assessed, in relation to clinical parameters and events, at a point soon after dialysis initiation and again 6 and 12 months later.

Results: The analysis consisted of 146 patients (107 planned, 39 unplanned, 119 HD, and 27 PD). The median dialysis vintage at the first assessment was 29.5 days (Inter Quartile Range IQR=37.5). Unplanned starters had significantly higher BDI scores (median=14.0 IQR=11.0) as compared to the planned (median=8.0 IQR=9.0, p=0.01). Depression (defined as BDI≥16) was more prevalent in the unplanned (44%), as compared to the planned (19%, p=0.005). Unplanned starters had weaker beliefs about the chronicity of ESRD (timeline, p=0.027), perceived their illness to be more unpredictable (cyclical timeline p=0.01), had greater emotional reaction (p=0.009) and, less understanding of their condition (illness coherence p=0.01). In regression analysis after controlling for gender, ethnicity, diabetes and cancer, age (p=0.02) and entry-path to dialysis, (p=0.01) significantly predicted BDI scores (R^2=0.102). In a second step, illness representations were added. Illness identity (p=0.001), consequences (p=0.001), and treatment control perceptions (p=0.047) predicted BDI scores (R^2 =0.392). Path to dialysis was no longer significant in this model, suggesting that illness representations mediate the relationship between entry-path and depression symptoms.

Conclusion: Unplanned starters experience more depressive symptoms compared to those with a planned dialysis initiation, which appears to be mediated by illness representations. This data highlights the importance of understanding personal illness beliefs in the aetiology of depression among initiating dialysis patients.

Acknowledgments: This study was supported by a joint British Renal Society-Kidney Research UK Fellowship

Poster Session

Wednesday 22 April

13:00 – 14:00

CKD & Cardiovascular Disease

Moderator Dr Robert MacTier

P44

Cardiovascular risk reduction strategies in Chronic Kidney Disease

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Background: Cardiovascular reduction is important management of chronic kidney disease. We assess the performance of the Wirral and Chester Renal services in achieving national risk reduction targets.

Method: Fifty consecutive inpatients with chronic kidney disease (CKD) stage 3 to 5 admitted under the care of the Wirral and Chester Renal services were included in this study. The study was prospective and data was collected on demographics, presenting symptoms, significant past history, blood pressure measurements, lipid profiles and urine protein measurements.

Results: Males comprised 60% of the study population and the mean age of the group was 66 years (range 22-88). 18 patients had CKD stage 3, 7 had CKD 4 and the remaining 25 patients were in CKD 5. The average systolic blood pressure was 134mmHg while the mean diastolic blood pressure was 76mmHg. Blood pressure management met NICE target criteria in 48% of our patients, including 7 of 14 patients with diabetes. 72% of patients with a previous history of cardiovascular, cerebrovascular or peripheral vascular disease were receiving antiplatelet agents. 48% of patients eligible for secondary prevention had statin therapy. 56% of patients with proteinuria were either on Angiotensin Converting Enzyme inhibitors or Angiotensin Receptor Blockers with 67% of patients with diabetes prescribed appropriate agents. Mean glycaemic control in 7 patients with diabetes was HbA1c of 7.5%. We identified 10% of our study population as active smokers.

Discussion: Management of cardiovascular risk factors is an area of significant importance in CKD. Our findings raise the need to renew our focus on appropriate cardiovascular risk reduction strategies for every individual patient with CKD, especially on smoking cessation, proteinuria management and secondary prevention. Patient education and a close collaboration with primary care would be crucial in achieving these objectives for the benefit of our patients.

P45

Chronic kidney disease; the association with cardiovascular disease in primary care.

Graham Baker, Philip El-Dalil, Indranil Dasgupta

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Introduction: Chronic kidney disease (CKD) affects 10% of the population, with a significant proportion progressing to ESRF and carries a high cardiovascular (CV) mortality. The development and progression of CKD is influenced by CV risk factors. The aim of this study was to identify the number of patients in primary care who suffer from CKD and CVD (hypertension [HTN], diabetes [DM], cerebrovascular disease [CVA], ischaemic heart disease [IHD], heart failure [HF] and peripheral vascular disease [PVD]) and to explore the association between these coexisting pathologies. The adequacy of management of CV risk factors was also evaluated.

Method: Data was collected from 2 General Practices using the EMIS database to identify patients with stages 3-5 CKD and patients on the CVD registers. Data were also collected on medication prescribed to treat HTN and dyslipidaemia, alongside a search for the latest; BP, HbA1c, total cholesterol and BMI for evaluation of patient management. These parameters were then compared with the recommended targets.

Results: The two practices served a total of 20,089 patients of which 547 were diagnosed with stages 3-5 CKD comprising 3% of the base population. In the CKD sample (n=547) the following CV co-morbidities were present; HTN 54%, IHD 32%, DM 26%, CVA 17 %, HF 12%, PVD 6%. The prevalence of these (except DM) was found to increase as the stage of CKD progressed and was statistically significant for PVD, HF and CVA ($p \leq 0.05$). Ninety percent of CKD patients were on at least 1 other CVD register. There were several inadequacies in the management of CV risk factors in CKD patients; 19% achieved a BP of < 130/80 and 58% ≤ 140/85. 49% of diabetics had an HbA1c <7%, 67% had a BMI >30, and 69% had a cholesterol of <5. Furthermore, 58% and 65% were prescribed statins and ACEi/ARBs respectively.

Conclusion: The results suggest significant under-diagnosis of CKD in the community. As 90% of CKD patients have other CV conditions, patients with these co-morbidities could be targeted for future screening initiatives. The number of CV co-morbidities increase with advancing CKD. The management of the CV risk factors was inadequate and need to be improved to slow progression of CKD and reduce CV mortality. This study lends support to introduction of screening for CKD in primary care. Acknowledgement of increased risk of CKD in CVD patients may allow earlier diagnosis and intervention.

P46

Elevated body mass index in advanced CKD patients: a large single centre study

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There has been a sharp rise in chronic kidney disease (CKD) rates that has paralleled the increase in the prevalence of obesity. CKD increases risk of cardiovascular disease (CVD), hospitalization and the development of ESRD. CKD has been reported to be more common in patients with high body mass index (BMI). Most of these studies involved patients with mild to moderate CKD (eGFR <60 ml/min/1.73m^2). Little is known of the prevalence of high BMI in patients with severe CKD (eGFR <30 ml/min/1.73m^2). This study assesses the prevalence of overweight and obesity in advanced CKD, and compares the prevalence of CVD risk factors and rate of CKD progression according to BMI.

We identified 210 patients with eGFR <30 ml/min/1.73m^2 but not on dialysis, attending the Low Clearance Clinic in our centre between 01/1996–12/2007. Data were extracted from electronic patient records. These included gender, age, ethnicity, eGFR, BMI, blood pressure (BP), smoking, lipid profile, diabetes, coronary artery disease (CAD), cerebrovascular disease, peripheral vascular disease; and use of antiplatelet, cholesterol-lowering, antidiabetic and antihypertensive agents. Patients were categorized according to BMI: Group 1. normal weight (18.5–24.9kg/m^2), Group 2. overweight (25–29.9kg/m^2) and Group 3. obese (≥30kg/m^2). Data analysis were done using StatsDirect statistical software version 2.6.5.

Overall the degree of CKD severity and age of patients were similar for the 3 BMI groups. The prevalence of overweight and obese patients was 32% and 44% respectively. BP (mean 140/78mmHg) was not different among all groups but more patients in Group 3 (44%) required >3 antihypertensives compared to Group1 (20%) and Group 2 (31%) (p=0.02). Diabetes and hypertension were more prevalent in the obese compared to those with lower BMI (p=0.002 and 0.03 respectively). Cigarette smoking was more common in Group 1 than other groups (p=0.003). Even though CAD was more prevalent with increasing BMI, it was not statistically significant (p=0.93). More patients in obese group were on statin (p=0.01). There was no significant difference in the rate of decline in kidney function across the 3 BMI groups over the preceeding 12 years.

High prevalence of overweight and obesity (76%) in our study population suggest a risk association between severe CKD and elevated BMI. There was a higher prevalence of CVD risk factors (diabetes, hypertension and dyslipidaemia) with increasing BMI but smoking was statistically significant in the normal weight group. The latter might be involved in the pathogenesis of the previously reported increased mortality in patients with normal weight commencing haemodialysis compared to overweight patients. Our study did not show a significant difference in the progression of CKD across BMI groups. The rate of CKD decline in the obese may have been circumvented by the group receiving more treatment (e.g. more antihypertensives and statin). CAD not being significant again could be because of more treatment for the obese group. A prospective study is needed to confirm these observations.

P47

Serum ADMA, SDMA, and Arginine levels: Prospective Study of the Relationships with Markers of Cardiovascular Dysfunction

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ADMA (endogenous inhibitor of NO synthase) predicts progression, cardiovascular (CV) complications and mortality in CKD. The roles of arginine (Arg) and SDMA (stereoisomer of ADMA) are less clear. We aimed to investigate the relationship between these factors and an extended suite of CV (largely functional) abnormalities, characteristic of CKD.

134 patients were recruited to a prospective study (46 CKD 4, 60 HD, 28 PD). Patients were well-matched for all general clinical and biochemical characteristics, as well as dialysis vintage (in the CKD 5 group). Advanced glycation end products (AGE) deposition within tissues was assessed by skin ultraviolet autofluoresence (AF) (AGE Reader®). Baroreflex sensitivity (BRS) was assessed by cross-correlation time-domain analysis of continuous digital artery waveform (Finometer®). Pulse wave velocity (PWV) was determined by applanation tonometry. OPG, fetuin, and hsCRP were measured using commercially available ELISA. Arg, ADMA, and SDMA were determined by liquid chromatography-mass spectrophotometry.

There were no associations between skin AF, or BRS, and Arg, ADMA or SDMA in this group. Both augmentation index (AIx) and augmentation pressure (AP) correlated with ADMA:SDMA ($r=0.33$, $p=0.001$; $r=0.33$, $p<0.001$ respectively), and negatively correlated with SDMA ($r=-0.22$, $p=0.02$; $r=-0.23$, $p<0.02$ respectively). The carotid-dorsalis pedis PWV (CD-PWV) relationships existed only within dialysis patients and related to treatment modality. In HD, baseline CD-PWV correlated with ADMA ($r=0.37$, $p=0.02$), and ADMA:SDMA ratio ($r=0.32$, $p=0.04$). In PD, CD-PWV negatively correlated with SDMA alone ($r=-0.58$, $p=0.01$). There were no significant relationships in the CKD 4 group.

Arterial stiffness is associated with reduced bioavailability of NO. This factor appears to have little effect on a number of the other CV abnormalities implicated in the high levels cardiovascular morbidity and mortality in this patient group. These data add important new information to our understanding of the pathophysiology of circulatory dysfunction in patients with late stage CKD.

P48

Patients with anti-neutrophil cytoplasm antibody associated vasculitis have an increased risk of cardiovascular disease

Matthew Morgan[1], Jennifer Turnbull[2], Umut Selamet[3], Peter Nightingale[4], Charles Ferro[4], Lorraine Harper[1]

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Objectives: To investigate the risk of cardiovascular disease (CVD) in patients with anti-neutrophil antibody associated vasculitis (ASV) and the risk factors for CVD in this group.

Introduction ASV is an autoimmune inflammatory disease causing chronic kidney disease (CKD) and associated with systemic inflammation. Both inflammation and CKD are recognised risk factors for CVD. Surrogate markers for CVD suggest there is an increased risk of CVD in ASV patients but no studies have looked at the incidence of CVD in ASV patients. The factors contributing to an increased risk of CVD in ASV patients have not been investigated. **Methods:** In this retrospective matched cohort study 113 patients with ANCA-associated vasculitis were matched 1:1 for renal function, age, gender, smoking, and previous cardiac history to patients with non-inflammatory CKD. Cardiovascular events including acute coronary syndrome, new angina, stroke or transient ischaemic attack, and clinically symptomatic peripheral vascular disease were recorded for both groups. Potential CVD risk factors were recorded in the ASV group; previous CVD events, renal function, serum cholesterol and C-reactive protein, hypertension, dialysis dependency, cumulative steroid dose, age, smoking history, diabetes and gender. **Results:** Median follow-up times were 3.6 years (interquartile range 2.6-6.8) for ASV and 4.2 (1.9-8.9) years for CKD. There were 23 CVD events in the ASV and 16 events in the CKD patients. Using Kaplan-Meier survival analysis the time to event was significantly shorter for the ASV group than the CKD group (median 1.8 vs 3.4 years, p=0.017). Cox-regression analysis showed a hazard ratio (HR) for ASV compared to CKD of 2.23 (95% confidence interval 1.1 to 4.4, p=0.017). Univariate analysis of risk factors was performed using the vasculitis cohort. The most strongly predictive factors were: pre-diagnosis cardiovascular disease HR 4 (95% CI 1.7 to 9.8); history of dialysis dependency HR 4.3 (1.5 to 10); Ever having smoked, HR 3.9 (1.5 to 10); older age HR 1.038 (1.006-1.072) /year; and remission eGFR HR 0.977 (0.957-0.998) /ml/min. **Conclusions:** Patients with ANCA-associated vasculitis have an increased risk of cardiovascular disease, with increased risk in those with pre-diagnosis cardiovascular disease, dialysis dependency, poor renal function at remission or a history of smoking. Cardiovascular risk should be aggressively managed in these patients.

P49

Post-dialysis mean arterial pressure is the best predictor of left ventricular hypertrophy in haemodialysis patients.

Philip Harvey[1], Ashley Holt[1], Hari Nair[1], Johann Nicholas[2], Indranil Dasgupta[1]

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Ninety percent of haemodialysis (HD) patients have hypertension yet less than 50% achieve the targets. Inadequately controlled hypertension is associated with left ventricular hypertrophy (LVH) and LVH is an independent predictor of cardiovascular mortality and sudden death in HD patients. The Renal Association Standards suggest 2 different BP targets for HD patients – pre-HD <140/90, post-HD <130/80. In this study, we aimed to assess which BP reading, pre or post HD, correlates with left ventricular mass index (LVMI), as a marker of LVH and a measure of long-term BP control taking into account other confounders of LVH in HD.

Of 648 patients with HD in 2 centres, those on HD <6 months, or history of significant CAD, or heart failure or valvular disease on echo were excluded. We also excluded all patients in whom appropriate M-mode study was not possible (n = 126). Of the 100 patients meeting the inclusion criteria, 35 were female, 65 Caucasian and 28 diabetic. Data on BP readings, antihypertensive medication, interdialytic weight gain, haemoglobin, phosphate, and PTH over preceding 3 months were collected and averaged for this analysis. All patients had M-mode echocardiogram and LVMI was calculated using the Penn Convention equation.

The mean pre-HD BP was 145/75 ± 21.5/13.6 and post-HD BP was 133/70 ± 22.0/11.8 mmHg; less than 50% patients achieved RA targets. The mean LVMI was 203.7g/m^2 ± 73.9g/m^2; 88% patients had LVH. On uni-variate analysis, mean pre and post HD systolic, diastolic and mean arterial (MAP) pressures, post-HD pulse pressure, and ethnicity significantly correlated with LVMI. However, on multiple regression analysis only mean post HD MAP correlated with LVMI ($p< 0.001$, $r=0.363$). The model included age, ethnicity, primary diagnosis, inter-dialytic weight gain, haemoglobin, phosphate, PTH, average BP, pulse pressure and use of RAS blocking agents.

In conclusion, in this study post-HD MAP was found to be the only predictor of LVH taking into account all putative causes of LVH in HD patients. We contend post-HD BP readings are more important than pre-HD BP in assessing BP control, and MAP as a measure of overall BP control is more important than either systolic and/ or diastolic BP and should be included in the recommended targets.

Poster Session

Thursday 23 April

13:30 – 14:30

Hypertension

Moderator Prof Alan Jardine

P50

High dose of bendroflumethiazide (BF2)- A risk factor for development of renal failure and electrolyte disturbance in general practice

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Diuretics are first line therapy in treatment of hypertension in people aged over 55 and in black population. BF2 is the commonest diuretic used in general practice and is available in 2.5mg and 5mg strengths. We decided to determine the efficacy and side effects of high dose (5 mg) BF2 in general practice.

Methods: We retrospectively analysed data over 12 months in our practice in all patients who had received at least one prescription of 5 mg BF2. Efficacy and adverse effects were noted. If drug was discontinued, reason for withdrawal was documented.

Results: 25 patients received 5 mg BF2 on repeat prescription and 1 new patient was started on treatment. 11 patients had significant improvement in their BP. BP did not improve in 6 patients and it actually increased in 4 patients. Data was not available for rest. 14 patients had their dose either changed or drug was completely stopped. 6 of these patients developed worsening renal failure, 1 had hyponateremia, one hypokalaemia, 3 were stopped due to lack of benefit, 1 had dizziness and data was missing for rest.

Conclusion: Higher dose BF2 is associated with significant risk of development of renal failure and electrolyte abnormalities, while improving BP control in less than 50% patients. Its use is not justified in general practice.

P51

Blood Pressure Control in a General Nephrology Clinic

Cathryn Robertson, Adnan Gebril, Julian Wright

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Background Good blood pressure control is a major factor in slowing the progression of CKD. Hypertension is also a major risk factor for cardiovascular disease which many renal patients will develop. The prescribing practice of renal physicians varies; we audited blood pressure control and antihypertensive prescriptions in the general nephrology clinic.

Methods All clinic letters were reviewed of patients who attended the general nephrology clinics of four renal physicians at Manchester Royal Infirmary in August 2008. Data was collected on eGFR, age, sex, blood pressure control, cause of CKD, antihypertensive medications and cardiovascular co-morbidity.

Results A total of 286 patients' clinic letters were reviewed. 92.3% of consultations were follow up clinic visits. In these letters blood pressure was documented in only 71.7% of cases. In 37.4% of clinic visits the patients was reviewed by the consultant. The clinics were made up of patients with a wide spectrum of renal disease: 19.7% of patients being in stage 2 CKD, 47.8% of patients were in CKD stage 3 with 22% being in stage 4 CKD.

Patient demographics were sex 56.3% male, mean age 61.8years, mean eGFR 46.1mls/min/m^2 and mean blood pressure138.7/74.8mmHg. Despite 22.5% of patients being diabetic, diabetic nephropathy was only recorded as the cause of CKD in 2.5% of patients. The cause of CKD was unknown in 40.3% of patients.

The mean blood pressure did not differ between the four consultants' patients however antihypertensive prescribing differed widely. Use of drugs affecting the renin-angiotensin system varied widely from 61.3-78.8% of patients dependent on their consultant as did prescriptions of alpha blockers (16.7-26%), beta blockers (25.8-39%) and calcium channel blockers (30.3-50%).

Cardiovascular co-morbidity was recorded in 26.1% of patients; prescriptions of aspirin (33.0%) and statins (48.8%) were recorded.

Conclusion In a diverse population of patients cared for in the general nephrology clinics overall blood pressure control did not differ between consultants but was higher than the UK Renal Association target of <130/80mmHg for patients with stable renal disease. There is differing antihypertensive prescribing practice in different consultant clinics. Increased emphasis should be placed on achieving improved blood pressure control in the general nephrology clinic; whether standardizing antihypertensive prescribing practice would improve blood pressure control is unknown.

P52

Spironolactone as an add-on treatment in resistant hypertension in patients with chronic kidney disease, its efficacy and safety.

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Background: Aldosterone antagonists provide significant additional blood pressure reduction when added to treatment regimens of patients with resistant hypertension independent of aldosterone levels. Hyperkalemia is uncommon, but can occur, and the risk increases in chronic kidney disease, diabetes, elderly patients and patients already receiving an angiotensin–converting enzyme inhibitor or angiotensin receptor blocker.

Aim: To determine the efficacy and safety of use of spironolactone in resistant hypertension in patients with chronic kidney disease.

Methods: We reviewed 20 consecutive patients attending a single nephrology clinic who were started on spironolactone as an add-on treatment for resistant hypertension in patients with chronic kidney disease stage 2 to 4. Resistant hypertension was defined as blood pressure that remained uncontrolled despite using at least 2-3 different anti-hypertensive medications in effective doses. Patients blood pressure, kidney function and serum electrolytes were monitored in an outpatient clinic and by the patients GP.

Results: 75% of subjects were male; mean age was 70.45 years; 40% were diabetic and 35% had renovascular disease. Most of them were initially started on 25 mg dose of spironolactone apart from 5 patients (2 were started on 12.5 mg and 3 on 50 mg). At the end of available follow-up, all patients were on the same dose, except one, whose dose was subsequently increased. Significant reduction in both systolic and diastolic blood pressure was found. At baseline mean systolic and diastolic blood pressure were 158 and 79 mm Hg. After 3 and 6 months of spironolactone treatment, BP was reduced to 139/71 mmHg (p value 0.0037 for systolic and 0.008 for diastolic blood pressure) and 136/72 mmHg (p=0.008 and 0.02). Serum potassium though rose significantly from their base line (3.8± 0.47mmol/l) but was still in the normal range (4.2 ± 0.4 at 1 month; 4.0 ±0.42 at 3 months; 4.14 ± 0.5mmol/l at 6 months). Serum creatinine at baseline was 164 ± 51µmol/l (equivalent to eGFR of 40 ±16 using MDRD formula) and 159 ± 46 µmol/l (at 3 months) and 168 ± 61µmol/l (at 6 months).Hence, kidney functions did not alter with spironolactone.

Conclusion: We conclude that spironolactone is a safe and effective drug in treating hypertension in CKD stage 2-4 and encourage its use in resistant hypertension.

P53

Hypertension and baseline creatinine predict pregnancy-associated loss of renal function

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INTRODUCTION AND AIMS: Pregnancy is associated with loss of renal function in some patients with chronic kidney disease. We aim to identify factors predictive of this to offer patients appropriate preconception counselling and obstetric management.

METHODS: Data from patients referred to our renal-obstetric clinic has been collected prospectively since 2004 as part of the United Kingdom Collaboration in Obstetrics and Renal Disease (UK-CORD). The rate of decline in renal function prior to conception was calculated by linear regression of 4-factor MDRD eGFR. At 6 months postpartum, patients with an eGFR below the lower 95% confidence interval predicted from the regression equation were defined as having Pregnancy-associated Accelerated Loss of Renal Function (PALRF). Continuous variables were compared by Student's t and Mann-Whitney U tests. Categorical variables were compared by Chi-squared and Fisher's Exact tests. Multivariate analyses were performed by linear or logistic regression.

RESULTS: Complete data was available on 27 patients from the Leicester cohort of UK-CORD; 6 had PALRF.PALRF was more common in patients receiving treatment for hypertension (83.3% vs 33.3%, OR=10, p=0.003). Diastolic blood pressure (DBP) was higher (81.0 vs 71.6 mmHg, p=0.009) prior to conception independent of blood pressure treatment. Receiver operating curve analysis identified 75mmHg as the optimum DBP predictive of PALRF (sensitivity 100%, specificity 57%, PPV 42%, NPV 100%). Serum creatinine prior to conception was higher in those going on to have PALRF (80.1 vs 110.6 mmHg, p=0.027). Estimated GFR was lower albeit not significant (78.8 vs 62.8 ml/min, p=0.077). Maternal age, proteinuria, gravidity and underlying kidney disease were not predictive of PALRF, nor interactive with the above associations.

CONCLUSIONS: Patients with more advanced renal excretory dysfunction or hypertension are more likely to have PALRF, even with relatively mild disease.

P54

Body composition and functional consequences of goal directed antihypertensive therapy in older people with chronic kidney disease

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Significant CKD is highly prevalent in the elderly. It is associated with changes in body composition, including hydration status, alteration in lean body mass and reduction in skeletal muscle function. These factors may be associated with worsening patient outcomes, having particular relevance for activities of daily living and falls propensity in older patients. Aggressive BP control is the cornerstone of CKD 3/4 management. As part of a prospective study of the effects of aggressive goal directed antihypertensive therapy (AHT) in elderly CKD patients we studied prospective changes in body composition and skeletal muscle function at baseline and after introduction and escalation of AHT agents.

We recruited 50 non-diabetic CKD 3/4 patients, over the age of 70 years; as well as non-CKD hypertensive control subjects. Recruitment was predominantly from primary care. Antihypertensives were withdrawn and discontinued for 2 weeks before the initial visit. At visit 1 patients underwent whole body DEXA, multisegmental, multifrequency bioimpedance analysis (BIA) and performed a Timed get Up and Go (TUG) test. Patients then restarted AHT to achieve target BP (130/80). At visit 2, four weeks later, BIA body composition analysis and TUG testing were repeated.

Baseline BIA and DEXA measurements of soft lean mass (SLM) and body fat mass (BFM) were highly correlated (r^2 =0.91, p<0.0001; r^2=0.94, p<0.0001). After drug reintroduction; mean BP was 126/69, mean BIA measured intra-& extra-cellular water were lower (0.4±1.5, p=0.037; 0.2±0.7L; p=0.035), BFM was unchanged, SLM reduced by a mean of 0.84±2.35kg (p=0.031), bone mineral reduced by 0.05±0.14kg (p=0.044) but there was no change in TUG function from baseline.

Aggressive management of hypertension in elderly patients is associated with a BIA measured reduction in SLM but did not seem to effect directed active functional assessment. Further prospective assessment of the global effects of AHT in elderly patients with CKD is ongoing.

P55

Blood Pressure and Proteinuria in the CKD Population: How Attained Levels Associate with Risk of Mortality

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Introduction

In this study we examine the association between systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg) and urinary protein to creatinine ratio (PCR, mg/mmol) on mortality in a CKD population over a 20-year period.

Methods

A retrospective analysis of data recorded on the electronic patient record (EPR) of the Glasgow Royal Infirmary Renal Unit was performed. The EPR contains routine clinical and laboratory data prospectively recorded for all patients seen by the renal services in this hospital from 31/07/1984 from the point of first clinical contact onwards. All patients registered on the EPR between 31/07/1984 and 11/01/2005 were examined. All patients with a creatinine clearance (CrCl) of <50mL/min (derived by Cockcroft & Gault formula) and progressive renal dysfunction were identified. Initial data and data averaged over the predialysis follow-up period were obtained for a range of variables including SBP, DBP and PCR. Univariate and multivariate analysis were performed with death as primary endpoint.

Results

1739 patients fulfilled our inclusion criteria with mean follow-up time of 78.3 months. 581/1739 (33.4%) died during follow-up. Univariate analysis demonstrated a significant association ($p<0.05$) between earlier mortality and primary renal diagnosis, increased age, calcium phosphate product, urate, eosinophil count, ferritin, HbA1C, urinary sodium, C-reactive protein, white cell count, initial and average SBP, average DBP, initial and average PCR and decreased initial CrCl and serum albumin.

Multivariate Cox regression analysis demonstrated an independent ($p<0.05$) association between earlier mortality and average SBP and initial and average PCR, urate, white cell count, creatinine clearance, ferritin, primary renal diagnosis and age. SBP of 120-129mmHg and 130-139mmHg were associated with lowest mortality (HR 0.29 and 0.31 compared with >170mmHg group, $p<0.001$). PCR of <100 was associated with lowest mortality with a stepwise increase in risk of early mortality for each 100 unit increase in PCR thereafter (HR 2.2 in PCR=100-199 group to 7.8 in PCR>500 group, $p<0.001$). On multivariate analysis averaged DBP was not associated with mortality.

Conclusion

SBP <119mmHg and levels of SBP >139mmHg and urinary PCR >100, as measured in routine clinical practice, have a particularly strong independent association with risk of earlier mortality in patients with progressive CKD. Risk of mortality escalates as achieved levels of SBP and PCR increasingly differ from the optimum levels described.

P56

Are different ethnic groups with hypertension and chronic kidney disease getting a fair deal in primary care?

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Introduction: The effect of ethnicity on the prevalence of hypertension and CKD has not been studied in the UK. Previous studies in a primary care setting have shown that the prevalence of diabetes mellitus (DM) and CKD are significantly different between ethnic groups. This study was undertaken to determine if similar disparities and care pathway variables exist between different ethnic groups with hypertension and CKD.

Methods: Routine audit data was collected from 146 GP surgeries in 3 Primary Care Trusts (City and Hackney, Newham and Tower Hamlets). 75,183 adults from a total population of 829,710 were identified as having a diagnostic Read Code for hypertension. 69,430 (92.3%) adults had a valid recording of ethnicity and 41,408 (55.1%) had an eGFR measurement during the study. Ethnicity was simplified into 5 groups – white (n=29,091), black (n=17,740), south Asian (n=16,783), other (n=5,198), unknown (n=618). Only whites, blacks and south Asians are included for analysis. Data was collected between 1/1/07 and 31/3/08. The 4 variable MDRD equation was used to generate eGFR values. Analysis is based on the last value recorded during the study period.

Results: The overall population prevalence of hypertension was 9.1%. Using Greater London Authority population data for East London, the prevalence of hypertension was 19.1% in blacks compared to 10.6% in whites and 15.8% in south Asians. The crude prevalence of CKD 3-5 in hypertensives was 21.5%. After adjusting for age, sex, clustering by practice, systolic BP and cholesterol, CKD 3-5 was more prevalent in black patients compared to whites and south Asians (OR 1.10, 95% CI 1.01-1.21). In hypertensives with CKD 3-5, systolic and diastolic BP (mmHg) were higher in black patients (139/78) compared to whites (136/74) and south Asians (134/75) - $p<0.001$ for SBP and DBP. South Asian patients were more likely to receive ACE-I, lipid lowering agents and aspirin compared to white and black groups ($p<0.001$) whereas black patients were more likely to receive α blockers, thiazides and calcium channel blockers ($p<0.001$).

Conclusion: Significant differences exist between ethnicities in this hypertensive cohort with concomitant CKD 3-5. Based on best practice guidelines, there are opportunities to improve the management of these conditions and reduce disparities between ethnicities.

P57

Salt reduction for blood pressure in diabetes

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Background

High blood pressure is the greatest predictor for heart attacks and strokes and tight control of blood pressure reduces the progression of diabetic kidney disease. Habitual consumption of salt increases blood pressure yet there is currently no consensus in restricting salt intake in diabetic patients. This study was performed as an attempt to answer this question.

Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library*, issue 3 2008), MEDLINE (1966 – Oct Week 1 2008) and EMBASE (1980 to 2008 Week 36) for randomised controlled trials of salt reduction in individuals with type 1 and type 2 diabetes. Trials were independently assessed by two authors and differences were resolved by discussion with a third independent author. Mean effect sizes were calculated using both fixed and random effects model.

Results

Six trials in individuals with type 1 diabetes (n=75) and 7 trails in individuals with type 2 diabetes (n=158) were included in the review. In individuals with type 1 diabetes there was a median reduction in urinary sodium was 203mmol/24h (11.9g/day). The mean reduction in blood pressure was -7.11 mmHg (95% CI -9.13, -5.10) for systolic and -3.13 mmHg (95% CI -4.28, -1.98) for diastolic. In individuals with type 2 diabetes, there was a median reduction in urinary sodium was 130mmol/24h (7.6g/day). The mean reduction in blood pressure was -6.90 mmHg (95% CI -9.84, -3.95) for systolic and -2.87mmHg (95% CI -4.39, -1.35) for diastolic. In all studies (n=245) median salt reduction was 145mmol/L and mean reduction in blood pressure was -7 mmHg (95% CI –8.71 to –5.38) for systolic and -3 mmHg (95% CI –3.16 to –2.24) for diastolic.

Conclusions

This study shows a large change in blood pressure with salt restriction, similar to single drug therapy, in both type 1 and type 2 diabetes and therefore all diabetics should be recommended to reduce salt intake to lower blood pressure and both cardiovascular disease and nephropathy.

Poster Session

Tuesday 21 April

11:30 – 12:30

Haemodialysis 1

Moderator Dr Chris McIntyre

P58

An audit of haemodialysis transport provision in a single centre and recommendations to improve its efficiency

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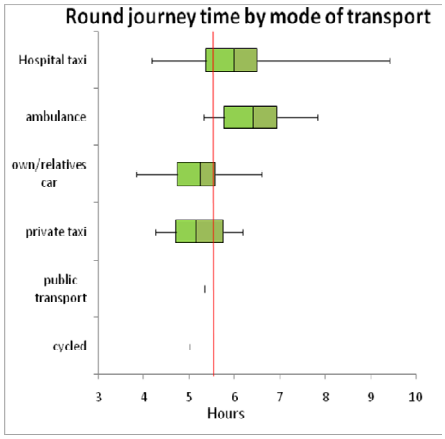
Background: To ensure equitable access to patients on haemodialysis (HD) then they should not be disadvantaged by where they live. Many patients consider transport as the most important factor determining their choice of dialysis modality. The national service framework and renal association clinical practice guidelines define that ≥75% of patients should travel for 30 minutes or less from home to the HD unit, with 30 minutes or less waiting time before starting or after finishing dialysis. This constitutes a 5.5 hour door-to-door time for a 3.5 hour HD session. We aimed to identify ways of improving the efficiency of HD transport by conducting an audit in a single centre dialysing 330 patients. Methods: Single page patient questionnaire for a single return journey detailing postcode, mode of transport, time asked to be ready, time collected from home and time returned home.

Results: 170 questionnaires sent, 106 returned. 45% achieved the target door-to-door time of 5.5 hours. This reduced to just 20% if the time at home waiting for transport to arrive was included. Crucially those travelling by independent means achieved the shortest times. Patients live up to 40 miles from the HD unit.



Conclusions: 1). Our centre failed to achieve the guideline standards for HD transport times. 2) Encouraging independent transport is one way to improve our performance 3) Improving communication between the patient and the transport provider may reduce redundant waiting time.

Relevance: This is the first such audit in our centre and has formed the basis of our action plan to redesign our HD transport service.

P59

Excellence in evolution! Forty years of renal replacement therapy in Northern Ireland.

Michael Quinn, A Peter Maxwell, Peter McNamee

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Background: Renal transplantation is recognised as the optimal form of therapy for patients suffering from end-stage renal disease (ESRD). Continued improvement in one year graft survival has been achieved principally by the prevention of early rejection. In the initial decade of the Northern Ireland renal replacement therapy (RRT) patient entry to the RRT programme was contingent on suitability for transplantation. More recently the majority of patients accepted for RRT are unfit for transplantation. Despite relaxing the acceptance criteria for RRT we have observed a substantial improvement in non-transplant ESRD patient survival.

Aims: To identify those factors which have changed significantly over the last forty years and to assess their impact on the survival of patients starting RRT in Northern Ireland

Design: Retrospective review of all patients commencing RRT in a single UK region.

Methods: Demographic details of all 4004 patients entering the renal replacement therapy programme between 1st January 1967 and 30th September 2008 were reviewed. Clinical data and outcomes were available from a prospectively recorded database. The study period was divided into 4 eras (A-1967-1979, B-1980-1989, C-1990-1999, D-2000-2009) to assess changes over time.

Results: The significant changes that have occurred include an increase in the number of patients starting RRT in each era, increased mean patient age and a fall in the proportion of RRT patients being transplanted. Compared to the first era (1967-1979) those patients who were transplanted in later eras have spent a longer period on dialysis therapy prior to their first transplant. Transplant provides significant survival advantage which has continued to increase in the most recent era. The most striking change however has been the improved survival of non-transplanted patients. The 5-year patient survival, calculated by adjusted Cox-proportional hazards model, has increased significantly when comparing the latest Era D (HR 0.21 [0.15-0.28]) to the earliest Era A (Ref 1.00).

Conclusions: Over four decades major changes have occurred in the management of ESRD patients. The changes have resulted in improved 5 year survival in non-transplanted dialysis patients despite their increasing age and complexity.

P60

Patient survival and the effects of ethnicity in haemodialysis patients with CVAs

Albert Power, Neill Duncan, Seema Singh, Michelle Willicombe, Damien Ashby, Tom Cairns, David Taube

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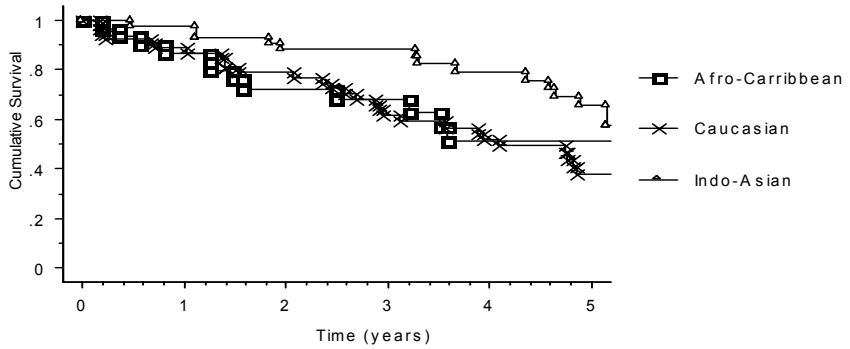
Background. This is the only large European study on the effect of stroke on haemodialysis patient survival in a large urban population.

Methods. We performed a retrospective analysis of 1,278 patients receiving maintenance haemodialysis at our centre. Stroke was defined by a clinical event explained by radiological findings on CT and/or MR.

Results. There were 121 strokes in 108 patients (72 male, age 62.4±12.1 years) with 5843 patient years of follow-up. The overall incidence of stroke was 20.7 / 1000 patient years. 95/121 (67%) were ischaemic and 43/121 (31%) haemorrhagic. Cumulative survival was 73% at 3 years, 52% at 5 years. Diabetes and gender had no effect on survival. Pre-event spKt/V>1.6 compared to spKt/V 1.2-1.6 was associated with better survival (logrank p<0.001). Indo-Asian patients survived significantly longer compared with Caucasians or Afro-Caribbeans: 65% 5-year survival vs 37% and 51% respectively (logrank p<0.02).

Conclusion. Stroke is 8 times more common in haemodialysis patients than the prevalent UK population. The mechanisms underlying the favourable impact of Indo-Asian ethnicity on survival after stroke are unclear and possibly relate to social support networks. Prospective studies on this and risk factor modification are required to reduce the impact of stroke in the haemodialysis population.



P61

Subclinical deficiency of Vitamin K status in chronic kidney disease

Kieran Voong, Maximilian Nerlander, Domonic Harrington, Padmini Manghat, Geeta Hampson, David Goldsmith, Martin Shearer

Kings Healthcare Partners, London, United Kingdom

Vitamin K serves as an essential cofactor for the enzyme gamma glutamyl carboxylase (GGC). This enzyme is pivotal to the formation of Gla residues on a small family of proteins, which can then bind calcium. Matrix Gla Protein (MGP) - one of these vitamin K dependent proteins (VKDP) - requires carboxylation to become active. MGP is an important inhibitor of vascular calcification (VC), which we know to be greatly increased in chronic kidney disease (CKD), and which can be increased by Warfarin (inhibiting Vitamin K dependent carboxylation). We wanted to examine the Vitamin K status of a group of stable patients with CKD (stages 1 through IV) to ascertain the extent of sub-clinical abnormalities of Vitamin K activity

Prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) is a sensitive and specific marker of Vitamin K activity and status. Serum PIVKA-II was determined using a MAb (C4B6) to PIVKA-II in an ELISA format. The C4B6 MAb used in this assay is conformation-specific such that in the presence of calcium ions it binds undercarboxylated species of prothrombin and does not cross-react with fully carboxylated native prothrombin. Results expressed as arbitrary units (Au)/ mL, where 1 AU is equivalent to 1 mg of multiple PIVKA-II species. Upper limit of the reference range and the lower limit of detection for PIVKA-II in adults was < 0.2 AU/mL (~200 ng/mL). The inter-assay coefficient of variation was <10%. We studied 141 ambulant patients (83 M and 58 F) (age mean [SD] 53 [14] years). 41 patients had CKD 1,2 (eGFR >60 ml/min; mean [SD] 78 [14]), 59 patients had CKD 3 (eGFR 30-59 ml/min; mean [SD] 45 [8]) and 45 patients had CKD 4 (eGFR <30 ml/min; mean [SD] 21[4]).

There were 12 patients with abnormal PIVKA-II levels. Four of these patients had PIVKA-II levels > 10 Au/mL - all four of these patients were anticoagulated with warfarin. Eight other non-anticoagulated patients had abnormal PIVKA-II levels (ranging from 0.247 to 1.226 Au/mL with GFR ranges 17 – 39 mls/min.

These results indicate that low-level vitamin K functional abnormalities can be detected in healthy ambulant CKD stage 1 - IV patients, but they are rare (8 out of 137 non-warfarinised patients). Such patients might be at enhanced risk for vascular calcification and this phenomenon should now be examined in a larger cohort with simultaneous quantification of vascular disease involvement.

P62

Atrial Natriuretic peptide (ANP) kinetics in high flux dialysis and its use a marker of volume status in Haemodialysis patients

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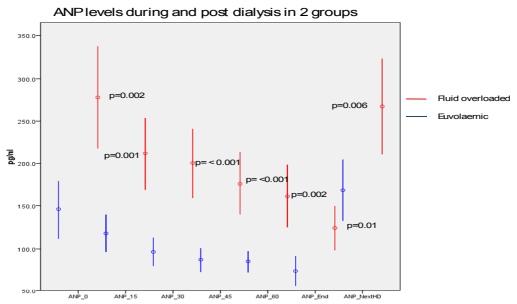
Lister Hospital, Stevenage, Herts, United Kingdom

ANP is released by the atria in response to volume overload. Chronic fluid overload in dialysis patients is associated with increased concentrations of ANP which fall significantly at the end of the dialysis due to clearance by high flux dialysis itself as well as decreased synthesis. We designed this study to evaluate the use of ANP in larger group of patients who are categorised to either being euvolaemic or fluid overloaded by clinical parameters.

60 chronic haemodialysis patients undergoing thrice weekly high flux HD were studied. Serum ANP was measured at start and then at 15 minute intervals for 60 minutes and then at the end of dialysis and another sample at the start of their next dialysis. Relative blood volume monitoring and whole body Bioimpedance were also performed.

29 patients were categorised as euvolaemic and 31 as being fluid overloaded. The mean serum ANP at the start of dialysis was 146 (SE 20) pg/ml in the euvolaemic patients and 278 (SE 36) in patients who were fluid overloaded (p= 0.003). ANP levels continued to fall during dialysis. Pre-dialysis ANP levels correlated strongly with the presence of pulmonary crackles (r = 0.445, p = <0.001) but not with elevated JVP or peripheral oedema. In 33 patients, the rate of fall in ANP during the first hour could be described by single pool exponential decay. In remaining patients, the kinetics were more complex. Single pool behaviour did not correlate with hydration status but those displaying single pool decay had higher predialysis ANP levels, 264 (SE 34) vs. 154 (SE 25) pg/ml (p=0.014). In these patients, it is likely that the dialysis clearance of ANP dominates the kinetics in the first hour of HD.

This study suggests that measurement of ANP can provide useful information regarding the volume status of dialysis patients.



P63

Demographic factors associated with stroke in haemodialysis patients - A large single-centre study

Albert Power, Neill Duncan, Michelle Willicombe, Seema Singh, Damien Ashby, Tom Cairns, David Taube

Imperial College Kidney and Transplant Institute, West London Renal and Transplant Centre, Hammersmith Hospital, DuCane Road, London, United Kingdom

Background. The age-adjusted incidence of stroke is 5-10 times greater in dialysis patients compared to the general population, and it is more likely to be haemorrhagic. Limited studies to date derive associated demographic factors from non-European (US & Japanese) populations.

Methods. We retrospectively analysed 1,278 patients receiving maintenance haemodialysis at our centre. Stroke was defined by a clinical event explained by radiological findings on CT and/or MR.

Results. We identified 121 strokes (CVAs) in 108 patients established (>90 days) on haemodialysis with 5843 patient years of follow-up. The incidence of CVA was 20.7 / 1000 patient years. 95/121 (67%) were ischaemic. Stroke was associated with a higher prevalence of diabetes (58% vs 41%, $p<0.001$), a diagnosis of hypertension (68% vs 55%, $p=0.01$), and ischaemic heart disease (42% vs 32%, $p=0.03$). Stroke was significantly associated with diabetic nephropathy as cause of end-stage renal disease (49% vs 31%, $p<0.001$). The association with hypertensive nephropathy or polycystic kidney disease was not significant.

Multivariate analysis (Cox regression) showed that age and diabetes was very strongly associated with a higher risk of stroke ($p<0.001$). Male sex and a diagnosis of hypertension were also associated with a greater stroke risk ($p<0.01$).

Conclusions. Stroke on haemodialysis is more common in older, male patients and in the presence of diabetes and hypertension. It is more frequent than in the general population, with a high prevalence of haemorrhage (33%). Prospective studies of the effects of blood pressure reduction and glycaemic control on stroke incidence in haemodialysis patients are required.

P64

Validation of longitudinal vector analysis of body composition with Deuterium dilution in haemodialysis patients.

Cian Chan[1], Kay B Tan[2], Christina Lam[5], Christopher McIntyre[3,4], Simon J Davies[2,5]

[1]Nottingham University Hospital NHS Trust, Nottingham, UK, [2]Institute for Science and Technology in Medicine, Keele University., Stoke on Trent, UK, [3]Derby City General Hospital, Derby, UK, [4]The University of Nottingham, Nottingham, UK, [5]University Hospital of North Staffordshire, Stoke on Trent, UK

INTRODUCTION AND AIMS: The use of conventional bioimpedance analysis (BIA) to assess body composition in renal failure is limited by the assumption that tissue hydration is normal. Bioimpedance vector analysis (BIVA) has been advocated as it avoids assumptions, using vector length (VL) and phase angle (θ) to measure tissue hydration. Currently there is a lack of longitudinal clinical validation with gold standard methods such as Deuterium dilution, TBW_D. The aim of the study is to compare changes in fluid status of HD patients over 12 months using single frequency BIVA with those obtained from absolute TBW_D measurement from Deuterium dilution using breath analysis by Flowing Afterglow Mass Spectrometer (Transpectra, UK) combined with conventional BIA.

METHODS: 59 HD patients were studied (17 female, mean age 58.4±16.1 years, mean BMI 27± 5.4). Body composition was determined post-dialysis. Resistance (R) and reactance (Xc) at 50 kHz normalised for body height (H) were plotted (H^2/Xc versus H^2/R) from which VL ($\propto$ to hydration) and θ (increased angle $\propto$ to overhydration). Comorbidity was stratified according to the validated Stoke Comorbidity Index. Normal reference values for H^2/Xc and H^2/R, standardised for age, sex and BMI were obtained from Bosy-Westphal et al (Am J Clin Nutr. 2005)

RESULTS: At baseline VL was not different to predicted values whereas θ was increased and H^2/R decreased ($p<0.001$). The higher the comorbidity the greater was the θ ($p=0.001$) and VL ($p= 0.037$, ANOVA). θ correlated with fluid excess as measured by Deuterium dilution, $R=0.42$, $p<0.001$ at baseline and $R=0.33$, $p<0.033$ at 12 months such that each degree of θ equated to 1kg of fluid excess. Longitudinal changes of VL and θ were not statistically significant but in directional agreement with the significant changes seen in TBW_D. VL lengthening was associated with a greater increase in TBW_D (mean 2.9kg) than VL shortening, (1.4 kg, $p=0.06$); patients in whom VL shortening was seen were more obese (BMI 29 v 25, $p<0.01$). In individuals with extreme changes in body composition BIVA was compatible with TBW_D.

CONCLUSIONS: Vector analysis at baseline indicates patients were overhydrated and muscle wasted proportional to their comorbidity in keeping with gold standard methods. BIVA is less sensitive to longitudinal changes in body composition and interpretation of changes in VL must take BMI and weight change into account.

P65

Socioeconomic status, ethnicity and regional variations in incidence of Renal Replacement Therapy in England and Wales

Udaya Udayaraj[1,5], Yoav Ben-Shlomo[2], Paul Roderick[3], Anna Casula[1], David Ansell[1], Charles Tomson[4,1], Fergus Caskey[4]

[1]UK Renal Registry, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom, [3]University of Southampton, Southampton, United Kingdom, [4]Southmead Hospital, Bristol, United Kingdom, [5]Churchill Hospital, Oxford, United Kingdom

Background: Regional variation in incidence of renal replacement therapy (RRT) in England and Wales (E&W) have been described but is not known if these variations can be fully explained by the socio-demographic characteristics of the population.

Methods: The age-gender standardised RRT rates in 2007 in Primary Care Trusts (PCT)/Local Health Boards (LHB) in E&W and Government Office regions (GOR) in England were calculated. We examined the association between area level deprivation (using Townsend index) and age-gender standardised RRT rate ratio in quintiles of PCT/LHBs ranked by their Townsend score in each region. The association between proportion of non-Whites in a PCT/LHBs and age-gender standardised rate ratio was examined using scatter plots and Spearman's correlation tests. Multivariable Poisson regression was used to examine the regional variations in age-gender standardised RRT rates controlling for PCT/LHB Townsend score and ethnic composition (% non-Whites) of PCT/LHBs in the regions.

Results: Increasing social deprivation was associated with higher RRT incidence rates in all regions. There was a correlation between RRT rates and proportion of non-Whites living in an area in England (correlation coefficient = 0.60, $p<0.0001$) but not in Wales. There were significant regional variations in the age-gender standardised RRT incidence rate ratio (95 %CI) with higher rate ratios in London 1.50 (1.41, 1.59), West Midlands 1.08 (1.01, 1.17), Wales 1.26 (1.15, 1.39) and lower rate ratios in North West England 0.81 (0.74, 0.87) and Yorkshire and Humberside 0.87 (0.79, 0.95). In Poisson regression analysis, adjusting for social deprivation and the proportion of non-Whites in the population abolished the high RRT rate ratio observed in London and West Midlands while RRT rate ratio remained higher in Wales (1.38, 95 %CI 1.22, 1.57) and lower in North West England (0.82, 95 %CI 0.74, 0.93) and Yorkshire and Humberside (0.86, 95% CI 0.77, 0.98)

Conclusions: Age, gender, ethnic composition of the population and area level social deprivation are important determinants of the need for RRT. However these factors only partly explain the regional variations in RRT incidence in E&W. The high incidence of RRT in Wales and the lower incidence in North West England and Yorkshire and Humberside warrant further study.

Poster Session

Wednesday 22 April

13:00 – 14:00

CKD 2

Moderator Dr Neeraj Dhaun

P66

Achieving 'NICE' blood pressure target was associated with lower microalbuminuria in diabetic patients with chronic kidney disease; a study in a general practice in the Northwest

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[1]Royal Liverpool University Hospital, Liverpool, Merseyside, United Kingdom, [2]Abercromby Health Centre, Liverpool, Merseyside, United Kingdom, [3]Aintree University Hospital, Liverpool, Merseyside, United Kingdom

Introduction: The prevalence of diabetic patients with chronic kidney disease (CKD) in the UK is rising rapidly. NICE (The National Institute for Clinical Excellence, UK) has set out guidelines for management and referral of patients with CKD. Many of these patients with early CKD stage 1-3 are managed in the general practice (GP). Majority of these patients do not progress to end stage renal disease but do have increased risks of cardiovascular disease (CVD). Optimal management of the risk factors including microalbuminuria reduces the risk of progression of CKD. We aim to study the prevalence of stage 3 CKD in patients with diabetes and evaluate their management in a GP according to the NICE guidelines. **Method:** A retrospective study of all diabetics in a GP practice in the north west of England was performed in 2008. Electronic data on demographics, CKD staging, blood pressure (BP) control, urine albumin creatinine ratio (ACR), lipid profile, HbA1C, anaemia, and the usage of aspirin, statin and anti-hypertensive medication were collected and analysed. **Results and discussion:** The total GP population was 6220 patients and 275 had diabetes (4.4%). Majority were type 2 diabetics (n=259, 94%) and 6% were type 1 diabetic. Thirty nine of these diabetic patients (14%) have stage 3 CKD. Their mean systolic BP was 132.38 ± 17 mm Hg and mean diastolic BP was 69 ± 9 mm Hg. The median Hb was 12.1 gm/dl (7.5-17), median cholesterol 3.5 mmol/l (2.5-5.2), median HbA1C 6.5 (5.2-12.7), median eGFR 47 (31-58) and median ACR was 3.4 (0.4-282). Among them, 85 % (33/39) patients were on statin, 82% (32/39) patients were on ACEI or ARB and 79% (31/39) patients were on aspirin. Systolic BP was above 130 mm Hg in 59% patients. The mean ACR in patients with SBP < 130 was 2 ±2.65, SBP between 130 -139 mm Hg was 17 ± 14.8 and SBP > 140 mm Hg was 38 ±32.4**. Conclusion:** There is a high prevalence of CKD 3 in diabetic population studied in a GP. Microalbuminuria is lower in those achieving the NICE target systolic BP control < 130 mm Hg. However, just below 50% achieved this target BP control. There is scope for improvement and achieving the NICE targets in the management of diabetic patents with CKD 3. A well designed prospective study would help to evaluate the outcome of these cardiovascular protective measures in diabetic patients with early CKD in primary care.

P67

Fatigue in Patients with Chronic Kidney Disease Stage 3-5 is Significant and Associates with Excessive Daytime Sleepiness but Not with Renal Disease Severity

TM Muniraju[1], Julia Newton[2], Ashley Brown[2], David Jones[2], Neil Sheerin[2,1]

[1]Renal Unit, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [2]Newcastle University, Newcastle upon Tyne, United Kingdom

It is recognised that uraemia is associated with many diverse symptoms. Fatigue is frequently reported by patients with chronic kidney disease (CKD). Here we quantify impact of fatigue, its associations and relationships in patients with CKD stages 3-5.

Methods: Consecutive patients (CKD stage 3-5) and matched controls completed symptom assessment tools. Fatigue was measured using the Fatigue Impact Scale (FIS), psychological distress by Hospital Anxiety and Depression Scale, autonomic symptom burden by the Composite Autonomic Symptom Scale (COMPASS), excessive daytime sleepiness by Epworth Sleepiness Scale (ESS) and co-morbidity using the Charlson Score. In all patients biochemical and haematological parameters were reviewed.

Results: 95 patients returned the completed symptom assessment tools (return rate 95/134;71%). Compared to controls, early renal disease patients were significantly more fatigued $p<0.0001$. When we considered the severity of potential biological associates of fatigue, the renal group experienced significantly more daytime sleepiness $p<0.0004$ and symptoms suggestive of autonomic dysfunction, these autonomic symptoms predominantly arose in response to standing. As has been seen in other disease increasing fatigue was associated with both increased daytime sleepiness and a higher prevalence of autonomic symptoms particularly related to standing ($p<0.0001;r2>0.2$). Increasing fatigue was unrelated to eGFR ($p=0.7;r2=0.002$) or comorbidity.

Conclusion: CKD is increasingly considered a global epidemic. This study has shown in a large well characterised cohort with early renal disease that the symptom of fatigue is a significant problem in this patient group and is comparable to that experienced by patients with other chronic diseases. Fatigue in CKD is associated with excessive daytime somnolence but is unrelated to the severity of the underlying chronic disease, measured by conventional parameters of disease severity.

P68

Leakage of potassium (K^+) and other molecules from cells in patients with chronic kidney disease (CKD)

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Royal Liverpool University Hospital NHS Trust Liverpool, Liverpool, United Kingdom

Introduction and hypothesis: Hyperkalemia is a life threatening electrolyte abnormality and common in patients with CKD. Spurious rise (cell leakage) in serum K^+ can be quite variable, either related to delay in centrifugation and or storage at 4^0C. We tested the hypothesis that stage of CKD, its aetiology or medications might influence the leakage of K^+ and other molecules (Mg, PO4, Cl , HCO3, Urea and Creatinine) from cell membranes.

Patients and Methods: We recruited 77 CKD patients (mean age 62, range 30 to 87 years, 40 male 37 female), mean GFR was 46, range 10 to 121 ml/min. Lithium Heparin samples were collected and analysed for urea and electrolytes at time zero, and after storage at 4^0C for 6 and 20 hours (h) respectively.

Results: There was a significant rise in K^+ at 6h (mean change +0.96, range -0.1 to +2.6 mmol/L) and at 20h (mean change +3.42, range 1.3 to 6.3 mmol/L). This rise was independent of CKD stage (mean change in K^+ was +0.7 ,+1.0 ,+1.0,+1.2 and +0.9 mmol/L in CKD 1,2,3,4 and 5 respectively at 6h).This rise in K^+ was independent of the cause of CKD (mean rise in K^+ after 6h was +0.97,+0.94,+1.0,+1.0 mmol/L in CKD secondary to diabetes, hypertension, glomerulonephritis and other causes respectively).The patients on ACE Inhibitors(ACEI) and Angiotensin Receptor Blockers (ARB) had higher K^+ at 0h (mean 4.6 mmol/L in comparison with mean of 4.25 mmol/L in patients not on them; p=0.026). Patients on ACEI/ARB also had higher leakage of K^+ at 6h (mean rise +1.1, range 0.1 to 2.6 mmol/L in comparison with mean rise of +0.79, range -0.1 to +1.8 mmol/L in those not on them; p value = 0.01). We also noted a fall in serum Na^+ (mean fall -0.5, range -6.0 to +6.0 mmol/L) at 6h.This fall was independent of both CKD stage and rise in K^+. Mg, PO4, Cl, HCO3, Urea and Creatinine did not change significantly with time in all stages of CKD.

Conclusions: This is the first reported study to investigate the relationship between CKD stage and cell leakage of nephrologically relevant molecules. K^+ rises significantly with time and this applies to all stages of CKD. It is therefore important to document the time of sample taking and any delay in laboratory processing to allow differentiations between hyperkalemia and pseudohyperkalemia. The rise in K^+ is greater in patients on ACEI/ARB but can not be attributed to the stage of CKD or its cause.

P69

Ethnic differences in renal referral patterns following national CKD guidelines.

Matt Hall[1], Emma Wilkinson[2], Peter Choi[4], Ken Farrington[3], Andrew Frankel[4], Roger Greenwood[3], Liz Lightstone[4], Paul Roderick[5], Joanna Willis[4], John Feehally[1], Gurch Randhawa[2]

[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom, [2]Institute for Health Research, University of Bedfordshire, Luton, United Kingdom, [3]Lister Renal Unit, North Herts NHS Trust, Stevenage, United Kingdom, [4]Imperial College Healthcare NHS Trust, Hammersmith Campus, London, United Kingdom, [5]Healthcare Research Unit, Southampton General Hospital, Southampton, United States

BACKGROUND: Amongst patients with type 2 diabetes mellitus (T2DM) in the UK, Indo-Asian (IA) ethnicity is associated with a 10-fold increased risk of developing end stage kidney disease (ESRD) compared to White Europeans (WE). Interventions to guide the management of kidney disease in the UK were introduced between 2005 and 2006; (a) publication of the National Service Framework (NSF), (b) publication of the UK CKD guidelines (RCP/Renal Association), (c) automated reporting of eGFR and (d) introduction of CKD parameter targets in primary care Quality Outcome Frameworks. Ethnicity was highlighted as a risk factor for progressive renal disease in the NSF We investigated the impact of these interventions on the status of IA and WE patients with T2DM at the time of referral to specialist renal services.

METHODS: Demographic and clinical data were collected from records of all patients with T2DM referred to specialist renal clinics in 4 UK centres in 2004 and 2007. Ethnicity was self-reported at clinics according to 2001 UK census ethnicity classification.

RESULTS: In 2007 30% fewer patients with T2DM were seen than in 2004 (251 vs 361) as a result of fewer patients with earlier CKD (stages 1 to 3) being accepted for review (150 vs 252). The reduction in total referrals was more marked for IA patients than WE (36% vs 25%, p=0.023). Of those accepted for review in 2007, IA patients were younger than WE (67.6 vs 70.5 years, p=0.035) with a longer history of T2DM (14.4 vs 11.4 years, p=0.014). Although preserved eGFR (>60ml/min) was more common in IA patients than WE (18% vs 3%, p<0.001) and had less advanced renal dysfunction (eGFR 42.8 vs 32.7ml/min, p<0.001), IA had more microvascular disease (45% vs 30%, p=0.015) and macrovascular disease (61% vs 46%, p=0.015), even after adjustment for age, sex and duration of diagnosed DM. Proteinuria, BP control and HbA1c were equivalent between ethnic cohorts. No differences in prescription of renoprotective, cardioprotective or hypertensive medication were found after adjusting for age, sex and cardiovascular comorbidity. A greater proportion of IA and WE patients were receiving treatment in 2007 than in 2004.

CONCLUSIONS: UK guidelines have led to a reduction in patients with T2DM attending renal clinics, particularly amongst IA patients. More patients received protective therapy at the time of referral, supporting success in transfer of early CKD management to primary care. We found increased prevalence of microvascular and macrovascular disease amongst IA, despite being younger. Prospective studies to evaluate the effect of these guidelines on rates of CKD progression and ESRD between ethnic groups are required.

P70

Differences in important risk factors support the division of CKD stage 3 into A & B

Natasha McIntyre[1], Richard Fluck[1], Christopher McIntyre[1,2], Maarten Taal[1]

[1]Department of Renal Medicine, Derby Hospitals NHS Trust, Derby, United Kingdom, [2]Department of Vascular Medicine, The University of Nottingham, Derby, United Kingdom

Introduction and aims: Evidence suggests that the risk of cardiovascular events, mortality and complications related to CKD increase significantly when the GFR falls below 45 mLs/min. In England, recent guidance from the National Institute for Health and Clinical Excellence (NICE) for the management of early CKD recommended the sub-classification of CKD stage 3 into 3A (45-59 L/min/1.73m^2) and 3B (30-44 mL/min/1.73m^2).

Methods: We studied 300 patients, recruited from primary care practices, to evaluate differences with respect to risk factors and clinical variables. Each participant underwent clinical assessment and serum as well as urine tests were performed. Albumin to creatinine ratio (ACR) and protein to creatinine ratio (PCR) were measured on three consecutive early morning urine specimens. Carotid to femoral arterial pulse wave velocity (PWV) was measured with a Vicorder™ device. Skin autofluorescence (AF), a measure of skin Advanced Glycation Endproduct (AGE) deposition that has been identified as a marker of cumulative metabolic stress, was assessed using the left forearm. Participants were divided into stages 3A (N=204) or 3B (N=57) for analysis

Results: Significant differences were observed between the groups with respect to urine ACR (P=<0.000), urine PCR (P=0.017), uric acid (P=<0.000), age (P=0.001), skin AF (P=0.017), serum potassium (P=0.017), bicarbonate (P=0.018) and haemoglobin (P=0.019). No significant differences were seen in blood pressure (diastolic or systolic), pulse wave velocity, deprivation score, waist to hip ratio, BMI, glucose, calcium phosphate or cholesterol. A small difference in albumin was of borderline significance (P=0.052).

Conclusions: Our results show significant differences in many of the risk factors associated with CKD complications, between CKD stage 3A and B. This confirms that division of stage 3 into A and B is clinically useful for identifying higher risk patients who may benefit from interventions to reduce renal and cardiovascular risk.

P71

Impact of latent TB in CKD Patients: accelerated decline of GFR in Diabetic Nephropathy

Catherine Lane[1], Anthony Ashcroft[2], Rosmarin Caryn[1], Graham Bothamley[2], Magdi M. Yaqoob[1], Stanley L-S Fan[1]

[1]Royal London Hospital, London, United Kingdom, [2]Homerton Hospital, London, United Kingdom

Introduction QuantiFERON-TB Gold (QF) detects IFN-γ made in response to specific TB antigens and may denote latent infection. We investigated if we could predict QF positivity in patients attending an inner city hospital and if this parameter affected the rate of renal function decline.

Methods QFs were performed on 96 CKD patients not on dialysis with any cause of chronic kidney disease. None was symptomatic of TB. We collected patient demographics, clinical and laboratory parameters. We calculated the rate of GFR (MDRD) decline.

Results QF positivity was found in 42% and age ($p<0.02$) but not ethnicity was predictive. QF result did not predict changes in rate of renal function decline when all causes of renal failure were examined. However, decline was significantly greater in QF positive diabetics (n=16) vs QF negative diabetics (n=19, $p<0.05$). PCR, ACE/A2RB use, CRP, vit D levels and presenting GFR did not differ significantly.

Comparison of characteristics of QuantiFERON positive and negative groups

	QF Positive	**QF Negative**	Signif.
Number	40	56	-
Age (y)	69.5	62	P<0.02
Ethnicity white/asian/black/other	0.45/0.30/0.22/0.05	0.45/0.36/0.12/0.07	NS
Prop. Diabetic Nephropathy	0.45	0.35	-
BP (mmHg)	138/77	137/76	NS
Presenting GFR all cause (ml/min)	32.7	36.0	NS
Presenting GFR Diabetics (ml/min)	28.0	32.0	NS
ΔGFR all cause (ml/min/yr)	-1.77	-0.71	NS
ΔGFR diabetics (ml/min/yr)	-4.42	0.500	P<0.05
PCR (mg/mmol)	282	250	NS
ACE/A2RB use	0.70	0.67	NS
Serum 25-Vit D (nmol/L)	36.6	31.0	NS
CRP (mg/L)	16.4	13.5	NS
No. on immunosuppressants	0	6	

Conclusion Age but not Ethnicity predicted QF positivity. Diabetic patients are at greater risk of TB and co-infection may accelerate renal decline through TIN. Our results are supportive; QF positivity correlates with a more rapid decline of GFR. If this data is confirmed in larger studies, a therapeutic trial of TB therapy in QF +ve, diabetic nephropaths is merited.

P72

Micro and Macrovascular complications of Diabetic non-nephropathy versus patients with Diabetic Nephropathy

Jamal Al Wakeel[1], Abdulkareem Al Suwaida[1], Arthur Isnani[1], Ali Al Harbi[2]

[1]King Khalid University Hospital-King Saud University, Riyadh, Saudi Arabia, [2]Security Forces Hospital, Riyadh, Saudi Arabia

Objective: To highlight the impact of nephropathy on microvascular and macrovascular complications among Type 2 diabetics.

Methods: A hospital-based retrospective study of 1,952 Type 2 diabetic patients followed-up from January 1989 to December 2004 at Security Forces Hospital, Riyadh, Saudi Arabia was reviewed. Study group was divided into the nephropathy (DN) and the non-nephropathy diabetic group (NND).

Results: Of 1952 patients, 626 patients (32.1%) had nephropathy (GFR<60 ml/min and/or SCr >130 umol/L and or persistent positive proteinuria for 2 years) and 1326 (67.9%) without nephropathy. Mean age at enrollment for all patients was 58.39 ± 14.2 years and mean duration of diabetes of 10.41 ± 7.45 years. Age at onset of diabetes was significantly older in nephropathy group (51.5 ± 12.3 vs. 46.4 ± 12.7 years, $p<0.0001$). Patients who had nephropathy had longer duration of diabetes compared to non-nephropathy group (15.4 ± 7.5 vs. 8.1 ± 6.2 years, $p<0.0001$). Complications were significantly more prevalent among the nephropathy group; such as background retinopathy (DN=22.4% vs. NND=6.3%, $p<0.0001$), proliferative retinopathy (DN=11.7% vs. NND=2.3%, $p<0.0001$), neuropathy (DN=24.9% vs. NND=8.4%, $p<0.0001$), acute coronary syndrome (DN=36.1% vs. NND=17%, $p<0.0001$), Myocardial infarction (DN=24.1% vs. NND=9.7%, $p<0.0001$) and stroke (DN=17.6% vs. NND=7%, $p<0.0001$). The development of persistent proteinuria and progressive decline in GFR significantly increased the propensity of developing macrovascular complications such as acute coronary syndrome (34.5% before nephropathy to 65.5% after onset of nephropathy, $p<0.0001$), MI (29.8% before and 70.2% after nephropathy, $p<0.0001$) and stroke (29.1% before and 70.9% after nephropathy, $p<0.0001$). Mortality rate from complicated diabetes significantly increased from 5.7% to 13.7% upon onset of nephropathy. ($p=0.0001$)

Conclusion: Diabetic Nephropathy is associated with higher prevalence of associated diabetic complications and increases the mortality rate from diabetes. Miicrovascular complications are significantly magnified with onset of nephropathy.

Poster Session

Thursday 23 April

13:30 – 14:30

Haemodialysis 3

Moderator Dr Pearl Pai

P73

Is it the end of the line for home based dialysis treatment in inner city regions?

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Introduction

The development of the various forms of Peritoneal Dialysis (PD) has enabled a considerable expansion of home based dialysis treatment previously limited by the cost, high spatial requirements and complexity of home based haemodialysis treatment.

Objectives

To assess the factors that determine suitability for home based dialysis treatment.

Method

A retrospective audit by a large inner city hospital was taken on 200 consecutive pre-dialysis home assessment visits to patients considered medically suitable for home based treatment. The audit was assessed using the following variables, household size, and household composition, housing type, housing condition, accessibility, and public health factors.

Results

Significant constraints in housing supply and deterioration in housing conditions were identified. No accommodation suitable to facilitate the spatial and installation demands of Home haemodialysis was identified. Only 41% of houses suitable for provision to support even the relatively low spatial demands of PD was identified. There was a very low success rate in re-housing patients to dialysis suitable accommodation. Of the few patients (n=6) re-housed to dialysis suitable accommodation, none subsequently went on to home based treatment. An increasing reluctance by patients to undertake self care therapy was identified.

Conclusion

The continued viability of home based dialysis treatment is dependent on the one element that health providers have absolutely no control, the supply of suitable housing. This study has highlighted that there is a considerable and increasing shortage of such housing even to support the low spatial demands of PD.

This has negative implications for the survival of Home based dialysis treatment as the dominant form of UK renal replacement therapy, and would appear to indicate that the Governments targets to substantially increase Home haemodialysis provision are completely unattainable in socially deprived inner city areas.

P74

A study of beta blocker usage in chronic haemodialysis patients.

Muhammad Shahed Ahmed, K Rafalia, P Pai

Royal Liverpool University Hospital, Liverpool, Merseyside, United Kingdom

Introduction: Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular (CV) mortality and cardiac arrhythmia is one of the leading causes of sudden death. In this retrospective study, we have examined the blood pressure (BP) control and calculated the potential scope of using BB in a cohort of haemodialysis (HD) patients.

Method: We analysed the computer records of 176 patients dialysing in a single HD centre. Patient demography, medications, pre and post dialysis systolic BP (SBP) and diastolic BP (DBP) were recorded. We also recorded all available echocardiogram (ECHO) findings of group of patients' dialysing in the afternoon shift.

Results: Among a total of 176 patients, M: F ratio 103:73 and 36/176 (20 %) was diabetic. Mean pre SBP was 142 ± 30 mm Hg and post HD SBP was 131±27 mm Hg. Only 76/176 (43%) patients were taking BB including atenolol (25/76, 33%), bisoprolol (35/76, 42%) and metoprolol (8/76, 10.5%). Among 100 patients not taking a BB, 52/100 (52%) were taking other anti hypertensive agents (p = 0.19) including ACE inhibitors (28/52, 54%), calcium channel blockers (25/ 52, 48%) and doxazosin (15/52, 29%) either as single agent or combination therapy. In addition, 77/176 (43.70%) were taking aspirin, 85/176 (48 %) were on statin. There was no significant BP difference in patients with or without BB usage, mostly as combination therapy (Pre HD SBP with BB was146 ± 30 and without BB is140 ± 28, p value 0.14). We were able to retrieve the ECHO report of 23 out of the 48 patients dialysing in afternoon shift. Among them, 50 % patients had variable degree of LV impairment; 43 % (14/32) patients had pulmonary hypertension (PHT). Patients who are on BB, 38% of them had features of LVH on ECHO compare to 50% without BB (p = 0.89).

onclusion: In this study, less than 50% of our HD patients were on a BB although many more patients were on other anti-hypertensive combinations. Atenolol, a hydrophilic BB was used in 33% patients. In theory, the lipophilic BB which penetrates the central nervous system indirectly mediates an increase in vagal tone and decreases sudden cardiac arrhythmia[1]. The reason why many of the HD patients were not on BB is beyond the scope of this study. However, there is potential scope of using BB in more HD patients. A randomized control trial is urgently required to assess the long term outcome of using BB in CKD and dialysis patients. Reference: [1]Furgeson SB et al. Semin Dial. 2008 Jan-Feb;21(1):43-8.

P75

Successful decolonisation of MRSA in Haemodialysis patients-a 12 month cohort study

Muhammad Shahed Ahmed, Y Shah, K Pitcher, M Heaton, J Davies, Mathew Howse

Royal Liverpool University Hospital, Liverpool, United Kingdom

Introduction: Infection is the second leading cause of death in patients on haemodialysis. Methicillin-resistant staphylococcus aureus (MRSA) strains cause serious nosocomial infections and approximately 20% of S. aureus isolates in Europe are reported as methicillin-resistant.[1] MRSA skin colonisation may be a prelude to MRSA bacteraemia. We studied the effect of MRSA screening and decolonisation programme in a cohort of patients dialysing in a single unit.

Methods: A new MRSA infection screening and decolonisation programme has been adopted in our dialysis unit in Feb 2008. We monitored monthly incidence of MRSA colonisation and kept records of successful decolonisation. The site of positive swab, time of decolonisation, any contributing factor and co-morbidity data were also recorded.

Results and discussion: Among a total of 176 patients dialysing in the unit, 32 patients had total 35 episodes of MRSA colonisation in 10 months. Male: female ratio was 27:8, 7/32 were diabetic. In 8/35 episodes, wound swab was positive. Rest were positive from standard nasal, throat and groin swab. None had bacteraemia. Contributory factors in MRSA infection included an in-patient stay in 11/35 patients and immunosuppressive medication in 6/35 patients. The average monthly incidence of MRSA colonisation was 2 per 100 patients on haemodialysis. Of the 31 available results, 26/31 (84%) had successful decolonisation and only 5/31 (16%) had persistent colonisation.

Conclusion: Our study highlights the importance of screening programme to identify positive cases promptly and also confirms the success of decolonisation programme. However, as MRSA bacteraemia rate was low, the effect of the screening policy on MRSA bacteraemia is not shown in this study and requires long term follow up. Reference: [1]P. C. Appelbaum. Clinical Microbiology and Infection. Volume 12 Issue s2, Pages 3 – 10.

P76

Tackling Haemodialysis associated bacteraemia

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Royal Preston Hospital, Preston, Lancashire, United Kingdom

Bacteraemia accounts for most antibiotic starts, hospital admissions and tunnelled-line loss in the haemodialysis population. We have audited bacteraemia for five years at a hub and five satellite Units. Infection rates are based on a census taken on the first two days of each month. In November 2006 we started a trial and increased the number of antimicrobial line locks (Taurolock). In April 2008 following an audit we instituted a protocol to remove all temporary lines before or on day 5 and all lines and venflons from patients transferred from peripheral hospitals or intensive care units on arrival. From early 2008, there was an effort to improve infection control protocols and blood culture technique.

Number of infections per 100 patient months

Access Type	Oct 03 – Sep 06	Oct 06 – Mar 07	Apr 07 – Sep 07	Oct 07 – Mar 08	Apr 08– Sep 08	**Population 1st Sep 08**
Temporary	67	130	150	120	0	**0**
Tunnelled	15	13	13	7	4.7	**61**
Fistulae	1.5	1.14	0.6	0.35	0.25	**332**
Grafts	3.1	4.76	7.6	1.4	1.7	**9**

Absolute number of blood cultures, positive cultures and antibiotic starts

	Oct 06–Mar07	Apr–Sep 07	Oct 07 – Mar 08	Apr–Sep 08
Blood Cultures	401	452	345	186
IV antibiotics	73	69	40	30
All Positive BC)	73	77	49	25
Coag Neg Staph	50	32	14	6
Other Gram Pos	6	18	12	4
MRSA	2	3	3	0
MSSA	10	14	13	6
Gram negative	19	20	12	10
Mean HD Patients	319	361	386	398

The data show a progressive reduction in the number of patients with symptoms warranting blood culture and the number of positive results across all types of vascular access despite a progressive increase in the number of patients on dialysis.

P77

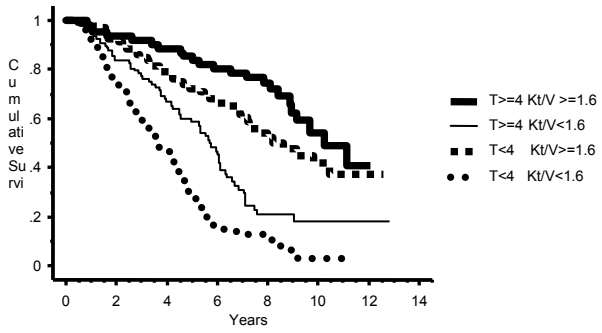
Dialysis hours have a significant effect on patient survival irrespective of Kt/V

Seema Singh, Neill Duncan, Albert Power, Tom Cairns, Andy Palmer, Megan Griffith, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

Background: Previous retrospective studies have shown a relationship between urea clearance and survival. HEMO demonstrated no survival advantage to standard versus high Kt/V, but highlighted the confounding effect of V. Method: Data on 451 incident patients >90d from 1/1996 – 12/2001 were followed to 12/2008. Our institution's target was for Kt/V >= 1.4 throughout this period without a ceiling dose. Average T derived from monthly prescriptions. Dry weights at start of dialysis correlated with average monthly Kt/V throughout the period of study. Patient survival was censored for change in modality and transfer to another centre and was correlated with average T and Kt/V over the period of study.

Results: All patient survival to 5 yrs was 56.5% [numbers at risk 170] and to 10 yrs was 26.3% [nar 26]. Kt/V correlated with dry weight at start of dialysis [R=0.4]. Patients were then stratified into groups with Kt/V <1.6 and Kt/V >=1.6. These groups were then subgrouped by T <4hrs and T>=4hrs.



Patients with Kt/V>=1.6 who achieved this adequacy with T >=4hrs had survival advantage at 5yrs 85.2% [nar 50] versus 72.3% [nar 50] [logrank p=0.05]. Patients with Kt/V<1.6 who achieved this adequacy with T >=4hrs had a survival advantage at 5yrs of 58.6% [nar 41] versus 29.4% [nar 29] [logrank p=0.0001]. Conclusion: Kt/V is strongly related to dry weight which is a surrogate for V. Irrespective of Kt/V <1.6, T has a dramatic effect on survival. This data will form the basis for a prospective randomised control study of high and low T.

P78

Unexplained haemolysis following haemodialysis in Northern Ireland

Michael Quinn[1], Brendan O'Brien[2], A Peter Maxwell[1], J Henry Brown[1]

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Introduction

Haemolysis is an extremely rare but potentially serious complication associated with the provision of haemodialysis. We report a recent cluster of 10 cases which have occurred in 4 of Northern Ireland's 6 dialysis units.

Method

An incident team was established by the Department of Health, Social Services and Public Safety (DHSSPS) to investigate the cases. Information letters were sent to all GP's and haemodialysis patients providing advice and details of a 24 hour advice line. Both industry and independent analysis was undertaken of the haemodialysis equipment used. A database was developed to act as a central repository of collated details of the identified cases. Following a review of the relevant case notes the incident team met to agree a case definition.

Results

Following the identification of an index case on the 11th of September 2008, a total of ten episodes of haemolysis have been reported. The patients had an average age of 57 years (range 44 to 82). Eight of the patients were male.

The ten cases have presented with varied symptoms but all had evidence, either clinical or laboratory, of haemolysis temporally related to an episode of haemodialysis. One case occurred in a patient with an AV fistula, the remaining affected individuals receive dialysis through tunnelled venous catheters. Four of the ten patients have been seriously ill presenting with acute pancreatitis and gross haemolysis. The remainder had a constellation of symptoms which included nausea, vomiting, haematuria, abdominal pain and headache. All patients had become acutely hypertensive during the preceding episode of haemodialysis. Review of the medications delivered and dialysis consumables used has not demonstrated a common link.

Conclusions

Despite all investigations to date no cause for the episodes of haemolysis has yet been identified. The nephrology community remains vigilant for further cases.

P79

The Epidemiology of Methicillin Resistant Staphylococcus Aureus Bacteraemia amongst patients receiving dialysis in England during 2007: a joint report of the Renal Registry and the Health Protection Agency.

Richard Fluck[1,4], Jennie Wilson[2], Ruth Blackburn[2], John Davies[2], Donal O'Donoghue[3], Charles Tomson[4]

[1]Derby City General Hospital, Derby, United Kingdom, [2]Health Protection Agency, England, United Kingdom, [3]Department of Health, England, United Kingdom, [4]UK Renal Registry, Bristol, United Kingdom

INTRODUCTION AND AIMS: It has been reported that ~8% of all episodes of Methicillin Resistant *Staphylococcus aureus* (MRSA) bacteraemia in the UK occur in patients with established renal failure (ERF) receiving dialysis [UK Renal Registry 8th Annual Report 2005] . The use of catheters for access to the circulation for haemodialysis is associated with increased risk of bacteraemia and consequent mortality and morbidity.

METHODS: Reporting of all MRSA bacteraemia (MRSAB) to the Health Protection Agency has been mandatory in England since 2001. From April 2007, all Renal centres in England provided additional data on patients with MRSAB using a secure web-based system. Data were recorded on modality of treatment, the type of vascular access and the use of venous catheters in the previous 28 days.

RESULTS: From April 2007 until March 2008 196 MRSAB were reported in patients receiving dialysis for established renal failure, of which 8 were duplicates. 4448 MRSAB were reported in England over the same period, indicating that 4.2% of all cases occur in dialysis patients. Additional data from the renal centre were available in 92/188 (49%). All 92 were on haemodialysis at the time of the bacteraemia. Of those 69 (75%) were using venous catheters, the majority tunneled lines (n=55, 59.8%), and 2 other cases had used venous catheters in the previous 28 days. The relative risk of MRSAB is about 100 fold higher for a dialysis patient in comparison to the general population and 8 fold higher for a patient using a catheter in comparison to a fistula. There was variation between renal centres in the rate of infection. The mean rate for all patients was 0.92 ±0.85 episodes/ 100 prevalent dialysis patients/year with a range of 0-3.28.In comparison with previous registry reports, the absolute numbers of reported MRSAB has fallen by approximately 62% from 2004

CONCLUSIONS: These data demonstrate that dialysis patients are at increased risk of MRSAB, and that this is closely associated with the use of venous catheters. The rate of MRSAB is falling substantially within the prevalent dialysis population, but with variation in performance between centres.

Poster Session

Wednesday 22 April

13:00 – 14:00

Miscellaneous 2

Moderator Dr Mick Kumwenda

P80

Prediction of renal functional outcome after revascularization with magnetic resonance imaging in atherosclerotic renovascular disease

Constantina Chrysochou[1], Ching Cheung[1], David L Buckley[2], Philip A Kalra[1]

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Renal functional outcomes after revascularization are unpredictable and many previous studies have shown that improvement will only occur in about 25% of patients; predicting which patients fall into this category can be very difficult. A pilot study suggested that kidneys with a larger parenchymal volume (PV) to single kidney GFR (SK-GFR) ratio were more likely to show renal improvement. Using a prospective case control study, the primary objective was to validate the hypothesis of whether the volume: GFR ratio (i.e. proportionality of PV: SK-GFR) is able to predict a patient's response to revascularization.

Methods

Using a power calculation, 35 patients and 15 control patients (suspected renovascular disease i.e. hypertension and CKD, but no evidence of renal artery stenosis) are to be recruited to confirm the reliability of this predictive test. 3D renal volumes were obtained on a 3.0 T Philips Achieva MR System using a phased-array body coil for signal reception. Kidney volumes were calculated manually with GraphPad using the voxel-count method applied to coronal MR images. Isotopic SK-GFR was calculated using ^{51}Cr-EDTA clearance and ^{99m}Tc-DMSA scintigraphy at baseline and 4 months follow up. Individual improvement was regarded as >1ml/min ± >15% post-revascularization in that kidney.

Results

22 patients undergoing revascularization and 12 control subjects have been recruited to date. Mean (SD) age of the group is 64 (12) years, 70% male, 95% hypertensive, 50% ischemic heart disease at baseline, mean eGFR 45.8 (22)ml/min. In 26 kidneys with complete follow up data, Responder kidneys had a PV: SK-GFR ratio on average 4 times greater than any of the control kidneys ($p=0.002$). Interestingly, contralateral kidneys with a large pre-revascularization PV: SK-GFR also manifested an improvement in renal function post procedure. Kidneys which showed an increase in renal function post revascularization also displayed a corresponding increase in renal volume

Conclusion

In this prospective study, patients with a larger PV to SK-GFR ratio in relation to a normal kidney are more likely to improve post renal revascularization and are postulated to have a 'hibernating parenchyma'. This method may allow appropriate selection of those patients most likely to benefit from revascularization procedures, and will also reduce the likelihood of those who will not benefit of being exposed to the risks associated with interventional procedures.

P81

Cyclosporin Induced Headache Due To Intracranial Hypertension

James Burton[1,2], Rakesh Patel[1], Sunil Daga[1], Bahar Arsalanizadeh[1], Nigel Brunskill[1,2]

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Case One: A 21-year-old woman with immune complex mediated glomerulonephritis (GN) associated with hypocomplementaemic urticarial vasculitis was initially treated with prednisolone and mycophenolate which was changed to cyclosporin when the rash and arthritis returned six months later. After four months she presented with a progressive generalised headache, blurred vision and vomiting. She was normotensive, had no focal neurology but fundoscopy revealed bilateral papilloedema. Cyclosporin levels were within therapeutic range. Opening cerebrospinal fluid pressure following lumbar puncture was >40cm. Magnetic resonance venography (MRV) excluded venous thrombosis and she was diagnosed with intracranial hypertension.

Case Two: A 46-year-old man presenting with nephrotic syndrome due to membranous GN was initially treated with antihypertensives, diuretics and a statin for 12 months before starting cyclosporin for persistent proteinuria. Six months on treatment improved his urinary protein leak, but soon after a switch from one brand of statin to another, he complained of progressive headache. He was hypertensive and fundoscopy revealed bilateral papilloedema. Drug levels were satisfactory and MRV excluded venous pathology. Lumbar puncture was postponed due to concomitant aspirin usage and his symptoms resolved following cessation of offending drugs. A diagnosis of cyclosporin induced intracranial hypertension was made.

Idiopathic intracranial hypertension or *pseudotumor cerebri* is a disorder of unknown aetiology affecting predominantly obese women of childbearing age. The primary problem is chronically elevated intracranial pressure which may lead to progressive optic atrophy and blindness. There are numerous reported risk factors which include chronic renal failure, corticosteroids and cyclosporine use.

Our case studies highlight that renal patients with symptoms of persistent headache, visual disturbance, nausea and vomiting who are on cyclosporin (either alone or in combination with glucocorticoids) should be promptly investigated by fundoscopic examination. Early diagnosis and management of intracranial hypertension in this setting could prevent potential visual loss.

P82

A review of current complications associated with percutaneous renal biopsy utilising a day-case admission protocol in a training centre.

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Introduction: In the last decade we have moved towards 'real-time' ultrasound guidance for percutaneous renal biopsy and utilise bedside histological analysis of biopsy specimens. We also now undertake a large proportion of these biopsies as 'day-cases'. In some centres biopsies are performed exclusively by consultant nephrologists or interventional radiologists. To assess the impact of these developments and the safety of our current practice we undertook a retrospective study of biopsy complications in our unit.

Methods: All biopsies were undertaken using real-time ultrasound guidance and assessed at the time of sampling using a mobile light microscope. A protocol was utilised for day-case admissions. We reviewed biopsies undertaken between January 1st 2007 and May 1st 2008, including discharge summaries, first clinic letter following the procedure, histopathology reports and any subsequent admissions.

Results: 399 biopsies were reviewed in total – 217 were native biopsies, 182 were transplant biopsies. There were 19 minor complications and no major complications. 7 (1.75%) patients had a proven perinephric haematoma. 7 (1.75%) patients had bowel in the biopsy specimen (though there was no associated morbidity). 3 (0.75%) patients went into urinary retention. 1 (0.25%) patient had frank haematuria, and 1 (0.25%) patient had an episode of hypotension. 140 of the 399 patients were performed as day case procedure without adverse outcome and no day-case patients required re-admission due to complications. No interventions to manage complications were required. All patients who developed a haematoma or frank haematuria had a creatinine over 200. Trainees took 83% of biopsies.

Conclusion: Complication rates for percutaneous renal biopsy were substantially lower than that generally quoted in current guidelines. Of note the rate for macroscopic haematuria was 40 times less common than the accepted rate of 10%. We feel the deployment of 'real-time' ultrasound and bedside histological examination has greatly improved complication rates and diagnostic yield. Native and transplant renal biopsies can be performed safely as a day case procedure. Not only can nephrologists perform renal biopsy effectively, but can train registrars to do so without compromising patient safety.

P83

Quantifying Renal Stone Risk: A Comparison Of Two Established Algorithms In Patients With A History Of Renal Stone Disease

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Ability to quantify renal stone risk (especially in the absence of data on stone composition) has been a major objective of medical management, given the sporadic nature of nephrolithiasis. We have had the opportunity to compare 2 stone risk algorithms SEQUIL (Ashby & Gyory, *Exp. Nephrol.* 1997, 5:246) and Psf (Robertson, *Front. Biosci.* 2003, 8:1330): SEQUIL has a physico-chemical basis, treating urine as a colloid and citrate as the major stabilizer; whereas Psf is probabilistic, based on the frequency distributions and 'risk curves' for 7 urinary components (UV, Ox, Ca, pH, UA, Mg, citrate) in stone-formers *versus* non-stone-formers. Although validated in small prospective studies, SEQUIL and Psf have not been compared in the same population of stone-formers. We compared data in 719 stone-formers. Although both algorithms generate numerical scores, SEQUIL (ratio of calcium solids to citrate) can be 'abnormal' if citrate is very low, even with low or normal calcium solids. Unlike SEQUIL, there are Psf values for each major stone type (UA, CaOx, CaP) or combination; previous data have shown that a value of >0.5 is 'abnormal'. For these reasons, we made both sets of scores categorical, normal *versus* abnormal, and compared these. SEQUIL scores were log-normally distributed. Multiple linear regression analysis for SEQUIL (y) *versus* Psf (x), R^2 was 0.54 with the most significant predictors being Psf scores for CaOx and CaP ($P<0.0001$). Using kappa analysis for agreement between 2 methods, Psf for CaOx, CaP and mixed were fair (>0.2), but poor for UA and UA mixed. Receiver Operator Curves (ROC) against SEQUIL as the determinant showed good discrimination for CaOx, CaP and mixed, but not for UA or mixed; moreover, ROC decision plots re-set Psf thresholds from 0.5 to 0.28, 0.45 and 0.37 for CaOx, CaP and mixed stones, respectively. Not surprisingly there is fair agreement between SEQUIL and Psf scores for CaOx, CaP and mixed stones, but not for UA or mixed stones, since these are not specifically accounted for in the SEQUIL calculation. Interestingly, of 23 patients selected solely on the basis of high Psf scores for UA (median 0.92), clinical records review showed that 14 (61%) had a history of gout or Crohn's disease. Although the outcomes for these algorithms are similar, they are complementary and used together could refine classification and better guide therapy, especially in the use of citrate or alkali.

P84

Dietetic monitoring and intensive nutritional support can improve nutritional status in eps: results of the West London eps prospective study

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Introduction - Encapsulating peritoneal sclerosis is a condition, which can seriously impact on patient's nutritional status. Our previous work has shown that regular monitoring and appropriate nutritional intervention can improve albumin levels and possibly other nutritional parameters and GI symptoms in prevalent patients. However newly diagnosed patients appear to have a poorer nutritional status than prevalent patients. The aim of this study was to see whether similar improvements can be achieved in newly diagnosed patients.

Method - All patients with a newly confirmed diagnosis of EPS from December 2006, identified through positive CT scans, were identified. Each patient was individually assessed and baseline data were then collected on nutritional status including weight, body mass index (BMI), albumin, percent weight change over 6 months and 7 point subjective global assessment (SGA) scale. Information on presence of 5 different gastrointestinal (GI) symptoms (nausea, vomiting, abdominal cramps/bloating, constipation and diarrhoea) and method of nutritional support received was also collected. This was repeated every 2 months for 1 year.

Results - 13 patients were diagnosed with EPS between December 2006 and January 2009. 7 of these have completed 12 months follow up. At time of diagnosis, 4 were transplanted, 2 were on haemodialysis and 1 was on peritoneal dialysis (PD). Mean age=52.8 years, mean duration on PD=6.0 years, mean time from stopping PD to diagnosis = 2.0 months.

Mean weight change over 1 year was –3.6kg (range –16.8-12.5). 5/7 patients experienced weight loss of 5% or greater at baseline in the preceding 6 months compared to only 2/7 patients at 1 year. Plasma albumin improved in 6 patients with 3 patients having albumin levels > 33g/l at 12 months. Improvements in handgrip strength were only seen in 3 patients. Mean at baseline and 12 months was 20.6 and 15.4 respectively. SGA scores were improved or maintained in 5 patients. At 12 months, 3 patients were classified as well nourished and 4 as moderately malnourished. 6 patients experienced 2 or more symptoms at baseline compared to only 1 at 12 months.

6 patients required hospital PN. Mean duration on PN was 7.1 months (range = 0.2 – 13.6 months). Of these 2 remain on home PN, 1 on nasojejunal feeding, 2 on oral nutritional supplements and 1 died 14.9 months after diagnosis.

Conclusions - The majority of patients experienced weight loss over the 12 month period but the rate of weight loss declined with regular monitoring and intensive dietetic support. Maintenance or improvement in albumin, SGA and number of GI symptoms was also observed for the majority of patients. Further data will be collected to increase the sample size and allow statistical testing to be performed.

P85

Lower extremity amputations in a UK haemodialysis unit and associations

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Introduction – It has been well documented that the incidence of non-traumatic lower extremity amputations in the ESRF population is in the order of 2 to 3 per 100 patients per year. There have been several large observational studies showing associations with lower extremity amputation in haemodialysis patients (1,2)

Aims – To assess the rate of lower extremity amputations in our haemodialysis population, and assess the prevalence of previously observed associations which include; diabetes mellitus, age, smoking, gender, duration on haemodialysis, pre-dialysis systolic hypertension, serum phosphate, low serum albumin and poor dialysis adequacy. We also assessed calcium phosphate product, which has not been previously studied as an association in this setting.

Method – Computer databases were used to collect data of all amputations performed between Jan 2002 and Jan 2008, those who were on haemodialysis at the time of operation were then entered into the study (n=20). Data for all associations studied was collected from computer records and paper notes, data for variables was collected for the year prior to amputation and a mean average calculated.

Results – Out of the 20 amputations, 14 were performed in association with a smoking history. 10 out of the 20 amputations were in diabetic patients. 16 out of the 20 patients had a phosphate mean average greater than 1.8 for the year preceding amputation.

15 out of the 20 amputations were seen to follow average calcium phosphate products greater than 4.4.

Conclusions – Lower extremity amputation is a major cause of morbidity and mortality in the haemodialysis population. In our patients the major risk factors were smoking, diabetes and calcium phosphate product. Calcium phosphate product has not previously been studied in this context. This requires further assessment to demonstrate if it is a true modifiable risk factor for future amputation risk.

References – 1) Eggers, PW et al. Kidney International 1999 **56**: 1524-1533

2) O'Hare AM et al. American Journal of Kidney Disease 2003 **41(1)**: 162-170

3) Speckman RA, Diabetes Care 2004 **27**:2198-2203

P86

Urine dipstick testing and the clinician's suspicion as predictors of positive urinary culture in unselected patients presenting acutely to a district general hospital.

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Background: Reagent strip bedside testing is well recognised as a tool for diagnosis of urinary tract infection (UTI), however the sensitivity and specificity of leucocyte esterase and/ or nitrites as predictors of UTI varies between population groups. Previous studies have suggested that clinical assessment in combination with dipstick urinalysis (DU) is superior to clinical assessment alone.

Aim: To analyse the predictive value of dipstick testing and clinical suspicion of UTI in patients admitted to a medical 'take' of a District General Hospital (DGH). Clinical suspicion was defined by inclusion of UTI in the differential diagnosis.

Methodology: Case note review for 121 patients was performed following the 'post take' ward round.

Results: 61% (74/121) had DU documented. Clinicians suspected UTI in 25% (30/121); 83% (25/30) were prescribed antibiotics. Urine was sent for microscopy culture and sensitivity (MC+S) in 41 %(n=50). A positive culture was defined as > 100,000 CFU/ml.

36% (18/50) samples sent for culture were positive for both leucocytes and nitrites; sensitivity 74%, specificity 87%. The Positive Predictive Value (PPV) was 78%; Negative Predictive Value (NPV) 84%. Exclusion of patients with recent or ongoing antibiotics at time of admission or with long term catheter did not significantly affect these figures.

The predictive value of leucocytes alone (10/50) vs. dipstick negative for leucocytes and nitrites (11/50) was less powerful; sensitivity 67%, specificity 60%, PPV 40% and NPV 82%.

Dipstick positive for nitrites alone was the least useful test, sensitivity 33%, specificity 50%, PPV 10% and NPV 82%.

Clinical suspicion of UTI had a PPV 81% and NPV 76%. Sensitivity was 62% but it was highly specific, 90%

Using a combination of clinical suspicion and a dipstick positive for leucocytes and nitrites did not confer additional benefit, Sensitivity 43%, specificity 86%, PPV 69% and NPV 67%. If patients with mixed growth were excluded, PPV was 60% and NPV was 71%

Conclusions: Positive nitrite DU or leucocyte DU in isolation were not predictive of a positive urine culture in our population.

Either the combination of a positive leucocyte and nitrite DU or clinical suspicion of UTI were highly specific for a positive urine culture in the context of unselected medical patients at time of admission.

Leucocyte and nitrite positive DU, whilst predictive for positive urine culture, may represent asymptomatic bacteruria. The addition of clinical suspicion in these cases should identify those with a significant UTI.

A clinical suspicion of UTI alone, in an acute unselected medical patient, irrespective of DU, should alert to a probable underlying UTI; in this context MC+S should always be requested.

P87

Asians have smaller kidneys than Whites independent of renal function

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Introduction: Estimation of renal size is part of the routine assessment of patients with kidney disease. "Small kidneys" (typically <9cm in length) infers chronicity of renal disease and frequently dissuades clinicians from pursuing further "unnecessary" investigation in the presence of reduced renal function. Renal length correlates with body height, and renal volume with body surface area. These parameters vary with ethnicity, but typically no adjustment is made for this when assessing the relevance of reduced kidney size.

At our large single centre in the UK, the number of patients diagnosed with chronic kidney disease of unknown aetiology ("small kidneys" with renal impairment) is disproportionately greater in Asians (32%) compared to Whites (20%), raising the possibility of under investigation of this group at presentation. The aim of the study was to accurately establish the kidney size of Asians and Whites with apparently "normal" renal function, to see whether an inherent difference in kidney size between these populations might explain this difference.

Methods: Renal size was assessed retrospectively in consecutive patients of White and Asian ethnicity using abdominal computed tomography. Ethnicity was self reported when patients attended for scans. Patients were excluded from review if they had evidence of any structural abnormalities on imaging, an eGFR<60mls/min/1.73m^2 (MDRD equation), or known renal disease. The study was powered to detect a difference in length of 1cm between the groups. Statistical analysis was performed using the independent sample *t*-test and simple correlations (SAS version 9.1.)

Results: Complete data was available on 48 Whites and 47 Asians. In both groups kidney length and volume correlated with patient height and weight, but not renal function, age or gender. After adjusting for age, gender, weight, height and eGFR, Whites had significantly longer left kidneys (10.56 v 9.89 cm, p=0.017) and also longer right kidneys (10.4 v 9.9 cm, p=0.09) than Asians. Similarly Whites had significantly larger left (147.4 v 125.4 cm^3, p=0.007) and right (144.7 v 124.9 cm^3, p= 0.013) adjusted kidney volumes than Asians. Despite both groups having normal renal function 18/47 Asians v 3/48 Whites had a renal length <9cm (p=0.0002 Fisher's & Chi^2).

Conclusions: Renal indexes such as length and volume are increasingly used in the assessment of renal disease, but may not provide an accurate reflection of true functional nephron mass in all populations. Renal length and volume in Asians with no evidence of kidney disease is significantly less than in Whites. Furthermore apparently "small kidneys" was a common finding in Asians but not Whites despite normal renal function. This inherent difference may affect the chances of Asians with kidney disease undergoing further evaluation including kidney biopsy when referred for assessment. Decisions regarding biopsy should be made according to the normal kidney size of a particular ethnic group within the local population.

Poster Session

Tuesday 21 April

11:30 – 12:30

Miscellaneous 1

Moderator Dr Andrew Mooney

P88

A survey of renal learning needs in Core Medical Trainees

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Objective :

Reduced exposure to renal medicine in undergraduate medical training has left many junior doctors lacking in confidence to deal with renal problems. We set out to identify areas of learning need related to the core medical curriculum learning goals for renal medicine, in order to provide optimum renal teaching for core medical trainees.

Method :

All core medical trainees in the Northern Deanery were asked to complete a questionnaire based on the required knowledge, skills and attitudes for renal aspects of competency for the Physician Level 1 GIM (Acute) Curriculum. 21 of the 45 trainees approached completed the questionnaire.

Results :

86% of trainees were able to categorise acute renal failure as pre-, renal or post-renal . When asked how they would manage acute kidney injury (acute tubular necrosis), over 80% would ensure circulating volume was optimised, would stop nephrotoxic drugs, and knew the significance of dipstick urinalysis and red and white cells casts on urine microscopy; fewer than 70% of trainees mentioned continued monitoring of fluid balance.

Only 33% of trainees could list the 3 main types of renal replacement therapy (RRT : haemodialysis, peritoneal dialysis, renal transplant) and only 10% were aware of the indications for urgent dialysis.

86% of trainees were aware of local protocols for avoidance of radiological contrast induced nephropathy ; the majority knew of potential nephrotoxicity of ACE inhibitors and non-steroidal anti-inflammatory drugs but <10% were aware of potential nephrotoxicity of proton pump inhibitors.

43% knew the classification of chronic kidney disease (CKD); 50% could list some long term complications of CKD & RRT, but only 33% were aware of the importance of sepsis.

Conclusion :

Indications for urgent dialysis, awareness of nephrotoxic medications and complications of CKD and RRT were identified as areas of learning need in core medical trainees.

P89

The Potential Impact of a Renal Stroke and Rehabilitation Unit

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Background:

The incidence of stroke is 20.7/1000 patient years in our total population of over 1200 haemodialysis patients. Specialist stroke units improve patient outcome, however, the need for dialysis and specialist care precluded the transfer of our patients to a general stroke unit lacking capacity to cope. Physio [PT], occupational [OT], speech and nutritional therapy within our renal centre was hindered by rotational staffing of therapists across 4 renal wards, and by thrice weekly HD or daily PD regimes.

Aim:

An 8 bed stroke and rehabilitation unit [SRU] was developed within our renal centre, with in-unit haemodialysis, a dedicated neurology/renal ward round and multidisciplinary team with additional funding for a Healthcare assistant, PT, OT, Discharge Support Nurse, and Pharmacist. The RehabRef system was used to judge admission for any renal patients with an acute stroke with rehabilitation potential. Spare capacity was used for other patients with reversible disability from other causes.

Results:

Between Apr – Nov 2008, 37 patients were admitted to SRU [mean age 69.5±10.1 yrs, 23males]. Length of stay 30.7±27.9 days. 15/37 [41%] were stroke patients, 2/37 [5%] were amputees, and 20/37 [54%] had other rehabilitation needs. 34/37 [92%] were haemodialysis patients with dialysis sessions organised around therapy. 20/37 [54%] were discharged; all patients went home, and none to placement in nursing/residential homes. 4/37 [11%] went on to community intermediate care, 5/37 [13%] patients died, and 8/37 [22%] remain as inpatients.

Conclusion:

SRU has accommodated all stroke patients with rehabilitation potential, a significant proportion of patients have been discharged to home and none to placement. Further analyses of the impact of this novel facility are underway.

P90

A Qualitative Analysis of the Attitudes of Trainers to the Case Based Discussion as an Assessment Tool for Foundation Trainees.

Elizabeth Garthwaite

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The publication of Modernising Medical Careers (http://www.mmc.nhs.uk) heralded a major change in postgraduate medical education and training. As part of the two-year Foundation Programme doctors are required to demonstrate their abilities and competence against set standards (www.foundationprogramme.nhs.uk). The case based discussion (CbD) is one of the four objective workplace based assessments. It was designed to assess generic skills undertaken as part of day-to-day clinical practice, with a trainee led discussion of his or her involvement in a particular chosen case. The assessor marks the CbD against specific criteria and feedback is given. Attitudes towards the assessment tool from assessors have been variable.

Semi-structured interviews of eight renal consultant colleagues of differing seniority to assess their attitudes and experiences towards the CbDs were undertaken.

All those interviewed demonstrated a satisfactory understanding of the Foundation Programme and the use of the assessments within it. There were misconceptions regarding the function of the CbD. Most thought it ought to assess knowledge rather than the generic skills for which it is intended in this trainee group. There were also evident inaccuracies towards the marking of the assessment, in particular the criteria and standards that should be used.

Attitudes towards the CbD were variable. They were largely dependent on the level of training in its use. Although some consultants had strong leanings towards traditional assessment methods (especially those who were more senior), all were realistic as to the reasons for change and were supportive of new strategies. Junior Consultants were in general more knowledgeable and optimistic about the use of the tool. This group were also the most experienced and highly trained group in terms of the assessment tools.

All those interviewed felt that changes were needed to improve the usefulness of the CbD as an assessment tool. Concerns regarding the validity and reliability of the assessments, the time burden and the feasibility of their undertaking within a busy clinical workload were discussed. Conversely however, there were positive attitudes towards the feedback opportunities that arise as a consequence of the assessments, their objective nature, the standardised format, the multiplicity of assessors and the educational benefits of the CbD. There was generalised concern that the training of the assessors was not standardised. Those who had received face-to-face training in the tool were more positive towards it.

Major barriers to the success of the tool seem to be related to training, a lack of time allocated for the assessments to occur and the trainee centred approach that may reduce the validity and reliability of the assessments.

Given that the CbD is being piloted for use in Renal Speciality Trainees, this has important implications, both in terms of it's functions as an educational tool and an aid to objective assessment and monitoring of progress.

P91

Validation of the protein: creatinine ratio to quantify proteinuria in pregnant patients with Chronic Kidney disease

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INTRODUCTION AND AIMS: Patients with chronic kidney disease (CKD) are at increased risk of pre-eclampsia during pregnancy and may have chronic proteinuria. Using protein: creatinine ratio (PCR) or albumin:creatinine ratio (ACR) to quantify proteinuria in these patients has not been validated. We hypothesise that PCR and ACR are valid tests to quantify proteinuria in pregnant patients with CKD.

METHODS: PCR and ACR were measured in random midstream urine specimens after exclusion of concurrent urinary tract infection from patients referred to renal-obstetric clinics in 3 UK centres. U24Pro and PCR/ACR were considered paired if samples were within 72 hours of each other. Correlation was assessed by Spearman rank correlation. Receiver operating curves (ROC) were constructed to calculate optimum cut-off values to predict proteinuria greater than 300mg/d and 1000mg/d.

RESULTS: 111 paired values of U24Pro and PCR and 84 paired values of U24Pro and ACR were available. Both ACR and PCR closely correlated with U24Pro (Spearman's ρ0.734 and 0.881 respectively, both $p<0.001$).ROC analysis identified a PCR of 28.5mg/mmol as the optimum value to predict U24Pro>300mg/d (sensitivity 97%, specificity 72.7%, area under curve (AUC) 0.939, $p<0.001$). A PCR of 89.5mg/mmol predicted U24Pro>1000mg/d with sensitivity 97% and specificity 86% (AUC 0.955, $p<0.001$) ACR was less accurate than PCR at predicting U24Pro>300mg/d (AUC 0.863, $p<0.001$) or U24Pro>1000mg/d (AUC 0.94, $p<0.001$).

CONCLUSIONS: PCR is more accurate than ACR at quantifying urine protein excretion in pregnancy and CKD. With optimum cut-off values, PCR will give false negative results in predicting U24Pro>300mg/d in 1 in 4 cases and in predicting U24Pro>1000mg/d in 1 in 7 cases. We conclude that PCR measurements are adequate for monitoring progression during pregnancy but should be supplemented by 24 hour urine collections at baseline and when accurate values are required for diagnostic criteria.

P92

Renal Patient View (RPV) A Patient Satisfaction Survey

Ruma Das, Drew Malloch, Kevin Howard, Mobin Mohteshamzadeh, Lindsey Barker, Emma Vaux, Ramesh Naik

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Background: RPV is an internet based system which extracts information directly from existing Renal Unit databases (e.g. Proton). Patients are able to access RPV using an individual password to view their own results online and obtain information on their renal condition. As the system is relatively new, regular patient feedback on its use would enhance its effectiveness in patient care. 210 out of 570 patients (36%) receiving renal replacement therapy in our unit have log-ins for RPV. **Aim:** The aim of the study was to promote the use of RPV through improving its accessibility based on recommendations from patients and exploring patient expectation and experience. **Method:** A questionnaire was sent to each of the 210 patients asking their opinion on ease of use, accuracy, practical applications and improvements. **Results:** 73/210 surveys (35%) were returned in the free post envelope provided. Patients accessed RPV either alone, with members of the family or with their General Practitioners. 49/73 (67%) had used RPV more than 5 times in the 11 month period, 20/73 (27%) between 1-5 times and 4/73 (5%) had never used RPV. 6/69 patients (9%) used RPV weekly and 31/69 patients (45%) used the system monthly. 32/69 patients (46%) accessed RPV less frequently. Patient responses to the questions asked can be seen in the attached table.

QUESTIONS	YES%	NO%
Is RPV easy to use	97	3
Are you satisfied with RPV	94	6
Do you use RPV to discuss treatment with your renal	50	50
Is the medication list accurate	89	11
Do letters reflect clinic discussion	90	10
Does RPV help you look after your health better	79	21
Do you have concerns about RPV	57	43
Did you raise these with unit	45	55
If so were you given appropriate advice	88	12

Comments: Some patients requested other results (urine tests and iron levels); an email facility for questions and advice would be welcomed. Patients felt RPV improves the efficiency of time usage and consultation with doctors; there were occasional inaccuracies in letters which sometimes did not reflect clinic discussion. Patients felt more in control of their condition and found results (93%), medical information (54%) and letters (54%) particularly helpful. **Conclusion:** Patient empowerment requires that information regarding clinical management is made available. The input of this data by clinicians needs to be accurate. The survey demonstrates that RPV is a useful tool in patient care and should be available to all renal replacement patients.

P93

Natural history of patients with renal cholesterol embolism

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Introduction Severe cholesterol embolisation syndrome is an uncommon cause of rapidly progressive renal failure associated with a high mortality. The outcome of patients, incidentally identified to have cholesterol emboli at renal histology, remains to be identified in a large contemporaneous cohort.

Methods All patients with histological evidence of cholesterol emboli on renal biopsy between 1994 and 2006 at a tertiary nephrology centre were included. Data regarding presenting features and co-morbidity in addition to outcome (renal function, morbidity and mortality) were obtained from hospital case notes, death certification and computer databases.

Results Seventy four patients (51M, 23F, mean age 70y, range 47-86) with histological features of renal cholesterol emboli were identified (median follow up 34 months). Twelve (16.2%) had classical cutaneous manifestations of cholesterol embolisation at time of renal biopsy. Common co-morbidities at time of biopsy were hypertension 67 (91%), ischaemic heart disease (IHD) 54 (73%), peripheral vascular disease 31 (42%) and diabetes mellitus 26 (35%). Twenty four (32%) patients progressed to end stage renal failure (ESRF) at time of last follow up. The remaining 50 patients demonstrated no significant decline in eGFR (median eGFR 25.5 vs 29.0 ml/min (IQ range 12.5-35.5 vs 18.5-36.0, p=0.294)). At the study endpoint 57 (77%) patients had died (median survival 39.0 months (95% CI 28-50)). Of these, 32 (56%) died as a result of vascular disease (17 IHD, 4 abdominal aortic aneurysm rupture, 4 ischaemic nephropathy, 3 peripheral vascular disease, 2 cerebrovascular accident and 2 ischaemic bowel).

Conclusion The incidental finding of cholesterol emboli on renal histology is associated with prevalent co-morbid vascular disease. These patients have a high risk of developing ESRF and of death from vascular disease. Aggressive cardiovascular risk factor reduction should be considered in this patient group.

P94

The influence of dietary salt on postprandial plasma sodium concentration

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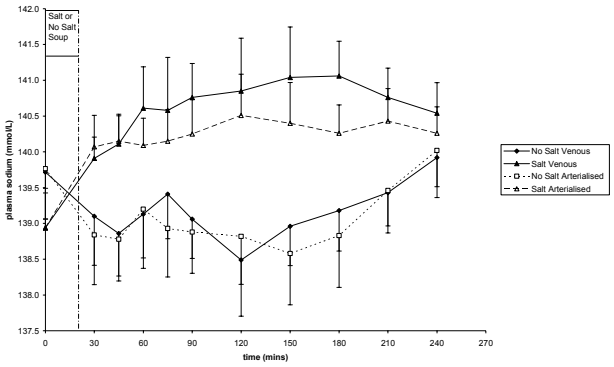
The mechanisms whereby dietary salt intake regulates blood pressure (BP) are not clear. Physiological increases in sodium in plasma or tissue culture are known to stimulate thirst and thereby fluid retention but also activate the local hypothalamic RAS, cellular changes in arterial smooth muscle and cardiac myocytes as well as endothelial stiffness.

Large changes in salt intake alter plasma sodium but the effects of smaller changes are not known. We therefore studied the effect in 10 normotensive subjects in a randomised crossover study of 400mls of soup with either 6gms of salt or no added salt.

Venous and arterialised blood samples and systolic and diastolic blood pressure were taken at baseline and at 30min intervals for 4 hours.

Results: Salt soup increases, at its maximum, venous sodium by 3.13±0.75mmol/L, osmolality by 6.975±1.145mosmol/L and chloride by 3.74±0.91mmol/L compared to control ($p<0.05$). This trend was also seen in arterialised samples.



Conclusions: Physiological increases in salt intake raise plasma sodium, chloride and osmolality by relatively large amounts from initial values and in comparison to control. These changes could be sufficient to directly alter endothelial stiffness as well as cellular changes in myocytes and smooth muscle and thereby affect blood pressure both acutely and chronically.

P95

Comparison between ultrasound and MRA in assessment of renal size

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Introduction: Reno vascular disease (RVD) accounts for a significant proportion of the chronic kidney disease population. Therapeutic decisions may be taken based on kidney size and disparities between the sizes of the two kidneys. Kidney size of >7.5cm is usually considered a meaningful nephron mass for intervention. Accurate and reproducible methods for assessing renal length are necessary for clinical decision making.

Aim and objective: This study aimed to assess whether there is any significant difference in measurement of renal length by ultrasound and MRA in relation to RVD.

Methods: All the patients who had renal ultrasound and MRA to investigate RVD at a single centre over an 18 month period were identified from radiology PACS. The time interval between the ultrasound and MRA was not recorded, however in all patients ultrasound was the first investigation performed. Renal length measurements by ultrasound were recorded as reported, MRA measurements were taken by a senior radiology SpR after 3D reformatting of the images.

Results: Fifty six out of a total of 107 patients had both ultrasound and MRA in our centre and were included for final analysis. Median age of this cohort was 70Y (43M, 13F).

Measurements on 109 kidneys were available for comparison (56R and 53 L kidneys). MRA measurements for the right kidney were significantly greater ($p<0.0001$) than the ultrasound measurements for the same kidneys with median of 10.7cm (10.2 - 11.6) compared to 10.3cm (9.6 - 11.3)].

For the left kidney, there was no significant difference in measurement by MRA or ultrasound with median of 10.7cm (9.4-11.4) compared to10.5cm (9.0-11.2), $p=0.06$. However for the 109 kidneys taken together, MRA measurement remained significantly greater ($p<0.0001$) than the ultrasound measurement with median of 10.7cm (10.2-11.6) compared to 10.3cm (9.6-11.3)].

Half of the renal MRA scans performed to investigate RVD did not show significant abnormality in the main vessels. Twenty two (40%) patients had >1.5cm difference in the size of kidneys on ultrasound and 70 % of those had abnormal renal vasculature on MRA. Thirty four (60%) patients had <1.5 cm difference in the size of kidneys on ultrasound and 37% of those had abnormal renal vasculature on MR.

Conclusions: Renal length measurements with MRA were significantly greater compared with ultrasound measurements for the same kidneys. This is probably because ultrasound measurements are not taken in the true longitudinal plane. Ultrasound will continue to be the method of choice for assessing renal size (accessible, cheap, no risk). Possible underestimation of renal length by ultrasound should be considered.

Poster Session

Wednesday 22 April

13:00 – 14:00

Haemodialysis & Cardiovascular Disease

Moderator Dr Paul Rylance

P96

Improved left ventricular function after starting haemodialysis; implications for transplant workup in pre dialysis patients.

Harikrishnan Nair, Stephen Smith, Stephen Ting, Bassam Fallouh, Indranil Dasgupta

Heartlands Hospital, Birmingham, United Kingdom

BACKGROUND: We recently observed a dramatic improvement in cardiac function in a patient following commencement of haemodialysis (HD) with the ejection fraction (EF) increasing from 24% to 63%. This retrospective observational study aimed to determine the clinical relevance of changes in cardiac function after starting HD.

METHODS: Records of all 678 patients starting HD in our unit between 2003 and 2007 were examined. 39 patients (27 male, 12 female, mean ages 63, and range 27-77 years) had transthoracic echocardiograms before and between 9 and 28 (mean 19.4) months after starting HD. Patients who had coronary revascularisation were excluded. Assessments included ejection fraction(EF), mean left ventricular internal diameter in diastole (LVIDd) and systole (LVIDs), left ventricular mass index (LVMI) and left ventricular fractional shortening (LVFS).

RESULTS: EF improved from 47 % to 63.3 % ($p < 0.001$). LVIDd decreased from 5.3 $\pm$ 1.3 cm to 4.96 $\pm$ 0.96 cm ($p< 0.005$) and LVISd decreased from 3.75 $\pm$ 1.02 cm to 3.13 $\pm$ 0.88 cm ($p< 0.005$). Interventricular septal thickness in diastole decreased from 1.23 cm to 1.08 cm ($p< 0.005$). LVMI improved from 264 $\pm$ 26.7g/m² to 171 $\pm$ 19.2 g/m² ($p< 0.005$). Before the start of dialysis treatment, 23.1% of the study population had LVFS of <25%. Only 4.9% had a LVFS of <25% after starting haemodialysis ($p < 0.005$). 3 patients with initial EF of <24% ultimately underwent successful renal transplantation after clinically significant improvements in cardiac function were demonstrated on serial echocardiograms.

CONCLUSION: These data show that clinically significant **i**mprovements in cardiac function occur after commencement of HD. This may be related to improvement in biochemistry, haemoglobin, blood pressure or fluid status. This is relevant when considering suitability for transplantation in the pre dialysis population.

P97

Predictors of intradialytic hypotension, 24 hour blood pressure control, and the prevalence of abnormal diurnal variation in blood pressure on haemodialysis.

Claire Edwards, Neill Duncan, Damir Tandaric, Seema Singh, Albert Power, Megan Griffith, David Taube, Tom Cairns

Imperial College Kidney and Transplant Institute, London, United Kingdom

Background: National standards for treatment are based upon static measures of pre- and post- dialysis blood pressure. Given the variability of blood pressure in a 24 hour period and the additional prognostic information that may be provided by the diurnal pattern of variation, ambulatory blood pressure monitoring has been made in many studies. Methods: 24 hour ambulatory blood pressure monitoring [ABPM] was made in 43 randomly selected patients at a single dialysis centre after a dialysis session [daytime 0700 to 2300, and night 2300 to 0700]. ABPM was correlated with means of static blood pressure measurements in the pre-, intra- and post- dialysis periods for the dialysis session preceeding the ABPM and the two following. Note was made of antihypertensive medications and interdialytic weight gain [IDWG]. Results: Intradialytic hypotension: There was a significant fall in mean SBP from 156±21 to 145±28mmHg [p=0.0005], but not mean DBP during haemodialysis, however this did not correlate with mean IDWG [R=0.03] or any particular class of antihypertensive agent or total number of agents. Static BP Predictors of 24 hour BP Control: Mean Daytime SBP and DBP on ABPM was most strongly correlated with post-dialysis SBP [R=0.79] and post-dialysis DBP [R=0.76] respectively. Pattern of ABPM: 38/43 and 33/43 patients had an abnormal absence of nocturnal dipping [defined by reduction in mean by >10%] of SBP and DBP from daytime to night respectively, an adverse prognostic sign. 2/43 patients showed extreme dipping of >20% by these measures and a morning blood pressure surge, an adverse prognostic sign. Conclusion: In keeping with several other studies, mean post-dialysis SBP and DBP are most strongly predictive of mean daytime SBP and DBP on ABPM, and post-dialysis measures may also be more strong predictors of outcome. Interdialytic weight gain and the number and type of antihypertensive medications did not influence intradialytic hypotension in this study. There were a high number of non-dippers, up to 88% of patients in this study of randomly selected patients. The loss of dipping has been associated with increased risk of adverse cardiovascular outcome. We advocate the use of ABPM to screen for hypertension and diurnal variation, and plan future work relating these to cardiovascular risk and its modification with treatment.

P98

Does Aldosterone have a Role in the Development of Left Ventricular Hypertrophy in End-Stage Renal Failure Patients?

Joanna Powell[1], Rajan Patel[1], Tracey Steedman[2], Henry Dargie[2], Alan Jardine[1]

[1]University of Glasgow, Glasgow, United Kingdom, [2]Western Infirmary, Glasgow, United Kingdom

Introduction and Aims: End stage renal failure patients have an increased risk of left ventricular hypertrophy and sudden cardiac death. The mechanisms for this are not fully understood. Aldosterone has been proposed as a causative factor for development of left ventricular hypertrophy (LVH) and cardiac fibrosis independent of blood pressure effects in patients with hypertension. Whether a similar relationship exists in end stage renal failure (ESRD) is not known. Our aim is to investigate the relationship between aldosterone and LVH in ESRD patients using cardiac MRI (CMR).

Methods: 73 patients who were being considered for renal transplantation were recruited (33 pre-dialysis (PRED) and 40 dialysis (HD)) between 2007 and 2009. Mean age = 54.9yrs (±12.9) and 74% male. Each patient underwent CMR (Siemens Sonata 1.5T scanner), exercise tolerance test, blood pressure, ECG for QT dispersal and venepuncture for routine tests and aldosterone measurement. Past medical history and therapeutics history was recorded using a questionnaire and checked using the electronic patient record. LVH was defined as a LV mass index (LV Mass/Body Surface Area) > 84.1g/m^2 (male) or 74.6g/m^2 (female), based on published normal LV dimensions for CMR.

Results: 49 patients had LVH (67.1%). No significant differences were found between the two groups (PRED and HD) for any of the CMR measurements including left ventricular mass index (LVMI) (38.7% vs. 51.4%, p=0.319). 46% patients were on an ACEI at the time of investigation (63.6% PRED and 32.5% HD) however the use of an ACEI was not associated with the level of aldosterone. Aldosterone was not found to correlate with blood pressure, LVMI, exercise time or QT dispersal.

Conclusions: Despite previous evidence of a positive association between aldosterone and LVH in hypertensive patients with normal renal function we did not find any evidence to confirm this suggestion in end-stage renal failure. There was also no significant association with QT dispersal; a possible prognostic indicator of sudden cardiac death.

P99

Incremental impairment of left ventricular longitudinal strain and diastolic function associated with hypertension with or without left ventricular hypertrophy (LVH) in chronic kidney disease (CKD 5) and normal renal function.

Eveline Lee[2], Kay B Tan[1], Biju John[2], Frauke Wenzelburger[2], Yu Ting Tan[2], Grant Heatlie[2], John E Sanderson[3], Simon J Davies[1]

[1]Institute for Science and Technology in Medicine, Keele University, Stoke on Trent, United Kingdom, [2]University Hospital of North Staffordshire, Stoke on Trent, United Kingdom, [3]University of Birmingham, Birmingham, United Kingdom

INTRODUCTION AND AIMS: The early effects of hypertension and CKD on left ventricular function measured by global longitudinal strain and diastolic function before the development of left ventricular hypertrophy (LVH) are not well known. We studied hypertensive patients with and without CKD 5 on peritoneal dialysis (PD) and/or LVH using 2 dimensional (2D) speckle tracking and tissue Doppler Imaging (TDI)

METHODS: 24 hypertensive patients with LVH (65±17years,13 female, 12 CKD 5, BMI 28±5, LVEF 58±6%, LVMI 133±17), 43 with no LVH (70±12years, 27 female, 9 CKD 5, BMI 29±5, LVEF 59±8%, LVMI 77±19) and 30 healthy controls (67±7years, 22 female, BMI 24±4, LVEF 63±8%, LVMI 78±19) underwent full echocardiography and images analysed offline. Apical four-chamber (4C) and two chamber (2C) images were used to study longitudinal strain with 2D speckle tracking. Global longitudinal strain was calculated from 4C and 2C data. Early diastolic velocity (E) and average septal and lateral annular diastolic velocities (E´) were recorded using pulse-wave Doppler and TDI. E/E´ was used as a marker of diastolic function.

RESULTS: There was incremental worsening of 4C and global longitudinal strain with and without LVH: 4C strain were -21.24±3.01 in controls, -19.82±2.57 in non LVH group and -17.57±4.11 in LVH group, p=0.003 (one way ANOVA). Global strain: -20.93±2.96 in controls, -19.49±2.29 in non LVH group and -17.60±3.47 in LVH group, p=0.002 (ANOVA). The same trend was observed for E/E: 8.14±1.98 in controls, 9.71±3.42 in non LVH group and 12.98±4.62 in LVH group, p=0.000. 4C strain, global strain and E/E´ in CKD 5 patients with or without LVH were not significantly different when compared with their counterparts with normal renal function.

CONCLUSIONS: Hypertension with and without LVH is associated with impaired longitudinal strain and diastolic function. The incremental differences suggest a progressive left ventricular dysfunction that is present before the development of LVH. These observations were similar in CKD 5 patients.

P100

Creation of an arteriovenous fistula is associated with significant potentially beneficial changes in systemic cardiovascular performance and arterial stiffness

Shvan Korsheed[1], Stephen John[1], Richard Fluck[1], Christopher McIntyre[1,2]

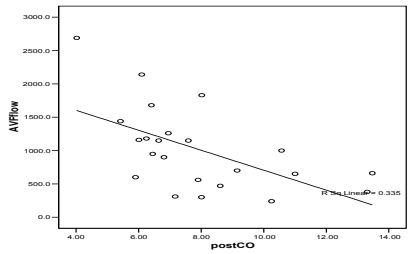
[1]Derby Hospitals NHS Foundation Trust, Derby, United Kingdom, [2]School of Graduate Entry Medicine and Health, Derby, United Kingdom

Native arteriovenous fistulae (AVF) remain the vascular access of choice for haemodialysis. The use of native access c.f. catheters is associated with sustained reduction in mortality. This may be due to factors above and beyond line related sepsis rates. The aim of this study is to investigate the impact of AVF formation on the spectrum of cardiovascular functional factors that might be important in the pathophysiology of cardiovascular disease in HD patients.

We recruited 31 CKD stage 4/5 predialysis patients who underwent AVF formation. This was primarily successful in 23/31 patients (18 brachiocephalic and 5 radiocephalic). All patients were studied 2 weeks prior to planned AVF operation and restudied 2 weeks postoperatively. Haemodynamic variables were measured non-invasively using pulse wave analysis. Central blood pressures (BP), Aortic Index (AIx) and carotid femoral pulse wave velocity (CF-PWV) were assessed using applanation tonometry. AVF blood flow (Qa) was measured using Doppler ultrasound. Bioimpedance analysis was performed using a multifrequency multisegmental method and patients underwent serial transthoracic echocardiography.

Two weeks postoperatively, total peripheral resistance decreased (-17±20%, p=0.004), stroke volume tended to increase (12±30ml, p=0.07), and heart rate increased (4±8.0bpm, p=0.03). This was associated with an increase in cardiac output (20±30%, p=0.006). Higher flow AVFs were not associated with higher cardiac outputs, indeed there was a negative correlation between AVF flow and post operative cardiac output (r= -0.591, p=0.003). Central systolic and diastolic BP were reduced (-11.3±17.9mmHg, p=0.008 and -6.7±8.5 mmHg, p=0.001 respectively). There was a significant reduction in both CF-PWV (-1.9±2.1m/s, p=0.01) and AIx (-3.8±5.65%, p=0.006). No change in body composition was observed.

Formation of an AVF resulted in a significant reduction in BP and arterial stiffness. Patients with lower cardiac outputs did not result in a low flow AVF, and patients with high flow AVFs were not subjected to high output cardiac states. Overall the post AVF adaptations might be characterised as potentially cardioprotective, and there was no evidence of acute cardiac decompensation.



P101

Indices of cardiac dysfunction in peritoneal dialysis patients are associated with relative increases in intravascular volume rather that extracellular water relative to total body water.

Kay B Tan[1], Biju John[2], Frauke Wenzelburger[2], Eveline Lee[2], Yu Ting Tan[2], John E Sanderson[3], Simon J Davies[1]

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INTRODUCTION AND AIMS: Secondary analysis of the ADEMEX study demonstrated that BNP, inflammation and poor fluid removal are independent predictors of survival in PD. To explore possible mechanisms further, we undertook a detailed analysis of the relationships between cardiac function, inflammation, intravascular and extracellular fluid status.

METHODS: 24 stable PD patients (12 men) were studied. Plasma volume (PVc) was measured using ^{125}I-albumin and corrected for BSA; extracellular (ECW) and total body water (TBW) were determined by Bioimpedance analysis (Xitron Hydra), inflammation from high sensitivity CRP. Left ventricular mass index (LVMI) and Left atrial volume index (LAVI) were determined using standard full Doppler-2D-echocardiography and Tissue-Doppler-Imaging.

RESULTS: LVMI correlated with systolic BP (0.49, P=0.035), PVc (r=0.63, P=0.006) and ECW:height (r=0.58, P=0.01) but not with ECW:TBW ratio or CRP. The LAVI also correlated with PVc (r=0.550, P<0.01) and BNP (r=0.66, P=0.004) but not with BP, ECW:height, ECW:TBW or CRP. A subgroup of 8 patients with heart failure and normal ejection fraction (HFNEF) according to European Society of Cardiology (ESC) guideline were identified. They had higher PVc than those without (1610 v 1381 ml, P=0.04) but similar CRP and ECW:TBW.

CONCLUSIONS: Echocardiographic abnormalities, especially increased LAVI and LVMI, were associated with a relatively expanded plasma volume. This is more marked in patients meeting HFNEF criteria. In contrast, these abnormalities were not related to the ECW:TBW ratio which is often elevated in PD patients and associated with worse survival. This suggests that there is more than one component to fluid excess in PD.

P102

Isothermic Haemodialysis Abrogates Myocardial Stunning and Optimises Intradialytic Haemodynamics with Excellent Patient Tolerability

Helen Jefferies[1], James Burton[1], Nicholas Selby[1], Christopher McIntyre[1,2]

[1]Renal Medicine, Derby City General Hospital, Derby, United Kingdom, [2]School of Graduate Entry Medicine and Health, University of Nottingham, Derby, United Kingdom

Recurrent haemodialysis (HD) induced cardiac injury is associated with markedly reduced survival and development of systolic dysfunction. We have previously demonstrated that lowering dialysate temperature from 37ºC to 35ºC significantly improved haemodynamic tolerability, and abrogated the development of acute dialysis-induced myocardial stunning, but at the expense of cold related symptoms. This study aimed to identify the optimal patient-tolerable dialysate temperature to reduce haemodynamic instability and abrogate myocardial stunning.

8 stable patients on chronic HD were studied at 37ºC, isothermic (dialysing at core body temperature), and subsequent incremental 0.5ºC reductions of temperature, to a minimum of 35ºC. Patients were blinded to dialysate temperature. Serial two-dimensional echocardiography was performed pre-dialysis, at peak stress, and post dialysis to identify left ventricular regional wall motion abnormalities (RWMA). Intra-dialytic haemodynamics were measured non-invasively with Finometer. Temperature tolerability was determined by validated symptom questionnaire.

Mean pre-dialysis core temperature was 35.75ºC (35.5-36.6ºC). Isothermic HD was associated with overall reduction in RWMAs compared to standard 37ºC. Systolic and diastolic BP were significantly higher during isothermic HD than at 37ºC (mean SBP +16 mmHg and +DBP 17 mmHg, $p<0.001$). Further reduction in temperature did not elicit further benefits in terms of BP, other haemodynamic parameters and development of myocardial stunning. Isothermic dialysis was well tolerated; patients reported feeling the same or better compared to dialysis at 37ºC, without thermal related symptoms. However, at lower temperatures patients reported adverse thermal symptoms.

This study defines the dose response relationship of systemic haemodynamics and HD induced cardiac injury with dialysate temperature. Isothermic dialysis provides optimal short-term improvement, without the development of symptomatic cold intolerability.

Poster Session

Tuesday 21 April

11:30 – 12:30

Haemodialysis & Inflammation

Moderator Dr Damien Fogarty

P103

Tissue Advanced Glycation Endproducts in two populations associated with increased oxidative stress: Normal in Cirrhosis but elevated in Haemodialysis patients

Kara Rye[1], Gerri Mortimore[1], Stephen John[2], Helen Jefferies[2], Shvan Korsheed[2], Paul Owen[2], Andrew Austin[1], Jan Freeman[1], Richard Fluck[2], Christopher McIntyre[2,3]

[1]Hepatology, Derby City General Hospital, Derby, United Kingdom, [2]Renal Medicine, Derby City General Hospital, Derby, United Kingdom, [3]School of Graduate Entry Medicine and Health, University of Nottingham, Derby, United Kingdom

Advanced glycation endproducts (AGE) result from non-enzymatic protein glycation and are a measure of cumulative metabolic stress. Tissue and serum AGE are known to predict cardiovascular (CV) mortality in end stage renal disease. Serum AGE levels are elevated in euglycaemic cirrhotics and correlate with disease severity, yet cirrhosis appears to be protective against coronary atherosclerosis. Tissue AGE has not been assessed in cirrhosis. We aimed to assess tissue AGE in two populations with increased oxidative stress: cirrhosis and haemodialysis (HD).

We studied 56 patients (28 cirrhotics, 28 age and sex matched HD patients) and compared with a normal control database (NC). Tissue AGE was measured using UV autofluorescence (AF) (AGE Reader®). 3 sequential readings were taken from the palmar aspect of the forearm, approximately 10cm below the elbow, avoiding pigmentation or vascular structures. History of diabetes mellitus (DM) and ischaemic heart disease (IHD) was noted and both Child-Pugh (CP) and Model for End Stage Liver Disease (MELD) scores calculated.

Mean age was 56±15 years, 64% male. The cause of cirrhosis was predominantly alcohol. Median CP score was 8, MELD 12. No cirrhotic patient had renal impairment. The prevalence of DM and IHD was similar in both groups. Mean AF correlated with age in all groups (HD R=0.52, p=0.016, cirrhosis R=0.709, p=<0.0001, NC R=0.995, p=<0.0001). Mean AF did not differ significantly between CP class in cirrhosis. Compared to NC, mean AF was significantly higher in both HD (3.264 vs 2.218, p=<0.0001) and cirrhosis (2.632 vs 2.218, p=0.016). When cirrhotic patients with DM and IHD were excluded, this difference became insignificant (2.352 vs 2.157, p=0.209).

Despite high levels of cumulative metabolic stress in both HD and cirrhosis, tissue AGE is only increased in HD. Both conditions are associated with elevated serum AGE levels but the mechanism underlying the differential tissue deposition is unknown. One hypothesis which may explain the reduced CV risk in cirrhosis is that soluble receptor for AGE (RAGE) acts as a decoy receptor preventing AGE-RAGE interaction and the resulting endothelial dysfunction.

P104

High cut-off haemodialysis improves pro-inflammatory status when used in a chronic haemodialysis schedule: an open-label crossover study

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Objectives: Retention of middle molecular weight molecules may contribute to the pro-inflammatory status of patients requiring chronic haemodialysis. This study firstly determined whether removal of middle molecular weight molecules is increased by using a dialyser with a high molecular cut-off (50kDa) compared with a high flux dialyser (10kDa). Secondly, the activation status of monocytes and levels of pro-inflammatory cytokines were analysed.

Methods: This was an open-label crossover study. Thirteen prevalent chronic haemodialysis patients on a standard 3x week haemodialysis prescription were recruited, underwent a two week wash-in period (6 dialysis sessions) using a standardised high flux dialyser (Gambro Polyflux 170H) and then received two weeks treatment (6 dialysis sessions) using the Gambro HCO 1100TM. Kappa and lambda serum free light chains (22.5 kDa and 45 kDa respectively) were measured pre- and post each dialysis session as markers of middle molecular weight proteins. Monocyte activation status as determined by expression of surface markers associated with cell trafficking and cell activation was assessed by flow cytometry. A panel of cytokines were measured using a 25-Plex AB Bead Kit (BioSource^{TM}).

Results: There were no clinical adverse events associated with high cut-off dialysis. Individual high cut-off dialysis sessions resulted in significantly greater reductions in serum concentrations of middle molecules than high flux dialysis sessions (both $P<0.001$). After two weeks high cut-off haemodialysis, pre-dialysis serum free kappa and lambda were both reduced significantly, by 15% (0-28) and 19% (3-24) respectively (both $P<0.01$). Expression of the monocyte cell surface trafficking and activation markers CCR2, CX3CR1, CD11b and CD163 were all down regulated (all $P<0.01$). Serum albumin was reduced by a median of 3g/L (range 0-8) ($P<0.01$). Across the panel of pro-inflammatory cytokines measured there was a significant decrease in serum concentrations after the two week treatment period ($P<0.01$).

Conclusion: High cut-off haemodialysis significantly reduces concentrations of middle molecular weight proteins in chronic haemodialysis patients. Further, there was a reduction of circulating determinants of systemic inflammation that may be important for accelerated cardiovascular disease. Longer-term clinical trials are now required to determine whether these effects translate to improved outcomes for chronic haemodialysis patients.

P105

Tissue Advanced Glycation Endproduct concentration in dialysis patients

Natasha McIntyre[1], Christopher McIntyre[1,2], Stephen John[1], Lindsay Chesterton[1], Helen Jefferies[1], Shvan Korsheed[1], Paul Owen[1], James Burton[1], Richard Fluck[1]

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Recent work has concentrated upon the role of oxidative stress, vascular change and their relative contributions to the overall cardiovascular morbidity and mortality in CKD. Several factors such as hyperglycaemia, oxidative stress and reduced renal clearance appear to increase the production of advanced glycation endproducts (AGE). These products result from the Maillard reaction, a biochemical process occurring in all tissues. Tissue AGE are a measure of cumulative metabolic stress. Assessment of tissue AGE by skin autofluorescence (AF) correlates well with cardiovascular outcomes in HD patients. This study aimed to measure and compare tissue AGE levels in HD and PD patients, and evaluate the impact of systemic PD glucose exposure.

115 established dialysis patients (62 HD, 53 PD) had tissue AGE measured using a cutaneous AF device (AGE Reader®). Values were compared with an age matched non-CKD database. Past medical history of diabetes mellitus and ischaemic heart disease (IHD), drug treatment, haematology and biochemistry results and 6 month time averaged dialysis adequacy were recorded. PD glucose exposure was determined from review of all previous PD solution delivery data.

There were no differences in IHD or smoking history, statin or ace-inhibitor use, lipids, biochemistry or prevalence of diabetes. >90% of both groups had met current dialysis adequacy targets. PD patients were similar in age to HD (62.5± 15.5 vs. 65.3±13.1 years, p=0.34) but had a shorter dialysis vintage (38.4±14.3 vs. 51.7±34.7 months, p<0.01). Skin AF correlated with age in both groups, but dialysis vintage only in PD. Despite PD patients being younger, with a lower vintage, skin AF was similar to HD (3.58±0.75 vs. 3.7±0.88, p=0.33). Skin AF in PD patients was associated strongly with the degree of historical PD glucose exposure.

Cumulative metabolic stress and transient hyperglycaemia results in grossly elevated levels of tissue AGE in dialysis patients. In PD patients this high level of AGE deposition is associated with historical glucose exposure. This observation provides a previously unappreciated potential link between PD exposure to glucose and systemic cardiovascular disease.

P106

Pre-emptive replacement of haemodialysis water treatment components results in increased haemoglobin at lower doses of erythropoiesis-stimulating agents.

Seema Singh, Peter Choi, Simon Beagle, Neill Duncan, David Taube, Thomas Cairns, Peter Hill, Marina Loucaidou

Imperial College Kidney and Transplant Institute, London, United Kingdom

Introduction: The provision of maintenance haemodialysis requires delivery of large volumes of water without microbial or chemical contaminants. Technical guidelines seek to identify safe thresholds for water quality and have been used to indicate a need for replacement of water treatment components.

Methodology: We performed a prospective analysis of clinical trends following pre-emptive replacement of water system filters, in the absence of prior microbiological failure.

Results: 518 patients received maintenance haemodialysis on five water treatment systems that underwent replacement of key components in 2008. Component replacement was performed when monthly Haemoglobin (Hb) trends were judged to show an adverse trend, despite the absence of microbiological failure, as judged by endotoxin levels and colony-forming unit counts.

The mean monthly Hb of the three months preceding component replacement was significantly lower than the mean monthly Hb of the following three months (12.07g/dL; 95% CI 11.98-12.17 v 12.32; 95% CI 12.20-12.43, $p<0.0001$ by paired t test) (figure 1). This Hb rise was not due to increased doses of Aranesp, as the average body mass and Hb-adjusted dose over three months after component replacement was significantly lower than for three months before (0.059mcg/kg/g/dL; 95%CI 0.055-0.062 v 0.055mcg/kg/g/dL; 95% CI 0.052-0.059, $p<0.0001$)(figure 2)

In keeping with microbiological results, there was no statistical difference in pre and post intervention average CRP (14.3; 95% CI 12.6-16.0 v 15.2; 95% CI 12.3-19.6). Mean single pool Kt/V of all units exceeded the institutional target of 1.6.

We also performed a comprehensive analysis for haemolysis in one unit, and detected no significant haemolytic process.

Conclusion: Replacement of water system components results in significant increases in Hb and falls in ESA dose, even in the absence of technical microbiological failure. Formal cost-effectiveness analysis of this practice should be performed.

Figure 1
Change in Hb pre and post

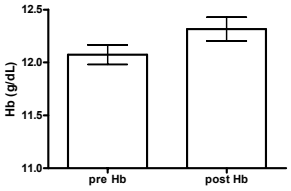
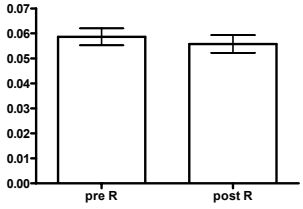


Figure 2
Change in R value



P107

Serum ADMA, SDMA and Arginine Levels and Vascular Calcification in CKD 4 and 5 Patients

Helen Jefferies[1], Stephen John[1], Mhairi Sigrist[1], Stefanie Bode-Boeger[2], Jan Kielstein[3], Christopher McIntyre[1,4]

[1]Renal Medicine, Derby City General Hospital, Derby, UK, [2]Institute of Clinical Pharmacology, Otto von Guericke University, Magdeburg, Germany, [3]Nephrology and Hypertension, University of Hannover, Hannover, Germany, [4]School of Graduate Entry Medicine and Health, University of Nottingham, Derby, UK

ADMA (endogenous inhibitor of NO synthase) is retained in renal failure and inadequately cleared by dialysis. ADMA predicts progression, CV complications and mortality in CKD. NO has been recently implicated as an initiator of VSMC transformation to an osteoblast like phenotype. Vascular calcification (VC) is an important risk factor for cardiovascular morbidity and mortality in CKD. The aim of this study was to investigate the relationships between VC, calcification inhibition (fetuin), and ADMA (with associated factors) in CKD 4, haemodialysis (HD) and peritoneal dialysis (PD) patients.

We studied 134 patients (46 CKD 4, 60 HD, 28 PD). Patients were well-matched for all general clinical and biochemical characteristics, as well as dialysis vintage (in the CKD 5 group). VC was quantitatively assessed by multi-slice CT of a standardised 5 cm segment of the superficial femoral artery. Arg, ADMA, and SDMA (μmol/L) were measured by liquid chromatography-mass spectrophotometry. Serum fetuin and OPG were quantitatively measured by commercially available ELISA.

Overall, ADMA was significantly correlated with calcification score ($r=0.33$, $p<0.001$).This effect was only seen within the HD patients, but ADMA levels were significantly higher in HD patients c.f. with the other groups. In HD patients alone, VC correlated with ADMA ($r=0.53$, $p=0.01$) and ADMA:SDMA ratio ($r=0.29$, $p<0.05$). When the analysis was restricted only to patients with significant VC these correlations were strengthened. The calcification score correlated with ADMA ($r=0.36$; $p=0.003$), SDMA ($r=0.47$, $p<0.001$), and ADMA:SDMA ratio ($r=-0.25$, $p<0.05$) in the whole patient group. Again though these relationships were largely confined to HD patients. In HD, VC correlated with ADMA ($r=0.44$, $p<0.01$) and SDMA ($r=0.38$, $p=0.03$). Fetuin levels negatively correlated with both Arg ($r=-0.21$, $p=0.04$) and ADMA:SDMA ratio ($r=-0.21$, $p=0.04$).

We have demonstrated for the first time that VC appears to be associated with reduced NO bioavailability in patients with CKD. Differences in ADMA levels between HD and PD/CKD 4 patients may be involved in the observed differences seen in severity and progression of VC between these groups.

P108

Serum ADMA, SDMA and Arginine levels: Prospective study of the effects of CKD and Dialysis Modality over 12 months

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ADMA, the most potent endogenous inhibitor of NO synthase (NOS), is increased in renal failure and predicts progression, cardiovascular (CV) complications and mortality in CKD. It is also implicated in reduced vasodilatory reserve and increased endothelial dysfunction. Longitudinal changes of ADMA as well as its structural isomer SDMA and the NOS substrate L-arginine (L-Arg) have not been investigated in patients with CKD yet.

134 patients (46 CKD 4, 60 HD, 28 PD) were studied at baseline and 12 months. Patients were well matched for all general clinical and biochemical characteristics as well as dialysis vintage (in the CKD 5 group). PD patients were treated with bicarbonate/lactate buffered fluid. HD patients received three sessions of at least 4 hours per week, utilising bicarbonate-based HD and low-flux polysulphone dialysers. L-Arg, ADMA, and SDMA were measured by liquid chromatography-mass spectrophotometry.

ADMA was higher in HD vs both PD (baseline 12%, 12 months 12%) and CKD 4 (24%, 17%). SDMA was lower in CKD 4 vs both PD (32%, 35%) and HD (36%, 28%). L-Arg was lower at 12 months in HD vs PD ($p=0.02$) and CKD 4 vs HD ($p=0.006$). L-Arg:ADMA ratio (indicative of bio-available NO) was lower in HD at 12 months vs PD ($p<0.001$) and CKD ($p<0.001$). Over 12 months L-Arg levels as well as Arg:ADMA ratio ($p<0.0001$) fell, SDMA increased and ADMA was unchanged. The effects varied by modality. The fall in serum L-Arg was particularly marked in HD patients.

In dialysis patients, ADMA is lower and L-Arg is higher on PD vs HD, indicating that PD is associated with higher relative NO bioavailability. The fall over 12 months in Arg:ADMA ratio is more marked in HD, apparently widening the separation in modality-related NO availability. The importance of SDMA, and the reasons for rising levels over 12 months require further investigation. These factors may be important in the development of structural and functional vascular disease.

P109

Serum ADMA, SDMA and Arginine levels: Associations with Fat, Muscle and Mortality in CKD 4 and 5

Stephen John[1], Helen Jefferies[1], Mhairi Sigrist[1], Stefanie Bode-Boeger[2], Jan Kielstein[3], Christopher McIntyre[1,4]

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ADMA (endogenous inhibitor of NO synthase) is retained in renal failure and inadequately cleared by dialysis. ADMA predicts progression, CV complications and mortality in CKD, and is implicated in reduced vasodilatory reserve and increased endothelial dysfunction. The roles of arginine (Arg) and SDMA (stereoisomer of ADMA) are less clear. Recent reports have associated fat mass with ADMA. The enzymatic machinery for production and degradation of ADMA is localised within adipocytes. We aimed to prospectively investigate these important vasoregulatory factors in CKD 4, HD and PD patients and their relationships with body composition (lean and fat mass) and mortality.

134 patients were studied at baseline and 12 months (46 CKD 4, 60 HD, 28 PD). Patients were well-matched for all general clinical and biochemical characteristics, as well as dialysis vintage. Vascular calcification (VC) and cross sectional muscle and fat areas were assessed by cross-sectional CT of a standardised section of the thigh. Arg, ADMA, and SDMA were measured by liquid chromatography-mass spectrophotometry. Outcome was assessed at 4 years.

At baseline and 12 months, fat area correlated with Arg (r=-0.22, p=0.03; r=-0.27, p=0.01 respectively) and Arg:ADMA ratio (r=-0.32, p=0.01; r=-0.25, p=0.02 respectively), and muscle:fat ratio correlated with Arg:ADMA ratio (r=0.31, p=0.002; r=-0.26, p=0.01). There were no consistent correlations with muscle area. Sub-analysis by modality did not reveal significant associations. Multivariate analysis demonstrated that Arg was predicted by gender (Adj R^2=0.043; p=0.022), SDMA by modality and age (Adj R^2=0.379; p<0.0001), Arg:ADMA by fat and VC (Adj R^2=0.081; p=0.007) and ADMA by gender, muscle, fat and modality (Adj R^2=0.352; p<0.0001). There were 38 deaths over 1495±121 days follow up. Cox-regression modelling demonstrated that mortality was predicted by gender, VC, modality, SDMA and muscle (overall model -2LL=196; p<0.0001).

These data demonstrate that nitric oxide bioavailability is associated with both fat and muscle mass in CKD 4 and 5. This is the first report of SDMA predicting mortality in preference to ADMA. Mortality risk is predicted by muscle mass and SDMA. Further quantification of the role of adipokines in this relationship will help to elucidate the pathophysiology resulting in this relationship more clearly.

Poster Session

Wednesday 22 April

13:00 – 14:00

Haemodialysis 2

Moderator Mr Ken Farrington

P110

Significant haemodialysis induced hypoglycaemia is seen in non-diabetic chronic dialysis patients dialysed using standard glucose dialysis solutions – a pilot study

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Introduction: Despite the wide usage of glucose containing (5.5 m mol/L) dialysis solutions, there is concern that significant intra and post dialysis hypoglycaemia may still be a problem on haemodialysis (HD), particularly in diabetics. Previous studies to assess the severity of the problem have yielded equivocal results. We used continuous glucose monitoring to ascertain the extent of this problem.

Method: 11 diabetic and 11 non-diabetic patients were studied. All had received high-flux HD thrice weekly for at least three months prior to the start of the study and were adequately dialysed. They were studied from the start of one dialysis session, during the post and interdialytic period (including two nights) and until the end of the next dialysis session - a continuous period of approximately 52 h. A dialysate glucose concentration of 5.5mmol/L was used.

Results: All 11 non-diabetic patients compared to 5 diabetic patients had blood sugars less than 5.5mmol/L on HD ($p = 0.035$). Similar differences extended into the two-hour post dialysis period. Non-diabetic patients experienced significantly more hypoglycaemia (blood sugar less than 3.5 mmol/l) during dialysis sessions than diabetics (18.9% of the sessions v 0.9%: $p = 0.048$). These differences extended into the period 2 hours post-dialysis (19.5% of the sessions v 3.4%: $p = 0.025$), though were not evident during the remainder of the interdialytic period. .

Conclusion: Despite the use of dialysis solutions containing 5.5mmol/L of glucose, significant hypoglycaemia occurs in non-diabetic patients during the dialysis session and in the immediate post-dialysis period. The mechanisms by which this occurs requires further study.

P111

Immunisation in Haemodialysis Patients: Fire Drills on Board the Titanic

S H Smith, J A McCaughan, N Leonard

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Introduction Infection is a major cause of morbidity and mortality in the haemodialysis population. The aetiology is multifactorial: uraemia, immunosuppressive therapy, comorbidities and advanced age all contribute.
It is the responsibility of primary care physicians to ensure that patients with chronic disease receive annual influenza immunisations and regular pneumococcal immunisations. A recent study demonstrated that an immunised cohort of patients had significantly fewer hospital admissions with influenza and pneumococcal infections, shorter lengths of stay in hospital and a lower all cause mortality when compared to an unimmunised cohort. It is the responsibility of nephrologists to ensure that patients on haemodialysis undergo a course of hepatitis B immunisation to minimise the risk of cross infection. There have been no outbreaks of hepatitis B infection in haemodialysis units in Northern Ireland in the past 30 years and there is a very low prevalence of hepatitis B in Northern Ireland.

Aim To ascertain what proportion of haemodialysis patients in a single centre received influenza, pneumococcal and hepatitis B immunisations within the recommended time frame.

Results There were 86 patients in our unit on haemodialysis. 69 patients (80%) had received an influenza immunisation in the preceding year. 30 patients (35%) had received a pneumococcal immunisation within the past 5 years. 86 (100%) had received or were receiving their hepatitis B immunisation course.

Discussion Infection provides a significant disease burden for the haemodialysis population and immunisation is a preventative measure which is highly successful in reducing the quantitiy and severity of infections. Immunisation against influenza and pneumococcal infection has been demonstrated to reduce morbidity and mortality in susceptible populations. Conversely, a similar effect has not been demonstrated since the introduction of hepatitis B immunisation. Our unit had a 100% immunisation rate for hepatitis B but there is scope to improve uptake of influenza and pneumococcal immunisations.

Immunisation in haemodialysis patients can be likened to fire drills on board the Titanic: significant resources are invested in minimising the risk of hepatitis B transmission in a population with a vanishingly low disease prevalence while simple immunizations for diseases with significant morbidity and mortality are overlooked. We are in danger of ignoring the iceberg in our midst.

P112

Effect of ethnicity on the causes of death in Haemodialysis (HD) patients- a single centre experience.

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There is some support from registry data that patients from Asian and Black ethnic groups have a survival advantage on HD. This may be a consequence of differing patterns of morbidity and mortality in ethnic groups. We conducted this prospective observational study from 2002-2007 of a prevalent HD population where cause of death was assigned in a weekly MDT of health professionals to ensure accuracy of recording the cause of death.
During this period, the prevalent population increased from 518 to 723.Approximately 50% of the population was Caucasoid with remaining population being evenly distributed between patients from the Indian Subcontinent (ISC) and Black Ethnic population. The total number of deaths observed during this period was 602 of which co-morbidity and mortality data was available in 476 patients (79.06%).These patients were divided in three groups based on their ethnicity. The three groups were similar in age, gender and duration of HD. However, the number of diabetic patients was higher in Black and ISC patients ($p<0.05$).The principle causes of death in these patient group is given in Table 1.

Principle causes of Death

Cause of Death	White (N=231)	ISC(N=110)	Black (N=63)
Myocardial Ischaemia and infarction	8(3.4%)	4(3.63%)	3 (4.76%)
Cardiac arrest/sudden death	36(15.8%)	19(17.2%)	8 (12.69%)
Cerebro-vascular accident	13(5.62%)	11(10%)	0 (0%)
All cause atherosclerotic cardiovascular mortality	59(25.5%)	37(33.63%)	12(19.04%)
Pulmonary infection (bacterial)	11(4.76%)	4(3.63%)	1(1.58%)
Septicaemia	38(16.45%)	18(16.36%)	20(31.74%)
All-cause infectious complications	50(21.64%)	24(21.81%)	23(36.5%)
Malignancies	16(6.92%)	2(1.81%)	2(3.17%)
Others	44(19.04%)	15(13.63%)	16(25.39%)

There was no difference in the causes of death in the three groups except for sepsis being commoner among the black ethnic groups. Contrary to previous literature, Cardiovascular mortality is lower in our cohort. This is important in power calculation of future RCTs on cardiovascular mortality and also highlights the importance of a dedicated mortality MDT in the assignment of accurate cause of death.

P113

The Burden of Transport on the "Dialysis Day": An Audit of Haemodialysis Patients in Berkshire

Helen Nye, David Meredith, Mobin Mohteshamzadeh, Emma Vaux, Lindsey Barker, Ramesh Naik

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Background

Reliance on transport is set to increase with an ageing dialysis population. Renal units are usually situated in urban areas with limited parking. Lack of local haemodialysis provision and inadequacy of transport are the commonest concerns cited by Kidney Patient Associations. Renal Association (RA) standards recommend that journey and waiting times for haemodialysis (HD) patients should be limited to 30 minutes.

Methods

Questionnaires were sent to 138 HD patients in December 2007 to assess our unit against RA standards. We measured the journey time to and from our unit and the distance travelled with predicted journey times using patient's postcodes and the Automotive Association (AA) Route Planner. Using t-tests, we compared differences between the time of dialysis slot (morning, afternoon, evening) and modes of transport (hospital, own, volunteer). The summation of journey time, waiting time and treatment time was used to gain an appreciation of the duration of a "dialysis day".

Results

112/138 (81%) patients responded. 54/112 (48%) patients live <5miles from the unit, 24 (21%) 5-10miles, 24 (21%)10-20miles, 10 (9%) 20-25miles and 1 patient >25miles. 39% of patients had a journey time longer than 30mins, and 71% waited more than 30min for transport before and after dialysis. On average, hospital transport journey times were 4.5 times those predicted by AA Route Planner, 2 times greater for own transport and 1.5 times greater for volunteer transport. The average dialysis day was 6 hours 50 minutes.

Average Time	Transport Modality			Dialysis Slot		
	Hospital	Own	Volunteer	Morning	Afternoon	Evening
Journey (mins)	39[a]	25	30	27	43[b]	29
Waiting (mins)	53.4[c]	38.5	54.2	40.9	55.6[d]	46.6

[a]p=0.0002 [b]p=0.004, [c]p=0.009, [d]p=0.0045

Discussion

A significant part of our patients' dialysis day is spent waiting for transport and travelling between our unit and home. Journey times are substantially longer than those predicted by AA Route Planner because of multiple pick-ups/set-downs for those using hospital transport, and traffic congestion for those dialysing in the afternoon slot. Transport issues should be addressed nationally if renal units are to reduce the increasing frustrations that patients are voicing through Kidney Patient Associations. Patients receiving pre-dialysis counselling should be aware of these issues when choosing haemodialysis as a modality.

P114

Defining Dialysis Dose Using "Standard Kt/V" in Incremental Haemodialysis

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Introduction: In an extension of the Kt/V urea concept, "Standard Kt/V" (Std Kt/V) has been proposed by Frank Gotch as a mathematical model allowing the combination of urea clearance from different dialysis modalities and residual renal function(RRF). Its use in incremental haemodialysis (HD) is recommended by the K/DOQI guidelines but this method is unvalidated in large studies. Recommended target Std Kt/V is 2 if residual renal urea clearance (KRU) is <2ml/min or 1.6 if >2ml/min for three times weekly HD. We aimed to establish the contribution of RRF to HD adequacy using the Std Kt/V model.

Methods: We analysed data from 650 patients starting incremental HD at our unit. Originally, dialyser clearance and RRF had been combined to achieve a target two-pool Kt/V of 1.2 (equivalent to Std Kt/V 2). We retrospectively applied the Std Kt/V model to calculate Total StdKt/V and its components from dialyser and RRF clearance.

Results: Mean Total Std Kt/V was 2.55 (SD 0.46) at 6 months after dialysis initiation and 2.33 (SD 0.29) at 5 years. Between 98.8% and 92.6% of patients achieved the target Std Kt/V in the first 5 years of HD. The proportion of patients failing to achieve minimum Std Kt/V adequacy targets was higher from 6 to 24 months in those with KRU<2ml/min compared to those with KRU>2 (1.5-12.6% versus 0-4% respectively, $p<0.001$ at each time point). Std Kt/V provided by RRF gradually declined from a median of 0.73 (interquartile range [IQR] 0.8) at 6 months to 0.19 (IQR 0.45) at 5 years. In those with KRU>2ml/min, RRF contributed a median Std Kt/V of 1.06 (IQR 0.59) at 6 months, declining to 0.92 (IQR 0.47) at 5 years. For those with KRU<2ml/min, the median Std Kt/V attributable to RRF was 0.27 (IQR 0.31) at 6 months and 0.14 (IQR 0.32) at 36 months.

Conclusion: Using this HD approach over 92% of patients achieve adequate dialysis. Failure to achieve target is more common if RRF is low and targets may need increasing. Further validation of the Std Kt/V methodology is required.

P115

Very High Incidence of Hepatitis C in Holiday Dialysis in Indian subcontinent – Follow-up

Durga Kanigicherla, R A Coward, L R Solomon

Royal Preston Hospital, Lancashire, United Kingdom

Seroconversion to Hepatitis C has significant implications on a) patient morbidity, b) prospects for renal transplantation and c) requirement for isolation facilities. We report our experience of haemodialysis patients taking holidays abroad – between Jan 2005 and June 2008.

58 patients took a total of 89 holidays during this period. 12 patients seroconverted to Hepatitis C on their return. The incidence was as follows

Europe / Americas / Aus & NZ	0/40 episodes	0%
Far East	0/3 episodes	0%
Mid East	0/14 episodes	0%
Africa	**1/10 episodes**	**10%**
Indian subcontinent	**11/22 episodes**	**50%**

All 11 (100%) patients had signs of biochemical hepatitis. The mean AST level was 6 times the upper limit of normal, 2-4 months after return. All these patients had to be isolated and dialysed at the central dialysis unit. The follow up data (upto 42 months) are as follows

Number Infected	12
Death	2 (17% - unrelated causes)
Spontaneous clearance	2 (17%)
Number treated with IFN	2 (After 1 yr of wait & watch')
Clearance with IFN	2 (100%)
Suspended from Transplant List	7 (58% - others were not on list)
Number Transplanted	1 out of 7 (14%)

Conclusion: Haemodilaysis patients travelling to Indian subcontinent have a very high risk of contracting Hepatitis C. This has major implications on morbidity, transplantation and subsequent dialysis on return.

P116

Investigating quality of life in matched older HD and PD patients: data from BOLDE study (Broadening Options for Long term Dialysis in the Elderly)

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Quality of life (QoL) is an important outcome in the older dialysis patient but there is limited data comparing haemodialysis (HD) and peritoneal dialysis (PD). The study aims to determine the impact of dialysis modality on QoL in 70 paired HD and PD patients aged ≥65 years, matched by sex, age, dialysis vintage, ethnicity and Index of Deprivation. We present results on the first 52 pairs. Mean age (72.9 v 73.3 years, range 65-89 years), sex (69 v 69% male), ethnicity (92% v 94% White European) and mean dialysis vintage (2.7 v 2.7 years, range 0.2-8.4 years) were similar in both groups demonstrating adequate matching. Social networks (those living alone or living with a partner), educational background (11.7 v 12.0 years), cognitive function (Trail Making Test-B and Mini Mental State Exam) and nutritional status (Subjective Global Assessment) were also similar in HD and PD. Patients on PD did have a lower co-morbidity score (mean Davis score 1.53 v 2.09: $p = 0.009$) and better physical functioning (Sit to Stand x 5, 63 v 40% completers: $p = 0.019$) but were similar in the Physical Component Score of the Short Form- 12 (SF-12) and hand grip strength. PD patients performed significantly better on the Mental Component Score of the SF-12 (55.3 ± 7.6 v 49.0 ± 15.1: $p = 0.004$) and had lower levels of probable clinical depression as assessed by the Hospital Anxiety Depression Scale (3.9 ± 2.7 v 6.1 ± 4.1: $p < 0.001$). The PD patients also experienced less illness intrusion as quantified by the Illness Intrusiveness Rating Scale (25 ± 10 v 31 ± 14: $p = 0.003$). We have demonstrated significant QoL advantages for older PD patients over HD patients when matched by sex, age, dialysis vintage, ethnicity and Index of Deprivation. Potential reasons for this observation could be that the PD group are a selected dialysis population that have managed on PD, 33% over 3 years. This will be addressed in the full data set by comparing HD and PD patients on dialysis ≤1 year. PD patients have commonly made an active modality choice and may have particular skills/traits that result in better adaptation to illness and/or treatment. The PD itself may result in less perceived treatment burden. The confounding effect of co-morbidity differences remains to be explored. The full data set from 70 pairs will amplify these findings.

P117

Factors affecting mortality in the first year of dialysis

Michael Wakefield, Julian Wright

Manchester Institute of Nephrology and Transplantation, Manchester, United Kingdom

An audit was performed to assess factors which determined mortality in the first year of dialysis.

Ninety seven patients commenced dialysis between May 2006 and May 2007. Average age was 53.7years (range 22-85); 65.3% male. Fifty nine percent of patients commenced haemodialysis and 41% peritoneal dialysis. The most common cause of end stage renal failure was diabetic nephropathy (24.4%) with IgA Nephropathy (15.6%) and Adult Polycystic Kidney Disease (10%) also being common.

The patients were at high risk of cardiovascular morbidity and mortality as at dialysis inception 28.6% of patients had ischaemic heart disease and 32.7% of patients were diabetic.

9.2% of patients commenced dialysis within three months of introduction to nephrology services; 45.8% of haemodialysis patients commenced dialysis with a functioning AV fistula or graft. In the first year of dialysis 8.3% of patients changed their dialysis modality, most commonly from peritoneal to haemodialysis. 20.6% of patients had died within one year of commencing dialysis.

Age (63.4±16.4 vs 51.9±16.9years; P=0.013) and non insulin dependent diabetes, (NIDDM) (36.8 vs 16.3%; P=0.044) were the only predictors of mortality within the first year of dialysis. Despite the high risks of cardiovascular complications, 63.6% of patients with NIDDM were prescribed calcium containing phosphate binders during the first year of dialysis.

This audit has led to a re-evaluation of cardiovascular risk stratification for diabetic patients commencing dialysis who are at high risk of cardiovascular complications. In light of the risk of coronary artery calcification for dialysis patients taking calcium containing phosphate binders, a new protocol for their use is being drawn up.

Poster Session

Thursday 23 April

13:30 – 14:30

Vascular Access – Catheters 1

Moderator Dr Gordon Bell

P118

The use of Confocal laser scanning microscopy (CLSM) to examine biofilm-containing catheters stained with DRAQ5 and Propidium iodide (PI)

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Introduction:

We have validated the use of CLSM to determine the number of live and dead cells of S*taphylococcus epidermidis* (CNS) and *Escherichia coli* (EC) in suspensions using a combination of the nucleic acid stains DRAQ5 and PI. We hypothesised that this technique could be used to determine the viability of cells within microbial biofilms on intravascular catheters and could serve as a tool to study the effects of substances on biofilms.

Objective:

To assess the performance of DRAQ5 (Biostatus Limited, UK) and PI (Invitrogen™ Corporation, USA) stains on biofilms formed on PVC catheters.

Method:

CNS and EC biofilms were grown on PVC catheters in the laboratory. Catheters were cut longitudinally and two millimetre segments were immersed in 1:1000 solutions of DRAQ5 and PI stains and examined with an upright CLSM (LSM510 META system, Carl Zeiss, UK) at 5, 10, and 20 minutes.

Results:

DRAQ5 appeared to penetrate cells of both species more efficiently than PI. PI appeared to be trapped within the biofilm material which might have prevented the stain from reaching the bacterial cells. Cells within biofilms were clustered together which made counting difficult.

Conclusion:

The combination of DRAQ5 and PI failed to determine the viability of bacterial cells within biofilms. Exopolysacharrides (EPS) produced by bacteria and a major component of the biofilm structure may prevent stains, especially PI, from reaching cells encased within the biofilm.

P119

Does the use of line locks lead to antibiotic resistant organisms as compared with systemic antibiotics alone in the treatment of haemodialysis catheter infections?

John Dixon, Maggi Steele, David Makanjuola

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INTRODUCTION - It has been suggested that instillation of a highly concentrated antibiotic solution (an antibiotic lock) into the catheter lumen after HD sessions, in conjunction with systemic antibiotics, may successfully treat episodes of Haemodialysis Catheter (HDC) infection and improve rates of catheter salvage. Some reports suggest that the repeated use of antibiotics leads to antibiotic-resistant organisms.

AIMS – to investigate whether our unit's policy of treating HDC infections with systemic antibiotics and inter-dialytic antibiotic-lock solutions has led to an increased prevalence of antimicrobial-resistant organisms above the rate expected with systemic treatment alone.

METHODS – Prospectively collected data of all HDC infections in our unit was analysed from 2003 to 2006. This included 8 months where HDC infections were treated with 2 weeks of systemic Vancomycin and Gentamicin, and the subsequent 36 months where a line-lock containing Vancomycin (10mg) and Gentamicin (8mg) was added to the systemic antibiotics during the inter-dialytic period. The organisms grown and their antibiotic sensitivities were analysed. Statistical analysis was performed using the Chi-Square test to detect a change in prevalence of infection, and Fisher's Exact test to assess for an increase in resistant organisms.

RESULTS – There were 265 positive blood cultures in the systemic antibiotics group (66% of 400 HDC's) and 662 in those treated with line-locks (32% of 2057 HDC's). The total number of HDC infections decreased from 66% to 24% ($p<0.0001$), but the proportion of gram +ve blood cultures increased ($p<0.0001$). The proportion of resistant gram +ve organisms did not change significantly: *MRSA* ($p=0.89$), vancomycin resistance ($p=1.00$). A significant increase in Gentamicin-resistance and Ciprofloxacin resistance was found in the *Enterobacter* group ($p<0.0001$ and <0.007 respectively), but not in the other gram negative groups. The number needed to treat to prevent a subsequent bacteraemia by using the line-lock technique was 3±0.4.

CONCLUSIONS - Our study demonstrates a statistically significant decrease in the number of HDC infections when using line locks, despite an increase in the total number of HDCs during the study period. The proportion of gram +ve organisms increased and there was an associated increase in the proportion of Gentamicin and Ciprofloxacin-resistant *Enterobacter* species.

P120

Long-term high adequacy haemodialysis can be delivered safely by Tesio-Caths

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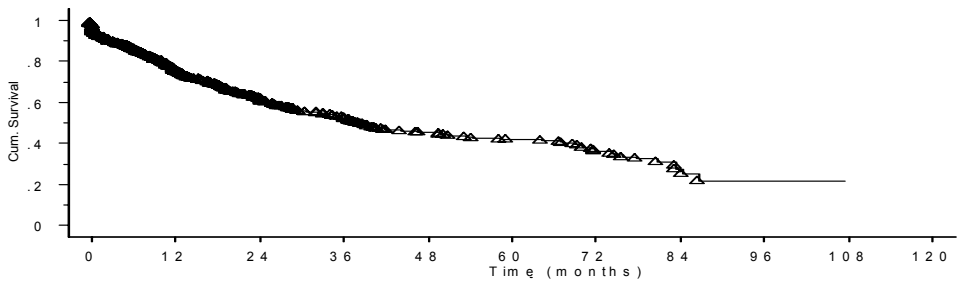
Imperial College Kidney and Transplant Institute, West London Renal and Transplant Centre, Hammersmith Hospital, DuCane Road, London, United Kingdom

Background. Despite a drive to form AVFs there has been a 50% increase in the use of central venous catheters, CVCs, 1998-2004 (USRDS 2007). 28% prevalent patients in DOPPS III used CVCs.

Methods. We prospectively studied Tesio-Cath (TC) insertions in 433 patients at our centre between Jan 1999-May 2008.

Methods. We studied 759 insertions (age 60±15yrs, 28% diabetic, 64% established on haemodialysis, mean dialysis duration 3.2±4.3yrs). At 1 year, 76% Tesio-Caths functioned compared with 68% AVFs and 49% AVGs (DOPPS II), and 42% functioned at 5 years. The mean spKt/V was 1.6±0.3. Unadjusted patient survival was: 87% at 1yr, 57% at 5yrs vs 81% and 44% respectively (UK Renal Registry 2007). There was no significant difference in patient and line survival in diabetics. 1, 2 and 3 year deaths per 1000 patient years were 143, 154 and 152 respectively. As a comparator at the same time points in USRDS 2007: 247, 211 and 214. There were 406 access-related admissions (0.47/1000 catheter days). 52% were for sepsis (9.7±15.8days), 48% for dysfunction (3.7±5.5days). As per CDC criteria, catheter-related sepsis rate was 0.34/1000 catheter days vs 0.8-2.4/1000 catheter days (published studies & USRDS 2007).

Conclusions. Use of Tesio-Caths at our centre is associated with low rates of infection and mortality and can deliver high dialysis adequacy. They offer an. effective dialysis access option for patients unsuitable or unwilling to have AVFs formed.



P121

An Observational Study of the Affect of Anticoagulation with Warfarin on Femoral Tunnelled Dialysis Catheter Associated Deep Venous Thrombosis and Patency.

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Aim: To establish whether anti-coagulation with warfarin reduces the incidence of femoral tunnelled dialysis catheter (TDC) associated deep venous thrombosis (DVT), increases catheter patency or improves dialysis adequacy.

Methods: A retrospective audit of all femoral TDCs from two renal units between 2003 and 2007 was undertaken. One renal unit routinely anti-coagulates all femoral TDCs with warfarin (target INR = 2.5) in patients without perceived contra-indication. The second renal unit anti-coagulates only in patients with a DVT or after requiring 2 urokinase locks.

Results: A total of 143 femoral TDCs were inserted. 7 lines were excluded from analysis due to incomplete data. A total of 14296 catheter days were analysed. 60 patients received warfarin and 76 did not. Patients on warfarin were older than those not on warfarin. Group demographics were otherwise comparable. Median INR was 1.9 (range 1.5 – 2.1) verses 1.0 (range 1.0-1.1) ($p< 0.0001$). 43% (n=33) not on warfarin were on anti-platelet therapy.

The incidence of DVT in both groups was equal at 8% (n= 5 versus 6; p=1.0). 20 (15%) patients died with a femoral TDC in place. There was no significant difference in mortality between the two groups (12% versus 17%; p=0.26). 14% of TDCs (n=19) were removed for infection. 30% of TDCs (n=41) were removed for other access. 8% of TDCs (n=11) were removed for other reasons. 31% of TDCs (n=43) were removed for loss of patency (one line remains in use). Of these TDCs, median patency was 54 days (range 19-190) on warfarin versus 48 days (range 26 – 71) off warfarin. There is a trend towards increased patency especially at 120 and 180 days. However this does not reach statistical significance, even when patients on anti-platelet agents are excluded from the analysis. Mean Kt/V is available in 52% of patients (n=71). Mean Kt/V was 1.28 in patients on warfarin versus 1.1 off warfarin (p=0.26).

Conclusions: Anticoagulation with warfarin does not or reduce the risk of clinically significant DVTs or improve dialysis adequacy with femoral TDCs. There is a trend towards increased patency of femoral TDCs in patients on warfarin. The unproven potential benefit of warfarin thus needs to be weighed carefully against the risk of harm from bleeding.

P122

Examination of tunnelled haemodialysis catheters using Scanning Electron Microscopy

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Background:

Tunnelled haemodialysis catheters (t-HDC) are prone to colonisation by micro-organisms resulting in increased morbidity and mortality. A previous study concluded that all culture-negative catheters removed from cancer patients were colonised by microbial biofilms when examined by scanning electron microscopy (SEM). Examination of t-HDC by SEM has not been published before.

Methods:

A total of 44 segments (0.5 cm each) from 11 *ex-vivo* t-HDC were examined by SEM prior to endoluminal brushing and quantitative culture to determine their colonisation status. An objective scoring system was used to record SEM findings.

Results:

Endoluminal brushing yielded a positive culture in two catheters. Meticillin-sensitive *Staphylococcus aureus* (MSSA) was grown from one catheter and a *Streptococcus* species was cultured from the second. SEM examination revealed universal endoluminal coverage by adherent biological material (ABM) which was composed of fibrin, platelets and other host-derived products. However, bacterial cells were visible on the two culture-positive catheters, two out of nine culture-negative catheters and were possibly present on one culture-negative catheter.

Conclusion:

In this study, the prevalence of microbial colonisation of *ex-vivo* t-HDC was 18% using the endoluminal brushing technique and 36% when examined by SEM. The previously reported universal microbial colonisation of central venous catheters is likely to represent coverage by ABM rather than by microbial biofilms.

Poster Session

Wednesday 22 April

13:00 – 14:00

Myeloma & CKD

Moderator Dr Paul Cockwell

P123

Incidence of significant haemorrhagic complications of renal biopsies in patients with and without monoclonal gammopathies.

Colin Hutchison[1], Jennifer Pinney[2], Poorva Jain[3], Tarek Ghonemy[1], Paul Cockwell[1]

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Background: Monoclonal gammopathies are frequently associated with renal pathologies. Principally the renal pathologies are a direct consequence of the excess free light chains produced by the clonal expansion of plasma cells. These monoclonal free light chains can result in a number of different renal pathologies which in turn can present in several different clinical presentations. In addition, patients with monoclonal gammopathies frequently have other potential causes of renal injuries such as hypercalcaemia and nephrotoxic medications. Therefore, renal injury in the context of monoclonal gammopathy is often investigated with a renal biopsy. However, patients with monoclonal gammopathies are believed to be at higher risk of developing haemorrhagic complications of a renal biopsy, although the incidence of this complication has not been clearly defined.

Study aim: The purpose of this study was to determine the incidence of severe bleeding episodes in patients with confirmed monoclonal gammopathies.

Methods: A retrospective audit of prospectively collected data from the renal units of three large teaching hospitals in the U.K. was undertaken. The rates of significant bleeding complications post renal biopsy were determined for unselected patients with and without monoclonal gammopathies. A significant bleeding complication was defined as macroscopic haematuria, a haematoma on radiological investigation or a drop in haemoglobin with no other cause identified.

Results: In total the outcomes of 728 patients were reviewed, of these 59 had monoclonal gammopathies identified as the cause of their renal injury. The renal pathologies of this group were: amyloidosis (10), cast nephropathy (40), light chain deposition disease (1), intraglomerular crystal formation (1); acute tubular necrosis (7). Two of these patients had significant bleeding post biopsy although neither required intervention. Of the remaining 669 patients 13 had significant bleeding post procedure. There was no significance difference between these event rates of 3.4% and 1.9%, respectively, P=0.54.

Conclusion: The incidence of significant bleeding episodes complicating renal biopsies in patients with monoclonal gammopathies was not significantly raised.

P124

Multiple myeloma induced renal disease - does renal histology affect outcome?

Richard Fish, James Adams, Chris Jones, Hugh Cairns, Satish Jayawardene

King's College Hospital, London, United Kingdom

Background: Cast Nephropathy (CN) is the commonest pathology in Multiple Myeloma (MM) induced renal failure. Native renal biopsy (NRbx) is not always performed despite its benefit in determining underlying histology and subsequent treatment strategies.

Aim: To describe the characteristics of CN and Other pathologies in MM, and whether renal histology predicts patient survival and recovery following acute renal event.

Method: Retrospective analysis of all patients with MM attending one renal unit between 1996 & 2007. Renal pathology was classed as either CN or Other, (Acute Tubular Necrosis, Amyloid, Glomerulonephritis, and Fibrosis/Ischaemia).

Results: 80 patients with MM were identified. 57(71%) underwent NRbx and classed as CN (41(72%)) or Other (16(28%)) pathology. There was no difference in characteristics, however those with CN were more likely to die or reach ESRD. Following an average (sd) follow-up of 2.5(3.5) years, death or progression to ESRD was significantly more likely in CN after adjustment for age and sex (RR 2.1; 95%CI 1.04-4.4; p=0.039).

	CN (41(72%))	**Other (16(28%))**	**All biopsy 57(100%))**	**P Value**
Male Gender	22(54%)	9(56%)	31(54%)	0.86
Age (mean sd)	66(11)	63(8)	65(10)	0.33
White race	34(83%)	11(69%)	45(79%)	0.61
Diabetic	2(5%)	1(7%)	3(5%)	0.79
Hypertension	6(15%)	5(31%)	11(19%)	0.15
Vascular Disease	5(13%)	3(20%)	8(15%)	0.53
Presenting GFR (median, IQR)	9(6-13)	13(7-28)	9(6-15)	0.09
ESRD	26(63%)	9(56%)	35(61%)	0.62
Death	29(73%)	7(44%)	36(63%)	0.05

Conclusion: This study confirms CN is the most common renal pathology in those with MM presenting to a renal service and is associated with significantly worse outcome. NRbx therefore has a role in determining both pathology and prognosis.

P125

Survival and renal prognosis in patients with multiple myeloma or MGUS attending a renal unit

James Adams, Richard Fish, Chris Jones, Hugh Cairns, Satish Jayawardene

King's College Hospital, London, United Kingdom

Background: Multiple myeloma (MM) and monoclonal gammopathy of uncertain significance (MGUS) are different ends of the spectrum of plasma cell dyscrasias, and usually present to either haematology or nephrology.
Aim: To compare the rate of death and progression to end-stage renal disease (ESRD) in patients presenting to a renal service with either MM or MGUS.
Method: This retrospective study analysed the characteristics of all patients with MM & MGUS attending a renal unit between 1996 & 2007.
Results: 161 patients with MM (80(49%)) or MGUS (81(51%)) were identified. At presentation MM were older with worse renal function but less comorbid illness than MGUS. After an average follow-up of 4.7(3.8) years, death or progression to ESRD was more likely in MM compared to MGUS (RR 3.7 (95% CI 2.4-5.9, p<0.001)), and remained despite adjustment for age, sex, comorbid illness, ethnicity, GFR, or paraprotein level (RR 3.7 (95% CI 1.7-7.9, p=0.001)). The only other factor independently predictive of death or ESRD was GFR at presentation (RR 0.95; 95%CI 0.93-0.97; p<0.001).

Characteristics & outcomes	**MM (80(49%))**	**MGUS 81(51%))**	**Total (161)**	**P value**
Male gender	49(61%)	50(62%)	99(62%)	0.54
Age (mean, sd)	70(11)	66(12)	68(12)	0.05
White race	62(78%)	44(54%)	106(66%)	0.01
Diabetic	4(5%)	20(25%)	24(15%)	0.001
Hypertension	21(26%)	53(68%)	74(47%)	<0.001
Vascular Disease	15(21%)	27(37%)	42(29%)	0.04
Presenting GFR (mean, sd)	15(14)	38(21)	27(21)	<0.001
ESRD	47(59%)	15(19%)	62(39%)	<0.001
Death	53(66%)	24(30%)	77(48%)	<0.001

Conclusion: MM presenting to renal service is associated with worse outcome than MGUS. Presenting GFR is also predictive of renal prognosis or death, hence prompt referral to nephrology services is recommended when there is evidence of renal involvement.

P126

Screening for Monoclonal Gammopathy in Patients with Unexplained Renal Failure

Michael Petchey[1], Simon Fletcher[1], Josie Hobbs[2]

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The quantitative measurement in serum of free immunoglobulin light chains (FLC) may be used in the investigation of multiple myeloma and related plasma cell disorders. FLC measurement has been recommended by the International Myeloma Working Group. Monoclonal FLC production is indicated by the presence of an abnormal κ to λ FLC ratio (reference range 0.26–1.65). Monoclonal FLC frequently cause kidney disease in patients with plasma cell disorders.

An increased κ to λ FLC ratio has been found in the presence of renal failure without any evidence of monoclonal gammopathy, caused by the loss of preferential clearance of κ FLC monomers over λ dimers by the kidneys. A modified reference range for use in renal patients has been suggested (κ to λ FLC ratio 0.37 – 3.1), to increase diagnostic specificity without loss of sensitivity.

The use of serum FLC measurements was investigated in patients (400 anticipated) screened for monoclonal gammopathy when presenting with unexplained acute or chronic renal failure to renal clinics between Sep 2008 and March 2009. The FLC measurements were compared with results from serum protein electrophoresis, immunofixation, and urine electrophoresis. The κ to λ FLC ratio was correlated to estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) stage to support the use of a modified reference range in renal failure patients. The serum FLC results were correlated with final diagnosis to enable calculation of diagnostic sensitivity and specificity of a modified renal reference range. Recommendation of the use of a serum only screening algorithm for investigation of monoclonal gammopathy in patients presenting with renal failure was evaluated.

P127

Hereditary fibrinogen A α-chain amyloidosis: phenotypic characterization of a systemic disease and the role of liver transplantation.

Arie J Stangou[1], John O'Grady[1], Mohamed Rela[1], Bernard Portmann[1], Elizabeth Sizer[1], Julia Wendon[1], Mark Monaghan[2], Nicholas Gall[2], Philip MacCarthy[2], Nicholas Banner[3], Muriel Buxton-Thomas[4], Christopher J Mathias[5], Nigel D Heaton[1], Bruce M Hendry[6], Merrill D Benson[7]

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Background: Variants of fibrinogen A α-chain (AFib) cause the commonest type of hereditary amyloid nephropathy in the UK. Variant fibrinogen is produced in the liver, and almost all isolated renal allografts reportedly fail within 1-7 years with recurrent amyloidosis.

Patients: We report the clinical features and outcome of 21 patients with AFib and stage 3-5 chronic kidney disease (CKD), who were assessed for combined liver and kidney transplantation (LKT). Twenty had E526V, and one the R554L variant.

Results: Coronary atherosclerosis was identified in 67 percent of cases, and carotid or aortic atheromatosis in 57 percent. Vascular atheroma excised at endarterectomy in one patient contained amyloid solely derived from variant fibrinogen. Endomyocardial biopsies in 3 patients, revealed fibrinogen amyloid. Half of cases had autonomic neuropathy. Eight patients received LKT between January 1996 - 2008, in 2 cases at stage 4 CKD pre-emptively before haemodialysis. Six patients are alive, with good dual allograft function and no progressive amyloidosis, after a median 49.5 (24-147) months' follow-up. In contrast to inexorable progression to complete ESRF in the disease natural course, dynamic and static renal scintigraphy in the 2 cases of pre-emptive LKT, demonstrate preserved native kidney residual function up to 5 years follow-up. Three explanted livers were used successfully for domino liver transplantation in patients with cirrhosis and hepatocellular cancer.

Conclusions: Fibrinogen A α-chain amyloidosis is a systemic disease with multi-visceral, vascular, cardiac and neurological amyloid involvement. Combined liver and kidney transplantation can be curative, however, cardiovascular disease may restrict successful access to this option. Our data encourage evaluation of pre-emptive solitary liver transplantation early in the course of amyloid nephropathy to prevent requirements for haemodialysis and kidney transplantation.

Poster Session

Thursday 23 April

13:30 – 14:30

PD 1

Moderator Prof Simon Davies

P128

Uptake of Peritoneal Dialysis in Northern Ireland: Analysis of Demographic, Clinical and Social Factors

Ying Kuan[1,2], Frank McCarroll[2]

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Introduction

Numerous studies have highlighted the equivalence and even superiority of peritoneal dialysis (PD) in comparison with haemodialysis (HD) in both clinical outcome and quality of life measures. Despite this however, the uptake in recent years of PD worldwide has continued to decline. This study assesses factors that influence the uptake of PD in Northern Ireland (NI), focusing on demographic, clinical and social influences.

Method

NI patients who commenced renal replacement therapy (RRT) between1st January 2005 and 31st of December 2006 were included in this study. Data, (age, gender, marital status, number of comorbidities, presence of diabetes and late presentation) were collected from the regional database system and analyzed.

Results

211 patients for whom there was complete data set were included in this analysis. The median age of the population was 68 years (16) and primarily male (133 vs 78 female). At commencement, the modality of choice was HD in 85% of this population. Using logistic regression, patients were more likely to commence RRT using HD if they were older, had larger numbers of comorbidities, female or if they presented late ($p<0.05$). Presence of diabetes did not influence this, and surprisingly despite the intuitive feeling that social support may favour uptake of PD, nor did marital status.

Conclusion

The study would suggest that the main drivers of PD uptake in our population are clinical factors, including significant presence of comorbidities. However, early access to education also positively influences the likelihood that patients will choose PD as the first modality. The impact of the National CKD initiative on number of late referrals, and how this may influence future patterns of modality choice remains to be seen. Contrary to expectation however, marital status and a presumed access to better social support does not influence the likelihood of patients embracing a home dialysis modality.

P129

Pneumoperitoneum in peritoneal dialysis patients; one centre's experience

Muhammad Imran, Rammohan Bhat, Hameed Anijeet

Royal Liverpool University Hospital NHS Trust, Liverpool, United Kingdom

Introduction: The pneumoperitoneum (PP) on upright chest x-ray usually indicates a perforated viscus. However its incidence and clinical significance in peritoneal dialysis (PD) patients has been the subject of debate in the literature (variable incidence from 4% to 34% reported in previous studies). With improvement in patient's training and connecting devices of PD catheter, technique related PP is quite rare. Following a recent patient with PP, We reviewed our three years data to evaluate the incidence and significance of this radiological sign in PD patients.

Patients and methods: We reviewed all upright chest x-rays, our PD patients had from 2006 to 2008, using electronic radiology database. Over 3 years our PD programme had total 156 patients (mean age 55, range 21 - 85 years, 67 female and 89 male, 83 patients were on automated PD and 73 on continuous ambulatory PD).We reviewed total 312 upright chest x-rays (mean 2 x-rays /patient) which were performed for various clinical reasons in the period when the patient had PD catheter in situ.

Results: 7 PD patients had 11 x-rays showing free air under the diaphragm (total incidence of PP 3% per PD patient and 4% per x-ray performed in PD patient). One patient had two episodes of PP with total 4 x-rays demonstrating free air .Two patients had surgical complications of PD catheter insertion and needed laparotomy. Five patients had incidental PP which was possibly technique related. One of these five was symptomatic (abdominal pain which was worse on eating and defecation and intolerance to day time dwell).We established that the cause of PP was faulty technique. Aspiration of PP (total 250 ml air was aspirated via PD catheter) in Trendelenburg position gave her immediate symptomatic relief. We also retrained her to prevent further episodes of PP.

Conclusions: This study demonstrates quite low and falling incidence of PP (<4%) possibly due to improvement in training and technique. The air should not enter the peritoneal cavity in normal, properly performed exchanges. Air under diaphragm in a PD patient requires appropriate evaluation to exclude visceral perforation. After that patient's technique for PD exchanges should be reviewed. However if PP persists aspiration of air can give symptomatic relief.

P130

What additional impact does end stage renal failure (ESRF) have in patients with heart failure and normal ejection fraction (HFNEF)?

Frauke Wenzelburger[1], Kay B Tan[2], Biju John[1], Eveline Lee[1], Yu Ting Tan[1], John E Sanderson[3]

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INTRODUCTION: Many patients with ESRF develop HFNEF. Whether their echocardiographic findings are comparable to hypertensive HFNEF patients with normal renal function is not known. We hypothesized that ESRF has an additional impact on the myocardial diastolic and systolic dysfunction.

METHODS: 17 peritoneal dialysis (PD) patients (9 female mean age 68±10years) and 17 age and gender matched hypertensive (HT) and HFNEF patients with normal renal function were recruited. Duration of HT: 12.2±10.6years in PD versus 11.8±10.1years in non-ESRF. Additionally a group of 17 age matched healthy control subjects were included. Full Doppler-2D-echocardiography and tissue-Doppler-Imaging were performed and images analysed off line (EchoPac-Software, GE). Left atrial volume index (LAVI) and LV mass index (LVMI) were derived from 2D images or M-Mode, respectively. Systolic (Sm_{colour}) and peak early diastolic annular velocities (Em_{colour}) were assessed by Colour-Tissue Doppler Imaging at the mitral annular level at septal, lateral, inferior and anterior wall and values averaged. Speckle tracking was performed tracking three cycles of apical short axis and 4-Chamber long axis images.

RESULTS:

	PD Patients	HT non-renal Patients	p value #	Healthy Controls
LV Ejection fraction (%)	58±7	61±9	0.237	62±8
LVMI (g/m2)	113.1±33.5	81.3±29.6	0.012	84±20*
LAVI (ml/m2)	27.8±11.1	28.7±8.2	0.772	22.9±8.4
E/A ratio	0.7±0.14	0.87±0.2	0.008	0.83±0.18*
E/E'pw ratio	10.4±3.6	10.2±4.0	0.885	7.5±1.8*
Smcolour	5.5±1.5	5.4±1.2	0.877	5.9±1.0
Emcolour	4.1±1.1	5.1±1.0	0.020	5.4±1.1*
Apical Rotation (◦)	10.5±4.1	11.2±3.4	0.620	13.9±3.0*
Global Long. Strain (%)	-19.4±2.3	-19.2±3.4	0.925	-21.8±2.3*

t-test comparing PD and HT non-renal; * p<0.05 One way ANOVA comparing patients with healthy controls

CONCLUSIONS: Subjects in both patient groups showed a reduced systolic and diastolic function compared to healthy controls. PD patients showed a significantly higher LVMI, E/A ratio and lower Em_{colour} compared to HT non-renal patients. Peritoneal dialysis seems to be a sufficient treatment to prevent fluid overload since E/E'pw ratio as a surrogate parameter for left atrial pressure was comparable in both patients groups.

P131

Predictive Value of Periscreen Strips and Dialysate Cell Counts Predicting Relapsing Peritonitis

Catherine Lane, Sally Punzalan, Ruby Tayab, Stanley L-S. Fan

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Introduction: Effective treatment of Peritoneal Dialysis (PD) peritonitis is the goal in the management of PD peritonitis. While factors predicting treatment failure are well established, predictors of relapse are not clearly defined. We aimed to identify these factors, which when present will allow modification for treatment, potentially reducing morbidity and mortality, with particular attention to the predictive value of leukocyte count (WCC) and point-of-care PeriScreen (leucocyte esterase) measurements on PD effluent.

Methods: We conducted a prospective study of 138 episodes of peritonitis. Effluent samples were analysed for WCC and PeriScreen score on days 3 and 5. Comorbidity data was collated from these patients.

Results: Effluent WCC and PeriScreen score were found to correlated closely ($p<0.0001$, figure 1). There were no statistically significant differences in age, dialysis vintage or sex. Patients who subsequently relapsed had a higher PeriScreen score at both day 3 and day 5 ($p<0.05$). The predictive power of the microscopic evaluation of WCC was inferior to the PeriScreen strip. The burden of co-morbidity and Karnofsky scores were similar for relapsers and non-relapsers.

Conclusion: We have shown that if a PeriScreen strip analysis of PD effluent on day 5 of PD peritonitis treatment is positive, the patient has a high risk of relapse of the peritonitis despite initial clinical response to treatment.

Figure 1 – Correlation between PeriScreen and White Cell Count

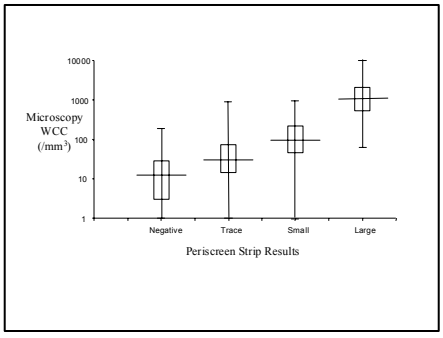

Table 1 – Sensitivity and specificity of PeriScreen Strips to predict relapse of PD peritonitis

Periscreen result	Sensitivity (%)	Specificity (%)
Trace	100	45
Small	50	98
Large	10	98

P132

A Retrospective Comparison Of Two Groups Of Long Term PD Patients – Why Do Some Develop Encapsulating Peritoneal Sclerosis and Others not?

Anne-Marie Habib, Emma Preston, Andrew Davenport

Royal Free Hospital, London, United Kingdom

INTRODUCTION AND AIMS: *Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis (PD) that has been suggested to be related to length of time on PD, number of peritonitis episodes and changes in peritoneal membrane permeability. Not all patients with these 'risk factors' though go on to develop EPS and other factors such as genetic susceptibility are likely to be involved.*

The aim of this study was to retrospectively compare two groups of patients who have had long term exposure to PD (4 years or more) and try to establish predictive markers for those that developed EPS compared to those that did not.

METHODS: *Retrospective data was collected on 37 patients with EPS and compared with data from 43 PD patients with a similar length of time on PD. Demographic characteristics, PD modality, length of time on PD, membrane characteristics, peritonitis episodes, co-morbidity and mortality data were collected.*

CA-125 levels were also measured as a marker of mesothelial mass.

RESULTS: *Demographic characteristics were similar between the two groups except for race (40% Caucasian in the EPS group vs. 70% in the control group; P<0.001).*

There were more patients on cycling PD with day time exchanges (CCPD) compared to continuous ambulatory PD (CAPD) in the EPS group (73% vs 50%; p=0.046).

There was no difference in the length of time on PD, number of peritonitis episodes, ultrafiltration or membrane characteristics in both groups.

Mean time on PD for both groups was 5.9 years.

The mean value of CA-125 was similar in both groups.

There was increased morbidity, hospital admissions and mortality in the EPS group.

CONCLUSIONS: *Exposure to higher volumes and concentration of dextrose with CCPD compared to CAPD appears to increase the risk for developing EPS.* Therefore patients initiating therapy should have peritoneal dialysis prescribed according to residual renal function and transporter status rather than as a lifestyle choice.

Poster Session

Wednesday 22 April

13:00 – 14:00

PD2

Moderator Dr Edwina Brown

P133

Substantial improvement in Peritoneal Dialysis survival compared with Haemodialysis in the Unites States; A Longitudinal Trend Analysis: 1995-2004

Austin Stack[1], Isam Yousif[2], Catherine Wall[1]

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Introduction and Aims: While mortality differences exist between peritoneal dialysis (PD) and haemodialysis (HD), the magnitude, extent and direction of these differences has not been evaluated in successive population-based cohorts.
The aim of this study was to evaluate mortality differences and period trends between HD and PD in three successive calendar periods: 1995-1998, 1999-2001 and 2002-2004.

Methods: National incidence data was collected on all new dialysis patients (N=1,003,305) who started treatment from 1995 to 2004 and were followed up to 4/10/2006. Interval Cox regression models allowing for non-proportional hazards evaluated the relative hazard of death by dialysis modality using intent-to-treat and as-treated analyses with a propensity –based multivariable risk adjustment.

Results: For younger patients (< 50 years), and middle age patients (50-70 years) adjusted mortality risks were significantly lower at for PD compared to HD in the 2002-2004 period (RR=0.71 95% CI 0.61-0.84) and RR=0.82, 95% CI 0.76-0.89) respectively) . For older patients (> 70 years), mortality risks were equivalent for PD and HD (RR=0.99, 95% CI 0.91-1.06).

In the trend analysis, for Peritoneal Dialysis, adjusted mortality risks were significantly lower in more recent cohorts who started therapy (1999-2001- RR=0.90, 95% CI 0.86-0.94 and 2002-2004- RR=0.79, 95% CI 0.76-0.84) compared with earlier cohorts (1995-1998 (RR=1.00, referent group).

For Haemodialysis, the improvement was less dramatic (1999-2001; RR=0.98, CI 0.97-0.98) and 2002-2004; RR=0.95, CI 0.94-0.96).

Conclusions: The survival of patients has increased significantly on PD relative to HD from 1995-2005, particularly in older age groups. This is likely due to more effective delivery of PD care and management of PD complications in recent cohorts.

P134

Use of mupirocin cream and tunnel scan to reduce the incidence of PD Peritonitis

Syed Atif Mohiuddin, Hameed Anijeet, Gordon Bell, Peter Livesley, Pearl Pai

Royal Liverpool Hospital, Liverpool, United Kingdom

Introduction: Peritonitis remains the most serious complication of peritoneal dialysis (PD) resulting in considerable morbidity and mortality. Staphylococcus aureus (s. aureus) and gram negative infections are associated with the worst outcome. We compared the incidence of PD peritonitis, after introduction of exit site prophylaxis with mupirocin cream and use of tunnel scan for management of catheter related infections, with historic control. **Methods:** All patients were advised to use 2% mupirocin cream daily. Tunnel scan was performed in all patients with clinical evidence of tunnel infection or exit site infection with s. aureus or gram negative organisms. Repeat scan was performed at the end of antibiotic course and treatment was prolonged if there was evidence of ongoing infection. We gathered six months data on incidence of PD peritonitis after introduction of these measures and comparison was made with historic control. **Results:** Average number of PD patients at our institute was ninety. 81 percent patients were prescribed exit site prophylaxis. PD peritonitis rate was 0.41 episodes per patient year which was a significant improvement compared to 0.69 episodes per patient year in the historic control. Staphylococcus aureus peritonitis was not observed after introduction of new measures. Gram negative infection rate was 0.04 episodes per patient year, compared to historic control (0.19episode/ patient year). Gram negative infection rate was also considerably better than previously reported by Bernardini et al in 2005 with mupirocin cream. **Conclusion:** Exit site prophylaxis with mupirocin cream and use of tunnel scan in PD population is associated with significant reduction in the incidence of PD peritonitis. These measures should form integral part of management of all PD patients.

P135

A sustained reduction in PD peritonitis rates achieved using a multidisciplinary team approach.

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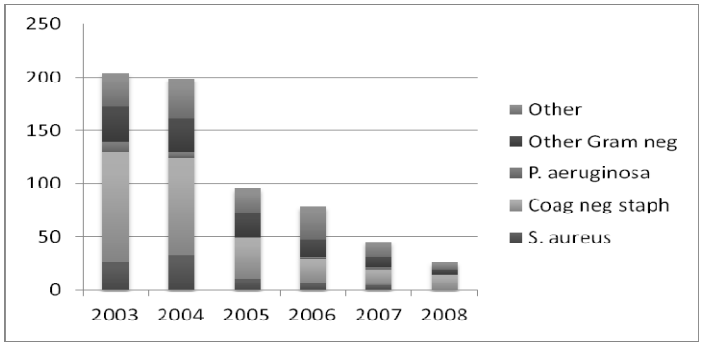
Peritonitis is a major cause of technique failure in peritoneal dialysis and may lead to serious complications including death. In 2004 our peritonitis rate was 1:14 patient months. In 2005 we adopted a multi-disciplinary approach to reduce infections associated with peritoneal dialysis. This involved introducing several simultaneous initiatives including pre-operative catheter insertion antibiotic prophylaxis with vancomycin; a peritonitis protocol that incorporated regular measurement of vancomycin levels; prophylactic use of mupirocin for exit site care; re-education of all team members; targeted re-training and routine refresher courses for patients and carers and regular reviews with the microbiology team. A patient care pathway was developed which assisted with root cause analysis of peritonitis episodes. Our results show that with careful attention to detail a sustained reduction in peritonitis rates including reductions in all isolates is achievable.

	2004	2005	2006	2007	2008
Patient months	**1949**	**1913**	**1913**	**1401**	**1033.5**
Peritonitis rate	**13.7**	**21.0**	**24.2**	**26.4**	**43.1**



P136

Seasonal variation in blood pressure in patients on peritoneal dialysis is mediated by temperature but not salt and water overload.

Sandhya Seneviratne, Stanley Fan, Arafat Mirza, Jakob Arhem

Royal London Hospital, Whitechapel, London, United Kingdom

Introduction: Seasonal changes of blood pressure in patients on haemodialysis have been studied in small groups of patients with equivocal results. We now study 619 patients on peritoneal dialysis from January 2003 to December 2008. The blood pressure variation due to changes in ambient temperature as well as the contribution due to fluid overload, sodium removal, residual renal function, age, ethnicity, gender and diabetes status are studied.

Method: Supine and standing blood pressures were measured at 26,101 hospital visits. Mean of supine and standing, systolic and diastolic blood pressures were calculated for each month. Estimate of fluid overload was made by calculating the difference between target weight and actual weight. It was assumed that patients were in steady state for sodium intake. Total sodium removed was the sum of sodium removed by ultrafiltration and of that passed in urine at a peritoneal equilibrium test. Average monthly temperatures were obtained from records published by UK Met. office.

Results: We showed a strong correlation between the changes in blood pressure and temperature . Linear regression analysis of mean blood pressure on mean temperature showed significant negative slopes. The inverse relationship was greatest for standing systolic blood pressure (regression coefficient -0.495 with t-value -5.48) and least for lying diastolic blood pressure (regression coefficient -0.183 with t-value -3.39). The effect of estimated fluid overload on blood pressure was much smaller and not significant. No correlation could be demonstrated between the amount of sodium removed and blood pressure. All ethnic groups did not show the same degree of correlation between blood pressure and ambient temperature.

Conclusion:A strong inverse correlation exists between ambient temperature and blood pressure. This was greatest for standing systolic blood pressures. Effect of temperature on blood pressure was not mediated by fluid overload or changes in sodium intake. Blood pressure in different ethnic groups behaves differently to changes in ambient temperature.

P137

Role of Tunnel sonography in detecting clinically asymptomatic catheter related tunnel infections in peritoneal dialysis patients with exit site infection and its outcome.

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Royal Liverpool and Broad Green University Teaching Hospital, Liverpool UK

Background: Catheter-related tunnel infection (CRTI) is an important cause of catheter loss in peritoneal dialysis (PD) patients. Both the type of cultured organism and the extent of inflammation are well known prognostic factors for the outcome of these infections.

Aim: Early detection by ultrasound and treatment of asymptomatic catheter-related tunnel infection in peritoneal dialysis patients with exit site infection and its outcome.

Methods: We performed tunnel ultrasound on 20 peritoneal dialysis patients with exit site infection and with no clinical evidence of tunnel inflammation. A positive ultrasound was defined as an area of hypoechogenicity (indicative of fluid collection) along any portion of the catheter tract. All patients had their exit site culture and sensitivity done and were treated with appropriate oral antibiotics and topical cream. We selected mainly patients with staphylococcus aureus and gram negative exit site infection. Patients with positive ultrasound were treated with more prolonged course of oral antibiotics (3 weeks) following microbiologist advice. Patients were followed up fortnightly for a repeat tunnel scan, exit site examination and to plan future management.

Results: Staphylococcus was the most common organism (n=15; 75%) and 53.3% (n=8) of them had positive tunnel ultrasound. 50% (n=4) of patients with positive ultrasound lost their PD cannula in the following 3 months either because of the development of PD peritonitis (n=2) or failed to eradicate infection (n=2) and the remaining 50% with positive scan were successfully treated. Of patients with gram negative exit site infection (n=5; 25%) the tunnel scan was only positive in one patient with pseudomonas exit site infection that also ended up in PD cannula removal due to PD peritonitis. All patients with negative scan (n=11), their exit site infection were treated successfully.

Conclusion: We conclude that ultrasound is a useful non-invasive test in detecting asymptomatic tunnel infections in patients with exit site infection. Patients with a positive scan have 50% chance of catheter loss despite prolonged antibiotic treatment. A negative ultrasound predicts excellent success for medical management. The routine use of tunnel scan in patients with exit site infection will assist in predicting patients at risk of losing catheter. We suggest treatment with close monitoring of such patients.

Poster Session

Tuesday 21 April

11:30 – 12:30

CKD & Survival

Moderator Dr Nerraj Dhaun

P138

The effect of medical comorbidities and use of predicted survival models in patients with Chronic Kidney Disease

Ram Prakash Narayanan[1], Pradeep Magapu[2], Alexander Crowe[3]

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Background : Renal patients are complex and have multiple comorbidities. We used recognised scores to assess the comorbidity profiles of our inpatients and predict survival outcomes.

Methods : We identified 50 consecutive inpatients with chronic kidney disease (stage 3 to 5) admitted to the Wirral and Chester Renal services for reasons other than dialysis alone. This project was conducted prospectively over a 6 week period in a cohort that would be representative of most district general hospital populations in the North West of England. Demographics, chronic kidney disease (CKD) class, the number of medications on admission, type of renal replacement therapy (if any), comorbidities on admission and major presenting symptoms were recorded. Comorbidity scoring was carried out using the Charlson Comorbidity Index comprising 19 weighted medical conditions. The above score was then age modified to calculate the predicted 10 year survival. The Davies Score, based on the presence of seven comorbid conditions was also calculated to stratify patients as low, medium or high risk groups with a maximal score of 7.

Results : Thirty of our subject were male and 23 patients were over the age of 70 years. 18 patients (CKD3), 7 (CKD4) and 25 (CKD5). 24 patients required renal replacement therapy. The mean number of different drugs per patient was 12.36 (range 3-21) with one patient on 21 different medications. 15 patients had a previous myocardial infarction and 14 had diabetes mellitus.

The mean Davies Score for the patients was 1.75 with 13 patients classed in the high risk group. The Charlson weighted index mean was 4.56 while the Charlson Age-Comorbidity Combined score was higher at 6.94 (range 2-13, SD 2.74) due to our proportion of older patients. Calculated likelihood of 10 year survival for the group mean was only 16.4 % (range 0-90 %, SD 28.15, SE 3.98).

Discussion : Patients admitted with chronic renal disease have other medical conditions which impact on survival, and are on numerous medications on a regular basis. Due consideration should be given to these issues while planning prescribing policies, ward staffing levels and community support arrangements for these patients.

P139

Using audit to effect change in a pre-dialysis service

Michelle Johnpulle, Julian Wright

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A repeat audit of the pre-dialysis service in Manchester was performed three years after the introduction of local guidelines for blood pressure and bone biochemistry management. 419 patients were audited (mean age 66.6years, range 20-95; 54.7% males).

The mean time attending the predialysis clinic was 21.6 months. Compared to 2005 data blood pressure had reduced by a mean of 6.0/5.2mmHg to a mean of 132.2/66.7mmHg. The use of both ACE inhibitors and Angiotensin II receptor blockers had increased by 2.2% ands 4.2% respectively to 32.9% and 23.5% respectively. Medications that must be used with caution in patient populations in whom there is a high prevalence of congestive cardiac failure such as alpha blockers had reduced from 44.3% to 33.6%. The use of the cardiovascular protective medications, aspirin and statins had also increased.

Over 95% of patients had phosphate within Renal Association guideline limits. Over 40% of patients required phosphate binder prescription and calcium containing binders were prescribed in 29.9% of patients. Despite previous local guidelines limiting the use of calcium containing binders, the use of non calcium containing phosphate binders was low, sevelamer 10.7% and lanthanum 1%. The proportion of diabetic patients was high, 41.1%, as was the prevalence of ischaemic heart disease, 25.8%. Despite this there were 50 diabetic patients still prescribed calcium containing binders. New guidelines will be produced reflecting the importance of reducing the calcium intake of patients at high risk of developing arterial stiffness.

Audit has effected an improvement in blood pressure control in the pre-dialysis population but this re-audit demonstrates the need for regular evaluation of this expanding service to ensure standards are adhered to and improvement sought across the whole range of measurable physiological and biochemical parameters.

P140

Effects of a six month exercise programme on uraemic symptoms and functional parameters of patients with chronic kidney disease.

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[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom, [2]Department of Infection, Immunity & Inflammation, University of Leicester,, Leicester, United Kingdom, [3]School of Sport and Exercise Sciences, Loughborough University, Loughborough, United Kingdom

INTRODUCTION AND AIMS: Patients with renal failure suffer from reduced physical capacity and muscle wasting associated with poor quality of life. Exercise in patients with renal failure can improve physical and functional performance as well as metabolic and cardiovascular factors. The aim of the present study was to evaluate the effects of an exercise programme on the frequency and intrusiveness of 11 uremic symptoms, as well as general concerns and parameters of physical, social, emotional and functional well-being.

METHODS: Eighteen patients (11M and 7F) aged 61.6±7.5 years (range 50-73 years) with CKD4 and 5 exercised for 30 minutes at least 5 times a week for six months. The exercise programme consisted of brisk walking at a speed adjusted to correlate to a Borg Rating of Perceived Exertion Rate (RPE) of 12-14, and a heart rate range that was elicited by the target RPE. Before and after the exercise period anthropometric haematological and biochemical parameters were measured as well as the arterial blood pressure and the questionnaires of the Leicester Uraemic Symptoms Score (LUSS) and Functional Assessment of Chronic Illness Therapy-Spirituality Scale Quality of Life Tool (FACIT-Sp; Pugh-Clarke et al. EDTNA-ERCA Journal 32,167-71,2006).

RESULTS: After 6 months of exercise there were no significant changes in haemoglobin or white cell count, or in the biochemical parameters (plasma urea, creatinine, eGFR calcium, phosphate, calcium-phosphate product or albumin). There was a significant reduction in the Body Mass Index ($p=0.006$), that was not accompanied by changes in the Mid Arm Circumference or the skin-fold thickness and there was a significant reduction in the systolic blood pressure ($p=0.008$). There was also, a significant improvement/reduction in the total of the uremic symptoms (LUSS) ($p=0.002$) as well as their frequency ($p<0.0001$) and intrusiveness ($p=0.03$). Additionally, there were improvements in two out of the four parts of FACIT-Sp that were concerned with physical ($p=0.004$) and social/family ($p=0.039$) well-being of the patients.

CONCLUSIONS: Six months of medium intensity exercise therapy can improve the perceived uremic symptoms and the emotional well-being as well as metabolic parameters of patients with chronic kidney disease.

P141

Survival outcomes in patients of different age-groups. Comparison of two different time periods.

James Medcalf, George Kosmadakis, Graham Warwick, John Feehally

John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom

Annual acceptance rate for RRT in UK is rising steadily from 20 pmp in the 1980s to 103 pmp in 2004[1]: The fastest growing group of patients with ESRD are those over 75 years old[2].

Aim. The aim of the present study was to compare the survival outcomes of the different patients' age groups in two different time-periods.

Patients and methods. The present study is a retrospective computer based study with data extracted from the renal patients' database. The studied patients initiating RRT were divided in two groups according to the time of initiation RRT (group 1-813 patients (517 M-296 F) initiating RRT from 1/1/1996 to 31/12/2000 and group 2- 894 patients (543 M- 351 F) initiating RRT from 1/1/2001 to 31/12/2005). Each group was divided into 3 subgroups according to the age of each patient initiating RRT- <65 years old, 65-74 years old and ≥75 years old. All subjects were followed up until the point of assessment (10/12/2008) or the time of death.

Results .90-days and 1-year survival: There were no significant differences in 90-days and one-year survival when we compared the total of the two time periods and the different age groups in the three periods.

Long-term survival: There was no significant difference in 5-years estimated survival for the 2001-2005 when we compared it against the 1996-2000 group. Six-years survival was significantly higher in the latest time period compared to the earlier one (Pearson Chi-Square 4.531, df 1, P=0.033). Five years survival was also significantly higher in the 2001-2005 group in the age group over 75 years old (Pearson Chi-Square 4,340, df 1, P=0.037). There was no significant difference concerning the five years survival of the under 65 years old age group and the 65-74 age group between the periods 1996-2000 and 2001-2005. Six years survival was also significantly higher in the 2001-2005 group in the ages under 65 years old (Pearson Chi-Square 5,713, df 1, P=0.017) in the 65-74 years old group (Pearson Chi-Square 3,814, df 1, P=0.05) and the over 75 years old group (Pearson Chi-Square 5,116, df 1, P=0.024).

Conclusions . The improvements in the RRT therapy have led to improvements in the long term (6year) survival of the patients. Short term survival has remained unchanged during the last 15 years and further studies are needed to address this issue.

1 Ansell D et al. UK Renal Registry Report 2005. Bristol, UK

2 Farrington K. et al. UK Renal Registry Report 2006.

P142

In patients with progressive renal disease, does urinary sodium excretion predict progression or survival?

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[1]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom, [2]Renal Unit, Monklands Hospital, Airdrie, United Kingdom, [3]Renal Unit, Glasgow Royal Infirmary, Glasgow, United Kingdom

Aim: It is widely believed that oral sodium intake influences progression of renal disease irrespective of changes in blood pressure. There is however little evidence to support this in clinical practice. We aimed to study whether urinary sodium correlates with disease progression in a cohort of patients with progressive renal dysfunction.

Methods: Adult patients attending the renal unit at Glasgow Royal Infirmary between 1992 and 2007 who had at least one 24h urinary sodium measurement were identified using the electronic patient record. We excluded patients who were receiving RRT at time of measurement; patients without a weight recording; patients without an MDRD6 GFR recording at time of measurement and at least one further reading; patients with a decline in GFR >10ml/min/yr and patients with a urinary sodium below 70mmol/24h. Date of death or renal replacement therapy was recorded as were subsequent MDRD6 GFR recordings. Urinary sodium per 24h was adjusted for weight in Kg. Kaplan Meier survival analysis was performed based on time to RRT or death for quartiles of urinary sodium mmol/Kg/24h. T-test was performed to compare the mean decline in GFR according to quartiles of urinary sodium.

Results: 172 patients were included. At baseline, mean age was 55.3y ± SD 15.7; mean MDRD6 GFR at 37.3ml/min ± 23.4; median albumin:creatinine ratio 135 (IQR 66-153); mean SBP 140.7mmHg ± 21mmHg; mean DBP 80.4mmHg ± 12.3mmHg; 47.7% were male; mean urinary sodium/24h 153.3mmol ± 63.6mmol; mean mmol Na/24h/Kg 2.1 ± 0.8. Median follow-up 8.5y (IQR 3.0-12.2). 63 patients required RRT, 55 patients died. Mean decline in GFR (MDRD6) 3.8ml/min/yr ± 2.5ml/min/yr. Mean number of GFR recordings 2.5. There was no significant difference, nor trend, in patient survival or decline in renal function between the quartiles of urinary sodium excretion. There was no significant difference in diuretic use between groups.

Conclusion: In this well defined cohort of patients with long follow-up there is no evidence of an association between urinary sodium excretion and progression of renal disease.

P143

Code Red – developing a common language to optimise recognition and response to an acutely unwell adult.

Arvind Ponnusamy, Julie Gorton, Gaynor Fereday, Minimol Santhosh, Maffida Hussain, Gillian Powell, Peter Murphy, Jane MacDonald, David Lewis, Janet Hegarty

Salford Royal NHS Foundation Trust, Salford, Manchester, United Kingdom

The Problem: Renal patients in Acute Trusts are often some of the sickest patients in level 1 and 2 care. Although a small number of cardiac arrests are unavoidable, research has demonstrated that most cardiac arrests have been presaged by physiological deterioration ie there is a window of opportunity to intervene before an arrest state ensues.

Aim: We were a pilot site in a Trust Quality Improvement Collaborative with the aim of halving our cardiac arrest rate, as a marker for improved care of the acutely unwell adult.

Assessment of problem: We conducted a retrospective review of a random sample of half our inpatient deaths (n=27) for 2006/7, using a modification of an evidence based tool (the Global Trigger Tool) to look for safety themes and any learning points. We also prospectively reviewed our cardiac arrest calls and any 'near misses' (ie when patients became more unwell and/or were escalated to a higher level of care) One key finding was that our Early warning score (EWS) was not triggered in a certain subset of patients who were nonetheless very unwell. A second finding was that other patients were readily recognized by experienced clinicians to be 'at risk' although no deterioration had necessarily occurred physiologically at a snapshot in time. .

Strategy for Change: We wished to develop a common language so that every member of staff could recognize an acutely unwell ***or*** at risk patient, and modify surveillance and care accordingly – regardless of whether they were triggering on an EWS system or not. We introduced the term" Code Red" as part of innovation testing as way of highlighting when such a patient exists in our care area. Critically any member of the staff including nursing staff, health care assistants, AHPs and doctors who are worried about a patient can 'Code Red' them, regardless of their EWS. Once a patient is tagged with Code Red, he or she is reviewed by a middle grade member of the medical staff immediately and a clear MDT action plan put in place.

Effect of Change: Initial concern were that the number of 'Codes' would be lead to overburdening of staff or dilution of perceived importance such that it stopped changing behaviour positively. In fact we have found only approximately 5-6 codes per month and the use of the term has led to improved situational awareness, better communication and planning. It is a powerful tool to allow nursing staff to message to doctors so they can triage their work appropriately; it also allows medical staff to get nursing engagement to expedite patient transfer, investigations or increased surveillance. As with other QI projects, we have tried a number of 'small tests of change' rapidly over the project period alongside Code Red. With these combined measures, during the 9 months of the project so far, we have reduced our cardiac arrest rate by 70%.

Future: The Renal Code Red patients are being kept as a learning bank for future MDT training including simulation. The QI Expert Faculty at the Trust have adopted Code Red in a best practice change package that will be rolled out across the organization.

P144

Reducing Cardiac Arrest Rates by 70% over 9 months on an Acute Renal Ward

Julie Gorton, Anthony Simmons, Gaynor Fereday, Gillian Powell, Maffida Hussain, Arvind Ponnusamy, Peter Murphy, Jane MacDonald, David Lewis, Janet Hegarty

Salford Royal NHS Foundation Trust, Salford,Manchester, United Kingdom

The Problem: Renal patients in Acute Trusts are often some of the sickest patients in level 1 and 2 care. Although a small number of cardiac arrests are unavoidable, research has demonstrated that most cardiac arrests have been presaged by physiological deterioration

Aim: We were a pilot site in a Trust Quality Improvement Collaborative with the aim of halving our cardiac arrest rate, as a marker for improved care of the acutely unwell adult.

Assessment of the problem: EWS systems are an evidence-based intervention leading to improved recognition and response to acute illness and less cardiac arrests as a marker of improved care. Despite there being an EWS system in use across the Trust including our acute ward (17 beds +3HDU beds), we had the highest levels of cardiac arrests in the organisation over a one year period.

Strategy for change: An improvement ward team was formed from the unit manager, consultant, nurse, trainee doctor and support worker. We used small tests of change (Plan, Do, Study, Act methodology) to improve how reliable our use of EWS was, MDT recognition and response to acute illness. Half of the previous years in-patient deaths retrospectively and all arrests, peri-arrests and near-misses were reviewed by the improvement team prospectively for learning. Regular staff meetings, patient safety huddles, CME, the staff newsletter and medical ward rounds were used to give updates on the project and to generate further ideas for tests of change. PDSAs have been tried on how clinical observations are taken, how oxygen is prescribed, how oxygen parameters are set by the medical team and recorded by the nursing team, on resuscitation orders, ceilings on escalation of care, recognition of acutely unwell or at risk patients who are not triggering on the EWS (Code Red).

Effects of changes: The cumulative effects of changes are a cultural shift within the ward. A raised awareness of the importance of diligence to clinical observations prevails. Every patient, every time, has a manual pulse and manual BP taken, getting staff reengaged and confident in the physical appearances and signs of illness. All patients have their oxygen prescribed to maintain oxygen saturation levels that are correct for the individual patient. Prioritisation of patients is now considered on routine ward rounds which are in the process of becoming structured so the sickest patients get seen first. A common language of ‘code red’ is used to alert the team to a deteriorating or at risk patient. We have conducted regular sample measures and over time we have achieved 100% completion of all clinical observations, 100% completion of oxygen therapy prescribing and a 70% reduction in cardiac arrests over the last 9 months. Tensions still exist as all changes have different impacts on long-established ways of working for different MDT members.

Future: Change is complex and hard work. However with leadership attention, and harnessing the focus of the energy and talent in our own staff teams to a highly visible challenging goal which is resonant with their core values, patient care can be demonstrably improved.

Poster Session

Wednesday 22 April

13:00 – 14:00

Proteinuria & Fibrosis

Moderator Dr Nigel Bruskill

P145

Identification of urinary biomarkers in proteinuric patients with focal segmental glomerulosclerosis (FSGS)

Ali Elfaitori, A Meguid El Nahas, John Haylor

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Proteomic analysis of urine from patients with chronic kidney disease (CKD) may help identify new biomarkers of renal progression. Using 2D-PAGE and mass spectrometry, we have previously matched proteins (from NCBI database) which, in addition to albumin, were elevated in urine from proteinuric patients with FSGS. Sequence matches included those to orosomucoid 1, transthyretin, α1-antitrypsin, hemopexin, transferrin and haptoglobin. The aim of the present study was to confirm the results of proteomic matching and identify possible urinary metabolites by Western blotting.

Protein was precipitated from pooled urine samples (n=5 per group) obtained from normal volunteers, proteinuric patients with FSGS or eGFR-matched CKD patients without proteinuria. Protein (10μg) was run on 10-12% gels and transferred to nitrocellulose membranes by electroblotting. Rabbit polyclonal antibodies (Abcam) to human orosomucoid 1, transthyretin, α1-antitrypsin, hemopexin and transferrin and a mouse polyclonal antibody (Abcam) to human haptoglobin were employed, Working dilution of primary antibodies ranged from 1:1,000 to 1:30,000.

Orosomucoid 1 is a heavily glycosylated 44kDa protein; antibodies gave a major band at 44kDa. Transthyretin is a tetrameric 55kDa protein; antibodies gave a major band at 55kDa. α1-antitrypsin is a single chain 52kDa protein; antibodies gave a major band at 52kDa but with multiple bands at lower molecular weights (MW). Hemopexin is a single chain 60kDa glycoprotein; antibodies gave a major 51kDa band together with multiple bands at lower MW's. Transferrin is a 80kDa glycoprotein; antibodies gave a major band at 75kDa but with multiple bands at lower MW's. Haptoglobin is a heterodimeric 90kDa protein; antibodies gave two major bands at 25kDa & 45kDa.

The results of Western blotting confirmed the sequence matching of proteins by 2D-PAGE and mass spectrometry for 6 major proteins, the excretion of which is increased in proteinuric patients with FSGS compared to either non-proteinuric CKD patients with a similar eGFR or normal volunteers. The presence of immunoreactive bands of lower molecular weight may indicate the increased excretion of urinary metabolites, particularly for hemopexin, transferrin and α1-antitrypsin.

P146

FSGS plasma initiates specific signalling pathways in podocytes – evidence for an imbalance of circulating proteases in the pathogenesis of nephrotic syndromes

Jessica Harris, Matthew Wherlock, Rohini Rattihalli, Rachel Lennon, Peter Mathieson, Gavin Welsh, Moin Saleem

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Focal segmental glomerulosclerosis (FSGS) is a nephrotic syndrome (NS) that often culminates in end-stage renal failure. The molecular cause of FSGS is as yet poorly understood, but may be the result of a circulating pathogenic plasma factor acting on the podocyte, or as we have previously suggested by the absence or deficit of a factor necessary for the maintenance of the podocyte slit diaphragm, and concomitantly the glomerular filtration barrier.

In this study we investigated the cellular effects of nephrotic human plasma on signalling pathways involved in the regulation of the actin cytoskeleton in conditionally immortalised human podocytes. We also considered the cellular response of podocytes to hemopexin, a circulating plasma protease raised in idiopathic NS and previously shown to induce a reversible proteinuria in animal models and cortical actin reorganisation exclusively in podocytes, mediated by the podocyte protein nephrin (Lennon et al, J Am Soc Nephrol, 2008).

FSGS relapse plasma (but not remission plasma) and hemopexin induced the phosphorylation of VASP in human podocytes, a protein known to be involved in the reorganisation of the actin cytoskeleton. Both FSGS plasma and hemopexin led to F-actin remodelling in podocytes. The presence of protease inhibitors in the cell culture medium decreased the phosphorylation of VASP in response to FSGS relapse plasma.

We decided to further investigate the possibility that protease activated receptors (PARs) on podocytes mediate the downstream cellular effects of circulating ‘factors’. We demonstrated that podocytes express PAR1, 2 and 4. Incubation with a synthetic activating peptide for PAR2, but not PAR1 or PAR4 leads to the phosphorylation of VASP in podocytes.

Our data therefore suggests that the cellular effects of FSGS plasma and hemopexin may therefore be mediated by the activation of PARs in human podocytes and activated by circulating plasma proteases. This is a novel concept that would suggest that correction of a protease imbalance in plasma provides therapeutic benefits in FSGS.

P147

Identification of urinary CKD biomarkers in the sub-total nephrectomised rat

Melissa Vickers, Meguid El-Nahas, John Haylor

The University of Sheffield, Sheffield, United Kingdom

Proteomic analysis of urine obtained from animal models may help to identify biomarkers of relevance to the diagnosis and prognosis of chronic kidney disease (CKD). Previous analysis of urinary proteins obtained from rats following sub-total nephrectomy (SNx) which were elevated on 2D-PAGE were matched following mass spectrometry to 16 known proteins. Matched proteins or their metabolites considered to be of particular interest to CKD pathophysiology included superoxide dismutase 3 (SOD3), fetuin b, fibrinogen and heparan sulphate proteoglycan 2 (HSPG).

Western blot analysis was performed on precipitated protein obtained from pooled urine collected from rats 90 days following either SNx (n=8) or sham operation (n=4). Goat polyclonal antibodies raised against human SOD3 (R & D Systems), fetuin b and the β chain of fibrinogen (Santa Cruz Biotechnology) were employed. For HSPG 2, a rat monoclonal antibody raised against murine tumour matrix HSPG (Abcam) was used.

By day 90, urine protein excretion from SNx rats had increased by 6 fold (19±3 vs 112±37mg/24h,$p<0.05$), glomerulosclerosis by 6 fold (28±13 vs 5±1%, $p<0.05$) and tubulointerstitial fibrosis by 11 fold (14±1 vs 1.3±0.3%,$p<0.05$) compared to sham. Creatinine clearance of SNx rats was more than 3 times lower that for sham controls (2.2±0.1 vs 0.6±0.1ml/min, $p<0.05$). Antibodies to SOD3, a 97kDa dimer, showed 3 bands representing dimeric, glycosylated and monomeric forms of the enzyme. Antibodies to fetuin b, a 63kDa glycoprotein, showed a single band at 50kDa. Fibrinogen is a 302kDa homodimer, each monomer containing 3 polypeptide chains. Antibodies to fibrinogen (β chain) showed 2 major bands at 40 and 50kDa representing c-terminal metabolites of the β chain. HSPG is a 460kDa single chain, glycoprotein containing 5 major domains. Antibodies to HSPG 2 showed a major band at 25kDa. Sequence matching of a 21kDa spot obtained by 2D-PAGE is consistent with this band representing the c-terminal subdomain (LG3) of domain 5 of the HSPG 2 protein.

Western blot analysis confirmed previous 2D-PAGE and mass spectrometry results showing an increase in SOD3, fetuin b, fibrinogen and HSPG 2 protein or protein metabolites in the urine of SNx rats with renal fibrosis.

P148

Role of IFNγ in the development of inflammation-induced peritoneal fibrosis

Ceri Fielding, Rachel McLoughlin, Gareth Jones, Anwen Williams, Chantal Colmont, John Williams, Simon Jones, Nicholas Topley

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Peritoneal dialysis (PD) is used to treat a significant proportion of patients with end-stage renal failure. In many patients the failure of the peritoneal membrane as a dialysing organ limits the effectiveness of the therapy and this is generally considered to result from the uraemic state, exposure to bio-incompatible dialysis solutions and to repeated episodic infection. Recurrent bacterial peritonitis, predominantly caused by *Staphylococcus* species, is the main complication of PD. Repeated peritonitis episodes are associated with retention of activated leukocytes within the peritoneal cavity, the development of peritoneal fibrosis, and loss of peritoneal function with resultant treatment failure. Recent data has identified that those patients with a history of episodic peritonitis have significantly more peritoneal membrane thickening than those who remain infection free. The frequency, duration and severity of these periodic infections may therefore promote tissue fibrosis, and thereby affect the capacity of the peritoneal membrane to allow adequate dialysis.

We have developed a murine model of repeated peritoneal inflammation to investigate the role of inflammation in the development of fibrosis of the peritoneal membrane. This model uses intraperitoneal injections of a cell-free supernatant of *Staphylococcus epidermidis* (SES) to induce repeated inflammation. These studies have identified increased lymphocyte activation following repeated inflammation and the eventual development of parietal peritoneal fibrosis. IL-6 was essential for the development of peritoneal fibrosis following repeated inflammation and skewing of STAT (signal transducers and activators of transcription) activation from STAT3 to STAT1 within the peritoneal membrane. This increase in STAT1 activation was dependent on the emergence of an IFNγ-producing lymphocyte population and IFNγ was found to be important for the development of peritoneal fibrosis. Our current studies are focused on identifying the mechanism involved in IFNγ and altered lymphocyte function in driving peritoneal fibrosis and whether IFNγ activity can be modulated for therapeutic gain.

P149

Tubulointerstitial inflammation and fibrosis is not influenced by deficiency of the regulatory transcription factor NFκB1

Amy Fearn, Derek Mann, Fiona Oakley, Neil Sheerin

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Tubulointerstitial inflammation and fibrosis is characteristic of progressive nephropathies. Inhibition of the archetypal pro-inflammatory transcription factor NFκB reduces injury in experimental animals. However, NFκB is a complex homo- or heterodimeric protein and it is clear that the different combinations of its 5 potential constituent subunits have different functions. Recently it has been shown that mice deficient in NFκB1 (p50) exhibit exaggerated inflammatory responses. We therefore tested whether mice deficient in NFκB1 (NFκB1-/-) would develop more severe tubulointerstitial inflammation and fibrosis in response to unilateral ureteric obstruction (UUO).

Methods: NFκB1-/- and age and sex matched C57Bl/6 mice were killed 3 and 10 days after UUO. Real time PCR was used to quantify gene expression of TGFβ, TNFα, Collagen I and Collagen III. Interstitial expansion and tubular dilatation were assessed on PAS sections. Immunochemistry was used to quantify Collagen I deposition, the number of α smooth muscle actin expressing myofibroblasts and macrophage, CD4+ and CD8+ T cell infiltration.

Results: There was no difference in the expression of the pro-fibrotic cytokine TGFβ, the pro-inflammatory cytokine TNFα or collagen genes I and III between the NFκB1-/- and wild type mice. By day 3 there was evidence of tubulointerstitial expansion and tubular dilatation in obstructed kidneys compared to contralateral kidneys. At both day 3 and 10 this was equivalent in the NFκB1-/- and wild type mice. Similarly there was no significant difference between the deposition of Collagens I and III and the number of αSMA positive myofibroblasts. Infiltration of macrophages, CD4+ and CD8+ cells was equivalent.

Conclusion: Deficiency of NFκB1 does not increase the severity of renal injury following UUO. Despite evidence that NFκB is involved in the injury following UUO and that NFκB1 reduces the severity of injury in other experimental tissue injury we were unable to demonstrate a role in UUO. Other NFκB subunits must compensate for the deficiency in NFκB1 (p50).

P150

Changes in Mesangial Cell Phenotype consequent to Extracellular Matrix attachment are mediated by the LIM protein Hic-5 independent of TGF-β.

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Central to the outcome of glomerular inflammation is the interplay between extracellular matrix (ECM), soluble factors, and their effects on cellular proliferation and apoptosis. Over recent years we have reported that mesangial cell attachment to Collagen I (which is over-expressed during glomerulosclerosis) results in an up-regulation of the LIM protein Hic-5. This increased expression of Hic-5 is associated with an increase in susceptibility to apoptosis and a "pro-sclerotic feedback loop" promoting further increased expression of Collagen I (Renal Association Annual Meeting, 2005, 2006, 2007).

The effects of TGF- β in glomerulosclerosis have been widely reported. TGF- β has been shown to promote apoptosis and also Collagen I expression in certain cellular models, and it is furthermore known to induce the expression of Hic-5 in some systems. Therefore we have sought to determine whether the observed effects of Hic-5 are regulated by TGF- β in our model.

We used a well characterised rat Mesangial Cell clone and created an siRNA Hic-5 knockdown line from this. These lines were cultured on Collagen I or Collagen IV and also with the addition of TGF- β or a specific inhibitor of SMAD-3. Lysates were tested for activation of TGF- β signaling, Hic-5 protein expression levels and expression of Collagen I mRNA, under all conditions. Our results indicate that the changes in Mesangial Cell phenotype consequent upon ECM attachment are independent of TGF- β signaling. These findings have important implications for the understanding of glomerular scarring and suggests non-TGF- β pro-sclerotic signaling pathways might be implicated.

This work was supported by KRUK, and The Yorkshire Kidney Research Fund.

Poster Session

Thursday 23 April

13:30 – 14:30

Cardiac & Vascular Biology

Moderator Dr Jeremy Hughes

P151

Creation of an arteriovenous fistula is associated with significant local and systemic changes in microvascular function

Shvan Korsheed[1], Stephen John[1], Richard Fluck[1], Christopher McIntyre[1,2]

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Native arteriovenous fistulae (AVF) remain the vascular access of choice for haemodialysis. AVF use is associated with a reduction in long term mortality (c.f. catheter use), but can result in vascular trophic effects and symptoms in the distal limb. The consequences of AVF formation on microvascular function, either in the subtended portion or systemically, are unknown.

We recruited 30 pre-dialysis CKD stage 4-5 patients who underwent AVF formation. This was primarily successful in 20/30. All patients were studied 2 weeks prior to planned AVF operation and restudied 2 weeks postoperatively. Patients with failed AVF procedures were utilised as sham operated controls. Laser Doppler Perfusion Imaging (LDPI) was used to measure subcutaneous microvascular blood flow. Microvascular function was assessed as increase in perfusion in response to iontophoretic administration of vasodilatory stimuli (acetylcholine (Ach) and sodium nitroprusside (SNP) to respectively assess endothelial dependant (ED) and non-endothelial dependant (NED) vasodilatation).

Patients with successful AVF formation had a significantly reduced ED vasodilatation in the fistula arm (-20±41%, p=0.004). Interestingly, only NED vasodilatation was significantly reduced in the non-fistula arm (-21±31%, p=0.009). On the other hand, patients who had unsuccessful AVF operation exhibited no recordable change at all.

The functional and structural consequences of forming an AVF are complex. In this prospectively studied patient group, formation of an AVF did not only result in significant reduction of ED vasodilatation locally in the fistula forearm, but it also produced a systemic effect, by reducing NED vasodilatation in the contralateral non fistula forearm. Further assessments are under way to examine the mechanistic contributions of local shear stress, bioavailability of vaso-reactive substances and central modification of the autonomic responses. Although the clinical significance of these findings are not yet clear, it is intriguing that local AVF formation is associated with such wide spread and profound changes in microperfusion. These may be important in determining the ischaemic threshold for sensitive and vital circulations such as the heart and brain.

P152

Myocardial Infarct Size Is Reduced Following Renal Ischaemia/Reperfusion in the Rat Model of Coronary Artery Ligation

Conor Byrne, Kieran McCafferty, Julius Kieswich, Christoph Thiemermann, Muhammad M Yaqoob

William Harvey Research Institute, QMUL, London, United Kingdom

The presence of CKD is well recognised as an important predictor of poor outcome in survivors of acute myocardial infarction and is included as a variable in several prognostic models e.g. GUSTO-1. However, it is unknown whether AKI has a bearing on prognosis.

Emerging data suggests that even small, in hospital, elevations in serum creatinine confer a poorer long-term prognosis. It is unknown whether these observations reflect greater severity of AMI or whether the presence of AKI influences the pathophysiology of AMI, altering the prognosis.

Animal models of AMI in the context of CKD have demonstrated an increase in infarct size in uraemic animals. We hypothesised that the inflammatory milieu that exists following kidney ischaemia-reperfusion (IR) injury might exacerbate cardiac IR injury.

Methods:

Male Wistar rats aged 7-8 weeks, underwent either bilateral renal ischaemia under ketamine/ Xylazine anaesthesia for 45 mins followed by 24 hours reperfusion, or a sham procedure where both kidneys were decapsulated. 24 hours after renal IR the animals underwent cardiac IR employing reversible LAD ligation, 25 minutes ischaemia followed by 2 hours reperfusion, at the end of which the animals were sacrificed and the infarct size was measured and expressed as a percentage of the area at risk.

Results: (median [IQR])

Both groups were similar in terms of blood pressure, weight and haematocrit. The renal IR group had significantly higher median creatinine than the sham group: 279 µmol/l [215-335] v 30.4 µmol/l [16.6-39.4](p=<0.01). Paradoxically we found a decrease in the size of myocardial infarction in the renal IR group compared with the sham operated group (52.6% [45.2-69.8] vs 34.0% [22.3-45.1]; p=<0.02).

Conclusion:

Lethal renal ischaemia reperfusion injury has not previously been reported to cause remote cardiac tissue protection. We believe this observation is the result of a phenomenon analogous to that of remote ischaemic pre-conditioning (RIPC). The signaling mechanism underlying this observation is the subject of ongoing investigation.

P153

The 'RISK' pathway does not appear to mediate the tissue protective effect of remote ischaemic preconditioning at a cellular level.

Kieran McCafferty, Conor Byrne, Julius Kiewsich, Chris Thiemermann, Magdi Yaqoob

WHRI, QMUL, London, United Kingdom

Remote ischaemic pre-conditioning (RIPC) is a powerful technique to limit the extent of tissue damage following ischaemia reperfusion injury (IRI). RIPC describes the phenomenon whereby repeated sub-lethal periods of ischaemia followed by reperfusion can confer protection in a remote tissue bed to a more prolonged ischaemic insult. We have previously published data confirming myocardial protection following both renal RIPC and IRI.

Although considerable evidence exists to indicate that the reperfusion injury salvage kinase (RISK) pathway, whose principal components are ERK-1/ 2 (p42/44) and Akt, is responsible for mediating the effect of direct ischaemic pre-conditioning (IPC). The mechanism by which RIPC primes the cell to resist subsequent IRI is not well understood.

We attempted to identify the signaling mechanism involved in RIPC of the heart by the kidney.

Methods: 6 week old male Wistar rats underwent renal IRI (45min ischaemia and either 2 hr or 24 hr reperfusion) or single kidney IPC (3x cycles of renal ischaemia for 5 min followed by 5 min reperfusion). Hearts and kidneys were harvested. Western blots for ERK1/2 and Akt, and ELISA for STAT 3,5a and 5b were performed on the tissue homogenates.

Results: There is no increase, over basal levels, of phosphorylated ERK-1/ 2 or Akt in the heart at either 24 hr or 2 hr post injury.

In the kidneys that received RIPC (contra-lateral to the kidney that received IPC), over the same time course, we found no increase in pERK-1/ 2 or pAkt. However, the kidneys that had undergone IRI or IPC demonstrated a significant increase in the levels of pERK-1/ 2 and pAkt. Stat 5a ELISA demonstrated increased phosphorlyation in the RIPC group only which approached significance ($p=0.069$, $n=3$).

Conclusions: Whilst the RISK pathway is important in both lethal IRI and IPC it does not appear to be involved in RIPC signalling. However STAT 5a may be important in transducing the RIPC signal between the kidney and heart.

P154

The impact of chronic uraemia on ischaemic preconditioning of the myocardium

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WHRI, QMUL, London, United Kingdom

Background: Direct ischaemic preconditioning (IPC) is a process by which brief non lethal periods of ischaemia render the dependant tissue resistant to subsequent lethal injury. This process has been extensively studied in animal models of tissue injury and this has led to human clinical trials showing a reduction in markers of myocardial injury following angioplasty in patients who have had IPC. There is emerging evidence to suggest that additional co-morbidities may render hearts more resistant to the beneficial effects of IPC. Published data suggest that hypertensive elderly rats and diabetic rats are resistant to IPC. There is no published data examining the effects of chronic uraemia on IPC. This is of clinical importance due to the burden of cardiovascular disease in CKD patients and due to the increasing use of preconditioning as a technique to improve the prognosis of patients following cardiac interventions.

Methods: The 5/6 nephrectomy model in male Wistar rats was used as a model of chronic uraemia. These rats were divided into 2 groups. The control group (n=15) underwent myocardial ischaemia using reversible LAD artery ligation. The LAD was occluded for 25 minutes after which time the heart was reperfused for 2 hours. The IPC group (n=4) had 1 cycle of 5 minutes LAD ligation and 5 minutes reperfusion followed by 25minutes ischaemia and 2 hours reperfusion. At the end of the experiment the animals were sacrificed and the infarct size was measured and expressed as a percentage of the area at risk (AAR).

Results: Median Infarct size was 61.2% and 7.5% in the control and IPC groups respectively (P=0.003): a relative reduction of 87.8%. The AAR (44 v 44%), blood pressure (148 v 176 mm/Hg) and serum creatinine (89.4 v 100.9 umol/l) was similar in the control and IPC groups respectively.

Conclusions: This is the first evidence that unlike ‘old’ hypertensive rats and diabetic rats, uraemic rats can respond to a preconditioning stimulus to reduce myocardial infarct size. This study suggests that clinical trials using IPC in uraemic patients could improve outcomes following cardiac interventions.

P155

Myocardial Infarct Size in Two Different Rodent Models of Chronic Uraemia

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Cardiovascular disease is the leading cause of death in patients with chronic kidney disease (CKD) and end stage renal disease (ESRD).

It has previously been suggested that this is due a reduced tolerance for ischaemia in the uraemic heart. Reversible left anterior descending artery (LAD) ligation was performed in 2 rat models of chronic uraemia; sub-total nephrectomy (SNx) and adenine induced uraemia.

Methods:

Male Wistar rats were fed a diet containing 0.75% adenine for 4 weeks or control diet.

Myocardial infarction was induced by occluding the LAD for 25 min and allowing the heart to reperfuse for 2 hr. At the end of reperfusion the LAD was re-occluded and Evans blue dye was infused IV to delineate the 'area at risk'. The heart was harvested and dissected; the non-perfused area was weighed and expressed as a percentage of the remaining left ventricle.

In the second experiment male wistar rats underwent a two stage sub-total nephrectomy, 4 weeks after the second procedure the rats underwent LAD ligation as above.

Results: (adenine v SNx v control; all expressed as mean +/- SD except creatinine)

Statistical analysis performed using one-way non-parametric ANOVA Kruskal-Wallis)

Serum creatinine was significantly higher in the animals with adenine induced renal failure (median 145 v 86 v 34.7 µmol/l; p=0.0001). Despite this there was no difference in infarct size between rats with adenine induced uraemia or those fed control diet (52.2% +/- 11.8 v 50.0% +/- 8.8).However, there was a significant increase in infarct size in the rats that underwent SNx (61.2% +/-12.8; p=<0.05). The SNx rats had significantly higher mean arterial blood pressures (MAP) compared with the other groups (141 +/- 17 v 150 +/- 12.4 v 143 +/- 19.7 mmHg), they also had the lowest mean haemoglobin of the 3 groups (11.4 +/- 1.84 v 13.8 +/- 1.85 v 8.7 +/- 1.68 g/dl).

Conclusion:

The degree of uraemia per se does not appear to have a significant impact on myocardial infarct size in these animal models of chronic kidney disease. Hypertension and degree of anaemia may well play a more significant role in determining infarct size.

P156

Cardiac morphology and inflammatory mediators in Chronic Kidney Disease (CKD)

Esha Sarkar[1], Angela Summers[1], Grant Heatlie[2], Julian Wright[1], Paul Brenchley[1]

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Background - There is significant cardiac comorbidity in patients both progressing to CKD 5 and on dialysis and this increased cardiovascular morbidity is not explained by known risk factors.

Hypothesis – Early changes in cardiac structure/function may be associated with the inflammatory environment that develops during progression of CKD.

Patients & Methods - 60 non-diabetic subjects (20 CKD3, 20 CKD4/5 and 20 age/gender matched controls) were subjected to a non-contrast cardiac magnetic resonance (MR) scan using a Philips 1.5 Tesla scanner. Inflammatory mediators IL-6, TNFα, and VEGF were measured in plasma by ELISA (Quantikine kit R & D systems).

Results - In the heart, there was a difference in left atrial area between the three groups (p=0.0116) with the CKD4/5 patients having the largest left atrial area indicative of elevated left ventricular end diastolic pressure. There were also differences in left ventricular longitudinal strain (p=0.0106) across the groups, greatest in the CKD4/5 group suggesting early systolic deformation abnormalities despite no difference in left ventricular mass index between the groups.

IL-6 (p=0.0106) and VEGF (p=0.0239), were significantly elevated in CKD3 compared to controls unrelated to level of eGFR. However, there was no difference between IL-6 and VEGF levels between the CKD3 and CKD4/5 groups. In CKD3, IL-6 and VEGF were significantly correlated (r=0.3501, p=0.0076). In contrast TNF α was elevated only in CKD4/5 (p=0.008 compared to controls). There was no association between cardiac changes and inflammatory mediators in any study group.

Conclusion - Even in the absence of an increased left ventricular mass index, there are early cardiac changes suggestive of both diastolic dysfunction and abnormalites of systolic function. VEGF and IL 6 are raised in CKD3 and there is a significant association between these inflammatory mediators. This was not observed in CKD4/5 suggesting that increased VEGF and IL-6 are unrelated to reduced excretory capacity of the kidney. As we could not demonstrate a link between the inflammatory milieu (plasma mediators) and cardiac changes in CKD3, other mechanisms, perhaps fibrotic in nature, might account for these early changes. A prospective study of a large cohort progressing from CKD3 - 5 is essential to define this mechanism in CKD.

Poster Session

Wednesday 22 April

13:00 – 14:00

Glomerulonephritis 2

Moderator Dr David Jayne

P157

Goodpasture's disease: a tale of two extremes!

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Introduction: Goodpasture's disease (GD) is a rare autoimmune disease characterised by rapidly progressive crescentic glomerulonephritis (GN), often accompanied by pulmonary haemorrhage in association with circulating antibody and linear deposition of IgG in the glomerular basement membrane (GBM).

Methodology: We report 2 GD cases with anti-GBM antibody levels at opposite ends of the spectrum. One patient was consistently negative and the other's levels were >100U/ml. A review of literature in Pubmed was made as regards the diagnostic and treatment modalities in our 2 cases. **Results: Case 1.** In February 2008, a 19 year old male presented with macrohaematuria and acute kidney injury (AKI) with serum creatinine of 250 µmol/L. Renal histology confirmed crescentic GN with linear IgG deposition in the GBM associated with negative anti-GBM antibodies (ELISA and Western blotting). Treatment was initiated with pulsed methylprednisolone, then oral prednisolone and cyclophosphamide (CYP) without plasma exchange (PE). At four months after presentation he remained well with stable renal dysfunction with a creatinine of 310µmol/L and eGFR 23ml/min and significant proteinuria 7.39g/day. A repeat renal biopsy confirmed active crescentic GN. He underwent 5 sessions of PE with concomitant CYP and prednisolone. Seven months after initial presentation he developed pulmonary haemorrhage despite treatment. He underwent further PE with intravenous immunoglobulin. His renal function deteriorated further and he was commenced on chronic haemodialysis. His anti-GBM antibodies remained negative throughout his clinical course to date. There is only 1 case series of 3 GD patients diagnosed with negative serology in the literature. **Case 2.** In July 2008, a 52 year old female presented AKI with creatinine of 633 µmol/L, microhaematuria and dyspnoea associated with anti-GBM antibodies > 100U/ml. She was empirically pulsed with methylprednisolone and oral CYP. Renal histology confirmed crescentic GN with linear IgG deposition in GBM. On the 3rd day she developed acute respiratory failure secondary to pulmonary haemorrhage and was intubated and ventilated. She was commenced on acute haemodialysis and PE. Later she developed Citrobacter freundii septicaemia and Clostridium difficile toxin colitis associated with thrombocytopaenia of 17x10^{9}/L. Her CYP was discontinued. When sepsis resolved she was administered 2 doses of rituximab 1g intravenously two weeks apart and her anti-GBM titres remained negative 5 months following treatment. Her clinical course was complicated by Charles Bonnet disease, hypertensive encephalopathy and heart failure. She remained haemodialysis dependent. There are 2 case reports of GD treated with rituximab successfully in the literature.

Discussion: Literature review regarding diagnostic and treatment dilemmas regarding our 2 cases will be included.

Conclusion: GD with negative serology should always be diagnosed with renal histology. The standard treatment in these patients remains uncertain. The use of rituximab in GD is novel and mandates further evaluation.

P158

Cryofiltration for cryoglobulinaemia: 2 cases

Mark Lambie[1], Nithya Krishnan[1], Stephen Bailey[2], Simon Fletcher[1], Rob Higgins[1]

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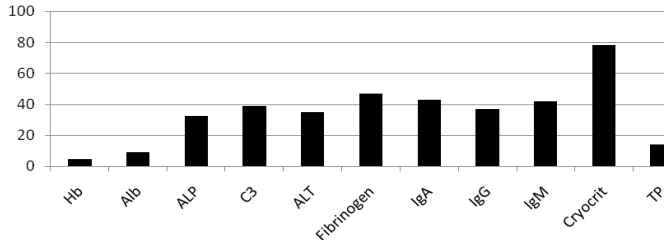
Cryofiltration is a modification of double filtration plasmapheresis, intended to selectively remove precipitate from cooled serum thereby avoiding some of the morbidity associated with non-selective plasma protein removal. Plasma is piped from the plasma separator through a cooled water bath before entering the second filter. This filter has a similar pore size to the plasma separator thereby only retaining proteins which have precipitated in the cold. Plasma is then rewarmed and returned to the patient. 2 different cryofiltration strategies have been described, essentially using different pore size filters for the second filter to remove either cryoglobulins (large pores) or 'cryogel', a composite of heparin, fibronectin, fibrinogen and possibly other proteins (smaller pores). The removal of cryogel has been used prior to ABO incompatible transplants as well as in the management of a variety of immunologically mediated conditions

We present the results of cryofiltration in 2 cases of cryoglobulinaemia. Both patients were treated with cyclophosphamide as well and in one case, rituximab was added. The Plasmacure membrane (pore size 0.2µm) was used for both filters. A total of 14 sessions were performed (5 sessions of mean 55.4 ml/kg plasma volume treated for patient 1 and 9 sessions of mean 43.1 ml/kg for patient 2), with no serious adverse effects (1 associated with mild light-headedness).

Figure 2: Mean percentage reduction in various markers post cryofiltration



Whilst cryoglobulins were substantially reduced compared to other proteins, the fact that other proteins were reduced implies some cryogel removal, compatible with published experience for membranes of this pore size. Both patients had a good clinical response temporally coincident with their cryofiltration. ABO titres, measured by flow cytometry, were reduced to a degree commensurate with overall immunoglobulin reduction.

We believe this is the first use of cryofiltration in Europe, and initial results suggest that it is safe, well tolerated and more selective than plasmapheresis for cryoglobulin removal.

P159

Re-biopsy in Lupus Nephritis after Treatment with a steroid sparing regime identifies quiescent disease

Marie Condon, Thomas Cairns, Megan Griffith, Ruth Pepper, Candice Roufosse, Terry Cook, Liz Lightstone

Imperial College Kidney and Transplant Institute, London, United Kingdom

Purpose: To review the benefit of re-biopsy in patients treated with Rituximab and MMF and minimal steroids, particularly in those patients with persistent proteinuria.
Methods: We identified all patients who had been rebiopsied having received our Rituximab-based treatment regimes for class III/IV/V lupus nephritis in the past 3 years. All patients receive Rituximab 1g twice + maintenance MMF. Protocol A: patients not on oral steroids at presentation receive 500mg methyl prednisolone (MP) IV twice & no oral steroids; Protocol B: patients on oral steroids were variably given MP as in Protocol A then steroid withdrawal was attempted.

Results: 22/62 patients with at least 6 months follow up have been rebiopsied (15/38 Protocol A, 7/24 Protocol B). Indications and timings of biopsies: non response (NR), relapse (R) or persistent proteinuria (PCR>100) despite stable serum creatinine + normal serum albumin at 1 year post treatment; Protocol A: NR=4 (7-24mths); R=2 (15-20mths); PCR>100=8 (12-24mths); other=1 (complete remission, patient request, 12 mths). Protocol B: NR=2 (19-20mths); R=2 (10-13mths); PCR>100=2 (12-21mths); other=1 (pre-pregnancy for MMF to Azathioprine switch, 18 mths). 2 patients on protocol A & 3 on protocol B with PCR >100 but stable creat and normal serum albumin at 12 months were not rebiopsied. 4 had falling proteinuria and 1 retreated empirically with Rituximab.

Biopsy findings & change in Rx	**Inactive disease**	**Ongoing or increase in disease activity**	**Increase in scarring** [defined as >20% increase in tubular atrophy]	**Re-Dose Rituximab +/- Methyl Pred**	**Cyclophosphamide based regime**	**Optimise MMF dose only**
Protocol A, No oral steroids	**9** [NR=1; PCR>100= 7; CR=1]	**6** [NR=3; R=2; PCR>100 =1]	**3** [2 with N GFR, 1 with stable impaired GFR]	**2** [R=1; PCR>100 =1]	**2** [NR=2]	**1** [R=1]
Protocol B, Steroid sparing	**3**[PCR>100=2; Pre-preg=1]	**4** [NR=2; R=2]	**1** [normal GFR]	**3** [NR=2 R=1]	**1** [R=1]	**0**

Conclusions: Rebiopsy of persistently proteinuric patients identifies achievement of renal remission, avoids empirical retreatment & provides a valuable baseline for future biopsies.

P160

Idiopathic membranous nephropathy (IMN) – Has our practice changed in the last 10 years?

Emily P McQuarrie, Catherine M Stirling

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Aim: Who, when and how to treat IMN remains contentious and the results of the MRC trial are awaited. We examined our practice in a single renal unit over the last 10 years and compared it with a previous cohort.

Methods: All patients with biopsy proven membranous nephropathy diagnosed between 1997 and 2007 were retrieved from our electronic database. Baseline and follow-up data were obtained, including details about immunosuppression and outcome. This was compared with a previously published series from the same unit, 1986 to 1996, n=53 [1].

Results: 65 patients were identified, of whom 48 had IMN. At diagnosis, mean age was 61.3y, mean eGFR 61 ml/min and mean proteinuria 6.4g/24hr. 58% were nephrotic and 80% were male. 12 patients (25%) were treated with immunosuppression, all of whom were nephrotic. 23 patients (52%) were in complete or partial remission at follow up (mean 5.1 y). 16 patients (36%) had a spontaneous remission. 3 progressed to ESRD (7%) and 5 died (11%). Patients who were treated with immunosuppression were significantly younger, more likely to be male, nephrotic and had better renal function at diagnosis. Median time to treatment was 329 days. 3 patients (25%) failed to complete treatment due to complications. Compared with the previous cohort, fewer patients were immunosuppressed (25% vs 36%). However they were also older (61.3 v 53.8y) and has less severe renal disease at diagnosis (mean QP 6.4g/24hr v 8.3g/24hr). Renal outcomes improved with 52% achieving remission at follow up (v 47%) and fewer patients developed end stage renal failure (7% v 13%) or died (11% v 15%).

Discussion: This study demonstrates that we are still conservative in our use of immunosuppression in patients with IMN (25% of patients), but that outcomes are similar or better compared with historical controls. There are a number of reasons for our selective approach to immunosuppression which include an older population, uncertainty about the evidence of benefit of immunosuppression and a high spontaneous remission rate (36%). We hope that the results from the MRC trial will help direct future treatment decisions.

1. C.M.Stirling, K Simpson, J.M. Boulton Jones. Q J Med 1998;91:159-164.

P161

VenoThrombotic Events in Idiopathic Membranous Nephropathy Patients: Incidence and Risk Factors

Sanjeev Kumar, Ananda Chapagain, Alistair Chesser, Raj Thuraisingham, Martin Raftery, Magdi Yaqoob, Michael Sheaff

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Background

Among the patients with nephrotic syndrome, those with membranous nephropathy are at the greatest risk of thromboembolism. The role of anti-coagulation in this patient group remains a clinical conundrum. However, little is known about its incidence rate and risk factors in idiopathic membranous nephropathy (IMN) patients.

Objectives

To measure the incidence of VTEs in patients with IMN and determine its risk factors. Incidence rate was calculated on the basis of time to first VTE.

Methods

A retrospective analysis of prospectively collected data on all 113 MN patients diagnosed over the last 20-year period at our centre.

Results

Eighty two (72%) patients had IMN. During 490 person-years of follow-up, 15 (18%) of 82 IMN had first-time thrombotic event yielding an incidence rate of 3.0 per 100 person-years. Twelve (80%) of 15 patients ***presented*** with venous thromboembolic event (VTE) and were subsequently, detected to be nephrotic. Compared with the 56 IMN patients with no VTE, the patients with VTE were significantly more hypoalbuminemic ($p<0.01$), hypercholesterolemic ($p<0.01$) with greater level of proteinuria ($p<0.05$) at presentation. The two groups were similar with respect to age, eGFR and medications. In univariate logistic regression analysis, proteinuria [Odds ratio(OR), 95% confidence interval; 1.24 (1.02 to 1.84); $p<0.05$], serum albumin (0.83, 0.71 to 0.97; $p<0.05$) and cholesterol levels (1.20, 1.02 to 1.47; $p<0.05$) were significantly associated with VTE but not age, sex, eGFR or s.globulins. Multivariate analysis revealed proteinuria (OR, 1.39, 95%CI 1.05 to 1.84 , $p<0.05$) and serum albumin (OR, 0.84, 95%CI 1.05 to 0.98, $p<0.05$) to be significantly associated with VTE.

Conclusions

Overall, the incidence rate of VTEs in patients with active IMN is high when compared with available rates in the general population (0.3 per 100 person-years) and lupus (1 per 100 person-years); however, similar to general population once the treatment for membranous nephropathy is initiated.

Serum albumin levels along with urine dipstick analysis for proteins should be included in the protocol of the management of patients with VTE as approximately one-fifth of the patient with IMN may present with VTE.

These results have important implications for clinical care of patients with IMN.

P162

Mesangiocapillary Glomerulonephritis: a 10 year single centre experience

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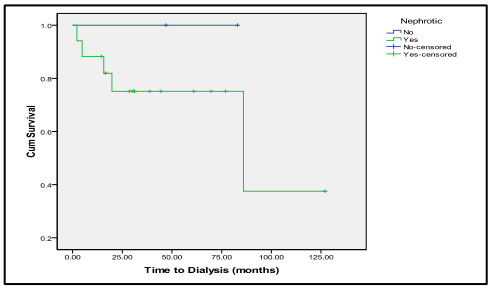
Introduction: Mesangiocapillary glomerulonephritis (MCGN) is a histopathological diagnosis that may be primary or secondary to infections, cryglobulinaemia, or autoimmune disease resulting in immune complex formation. The aim of this review was to examine all incident patients over a 10 year period in a single UK Renal Centre.

Method: A retrospective analysis was undertaken of all patients presenting to our renal centre with biopsy proven MCGN from 1998 to 2007, inclusive, allowing for at least one year follow-up.19 case notes were reviewed using the electronic patient record. Patients were divided into 2 categories, those with idiopathic MCGN and secondary MCGN

Results: The mean age at diagnosis was 53 ±17 [Mean ± SD] .52% were female and mean follow up was 36.5 ±31/9 months. 15(79%) patients presented with renal impairment; mean creatinine at presentation was 207 ±110umol/l. Proteinuria at presentation was 5.1± 3.1 gm/day with 89 % of patients having nephrotic range proteinuria. The causes of MCGN were as follows - SLE(4 cases),Light chain nephropathy(1),Chronic lymphocytic leukaemia(1), Sjogren's disease(1) , Hepatitis C (1) and Essential cryglobulinaemia(2). In the other 9 cases no cause was identified and they were classified as idiopathic.Cryoglobulins were detected in 4 patients; this was in association with hepatitis C and light chain nephropathy (one patient each). Low complement (C3/C4) was found in 11 (57%) patients. 12 patients had Type 1 MCGN,1 Type 2,and there were 2 patients diagnosed as type 3.Patients with SLE were not classified

Outcomes: Patient and renal survival at last follow-up were both 74%. Mean time to ESRD was 24 ±34.4 months. 60% of patients with nephrotic syndrome at time of diagnosis progressed to ESKD requiring dialysis within 8 years (see Kaplan Meier Plot). One patient had a pre-emptive transplant and another patient was transplanted after 4 years on dialysis. Neither has had recurrence of MCGN in the allograft.

Treatment: 16 (84 %) patients were treated with RAAS blockade.Immunosupressive treatment was very variable;prednisolone and MMF was instituted for MCGN patients with secondary SLE, all of whom had reduction in proteinuria and improved renal function. Prednisolone with chlorambucil was given to patients with Light chain Nephropathy and CLL and with Cyclophosphomide to one of the essential cryoglobulinaemia patients. Only one patient with idiopathic MCGN received treatment (Prednisolone) – they had crescentic change



Graph 1: Time to ESRD for MCGN comparing Nephrotic and non Nephrotic patients

Poster Session

Thursday 23 April

13:30 – 14:30

Vascular Access – Catheters 2

Moderator Dr Rob Mactier

P163

Previous Central Lines Don't Affect Short Term Fistula Outcome

Lesley Brown, Marc Clancy

Western Infirmary, Glasgow, United Kingdom

Aim: Arteriovenous fistulae are the preferred form of dialysis access but need time to mature. Many patients require central lines to allow immediate dialysis and it is well known that these in-dwelling lines promote stenosis or occlusion of the central veins. This study aimed to see if previous central line insertion was associated with poorer 6 week fistula patency.

Methodology: : Demographic and clinical data for all patients having upper limb autologous fistulae created between October 2007 and July 2008 was assembled in a dedicated database (MS EXCEL) using information from the prospective unit database (proton) supplemented by clinical records. Patency at 6 weeks was compared between the group with previous line insertion and the group with no previous line.

Results: 93 access episodes were looked at. Fifty of these episodes had a history of previous line insertion. There were no significant demographic differences between the groups in terms of age, sex, number of previous access procedures or the level of fistula created but there were more predialysis patients in the group without previous ($P<0.0001$) lines. Patency results are shown in the Table below.

	Total Number	**Working**	**Failed**	**Other outcome**
No line, wrist fistula	25	15(60%)	10(40%)	0
No line, elbow fistula	18	10(55.56%)	7(38.89%)	1(5.56%)
Previous line, wrist fistula	20	12(60%)	7(35%)	1(5%)
Previous line, elbow fistula	30	16(53.33%)	9(30%)	5(16.67%)

Conclusion: A previous central line history was not associated with reduced 6 week patency. Assessment of any effect on longer term success rates and complication rates will require longer follow up and a larger sample.

P164

Exit site care with topical Mupirocin ointment for cuffed central venous catheters is associated with lower rates of exit site infection

Seema Singh, Neill Duncan, Albert Power, Damien Ashby, David Taube, Thomas Cairns

Imperial College Kidney and Transplant Institute, London, United Kingdom

Our centre's haemodialysis programme is composed of 9 satellite haemodialysis units, 5 units routinely apply Mupirocin ointment to the exit site of cuffed central venous catheters and 4 units do not. All units clean the exit site area with 4% Chlorhexidine solution. We assessed the impact of the two exit site care regimens on incidence of: exit site and tunnel infections and bacteraemia; organisms associated with local infection and bacteraemia; antibiotic starts. Data were collected prospectively from 1st June 06- 31st May 08 representing 180,835 catheter days (cath days) in the Mupirocin group and 354,113 in the Chlorhexidine group. Infection return forms were completed by haemodialysis nursing staff and collated centrally. Mupirocin use was associated with significantly less exit site infections, 0.25 v 0.77 /1000 cath days ($p<0.0001$), but there was no significant difference in bacteraemia rates, 0.41 v 0.50 /1000 cath days ($p=0.16$). Mupirocin use was associated with significantly fewer antibiotic starts, 1.06 v 1.76 /1000 cath days ($p<0.0001$) and in particular, fewer vancomycin starts 0.74 v 1.10 /1000 cath days ($p<0.0001$). The use of Mupirocin significantly reduces Staphylococcal exit site infections, but does not have an effect on other gram +ve and also gram –ve organisms. The treatment effect of Mupirocin at the exit site does not translate into a reduction in Staphylococcal bacteraemia. This maybe due to basal bacteraemia rates being significantly lower than published data. The routine use of Mupirocin is associated with significantly: lower exit site infections; fewer antibiotic starts; fewer Vancomycin starts but does not affect rates of bacteraemia. A randomised trial is necessary to elucidate optimal use of Mupirocin: routinely versus clinically indicated to avoid risk of development of Mupirocin resistance.

P165

Review of Damaged Haemodialysis Catheters Due to Cracked Luer Lock Mechanism

Joanne Shields, Ronan Cunningham, Camille Harron, Robert Mullan

Antrim Area Hospital, Co Antrim, Northern Ireland, United Kingdom

Introduction

The type of long-term vascular access for haemodialysis (HD) patients is critical in both the provision of adequate dialysis and the minimisation of complications such as sepsis. Clear evidence exists indicating that HD access in the form of an arteriovenous (AV) fistula is superior to that of a tunnelled haemodialysis catheter (THDC). Despite this many HD patients continue to use THDCs indefinitely over many months or years because of the inability to obtain more permanent access. As a result unique complications related to catheter aging have been noted such as cracks developing in the luer lock mechanism, which can compromise the seal and cause leaks, creating the potential for infection and air embolism.

Aim

The aim of this study was to assess the rate of this specific complication and whether or not the THDC could be salvaged or required full replacement.

Methods

The population studied was HD patients at Antrim Renal Unit in Northern Ireland, servicing a population of 440,000 and which had been reported in the 2006 United Kingdom Registry Report (UKRR) to have the highest percentage of patients using THDC, currently 64% of the total HD population. We reviewed the HD medical and nursing records of patients at Antrim Renal Unit from 1st January 2007 to 1st June 2008 to identify episodes of cracked luer locks and their subsequent management. The insertion date of THDCs identified with cracks and complications related to the repair of luer locks were also recorded for analysis.

Results

15 episodes of cracked luer locks were identified over the time period with an increase in frequency occurring in the past 6 months (n=8 in 2008). The median age of the patients was higher than that for the whole HD population (71 years vrs 67 years). The median time from THDC insertion to crack was 14 months (4-58 months). All locks were repaired by localised excision and replacement with a new luer lock. No THDC required full replacement. No complications from the repair such as sepsis or secondary leak were observed.

Conclusions

This study indicates that the integrity of luer locks on THDCs suffers over time. Although this has the potential for serious complications, localised repair to the lock appears successful.

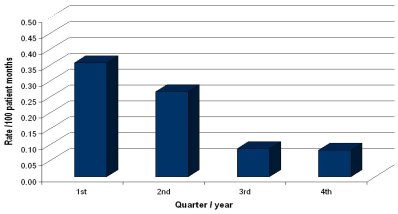
P166

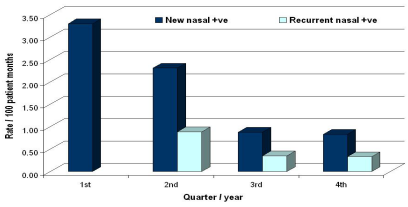
Screening and eradication of nasal and exit site MRSA colonisation is effective and associated with a significant reduction in clinical infection.

Seema Singh, Neill Duncan, Albert Power, Damien Ashby, David Taube, Thomas Cairns

Imperial college kidney and transplant institute, London, United Kingdom

We initiated 3 monthly screening for nasal and exit site colonisation with MRSA for the prevalent haemodialysis population, established for > 90days from July 07 to June 08. 1120 patients were on dialysis in the first quarter, 63% had cuffed central venous catheters, 36% arterio-venous fistulas and 1% arterio-venous grafts. Screen positive patients had eradication treatment comprising Mupirocin 2% ointment to nose 4x daily and Chlorhexidine 4% body scrubs daily both for 5 days. In the event of a positive exit site swab Mupirocin ointment was applied to exit sites indefinitely. Recurrent infection was defined as two consecutive screen positives. Nasal site colonisation decreased by 75% from 3.30/100 patient months in the 1st quarter to 0.83/100 patient months in the 4th quarter ($p<0.0001$). Recurrent nasal site colonisation also decreased from 0.89/100 patient months in the 2nd quarter to 0.33 in the 4th quarter [Figure 1]. There was a downward trend in exit site colonisation from 0.27/100 patient months in the 1st quarter to 0.08/100 patient months in the 4th quarter ($p=0.18$) [Figure 2]. Clinical episodes of MRSA bacteraemia decreased from 0.17 /100 patient months in the 2nd Quarter to 0 in the 3rd and 4th quarters. There were no MRSA exit site infections during the period of study. Routine MRSA screening and subsequent eradication effectively reduces colonisation rates and is associated with a significant reduction in clinical infection.





P167

Tal PALINDROME™ dual lumen tunnelled cuffed catheters are associated with increased catheter-related bacteraemia rates in prevalent haemodialysis patients.

Shalabh Srivastava, Shreya Raman, Mark Blunden, Neil Ashman

The Royal London Hospital, London, United Kingdom

Introduction: Tunnelled Cuffed Catheters (TCC) are important in providing vascular access for haemodialysis requiring renal failure. They serve as a bridge to the more definitive access i.e. Arteriovenous Fistula. There are many commercially available TCC and we compared the efficacy of Medcomp® Split Cath® and Tal Palindrome™ (Covidien) dual lumen catheter in prevalent haemodialysis patients.

Methods: We analysed data from 21 patients in the Medcomp® group and 15 patients in the Palindrome™ group at the Royal London Hospital Renal Unit. Palindrome™ catheters were introduced in our unit as the TCC of choice in April 2008 completely replacing Medcomp® catheters. We collected monthly Hb, CRP, EPO requirements, Blood Flow Rate, Venous Pressure, Dialysate Flow Rate, Litres Processed, URR, Kt/v, Alteplase usage, blood culture proven episodes of catheter-related bacteraemia (CRB).This data was collected over a period of 12 months for the Medcomp® group and over 8 months for the Palindrome™ group. Patients who died, changed to arteriovenous access or changed mode of renal replacement therapy were excluded.

Results: We analysed 3850 at risk patient days in the Palindrome™ group and 7300 in the Medcomp® group.CRB rates were 2.34 per 1000 patient days in the Palindrome group and 0.27 per 1000 patient days in the Medcomp® group ($p<0.01$).Median C-reactive protein was 25.06 in the Palindrome™ group and 7.29 in the Medcomp® group ($p<0.004$).No significant difference was observed in Hb, EPO requirements, Alteplase requirements, Blood Flow Rate, Venous Pressure, Dialysate Flow Rate, Litres Processed, URR and Kt/v between the two groups.

Discussion: A significant increase in CRB rates in the Palindrome™ group was observed.46.7% Trisodium citrate (TSC) is uniformly used as a catheter lock solution in our unit. We postulate that this clinically significant finding can be explained by leakage of catheter lock solution from the lumen of Palindrome™ catheters. Further investigation of the catheter dynamics and longer follow up with a greater number of patients may be required to confirm this important observation.

Conclusion: Tal Palindrome™ dual lumen catheters are associated with a significantly higher incidence of catheter-related bacteraemia episodes in prevalent patients.

Poster Session

Wednesday 22 April

13:00 – 14:00

Vascular Access – Fistulas

Moderator Dr Mark Harbor

P168

The effect of Erythropoietin on short term fistula outcome

Lesley Brown, Marc Clancy

Western Infirmary, Glasgow, United Kingdom

Aim: Arteriovenous fistulae(AVF) are the preferred form of dialysis access with superior patency and lower complication rates than lines or grafts. If these fail it becomes a major clinical problem with significant morbidity and financial implications. Erythropoietin(EPO) has both haemodynamic effects and effects on survival on rapidly dividing cells such as those comprising a new vascular anastomosis. The aim of this study is to assess the effect of exogenous EPO on the short term outcome of native arteriovenous fistulas.

Methodology: Demographic and clinical data for all patients having upper limb autologous fistulae created between October 2007 and July 2008 was assembled in a dedicated database(MS EXCEL) using information from the prospective unit database(proton) supplemented by clinical records. Patency at 6 weeks was compared between the group treated with EPO and those not receiving the agent.

Results: 93 vascular access episodes were analysed. There were no significant demographic differences between the groups in terms of age, sex, number of previous access procedures or the level of fistula created. Tables 1 & 2 show patency results.

Table One – Wrist Fistulae

	Total Number	**Working**	**Failed**	**Other Outcome**
Epo	33	25(75.76%)	8(24.24%)	0
No Epo	12	4(33.33%)	8(66.66%)	0

Table Two – Elbow Fistulae

	Total Number	**Working**	**Failed**	**Other Outcome**
Epo	39	22(56.41%)	12(30.77%)	5(12.82%)
No Epo	9	6(66.67%)	2(22.22%)	1(11.11%)

Conclusion: EPO treatment is associated with a significant increase in wrist fistula patency (P 0.0086) at 6 weeks. In this short time frame, haemodynamic effect seems the most likely explanation.

P169

Can average weekly blood flow rate and venous pressure on dialysis predict fistula and graft thrombosis occurring?

Olivia Worthington, Muhammed Wadood, Steven Powell, Yaser Shah, Qi Bing

Royal Liverpool University Hospital, Liverpool, United Kingdom

AIM To look at the average weekly flow rates and venous pressures on dialysis one month prior to fistula/ graft thrombosis and to assess if a reduction in flow rate and/ or increase in venous pressure occurs prior to thrombosis and can therefore aid in its prediction.

BACKGROUND Fistula and graft thrombosis is one of the major causes of morbidity and mortality in dialysis patients and is one of the most common dialysis emergencies. Various methods of fistula surveillance have been developed but there is not yet a consensus as to which factors best predict access failure. It is known that poor dialysis flow and high venous pressures occur when there is impedance to blood flow on dialysis and this audit therefore looked to see if these factors could be used to predict access failure.

METHOD The computerised dialysis records of 34 patients who presented with primary fistula/ graft failure requiring radiological thrombectomy between October 2006 and January 2008 were analysed. Average weekly values for flow rate and venous pressure in the 4 weeks prior to graft failure were analysed for each patient and then the average group values were compared.

RESULTS The average flow rate on dialysis was 332ml/min 4 weeks prior to fistula/ graft failure, compared to 342 ml/min 3 weeks before, 282ml/min 2 weeks before and 306 ml/min 1 week before. The average venous pressure 4 weeks previously was 148mmHg compared to 167mmHg 3 weeks previously, 149mmHg previously and 152mmHg 1 week previously.

CONCLUSION There was found to be no significant difference between average blood flow or venous pressure 1 week prior to fistula/ graft thrombosis when compared to 4 weeks previously, although the 4 week flow rate is slightly higher and the venous pressure slightly lower when compared with the week 1 values. However this study could be reproduced with a larger group of patients studied over a longer period so as to more accurately determine any significant differences between normal and impeded blood flow. Separation of the groups into graft and fistula may also provide greater accuracy in future studies and a specific target minimum blood flow and maximum venous pressure would lead to more reliable comparison.

P170

The use of ACE- inhibitors has no impact on short term fistula outcome

Lesley Brown, Marc Clancy

Western Infirmary, Glasgow, United Kingdom

Aim: Arteriovenous fistulae (AVF) are the preferred form of dialysis access with superior patency and lower complication rates than lines or grafts. If these fail it becomes a major clinical problem with significant morbidity and financial implications. One of many factors suggested as potentially protective against failure are ACE-inhibitors. The aim of this study is to see if this is true in short term outcome of native arteriovenous fistulas.

Methodology: Demographic and clinical data for all patients having upper limb autologous fistulae created between October 2007 and July 2008 was assembled in a dedicated database (MS EXCEL) using information from the prospective unit database (proton) supplemented by clinical records. Patency at 6 weeks was compared between the group treated with ACE/ARB and those receiving no such agent.

Results: There were no significant demographic differences between the groups in terms of age, sex, number of previous access procedures or the level of fistula created. Patency results are shown in Tables One and Two.

Table One – Wrist Fistulae

	Total Number	**Working at 6 weeks**	**Failed at 6 weeks**	**Other outcome**
ACE/ARB	14	8(57.14%)	6(42.86%)	0
No ACE/ARB	31	21(67.74%)	10(32.26%)	0

Table Two – Elbow Fistulae

	Total Number	**Working at 6 weeks**	**Failed at 6 weeks**	**Other outcome**
ACE/ARB	13	6(46.15%)	5(38.46%)	2(15.38%)
No ACE/ARB	35	22(62.86%)	9(25.71%)	4(11.43%)

Conclusion: The use of an ACE-inhibitor is not associated with any significant difference in the 6 week patency rates of AVF's. Whilst it is reassuring that the powerful antihypertensive action of these agents doesn't affect short-term outcomes, any long term benefit on patency will require longer follow-up and greater patient numbers to assess.

P171

Retrospective survey of vascular access provision for patients starting on haemodialysis at Birmingham Heartlands Hospital in 2007.

Khai Ng, Steve Ting, Prince George, Jyoti Baharani

Birmingham Heartlands Hospital, Birmingham, United Kingdom

Introduction

Arteriovenous fistula (AVF) is the preferred form of vascular access for haemodialysis due to its lower infection risk and better long term dialysis performance compared to dialysis catheter [1, 4]. Nevertheless, the Dialysis Outcomes and Practice Patterns Study (DOPPS) published in 2002 undoubtedly illustrated the need of improvement in UK renal vascular access provision as we have the lowest incidence and prevalence of AVF access use compared to other European countries [DOPPS].

National Kidney Foundation 2006 advocated early planning for renal failure [2]. Renal Association Clinical Practice Guidelines 2007 aim for least 65% of patients presenting more than 3 months before initiation of dialysis to have usable AVF upon starting haemodialysis and expect all patients on dialysis, including those patients who present late, to wait no more than 4 weeks for AVF construction.

Aims

Our audit aims to examine the service provision of vascular access for patients starting on haemodialysis in Birmingham Heartlands Hospital in 2007 against the current renal association clinical practice standards and to compare the outcome with previous local audit results in 2001 and 2004.

Methods

This was a retrospective study of all patients who first commenced on haemodialysis from 1st January 2007 to 31st December 2007 in Birmingham Heartlands Hospital using electronic hospital record and renal database.

Results

There were 82 patients identified, mean age 62.3 +/- 16.8 year-old. Male to female ratio was 1.7:1. The average eGFR on commencement of haemodialysis was 8.4 +/- 3.1. 70% of patients received first haemodialysis via AVF, compared to 59% and 64% in 2001 and 2004, respectively. 3 months after the initiation of the haemodialysis, 14% of the patients were still receiving haemodialysis via non-AVF access. 59% of the patients who did not have AVF access on first haemodialysis waited longer than 4 weeks for AVF construction. The average waiting time for AVF formation was 2 ½ months.

Conclusion

There was marked improvement of vascular access service provision from 2001 to 2007. The introduction of renal vascular access specialist nurse in 2003 played a crucial role in this achievement. On the other hand, we failed to achieve the waiting time target of 4 weeks for AVF formation. This resulted in a significant proportion of patients with established end-stage renal failure remained on dialysis catheter 3 months after their first haemodialysis session. This audit outcome prompted the urgent need for expansion of AVF formation surgery capacity. It also concluded the importance of the role of dedicated specialist nurse service and recommended the maintenance or increment of the number of vascular access specialist nurses for the unit.

P172

Approaching an 80% fistula prevalence with an enhanced Multidisciplinary team

Rosie Donne[1], Lourinti Fletchman[1], Zulfikar Pondor[1], Hilary Robinson[1], Paula Gleave[1], David Lewis[1], Ravi Pararajasingam[2], Afshin Tavakoli[2], Babatunde Campbell[2]

[1]Salford Royal NHS Foundation Trust, Greater Manchester, United Kingdom, [2]Central Manchester NHS Foundation Trust, Greater Manchester, United Kingdom

Introduction

The risks associated with dialysis via a central venous catheter are well recognised. The Renal Association standard of permanent vascular access in 80% of prevalent haemodialysis patients has been a challenge for many units across the UK. Like many regions, the Greater Manchester West Sector (Salford Royal and its satellites) has experienced a rapid expansion in haemodialysis numbers, with 340 prevalent patients in 2009. Although this has been accompanied by the appointment of 2 vascular access nurses and an expansion in vascular access surgeons, the fistula prevalence had remained at 65-67% over the preceding 5 years. The "Modernising Services for Renal Patients" 2005 report focussed on strategies to improve patient pathways and maximise use of resources. The aim of our work was to improve vascular access prevalence by streamlining the vascular access pathway accompanied by continuous audit to guide future service improvement.

Methods

A vascular access co-ordinator was appointed to track patients' progress and record data. The multidisciplinary vascular access team was defined, including co-ordinator, access nurses, surgeons, nephrologists, radiologist, anaesthetist and manager. The team worked closely to identify current problems and redesign the patients' pathway, incorporating protocols for referral, investigation and perioperative management. The role of the vascular access nurses was enhanced to include attendance in access clinics, renal unit ward rounds, pre-operative assessment clinics, and complete a weekly telephone-based audit of prevalent vascular access usage.

Results

Preliminary data 8 months following the introduction of these strategies demonstrated an increase in prevalence of permanent vascular access from 67% to 78% accompanied by enhanced motivation of the vascular access team.

Conclusions

A significant improvement in fistula prevalence was achieved by multidisciplinary working to maximise the use of existing resources. The appointment of a co-ordinator proved invaluable and the data collected will guide our future service development.

P173

Timeliness and technical success of angioplasty are important for endovascular salvage of arterio-venous fistulae with stenosis

Nasim Bahaei, Basavaraju Sujatha, Martin Ferring, John Henderson, Vijay Suresh

Birmingham Heartlands Hospital, Birmingham, United Kingdom

Background:

Stenosis is a frequent cause of dysfunction of arterio-venous fistulae (AVF), but can often be treated by appropriate intervention. Endovascular and surgical repair are two widely used salvage strategies. We evaluated how initial technical success and timeliness of intervention affected the outcome of angioplasty of dysfunctional AVF.

Methods:

We examined all haemodialysis patients who presented with a clinically dysfunctional AVF at our hospital during a 9-month period. We recorded time to radiological assessment and intervention, as well as technical success and dialysis use of the AVF from electronic patient and electronic dialysis session records.

Results:

Of 34 patients presenting with dysfunctional AVF (59% brachiocephalic, 21% brachiobasilic, 15% radiocephalic), 31 underwent fistulography after a mean of 15 days (range 0-90 days). In 27 (84%), the cause of AVF dysfunction was due to stenosis. Of those, 13 (48%) had angioplasty after a median of 40 days (range 0-180 days). Angioplasty had technical success in 80% (12/15) of AVF. Short term patency was 86% with early (≤ 14 days) angioplasty, compared to 75% with late angioplasty and 63% with no intervention, although this did not reach statistical significance. Overall, 80% (12/15) of salvaged AVF became usable for dialysis and remained functional for a mean of 10.7 months. By 6 months post angioplasty, 55% of our AVF were patent, but by one year, only 36 % (8/22) were patent. Almost half (47%) of the salvaged AVF subsequently required further salvage intervention.

Conclusions:

AVF dysfunction in haemodialysis patients is largely due to stenosis and this responds well to angioplasty. Our data suggest that early endovascular repair is an important factor for better short term AVF patency. Despite good short-term results, nearly half of the patient need further repair in future. Therefore, patients after AVF angioplasty may particularly benefit from close vascular access surveillance.

P174

The impact of a multi-professional vascular access pathway on local anaesthetic vascular access surgery waiting times

Tessa Savage[1], Simon Daniel[2], Matthew Bell[1], Mark Thornton[3], Alison Armitage[2], David Mitchell[1]

[1]Department Surgery,Southmead Hospital, Bristol, United Kingdom, [2]Department Renal Medicine & Transplantation, Southmead Hospital, Bristol, United Kingdom, [3]Department Radiology, Southmead Hospital, Bristol, United Kingdom

In North Bristol NHS Trust, a Vascular Access (VA) Steering group was set up in 2005 to identify the needs and initiatives required to ensure "timely and appropriate" VA to CKD patients. This resulted in the appointment of a new post, the Renal Access Specialist (RAS), in June 2006 and subsequent introduction of the multi-care professional VA Pathway in October 2006. A weekly meeting between the vascular surgeon and RAS was introduced to put clinical plans in place and streamline the referral process.

Within 3 months of initiating the VA pathway, waiting time (WT) for VA surgery had halved (Apr-Jun 2006 median 132 days (range 1-245 days) - 58 days (Jan 2007 range 0-197 days, $p<0.0001$).

Two further measures have been incorporated into the VA pathway. In November 2007, a weekly multi-disciplinary team meeting between Radiology, Renal Medicine and Surgery was started to discuss complex cases. In April 2008 waiting time management for LA procedures was transferred to a dedicated waiting list co-ordinator in Dept Surgery. This has resulted in a further fall in WT for VA surgery to a median 25 days (Aug-Oct 2008, range 0-76 days, $p<0.00001$). These measures have resulted in an 81% reduction in WT for VA surgery in 2 years.

These results show that an multi-professional approach with dedicated nurse specialist and waiting list co-ordination have a significant impact on waiting times for vascular access surgery.

P175

Sub-Clinical Steal Syndrome in Haemodialysis Patients with Established Arterio-Venous Fistula.

Sameer Sharma, Rebecca Roberts, Joana Vasconcelos, Gavin Pettigrew

Department of Surgery, University of Cambridge, Cambridge, United Kingdom

Objectives

Creation of an arterio-venous fistula for haemodialysis risks the development of hand ischaemia due to steal syndrome. Here we assess how the presence of a mature fistula influences distal digital blood pressures (DBP) and fistula flow rates (FFR).

Methods

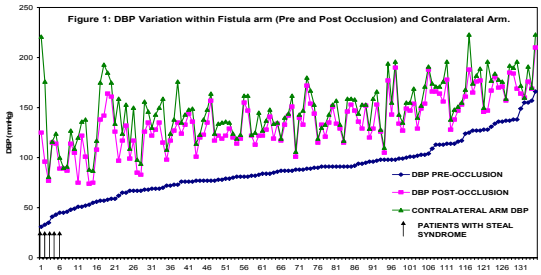
135 haemodialysis patients with established fistulae were assessed clinically for the presence of hand ischaemia. The systolic digital and brachial blood pressures were measured on the fistula and contra-lateral arm, and then re-measured after occlusion of the fistula for 30 seconds. FFR were measured by using ultrasound indicator dilution principles (Transonic™ – Hemodialysis Flow Monitor).

Results

In all but one patient, the DBP in the fistula arm was less than in the contralateral arm (Figure 1); pressures approximated upon fistula occlusion. Digital pressures in the contra-lateral arm ranged widely (81.0mmHg to 221.1mmHg), and, notably, correlated with the pre-occlusion DBP on the fistula arm. Although there was an inverse relationship between FFR and DBP (Pearsons correlation coefficient -0.35, p= 0.008), Fistula site (elbow or wrist) did not influence DBP, presumably because mean FFR for wrist and elbow fistulae were similar. Only five patients had clinical evidence of hand ischaemia; their digital pressure measurements were commensurately low (33 - 42mmHg).

Conclusions

Although largely asymptomatic, digital pressures are reduced in the fistula arm. This reduction is influenced by flow through the fistula, but the correlation with pressures on the contralateral arm suggests that a critical factor in the development of symptomatic steal is co-existent peripheral atherosclerotic disease.



Poster Session

Tuesday 21 April

11:30 – 12:30

Tubular Cell Biology

Moderator Dr Mark Dockrell

P176

Albumin – stimulated epithelial mesenchymal transformation

J Ibrini, S Darwish, R.S Chana, T Johnson, N Brunskill, A.M El Nahas

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Background: Progression of CKD is associated with albuminuria and progressive renal fibrosis. The latter is linked to accumulation of myofibroblasts and subsequent increased production of extracellular matrix (ECM). Renal myofibroblasts are derived from a number of cells including renal proximal tubular epithelial cells (PTCs) through Epithelial Mesenchymal transformation (EMT). This study explores the hypothesis that exposure of PTCs to albumin *in vitro* induces EMT.

Method: Normal rat PTC line (NRK52E) was cultured on plastic six-well plates until they reached 70% or complete confluency. The cells were then starved for 24hr and then exposed to de-lipidated bovine serum albumin (dBSA; 10mg/ml)) for 2, 4 and 6 days. Mannitol (20mg/ml) was used as osmotic control. Transdifferentiation of tubular cells into myofibroblasts was assessed by light & electron microscopy (EM), immunofluorescence (IF) and Western blotting for the neo-expression of α-smooth muscle actin (α-SMA); a myofibroblast marker and downregulation of E-cadherin; a PTC marker. We also examined collagen I, III and IV expression by IF. TGF-β_1 expression after dBSA stimulation was assessed by Northern and Western blotting. 10μg/ml neutralizing anti-TGF-β_1 antibody was used to test if albumin-stimulated EMT was TGF- β_1 dependent. Results are expressed as mean ± SEM. Differences between groups were assessed by using t-test or ANOVA test.

Results: Exposure to dBSA led to binding and uptake by PTCs in culture. Light microscopy showed changes involving hypertrophy with cells becoming elongated. Scanning EM showed loss of epithelial cell morphology with cell elongation and loss of cell-cell contact. Transmission EM showed few bundles of actin filaments in treated cells. Immunofluorescence staining and Western blot analysis showed that the addition of dBSA to PTCs caused a significant reduction of expression of the epithelial marker E-Cadherin (ANOVA p= 0.0002) and de novo expression of the mesenchymal marker α-SMA (ANOVA p= 0.0001) in a time-dependent manner. Incubation of PTCs with dBSA increased expression of collagen I, III and IV by 8.1 ± 1.63 fold, 6.99 ± 2.1 fold and 2.1 ± 0.18 fold, respectively in a time-dependent manner($p<0.05$). Incubation with dBSA increased TGF-β1 mRNA expression (1.8 fold compared to control [P=0.005]), TGF-β1 protein and activity. The application of 10μg/ml anti-TGF-β1 neutralizing antibody to PTCs treated with dBSA for 6 days caused significant preservation of the expression of E-cadherin and blunted the increase in α-SMA. Osmotic control studies with mannitol had no effect on EMT.

Conclusion: This study demonstrated that albumin induces in *vitro*, in a TGF-β_1-dependent manner the trans-differentiation of PTCs into myofibroblasts.

P177

Homophilic and Heterophilic Polycystin-1 interactions regulate E-cadherin recruitment and junction assembly in MDCK cells

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited human renal disease and is caused by mutations in two genes, *PKD1* (85%) and *PKD2* (15%). Cyst epithelial cells are characterised by a complex cellular phenotype including changes in proliferation, apoptosis, basement membrane composition and apicobasal polarity. Since polycystin-1, the PKD1 protein, has been localised to the basolateral membrane of kidney epithelial cells, we hypothesised that polycystin-1 might play a key role in mediating or stabilising cell-cell interactions.

We first investigated whether surface expression of the polycystin-1 extracellular domain alone was sufficient to confer an adhesive phenotype in non-adhesive L929 fibroblasts. Secondly, we investigated the trafficking of polycystin-1 during junction re-assembly following 'calcium switch' in MDCK cells.

Stable L929 clones were generated expressing the extracellular domain of polycystin-1 in frame with a GPI anchor signal sequence (NT1-GPI) which localises it to the plasma membrane. Cell surface expression was demonstrated by FACS, immunofluorescence and electron microscopy. L929 aggregation assays were used to assess the ability of polycystin-1 to mediate cell-adhesion in the absence of classical cell adhesion molecules. The trafficking of endogenous polycystin-1 during junction re-assembly was observed by confocal microscopy using a calcium switch assay.

Expression of NT1-GPI induced aggregation and junction formation in L929 cells confirming that homophilic interactions of the extracellular domain of polycystin-1 is sufficient to confer an adhesive phenotype. In MDCK cells, polycystin-1 co-localised with E-cadherin at lateral cell borders during junction reassembly within 30 min following a calcium switch. Recruitment of E-cadherin to intercellular junctions was delayed when cells were treated with a polycystin-1 blocking antibody. Finally, polycystin-1 and E-cadherin could be co-immunoprecipitated together from MDCK cells. We conclude that polycystin-1 plays a key role in initiating junction formation via initial homophilic interactions and facilitates junction assembly and the establishment of apicobasal polarity by E-cadherin recruitment.

P178

Statins regulate cell function by altering membrane cholesterol rafts and isoprenoids

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The cell membrane supports functional cholesterol-rich microdomains ("rafts") which concentrate receptors and signal transduction molecules to facilitate high efficiency signal transduction. Statins inhibit cholesterol synthesis by HMG-CoA reductase and have proven benefits in the prevention of cardiovascular events beyond lowering plasma lipids, notably immunosuppressive functions as well as anti-inflammatory effects and attenuation of fibrosis in cyclosporine toxicity Reduced production of isoprenoid intermediates (that play a key role in cell signalling), and depletion of cell membrane rafts have been proposed to explain these "pleiotropic" actions. This study sought to differentiate between the effects of reduced isoprenoid groups and disrupted cholesterol rafts.

HK2 proximal tubular cells treated with statins reduced the production of inflammatory cytokines, IL-6, IL-8, GMCSF and fibronectin. The functional effect of raft disruption on immune cells (NK92 cells) was investigated by cytotoxicity assay. Cytotoxicity increased with time exposed to soluble cholesterol. However, cytotoxicity levels did not return to baseline with overnight incubation, despite changes in membrane cholesterol and raft associated proteins. We therefore measured active Ras (a small-G protein that is localised by isoprenylation in membrane rafts when activated). Treatment with simvastatin reduced Ras within the raft, and is not reversed by the addition of membrane cholesterol. NK92 cells were treated with increasing concentrations and length of time of soluble cholesterol. Cholesterol incorporated into the membrane was concentration dependent and short incubations doubled the incorporation of cholesterol into NK cell membranes. Addition of soluble cholesterol reversed the effects of simvastatin on membrane cholesterol content. Raft cholesterol content was similarly increased. Isolated rafts were Western blotted, to measure raft-associated signal proteins. LAT and Lyn levels were both reduced by simvastatin treatment. Short term exposure to soluble cholesterol increased both LAT and Lyn levels in the raft fraction. Overall these findings suggest that statins deplete membrane cholesterol and raft-associated proteins as well as isoprenylation. Replenishment of membrane cholesterol restores non-isoprenylated, raft-associated proteins such as LAT and lyn, but does not necessarily correct the functional effects of statins.

P179

Protease leak from proximal tubular epithelial cells (LLC-PK$_1$)

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Our recent work has indicated that high ambient glucose concentrations (25 mM) can elicit a calpain mediated necrotic injury occurs prior to the onset of apoptosis in cultured proximal tubular epithelial cells (PTEC). In this study we attempt to further elucidate the time course of this early injury and to examine the role of calpain in this death cascade.

PTEC were treated with 5 mM (control, C) and 25 mM D-glucose (high glucose, HG) as before but here LDH activity was measured in cell culture media at 30 min, 3 h and 24 h. Necrotic injury (% cytotoxicity) was found to be greatly elevated in those cultures treated with HG. Surprisingly, the degree of injury was almost identical over time (30 min C 3.83±2.12 HG 20.97±4.7, 3 h C 3.91±2.76, HG 22.99±6.2, 24 h C 6.07±3.28, 24 h 24.92±6.23, C vs HG $p<0.00002$, 0.0005, and 0.0002 respectively, n=6). We therefore examined the cell culture media of PTEC incubated in HG supplemented media (3 h) and found an appreciable quantity of calpain protein present (calpain 2 immunoreactivity) and a significant elevation in calpain activity was detected by fluorescent substrate assay (C 12.7± 7.5, HG 19.6±2.1, nM AMC released/min, $p<0.02$, n=12). Lysates derived from PTEC incubated with HG had a concomitant reduction in total protein concentration (C 0.6756±0.07, HG 0.5304±0.08, mg/L, $p<0.0005$, n=12) indicating substantial protein leakage from the cells. In order to discover if this protease leak was specific for HG induced injury we studied the same cells but here cultured them in the absence of fetal calf serum. % cytotoxicity (0 h 4.2%±2.3, 3 h 15.9±10.7, $p<0.002$, n=12), calpain activity (0 h 7.25±4.4, 3 h 12.7±16.8, nM AMC released/min, $p<0.05$) and caspase-3 activity (0 h 8.8±8.2, 3 h 31.6±26.5, nM AMC released/min, $p<0.01$) were all significantly elevated in cell culture media within 3 h of serum starvation. This work demonstrates that the recently described early HG induced calpain mediated necrosis occurs more rapidly than first thought. Furthermore, the externalized of proteases in response to serum starvation injury suggests that calpain leak in PTEC is not specific to HG induced injury but is likely to be a non-specific response to cell cytotoxicity As calpain externalized has been associated with PTEC repair *in vivo* this indicates that this area of study may have therapeutic implications.

P180

α-Linolenic acid Protects Renal Proximal Tubular Cells against Palmitic Acid Lipotoxicity via Inhibition of Endoplasmic Reticulum Stress

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Background/Aims: Hyperlipidaemia is relatively common in the general population and can promote renal disease. Recent evidence suggests that unsaturated fatty acids may counteract the lipotoxicity associated with saturated fatty acids. The aims of this study were to investigate (i) the mechanisms of the lipotoxicity produced by palmitic acid (PA), a dietary saturated fatty acid, in a renal proximal tubular cell-line and (ii) whether α-linolenic acid (ALA), an unsaturated fatty acid, could protect against the renal toxicity of PA.

Methods: NRK-52E cells were incubated with increasing concentrations of PA (0 – 1000 μmol/L) for 24 h after which cell viability was assessed via measurement of the mitochondrial-dependent conversion of 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide into formazan. Hoechst-propidium iodide staining and lactate dehydrogenase release were used to evaluate apoptosis and necrosis. Western blotting was used to measure the expression of markers of endoplasmic reticulum (ER) stress, specifically, levels of the phosphorylated form of eukaryotic initiation factor 2α (eIF2α), C/EBP homologous protein (CHOP) and glucose regulated protein 78 (GRP78). NRK-52E cells were also incubated with PA (300 μmol/L) for 24 h in the presence or absence of ALA (100 and 300 μmol/L) after which levels of cell viability, death and ER stress were measured.

Results: PA induced substantial ER stress and caused both apoptotic and necrotic cell death in NRK-52E cells. Specifically, PA (300 μmol/L) increased levels of all three markers of ER stress - p-eIF2α, CHOP and GRP78. ALA (100 or 300 μmol/L) restored cellular function and markedly reduced cell death and levels of all three indicators of ER stress brought about by PA. Tunicamycin (10 μg/mL), which induces ER stress via glycosylation of proteins, produced effects similar to those obtained using PA. These were reversed by ALA (300 μmol/L). Furthermore, the effects of salubrinal, a phosphatase inhibitor which increases levels of the p-eIF2α, were also reversed by ALA (300 μmol/L).

Conclusions: These results suggest that unsaturated fatty acids such as α-linolenic acid can protect the kidney against the lipotoxic actions of unsaturated fatty acids such as palmitic acid via inhibition of ER stress, eIF2α phosphorylation and consequential reduction of CHOP protein expression and apoptotic renal cell death.

P181

Reactive oxygen species in human proximal tubular cells overloaded with albumin.

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Introduction: Proteinuria is pathogenic to proximal tubular cells (PTC) and linked with progression to renal failure. The mechanisms involved are multifactorial and result in the release of multiple mediators which promote tubulointerstitial fibrosis (TIF). TIF is the hallmark of progressive renal failure. We have recently shown that human serum albumin (HSA) overload in PTC caused increased oxidative stress and upregulation of stress-related genes. We hypothesise that the pathogenic effects of HSA in the PTC occur through the modulation of reactive oxygen species (ROS) leading to changes in gene expression and cell signalling.

Aims: To directly measure ROS generation in primary human PTC in response to HSA. To define the source of ROS production and determine its role in stimulating adaptive changes in cell signalling and gene expression.

Methods: ROS generation following 30min incubation with HSA was measured using a redox sensitive fluorophore (DCFH) and at 4-48h using Electron Paramagnetic Resonance spectroscopy. The source of ROS generation was investigated using the following inhibitors: mitochondria (rotenone), NADPH oxidase (DPI), xanthine oxidase (allopurinol), nitric oxide synthase (L-NAME). IL-8 and MCP-1 release were measured by ELISA.

Results: There is no increase in ROS following incubation of PTC with HSA for 30min. Incubation with HSA for 4-48h causes a dose-related increase in PTC ROS generation ($p<0.05$) as well as IL-8 ($p<0.001$) and MCP-1 production ($p<0.005$). DPI, rotenone and L-NAME prevent the increase in ROS in response to HSA. However, inhibition of ROS generation does not reduce the increase in IL-8 and MCP-1 in response to HSA.

Conclusions: HSA overload of primary human PTC causes a dose-dependent increase in ROS generation that can be demonstrated directly after 4-48h incubation. This increase in ROS is prevented by inhibition of NADPH oxidase, mitochondrial electron transport and nitric oxide synthase, but not xanthine oxidase. The secretion of IL-8 and MCP-1 by PTC in response to HSA is not critically dependent on ROS generation as inhibition of ROS generation does not affect cytokine secretion.

Poster Session

Thursday 23 April

13:30 – 14:30

Inflammation & Leukocytes

Moderator Dr David Kluth

P182

Circulating Microparticles and Platelet-Monocyte Aggregates in Renal Transplant Patients Does erythropoietin use have an effect?

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BACKGROUND: Platelet-monocyte aggregates (PMAs), Endothelial Microparticles (EMPs) and Platelet Microparticles (PMPs) are thought to be markers of cardiovascular disease and endothelial dysfunction. They have been shown to be raised in patients with CKD and on dialysis. Increased levels of these markers are thought to be associated with increased cardiovascular morbidity in these patients. The effect of erythropoietin in the cardiovascular biomarker profile of anaemic transplant patients has not been studied. The aim of this study was to assess this effect.

METHOD: Cross-sectional and longitudinal analysis of renal transplant patients enrolled in a RCT was performed. Flow cytometry was used to analyse whole blood. PMA were calculated as the percentage of CD42a+CD 14+ positive monocytes. EMPS were measured as a percentage of CD31+CD42a- microparticles. PMP were measured as the percentage of CD42a+/62p+ microparticles.

RESULTS: 27 patients were assessed for the cross-sectional analysis [n=13 non-treated vs. 14 treated with EPO for > 4 months]. The demographics of the control and treatment group were similar. There was no statistical difference in the percentage of PMAs [12.2 ± 11.94 vs. 10.64 ± 3.6, p=0.54], EMPs [0.065 ± 0.03 vs. 0.063 ± 0.07, p = 0.16] or PMPs [0.041 ± 0.025 vs. 0.039 ± 0.034] between the groups.

20 patients were available for longitudinal analysis [Control: n=9, Treatment: n=11]. The demographics of the two groups were similar. There was no statistical difference between the control and treatment groups on initiation of treatment: PMAs [14.17 ± 2.98 vs. 12.45 ± 2.68, p=0.67]; EMPs [0.1229 ± 0.033 vs. 0.07 ± 0.009, p=0.07] or PMPs [0.042 ± 0.016 vs. 0.09 ± 0.024, p=0.15]. There was no statistical difference between the 2 groups at 4 months post-intervention: PMAs [16.64 ± 7.66 vs 10.86 ± 1.804, p= 0.4], EMPs [0.071 ± 0.0076 vs. 0.072 ± 0.014, p=0.99], PMPs [0.35 ± 0.29 vs. 0.052 ± 0.011, p = 0.19].

CONCLUSION: Renal transplant patients receiving EPO have a similar cardiovascular biomarker profile to those anaemic renal transplant patients not receiving EPO. This data is reassuring as EPO use does not appear to adversely affect cardiovascular biomarker profile of renal transplant patients.

P183

Differentiating between macrophages and dendritic cells *in vitro* and in the inflamed kidney.

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Introduction and Aims

Although cell surface markers are used to identify cell types *in vitro* and *in vivo*, recent work has indicated that certain markers may be less specific than previously thought e.g. F4/80 has been generally regarded as a macrophage (Mϕ) marker but may also be expressed by dendritic cells (DC). CD11c has been extensively used to define dendritic cells (DCs) and we examined the specificity of CD11c *in vitro* and *in vivo*.

Methods

Murine bone marrow (BM) derived Mϕ or DCs were generated by culture of bone marrow with M-CSF or GM-CSF respectively for 7 days. Murine kidneys underwent unilateral ureteric obstruction and kidneys were removed at day 7. Kidneys were enzymatically dissociated to a single cell suspension. Cells were analysed by flow cytometry for F4/80, CD11c, MHC Class II and CD86 with appropriate isotype antibody controls.

Results

BM-derived DCs strongly expressed CD11c (~80%) with a minority expressing F4/80 (~20%). Also, ~75% of BM-derived DCs were both CD86+ and MHC class II+. In contrast, BM-derived Mϕ strongly expressed F4/80 (~100%) and CD11c (~70%) but exhibited little co-expression of CD86/MHC class II (<5%). At day 7 following UUO, analysis of total kidney cells indicated that ~20% of total kidney cells were F4/80+ whilst ~15% were CD11c+. 8-10% of total cells co-expressed F4/80 and CD11c. The majority (~70%) of F4/80+CD11c+ cells exhibited co-expression of CD86/MHC class II. Interestingly, however, ~60% of F4/80+CD11c- cells and ~75% of F4/80-CD11c+ cells also exhibited co-expression of CD86/MHC class II.

Conclusion

Single staining for CD11c is inadequate to differentiate Mϕ and DC *in vitro* or *in vivo*. Combinations of cell surface markers are more informative and this work suggests that CD86/MHC Class II co-expression (associated with various combinations of F4/80 or CD11c staining) may identify DCs *in vitro* and *in vivo*. Further work will explore the functional properties of these infiltrating leukocyte populations in obstructed kidneys.

P184

Influence of IgG subclass on neutrophil adhesive behaviour and relevance to anti-neutrophil cytoplasm antibody (ANCA)

Tanya Pankhurst[1], Gerard Nash[2], Julie Williams[1], Rachael Coleman[1], Abdullah Hussain[1], Caroline Savage[1]

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In small vessel vasculitis, ANCA are detectable in all four IgG subclasses but opinions vary about their relative pathogenicity. We investigated whether subclass influenced neutrophil activation using a flow model. In vasculitis, neutrophil activation depends on dual signals from antibody Fc engagement with constitutive Fc receptors (FcγRIIa/CD32 and FcγRIIIb/CD16) and by antibody Fab engagement with target antigens, effectively causing receptor cross-linking.Initial experiments examined neutrophil adhesion to and activation via Fc receptors alone. Pure human IgG subclasses 1 to 4 were coated onto glass microslides and neutrophils flowed across. IgG3 captured neutrophils efficiently and induced activation, seen as spreading. IgG1 captured and activated neutrophils but less efficiently, and IgG2 or 4 were poor mediators of capture (1 v. 2 $p=0.004$; 3 v. 1,2 and 4 $p<0.001$). Blocking CD32 and CD16 reduced capture by all subclasses, but CD16 was more effective for IgG3 and CD32 for IgG1. To examine the effects of ANCA IgG that engage dual signalling pathways, neutrophils were flowed across a P-selectin coated microslide and then over activated human umbilical vein endothelial cells (HUVEC). Neutrophils were exposed to chimeric PR3-ANCA (i.e. ANCA reactive with proteinase 3) of IgG subclasses 1, 3 and 4 (IgG2 subclass was not available). IgG1 ($p<0.001$ v. control) and IgG3 ($p=0.005$) PR3-ANCA caused neutrophils to change from rolling to static adhesion on a P-selectin surface. Unexpectedly, IgG4 also had this effect ($p=0.01$), although it was less potent ($p=0.004$ compared to IgG1).

On HUVEC, all three PR3-ANCAs converted neutrophils from rolling to static adhesion (1, $p=0.006$; 3, $p=0.011$; 4, $p<0.001$) and caused significantly more migration. IgG1 and IgG3 were similar although IgG4 was less potent (capture by 1 v. 4 $p=0.016$). Thus, the behaviour of neutrophils was similar with all three subclasses. In conclusion, IgG3 and IgG1 capture flowing neutrophils and deliver activating signals via Fc receptors that lead to cell spreading, while IgG2 and IgG4 are only weakly functional. In contrast, PR3-ANCA IgG1, 3 and 4 have major effects on adhesion (and migration) of flowing neutrophils, suggesting that binding of PR3 antigen by autoantibody permits the IgG4 subclass to acquire functionality, albeit less than IgG1 and 3, that may have pathogenic consequences.

P185

Neutrophil function and systemic inflammation in chronic kidney disease : effect of a one-month programme of moderate intensity exercise

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Chronic kidney disease (CKD) is associated with immune dysfunction and chronic systemic inflammation. Neutrophil function is impaired in CKD and this may contribute to the high incidence of infection, a major cause of morbidity and mortality in these patients. In addition, plasma levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are elevated in CKD and have been shown to predict cardiovascular mortality. It has been suggested that regular moderate exercise may exert anti-inflammatory effects, but strenuous exercise can suppress immune resistance to infection. Therefore, moderate exercise may be beneficial in CKD, but to date, its influence on immune and inflammatory status is yet to be determined. The aim of this study was to investigate the effects of 1 month of regular moderate aerobic exercise on neutrophil degranulation and plasma CRP and IL-6 in CKD patients.

Sixteen CKD (stage 4 and 5 pre-dialysis) patients (11M and 5F), mean age 60 years (range 50-73 yrs), exercised for 30 min at least 5 times per week for a total period of 1 month. The exercise programme consisted of brisk walking at a Rating of Perceived Exertion (RPE) in the range of 12-14 (“somewhat hard”). Patients kept exercise diaries and were monitored to ensure compliance. Before (baseline) and after 1 month of regular exercise patients performed a standard 30 min treadmill exercise test. Resting venous blood samples were collected on both occasions. Elastase release from unstimulated (plasma elastase) and bacterially-stimulated neutrophils, and plasma CRP and IL-6 concentrations were determined by ELISA. Results were analysed using Student's paired t-tests. Values are mean±SEM.

Average RPE response to the exercise test at 1 month was lower than at baseline (baseline: 13±0 vs 1 month: 11±0, $P < 0.001$), indicating an improvement in “fitness”. After 1 month of exercise, plasma IL-6 levels were reduced (baseline: 4.1±0.9 pg/mL vs 1 month: 2.9±0.5 pg/mL, P=0.041), but plasma CRP levels had not significantly changed (baseline: 6.3±2.4µg/mL vs 1 month: 5.1±1.6µg/mL, P=0.440). Plasma elastase concentration (baseline: 88±10µg/mL vs 1 month: 81±9µg/mL, P=0.535) and bacterially-stimulated elastase release per neutrophil (baseline: 551±43 fg/cell vs 1 month: 546±67 fg/cell, P=0.944) also remained unchanged.

These results suggest that regular moderate aerobic exercise might exert anti-inflammatory effects in CKD patients. After 1 month of exercise, there was a significant reduction in plasma IL-6 levels, but CRP did not change. CRP production is partly regulated by IL-6, so continuing this exercise regimen may lead to reduced CRP in the longer term. Neutrophil function was unaffected, indicating that this level and frequency of exercise does not have a negative impact on phagocyte function which might lead to increased susceptibility to infection.

P186

Neutrophil and T cell function in chronic kidney disease : acute effect of a bout of moderate intensity exercise

Joao L Viana[2], Nicolette C Bishop[2], George Kosmadakis[1], Emma L Clapp[2], Alan Bevington[1], John Feehally[1], Alice C Smith[1]

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Chronic kidney disease (CKD) is associated with reduced levels of physical activity, deconditioning and impaired immunity. Exercise is increasingly accepted as beneficial in many chronic diseases, including CKD. In healthy people, it has been demonstrated that a bout of acute intensive exercise temporarily depresses many aspects of immune function, whereas moderate exercise exerts little influence on these measures. However, it is not clear what effect moderate intensity exercise may have in CKD patients given their deconditioned state and compromised immunity. Therefore, the aim of this study was to determine the effects of acute moderate aerobic exercise on neutrophil degranulation and T helper (CD4+) lymphocyte activation in CKD patients.

Eighteen CKD (stage 4 and 5 pre-dialysis) patients (14M and 4F), mean age 59 years (range 38-76 yrs), walked for 30 min on a motorised treadmill at a 1% gradient and at a speed that elicited a subjective rating of perceived exertion (RPE) in the range of 12-14 (“somewhat hard”). Venous blood samples were collected before (pre-ex), immediately after (post-ex) and 1 h after exercise (1 h post). Elastase release from unstimulated (plasma elastase) and bacterially-stimulated neutrophils was determined by ELISA. CD4+ lymphocyte activation (CD69 expression) was determined by flow cytometry following 20 h in vitro stimulation by staphylococcal enterotoxin B. Results were analysed using a one-factor repeated measures ANOVA with post-hoc Student's paired t-tests with Holm-Bonferroni adjustment applied. Values are mean±SEM.

Exercise induced an increase in plasma elastase concentration (pre-ex: 49±7µg/l vs post-ex: 74±14µg/l, P=0.042) yet values returned to resting levels 1 h after exercise (1 h post: 46±5µg/l, P=0.449 vs pre-ex). Bacterially-stimulated elastase release per neutrophil was temporarily suppressed immediately after exercise (pre-ex: 756±110 fg/cell vs post-ex: 560 ±81 fg/cell, P=0.006) but there was a trend for an increase 1 h after exercise (1 h post: 1115±264 fg/cell, P=0.076 vs. pre-ex). Similarly, exercise induced a transient decrease in the geometric mean of fluorescence intensity (GMFI) of CD69 in CD4+ lymphocytes (pre-ex: 118±11 vs post-ex: 106±10, P=0.046) but this was also recovered within 1 h (1 h post: 120±17, P=0.758 vs pre-ex). There was no effect of exercise on the percentage of CD4+ lymphocytes expressing CD69 (pre-ex: 25.4±3.0%, ANOVA P=0.936).

These findings suggest that neutrophil and CD4+ lymphocyte functions in CKD patients are not compromised by an acute bout of moderate intensity exercise, indicating that this level of exercise appears to be safe from an immune point of view.

P187

Inflammation causes statin resistance *in vivo*: a potential mechanism for ineffectiveness of statin therapy

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HMGCoA reductase is an important rate-limiting enzyme for cholesterol biosynthesis and the target for cholesterol lowering drug statins which lower plasma cholesterol concentrations by upregulating hepatocyte LDL receptors. The clinical effects of statins may be reducing in patients with chronic inflammatory diseases, such as those with renal dysfunction and type 2 diabetes. The present study was carried out to investigate whether a degree of resistance to statins is present in the presence of inflammatory stress *in vivo*.

Eight-week old ApoE/Scavenger receptor typeA/CD36 triple knockout (KO) mice fed a Western Diet were randomly assigned to either daily subcutaneous injections of 10% casein to induce inflammation or vehicle. Animals were sacrificed after 14 weeks and terminal blood samples were assayed for lipid profile, serum amyloid A (SAA) and TNFα. Liver, aorta and kidney were harvested and tissue lipid levels measured by enzymatic assay and Oil Red O staining.

Casein injected mice required atorvastatin 10mg/kg/day to obtain the same effect as a 2mg/kg/day dose in non-casein injected mice, to attain similar levels of serum total cholesterol □TC□and LDL cholesterol. Serum SAA and IL-6 were also higher in the casein injected mice given atorvastatin 2 mg/kg/day compared with mice receiving atorvastatin of 10 mg/kg/day. Lipid accumulation in the liver, aorta and kidney was more extensive in casein-injected animals. Atorvastatin 2 mg/kg/day reduced lipid accumulation in kidney in non-casein injected mice, but higher doses of atorvastatin (10 mg/kg) were required to achieve an equivalent effect under inflammatory stress, suggesting that inflammatory stress causes atorvastatin resistance.

Inflammation overrides the suppression of HMGCoA reductase activity by statins and causes statin resistance in vivo. Hence a higher concentration of statin may be required to achieve the same biological and clinical effects in inflammatory states. Furthermore results from triple KO mice show the importance of LDL receptor and HMGCoA reductase pathways in the genesis of atherosclerosis under inflammatory stress.

Poster Session

Wednesday 22 April

13:00 – 14:00

Genetic Disease & the Endothelium

Moderator Prof Peter Mathieson

P188

Inherited glomerulonephritis from the Troodos Mountains is genetically distinct from the Peutz Jeghers syndrome

Daniel Gale[1,2], Elena Goicoechea de Jorge[3,4], Terry Cook[3], Ruben Martinez-Barricarte[4], Veronique Frémeaux-Bacchi[5], Charles Pusey[2], Andrew Palmer[2], Santiago Rodriguez de Cordoba[4], Patrick Maxwell[1], Matthew Pickering[3]

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Glomerulonephritis is often associated with the deposition of complement components, such as C3, in the glomerulus. In almost all these cases, this is associated with the production of circulating immunoglobulins (related to infection, autoimmunity or malignancy) and immunoglobulins are present in the glomerular deposits. The reasons why some individuals develop severe glomerular injury in the setting of increased immunoglobulin production while the great majority do not are poorly understood. Insight into the mechanisms underlying this has come from the observation that acquired or inherited conditions in which there is dysregulation of the complement alternate pathway may cause deposition of complement in the kidney in the absence of immunoglobulins, as seen in the diseases haemolytic uraemic syndrome, dense deposit disease and C3 glomerulonephritis.

We have identified individuals from two families from the Troodos region of Cyprus in which there is autosomal dominant inheritance of renal disease characterised by isolated glomerular deposits of complement C3. Atypical gastrointestinal polyposis with juvenile buccal pigmentation was noted in some individuals in family 1 and sequencing revealed a novel premature termination codon in exon 1 of the STK11 gene, confirming Peutz Jeghers Syndrome in these individuals. This genotype did not cosegregate with the renal disease.

Direct exon sequencing of Complement Factor H, Factor I, Membrane Cofactor Protein 1, C3, Factor B and Factor H Related-1 and -5 genes has not revealed any mutations cosegregating with renal disease. A genome-wide linkage study demonstrated linkage to the Regulators of Complement Activation gene cluster of chromosome 1 with LOD of 2.67. In addition an identical haplotype across this region was present in affected individuals from both families. Ongoing work aims to identify the causative mutation and understand how it causes disease.

P189

Whole-genome linkage and association scan in primary, non-syndromic vesicoureteric reflux (VUR) and reflux nephropathy

Heather Cordell[1], Rebecca Darlay[1], Pimphen Charoen[2], Aisling Stewart[1], Ambrose Gullett[3], Heather Lambert[4], The UK VUR Study Group[1], Sue Malcolm[3], Sally Feather[5], Tim Goodship[1], Adrian Woolf[3], Rajko Kenda[6], Judith Goodship[1]

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In this sib-pair study 316 families (including 694 affected individuals) from two populations (UK and Slovenian) were analysed using linkage and family-based association approaches, at between 124,032 and 140,484 single nucleotide polymorphisms (SNPs) across the genome. We also carried out case/control association analysis at these SNPs using our cases together with a publicly available UK control sample from the Wellcome Trust Case Control Consortium. We found only modest evidence of linkage (maximum LOD scores in the range 2.32–2.63) but we did find significant association at six SNPs passing our very stringent, stringent or medium quality control criteria. In our UK families we found association ($p=3.06x10^{-6}$) at rs11083021 in intron 3 of OSBPL1A (oxysterol binding protein-like 1A) which is a member of the OSBP family of intracellular lipid receptors. In our Slovenian families we found association ($p=2.55x10^{-6}$ and $p=5.81x10^{-7}$) at two intronic SNPs (rs4895183 and 17144806) in the gene DTWD2, while in the combined (UK and Slovenian) families we found association at a SNP (rs2102860, $p=7.43x10^{-7}$) in linkage disequilibrium with RTP4 (a Golgi chaperone) and at two further SNPs of unknown function (rs1696803, $p=2.25x10^{-6}$, and rs11029158, $p=1.82x10^{-6}$). Overall there was relatively little overlap between the results from our linkage and association analyses, the results from our UK and Slovenian cohorts, or between our results and those reported by a previous genome-wide linkage study (based on a smaller Irish sample collection). Our findings require replication and re-analysis in larger cohorts, preferably scanned using a denser set of polymorphisms, to allow increased power for detection of effects in this genetically heterogeneous disease.

P190

Are anti-factor H autoantibodies in atypical haemolytic uraemic syndrome always associated with *CFHR1/3* copy number?

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Atypical haemolytic-uraemic syndrome (aHUS) may be sporadic or clearly associated with a family history. It is associated with defects in complement regulators and activators, including factor H (fH), factor I (CFI), membrane cofactor protein (MCP, CD46) factor B (CFB) and C3. Anti-fH autoantibodies have been reported in ~10% of aHUS patients. Recently, an association has been described between the presence of such antibodies and complete deficiency of factor H-related proteins CFHR1 and CFHR3.

We have attempted to replicate this finding in the Newcastle aHUS cohort. In both patients and normal controls we have screened for anti-FH autoantibodies by enzyme-linked immunosorbent assay (ELISA). Multiplex ligation-dependent probe amplification (MLPA) was used to determine *CFHR1/3* copy number in both patients and controls. We screened serum from 150 aHUS patients in the Newcastle cohort and 100 normal controls.

IgG anti-fH autoantibodies were detectable in the sera of 14 aHUS patients (aged 4-45yrs.) Four were strongly positive, 5 positive and 5 weakly positive (greater than 2x the mean of a known negative +1 SD). Our results were confirmed by titration and western blotting. Of these 14 patients, 9 had zero copies, 1 had a single copy of both and 3 had 2 copies of *CFHR1/3*. One DNA sample was unavailable. Other groups have reported a solid correlation between presence of anti-fH autoantibodies and deficiency of proteins CFHR1/3.

We conclude that ~10% of patients in the Newcastle aHUS cohort have anti-fH autoantibodies, in keeping with the reported prevalence in other groups. Unlike these other groups, we have, however, not found the presence of anti-fH autoantibodies to have as strong an association with *CFHR1/3* copy number.

P191

Glomerular endothelium expresses very low levels of VCAM-1 that supports only minimal lymphocyte binding

Tanya Pankhurst[1], Gerard Nash[2], Julie Williams[1], Matthew Morgan[1], Simon Satchell[3], Peter Mathieson[3], Caroline Savage[1]

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Endothelial cell phenotype differs between organs and is likely to be important for the behaviour of the endothelium in health and disease. We have investigated leukocyte capture by human umbilical vein endothelial cells (HUVEC), primary glomerular endothelial cells and an immortalised glomerular endothelial cell line.

Presence of CD31 and vWF were detected using FACS and immunocytochemistry on all three cell types, confirming their endothelial derivation. The ICAM-1 adhesion molecule was present on resting cells as demonstrated by FACS, immunocytochemistry and ELISA, while both ICAM-1 and E-selectin were up-regulated by TNFα and IL-1β. VCAM-1 was induced on HUVEC by cytokine activation but was not found on the surface of resting or cytokine-activated glomerular endothelia. Western blotting confirmed the presence of VCAM-1 in all three cell types.

Functional studies of leukocyte-endothelial cell interactions in a flow model using TNFα activated endothelium, demonstrated similar neutrophil capture, rolling, static adhesion and migration by both HUVEC and glomerular endothelium. These interactions are likely to be dependent on selectins and ICAM-1. Peripheral blood lymphocytes (PBL) were not efficiently captured by glomerular endothelium compared to HUVEC, which, since this is a VCAM-1 dependent process, we postulate is due to the low surface expressed levels of VCAM-1 on glomerular endothelium, even after TNFα stimulation. Blockade of endothelial VCAM-1 or its leukocyte ligand VLA4, resulted in significantly reduced adhesion of PBL to HUVEC, while even the low levels PBL adhesion to glomerular endothelium were significantly reduced, suggesting that VCAM-1 does contribute to PBL capture by glomerular endothelium.

In conclusion, these studies demonstrate many similarities between glomerular endothelial cells and those derived from a large conduit vessel, but glomerular endothelia also display some unexpected properties, particularly low expressed levels of VCAM-1 that reduce PBL adhesion. If these findings translate in vivo, reduced VCAM-1 expression by glomerular endothelial cells may be a protective mechanism to reduce inflammatory responses, a process potentially disrupted in disease.

P192

Molecular mechanisms of TNF-induced immune damage to endothelial cells.

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Chronic kidney disease is an independent risk factor for cardiovascular disease, but the mechanism of this association is unclear. We are studying possible mechanisms underlying this additional risk in chronic kidney disease. There is good evidence that inflammation is associated with an increased incidence of cardiovascular disease. Endothelial damage is an early event in the development of atherosclerotic plaque development. We hypothesised that inflammation may induce changes in endothelial cells that will render them vulnerable to direct immune attack.

Tumour necrosis factor alpha (TNF) levels are elevated in chronic kidney disease and in atherosclerotic disease. In this study we have demonstrated that tumour necrosis factor alpha (TNF) upregulates an immune ligand (MICA) on human endothelial cells. MICA which is expressed on the endothelial cells is recognised by natural killer cells using the innate immune receptor NKG2D. This immune recognition interaction triggers destruction of the endothelial cells by natural killer cells. We have analysed the molecular mechanism of this effect and demonstrate that it involves the NFkappaB pathway. p50/p65 heterodimers bind to specific regulatory regions of the MICA gene. We have used luciferase reporter constructs and electrophoretic mobility shift assays to define these regulatory regions of the MICA gene precisely. We have further shown that an additional transcriptional cofactor is required for optimal induction of MICA. Therapy targeted at suppressing the pathway leading to MICA expression in endothelial cells could be of benefit in reducing cardiovascular disease.

P193

Engineering the Glomerular Filtration Barrier In Vitro

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The glomerular filtration barrier (GFB) comprised of glomerular endothelial cells (GEnC), glomerular basement membrane (GBM) and podocytes, functions as a whole to filter the blood. We have developed models of the human GFB to study its barrier properties and cross-talk between cellular components. In existing models based on tissue culture inserts, the GBM is represented by a synthetic porous support much thicker than the GBM in vivo.

Aim: To identify a suitable biocompatible material to replace the porous support to produce a model more closely mimicking the in vivo GFB. We have previously developed unique conditionally immortalised (ci) human GEnC and podocytes (ciPod). The new membrane needs to support growth of both cell types in monolayers on either side.

Initially ciGEnC and ciPod were seeded onto gelatin, collagen type I, and matrigel gels. Subsequently we employed a technique from tissue engineering, electrospinning, to produce nanofibre membranes of alginate, chitosan or type 1 collagen. The ability of cells to a form monolayer was monitored by both light and fluorescent microscopy. Cell survival and proliferation was measured using a WST-1 proliferation assay.

Neither cell type formed a confluent monolayer on any gel form of matrix protein. Few cells attached to electrospun alginate. Both cell types adhered to and proliferated on nanofibre membranes made of collagen I or a collagen I /chitosan mix, however a confluent monolayer was only formed on the collagen I membrane. A WST-1 assay showed cell proliferation on collagen I electrospun membrane was similar to that on plastic.

We have identified electrospun type I collagen nanofibre membrane as a suitable material to act as the GBM in a tri-layer in vitro model of the GFB. Both ciGEnC and ciPod will adhere to, proliferate, and form a confluent monolayer on this material. This membrane can now be used to produce a more physiological model of the GFB, enabling more representative studies of its function.

Poster Session

Tuesday 21 April

11:30 – 12:30

Immunological Disease

Moderator Prof Caroline Savage

P194

Urinary Cytokines and Different Protein Subtypes as Early Prognostic Markers in Pauci Immune Rapidly Progressive Glomerulonephritis (RPGN)

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Pauci immune RPGN is characterised by severe inflammatory reaction in renal tissue, and rapid deterioration in renal function. Severe glomerular inflammation is followed by increased urinary excretion of cytokines and other protein fragments of unknown origin. In the present study, urine from 33 patients with RPGN, [15 male, age 54.5yrs (25-80)] taken at the day of renal biopsy, and before any treatment was applied, SDS PAGE analysis were used in order to detect excretion of molecules other than albumin. EGF and VEGF were also measured as factors which induce epithelial and endothelial regeneration respectively. The same treatment protocol was applied in all patients and their renal function was estimated at day of admission, 3, 6, 12 months of follow up and at the end of the study, after 39.4±45mo. RPGN patients were found to excrete several proteins in the urine, and their molecular weights were estimated to 90, 96, 105, 133, 148 and 174KD. On admission GFR correlated with the number of high-molecular weight proteins in the urine, GFR in patients excreting 0molecules was 39±33, 1molecule=23±22, 2molecules=24±18 and 3molecules=21±10ml/min. Similarly, at the end of the study GFR in 0mol=45±16, 1mol=35±37, 2mol=24±19, 3mol=29±25ml/min. Urinary EGF also showed inverse relation with the number of protein molecules in the urine. Interestingly, urinary levels of EGF significantly correlated with GFR at all stages [(biopsy): r=0.7, p=0.001, (3mo): r=0.7, p=0.001, (6mo): r=0.7, p=0.001, (12mo): r=0.7, p=0.003, (last): r=0.7, p=0.003]. Patients with extrarenal manifestations had increased serum VEGF levels compared to those with renal limited disease (937±590pg/dl vs.387±139pg/dl, p=0.001). RPGN patients excrete a number of proteins with different molecular weights in the urine. Increased number of excreted molecules is correlated with the severity of renal function impairment. EGF excretion in the urine of RPGN patients is an early prognostic indicator of disease outcome.

P195

B cell cytokine levels in patients with SLE and ANCA-associated vasculitis

Amit Shah[1,2], Sarah Harford[2], Eoin McKinney[1,2], Faustra Cataponi[1], Rachel Jones[1,2], David Jayne[1,2], Ken Smith[1,2], Menna Clatworthy[1,2]

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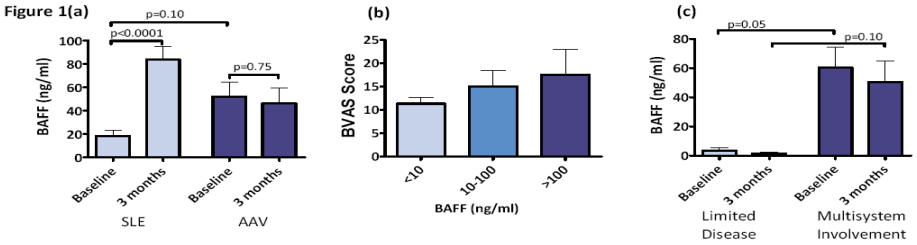
Introduction: B-cell activation factor of the tumour necrosis family (BAFF) is a cytokine which drives B cell survival and proliferation. We wished to determine serum levels of BAFF in patients with antibody/immune complex-mediated autoimmune disease (SLE and ANCA-associated vasculitis(AAV)), both at the time of initial presentation/disease flare, and 3 months following treatment with immunosuppression. Given that BAFF drives B cell activation, we wanted to assess whether serum BAFF levels correlate with disease activity or relapse.

Methods: Serum samples were obtained from 14 patients with SLE and 35 patients with AAV at induction and three months post-immunosuppression with prednisolone +/- cyclophosphamide +/- MMF +/- rituximab. Data on disease relapse and activity (British Isles Lupus Assessment Group (BILAG) for SLE and Birmingham Vasculitis Activity Score (BVAS) for AAV) were obtained from patient records.

Results: At time of disease flare, mean serum BAFF levels were non significantly higher in patients with AAV than in those with SLE (Figure 1a, 52.2ng/ml and 18.4ng/ml respectively, p=0.10). Following treatment, BAFF levels increased in patients with SLE, from 18.4ng/ml to 83.8ng/ml (Figure 1a, $p < 0.0001$) but not in patients with AAV (52.2ng/ml at time 0, 46.4ng/ml at 3 months, p=0.75). In rituximab-treated SLE patients (10/14), BAFF levels increased from 17.3ng/ml to 73.5ng/ml ($p<0.002$). In rituximab-treated AAV patients (7/35), BAFF levels decreased from 74.6ng/ml to 42.4ng/ml ($p = 0.48$). At time of disease flare, higher BAFF levels were not associated with higher BILAG scores in SLE, but were associated with higher BVAS scores in AAV (Figure 1b). AAV patients with multisystem involvement had higher BAFF levels than those with limited disease (Figure 1c). High BAFF levels at presentation were not associated with disease relapse in either SLE or AAV patients.



Conclusions: In patients with SLE, BAFF levels significantly increase post-treatment (with both rituximab and standard immunosuppression). No such increase is seen in AAV. In AAV patients, higher serum BAFF levels during disease flare are associated with increased disease activity, as measured by BVAS and multisystem involvement. Serum BAFF at presentation does not predict disease flare in either SLE or AAV.

P196

Mesangial cell mannose receptor deficiency promotes cell apoptosis and generation of anti-inflammatory macrophages, abrogating nephrotoxic nephritis.

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Crescentic glomerulonephritis (CGN) is characterised by macrophage and T cell glomerular infiltration. Mannose receptor (MR) is a scavenger receptor expressed on macrophages and mesangial cells (MC) and implicated in resolution of inflammation. Our previous data demonstrated that MR-deficient mice ($MR^{-/-}$) were protected from CGN in a model of nephrotoxic nephritis (NTN) and this was dependent on intrinsic renal cell MR expression. Since MR is only expressed in the kidney on mesangial cells, we investigated differences in WT and $MR^{-/-}$MC responses. Importantly, in WTMC unlike macrophages, IFN-γ and TNF-α upregulates MR expression while IL-4 has little effect. Unstimulated and IFN-γ/TNF-α stimulated MC demonstrated increased rates of apoptosis in $MR^{-/-}$ compared to WT (unstimulated % Annexin V positive cells 7.99±1.5 vs 4.3±0.7, $p< 0.008$, stimulated 29.2±4.7 vs 6.9±0.9, $p=0.0002$), this was also associated with diminished AKT phosphorylation (a key factor in regulating cell survival and apoptosis) under serum free conditions and following FCS stimulation. However, $MR^{-/-}$MC demonstrated greater rates of proliferation in complete medium compared to WTMC (CCMP: 219100±27300 vs 110900±21220, $p<0.0001$). In addition, cytokine and immune complex stimulated MC induced greater levels of MCP-1 in $MR^{-/-}$MC than WTMC (1546±1049.7 vs 113.5±116pg/ml, $p=0.0012$). Stimulation of $MR^{-/-}$MC but not WTMC with recombinant MCP-1 induced greater apoptosis (% Annexin V cells: 13.7±3.1 vs 10.5±1.9, $p<0.0001$) suggesting altered responses to MCP-1. In turn, ingestion of apoptotic MC by $MR^{-/-}$ macrophages induced a greater anti-inflammatory response compared to WT, with diminished TNF-α (133±24 vs 190±13.7pg/ml, $p=0.02$) and increased IL-10 (253 ±64 vs 133±8.7pg/ml, $p=0.02$) production. These changes were reflected in vivo as greater glomerular apoptosis was observed in $MR^{-/-}$ mice with NTN compared to WT. Overall, our data suggest that following induction of nephrotoxic nephritis, augmented MC apoptosis in $MR^{-/-}$ mice, in part through MCP-1 overexpression, generates anti-inflammatory macrophages and abrogates disease. Hence, MR represents a novel therapeutic target for treatment of CGN.

P197

Are Human Endogenous Retroviruses (HERVs) triggers for Systemic Lupus Erythematosus and other autoimmune diseases?

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The aetiology of autoimmune diseases, such as Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA), remains unclear, but recently human endogenous retroviruses (HERVs) incorporated into the human genome have been implicated. These viruses are transmitted on through generations, can be activated, and may mediate their effects through molecular mimicry.

Bioinformatics computer programmes were employed to predict the most antigenic components of the viral proteins of HERV-K10. A key immunodominant region was found in the Gag (capsid) region. As a novel assay technique, a biotinylated synthetic peptide of the capsid region was produced, which was tethered to streptavidin-coated ELISA plates. This synthetic peptide was used to investigate the presence of antibodies to HERV-K10 in patients with SLE with associated renal disease (n=30), and also in patients with RA (n=40). These were compared with control groups of patients with inflammatory bowel disease (IBD) (n=45), and normal healthy controls (n=50).

High levels of serum antibody (IgG) to HERV-K10 Gag were identified in patients with SLE ($p=0.06$) and RA ($p=0.04$), compared with low levels in control groups with IBD and healthy controls. Molecular modelling suggests that it is possible that there could be similarity in molecular structure of viruses and autoantigens. The similarity of shape could effect an unwanted immune reaction which once initiated mediates progression of the disease. The role of HERVs could also explain the familial nature of autoimmune diseases such as SLE.

Continuing research is being focused in establishing a larger cohort of patients to determine whether antibody levels correlate with disease activity and also investigating the potential of other viruses and HERVs, e.g. ERV3 (HERV-R), also being involved as triggers of autoimmune disease. In addition, the phenomenon of epitope spreading will be assessed, that could help explain the variety of autoantibodies found in SLE and RA.

P198

Critical role of IL-17 in accelerated nephrotoxic nephritis

Sally Hamour[1], Terence Cook[1], Yoichiro Iwakura[2], Charles Pusey[1], Alan Salama[1]

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Objectives Accelerated nephrotoxic nephritis (NTN) is well-established as an animal model of immune-complex mediated glomerulonephritis. Th17 cells have recently been described as a distinct lineage of CD4+ T-helper cells with a role in the pathogenesis of a number of animal models and human autoimmune diseases. To date the role of Th17 in NTN has not been characterised. We compared NTN in wild-type (WT) and IL-17 knock-out (IL-17$^{-/-}$) mice.

Methods NTN was induced in female mice: 10 WT C57B6 and 10 IL-17$^{-/-}$, according to standard protocol. Animals were pre-immunised with sheep IgG and complete Freund's adjuvant; injected with nephrotoxic serum (NTS) 5 days later (1:4 or 1:1 dilution) and sacrificed 9 days after NTS. We measured albuminuria, serum urea and creatinine and ELISA for mouse anti-sheep IgG antibodies. Renal histology was scored for thrombosis.

Results Proteinuria was significantly reduced in IL-17$^{-/-}$ mice. At 1:4 NTS concentration, mean proteinuria in IL-17$^{-/-}$ was 0.26 mg/24hr (±0.15) compared to 3.2mg/24hr (±3.3) in WT ($p<0.05$). At higher 1:1 NTS concentration, IL-17$^{-/-}$ mice were still protected from disease with mean proteinuria 0.29mg/24hr (±0.06) compared to 11.4mg/24hr (±8.16) in WT ($p<0.05$). Serum urea was reduced in IL-17$^{-/-}$ mice although this did not reach statistical significance. At lower 1:4 NTS, mean urea was 8.83mmol/l (±0.98) in IL-17$^{-/-}$ compared to 66.8mol/l (±48.4) in WT. At higher 1:1 NTS, mean urea 9.1mmol/l (±1.94) in IL-17$^{-/-}$ and 21.0 (±22.8) in WT. Thrombosis scores were lower in IL-17$^{-/-}$ but this did not reach statistical significance. At lower NTS concentration, mean thrombosis score 0.88 (±0.53) in IL-17$^{-/-}$ mice compared to 1.80 (±1.0) in WT. At higher NTS concentration, thrombosis score 1.05 (±0.62) in IL-17$^{-/-}$ mice and 1.64 (±0.87) in WT. There were no differences in anti-sheep IgG antibody response suggesting that cellular effectors mediate the protection in IL-17$^{-/-}$ mice. T cell transfer experiments are ongoing to confirm the key role of CD4 Th17 cells in mediating glomerulonephritis.

Conclusion IL-17 plays a critical role in the pathogenesis of accelerated nephrotoxic nephritis. Further work is required to characterise the potential role of Th17 and IL-17 in this model and hence its' potential as a therapeutic target in human disease.

P199

IL-17 is elevated in patients with ANCA-associated vasculitis and persists during disease convalescence.

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Objective Th17 cells have recently been described as a distinct lineage of CD4+ T-helper cells and implicated in the pathogenesis of a number of autoimmune diseases and animal models of human disease. Thus far, little is known about their role in the evolution of ANCA-associated vasculitis (AAV). We analysed serum levels of IL-17 and its associated cytokines in acute and convalescent patients with AAV and assessed the frequency of autoantigen-specific peripheral blood mononuclear cells (PBMC) producing IL-17.

Methods ELISA on sera from acute (n=28) and convalescent (n=65) patients with AAV was performed for IL-17 (Th17); IL-23 (Th17 maintenance); IL-6 (Th17 differentiation); IL-1β (Th17 differentiation) and IFN-γ (Th1). Three control populations (healthy volunteers, sepsis, anti-GBM disease) were used for comparison. PBMC from convalescent AAV patients (n=17) and healthy volunteers were isolated and stimulated in-vitro with phytohaemagglutinin (PHA), diphtheria/tetanus/pertussis (DTP) and MPO- or PR3-ANCA autoantigen. Frequency of IL-17 and IFN-γ producing cells following stimulation was determined by ELISPOT.

Results Serum IL-17 and IL-23 levels were significantly elevated in acute patients with AAV compared to healthy controls ($p<0.01$ and $p<0.001$, respectively) and fell rapidly with treatment of disease. IL-17 levels remained elevated (>mean+2SD of healthy controls) in 48% of convalescent patients. Overall IL-1β and IL-6 levels tended to be higher in AAV patients compared to controls, but this was only significant in PR3-ANCA positive patients ($p<0.05$). There was no difference in IFN-γ levels between any of the groups.

In convalescent patients, PBMCs had a higher absolute frequency of IL-17 producing cells in response to stimulation with ANCA autoantigen than controls ($p<0.05$). There was no difference in IFN-γ producing cells.

Conclusion Elevated levels of IL-17 and IL-17 producing memory cells in response to autoantigen were found in a significant proportion of patients with AAV. Further investigation is required to characterise the potential role of Th17 cells and IL-17 in the pathogenesis of AAV.

Poster Session

Thursday 23 April

13:30 – 14:30

Physiology

Moderator Prof Robert Unwin

P200

Diffusive solute permeability coefficient of single isolated perfused glomeruli

Andy Salmon[1], Ildiko Toma[2], Dave Bates[1], Steve Harper[1], Janos Peti-Peterdi[2]

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Proteinuria is the hallmark of glomerular disease. Proteinuria may arise because of increased convection or increased diffusion of albumin across the glomerular capillary wall. We have devised assays for measuring the contribution of convective albumin flux in glomeruli (L_PA & sigma), independent of the confounding influences of haemodynamics or tubular reabsorption. However diffusion also contributes to albumin transport across the glomerular capillary wall[1]: here we report a method for measuring diffusive solute permeability in single isolated glomeruli.

Single glomeruli were manually dissected from fresh cortical slices of New Zealand rabbit kidneys, cannulated using a triple-barrelled concentric pipette apparatus, and perfused through the afferent arteriole with 500 nM TMA-DPH and 3 μM Hoechst 33342 to label cell membranes and nuclei respectively. Lucifer Yellow (LY) was introduced to the perfusate at time t_0. Fluorescence intensity (I_f) was measured in a reference window incorporating a single glomerular capillary lumen and the adjacent urinary space.

I_f rose in a stepwise fashion (to ΔI_{f0}) as the glomerular capillary lumen filled with LY. The rate of the subsequent slow rise in fluorescence intensity ($(dI_f/dt)_0$) reflects diffusive transfer of solute across the glomerular capillary wall, from which the diffusive solute permeability coefficient of LY (P_S^{LY}) is calculated according to the relation $1/\Delta I_{f0} * (dI_f/dt)_0 * r/2$.

Mean±s.e.m. P_S^{LY} was 7.4±3.0 * 10^{-5} cm.s^{-1} (n=4). Glomerular P_S^{LY} is 3 - 7.5 -fold higher than P_S for similarly-sized solutes in mesenteric capillaries (with continuous endothelium[2]). This assay provides a new avenue for investigating glomerular permeability, and can be used to measure P_S of pathophysiological-relevant substances (i.e. albumin) in a wide variety of settings. The assay may also provide simultaneous information about glomerular function (e.g. P_S) and structure (e.g. sub-podocyte space[3]) and cell signalling (e.g. calcium flux[4]), expanding the opportunities for research into glomerular physiology.

[1]Haraldsson *Physiol Rev*(2008):88;451 **[2]Fu** *Microvasc Res*(2004):68;51

[3]Salmon *Am J Physiol Renal Physiol*(2007):293;F1777 **[4]Peti-Peterdi** *Am J Physiol Renal Physiol*(2006):291;F473

P201

Proteinuria is associated with increased WATER PERMEABILITY IN glomerular and systemic Microvessels

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Proteinuria is associated with an increased prevalence of vascular disease in both diabetic and non-diabetic populations. Evidence suggests that proteinuria reflects systemic endothelial dysfunction as well as renal pathology. The Munich Wistar Fromter (MWF) rat strain develops spontaneous proteinuria, permitting study of altered endothelial function under conditions of increased proteinuria. Male MWF rats (15-24 wks) were significantly proteinuric (MWF:15.0±1.5 n=14 Wistar: 1.8±0.20 n=10, p<0.0001). Hydraulic water permeability (L_p) and effective oncotic pressure ($\sigma\Delta\pi$), describing protein permeability, were measured in individually perfused microvessels of the mesentery. Male MWF rats had significantly increased L_p (x10^{-7} cm s^{-1} cmH_20^{-1}) but unchanged $\sigma\Delta\pi$ (cmH_20) compared with age matched wistar rats (L_p MWF:6.4±1.8 n=7; Wistar: 2.8±0.4 n=15, p<0.05) ($\sigma\Delta\pi$ MWF:24.6±2.0 n=7; Wistar:23.7±0.9 n=7). Normalised glomerular ultrafiltration coefficient (L_pA/V_i) was measured using an oncometric assay. The increase in systemic L_p was mirrored by a significant increase in glomerular L_pA/V_i (MWF: 1.5±0.1 $min^{-1}mmHg^{-1}$ n=58; Wistar: 1.0±0.1 $min^{-1}mmHg^{-1}$ n=24, p<0.01). These results suggest proteinuria is associated with increased glomerular and systemic water permeability. The mechanistic links require further investigation and may provide insight into the predictive link between proteinuria and increased cardiovascular mortality.

Supported by BHF

P202

Segmental Sodium Reabsorption in Programmed Hypertension

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Programmed hypertension is associated with increased renal expression of the $Na^+K^+2Cl^-$ type 2 (NKCC2) transporter, which has led to the suggestion that sodium retention underlies this form of hypertension. However, we have recently reported (Clin Sci 2009 doi:10.1042/CS20080294) that absolute and fractional excretion of sodium (FE_{Na}) are increased in rats with programmed hypertension. This was associated with a 20% reduction in whole kidney Na^+:K^+ATPase activity and the loss of pump expression in the inner medulla. The aim of the current study was to quantify segmental sodium reabsorption *in vivo*. Programmed hypertension was induced by exposure to a low (9%, LP) maternal protein diet during gestation (N = 5 litters); controls (C) were exposed to an 18% protein diet (N = 5 litters). 4 week old male offspring received LiCl-supplemented rat chow (12 mmol/kg chow) for 48 h prior to making standard clearance measurements under Inactin anaesthesia. Servo-controlled fluid replacement was employed: after 90 mins equilibration and a 30 min control period, rats received either amiloride (AM: 2 mg/kg/h) for 1 h followed by AM and bendroflumethiazide (BF: 1.25 mg/kg/h) for 1 h or AM and BF for 1 h followed by AM and BF and furosemide (FUR: 2.5 mg/kg/h) for 1 h. Mean arterial pressure was increased in LP rats (102±1) compared with controls (87±2 mmHg P<0.001). During vehicle infusion FE_{Na} was increased in LP rats (Table); however, there was no significant difference between LP and control rats during infusion of any combination of diuretic.

FE_{Na} (%)	Vehicle	AM	AM + BF	AM + BF + FUR
C (n = 6-14)	1.7 ± 0.5	6.9 ± 0.7	11.2 ± 1.9	34.3 ± 4.5
LP (n = 8-17)	3.0 ± 0.3*	7.6 ± 1.6	11.4 ± 1.7	30.9 ± 3.3

FE_{Na} by the proximal tubule (FE_{Li}: C 37.4±7.1 vs LP 49.2±5.8%) and end proximal fluid delivery (C_{Li}: C 201.6±27.0 vs LP 246.1±28.0 µl/min/100g bwt) tended to be greater in LP rats, but this did not achieve statistical significance. These data show that despite increased expression of the loop transporter NKCC2, FE_{Na} is greater in LP rats. Assessment of segmental sodium reabsorption suggests that the greater sodium loss was incurred in the IMCD, as FE_{Na} only differed in the absence of diuretic drugs. These data are consistent with our earlier report of the loss of Na^+:K^+ATPase expression in the IMCD.

P203

Salt and water handling after Roux-en-Y gastric bypass in rats

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Background: Regulation of sodium and water excretion is critical for normal physiology and blood pressure. However, the interaction between gastrointestinal tract and renal excretion of sodium and water is poorly understood. It has been recognised that oral salt loading induces greater natriuresis than intravenous salt loading in rats and humans (Lennane RJ et al, 1975). We hypothesized that Roux-en-Y gastric bypass (gastric bypass) would alter salt and water handling.

Methods: 21 male wistar rats (Body weight (BW) 348 ±19g) were scheduled to undergo either gastric bypass (n=14) or sham operation (n=7). Animals were kept on a diet low in sodium content (DO2051701, Research Diets, Inc., New Brunswick, USA) and deionized water ad libitum. Before and after surgery rats received oral hypertonic sodium solution (1.5 mmol/ kg BW). During each of the interventions, rats were placed individually in metabolic cages to measure urine production and water intake for 8 h after sodium load. Urine sodium concentration was measured by Integrated Chip Technology (ICT) using the Architect ci16200® (Abbott, Illinois, USA).

Results: Three weeks after surgery, gastric bypass compared to sham led to reduced weight (95.8±12% vs. 116.5±4%, $p<0.01$) and food intake (57.3±14.6 vs. 88.5±8.3 kcal, $p<0.01$). In the gastric bypass rats after the operation, the oral sodium solution lead to an increase in water intake (0.06±0.01 vs. 0.03±0.01 ml/g BW, $p=0.02$), urine output (0.04±0.01 vs. 0.02±0.004 ml/g BW, $p=0.01$) and natriuresis (70.2±18 vs. 30.1±8 µmol, $p=0.04$). The sham operated animals showed no changes in water intake, urine production or sodium excretion after surgery.

Conclusions: Urine production, sodium excretion and water intake are increased after gastric bypass in rats on sodium restriction. This might contribute to the improvement of hypertension after gastric bypass.

P204

Enhanced anti-natriuretic action of urotensin II during the development of hypertension

Ellen Forty, Nick Ashton

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Urotensin II (UII) acts on both the renal vasculature and tubular epithelia to conserve salt and water. The adult spontaneously hypertensive rat (SHR) responds to infusion of rat UII with greater decreases in renal water and sodium excretion compared to normotensive Wistar-Kyoto (WKY) rats (Abdel-Razik *et al*., 2008, Am J Physiol 295:F1239-47). These data suggest that UII may play a role in established hypertension; however, its role in the development of hypertension is unknown. Young 4-5-week-old WKY and pre-hypertensive SHR were prepared for standard renal clearance experiments. Following a 2h equilibration period animals were randomly assigned to receive vehicle (NaCl 0.154M at 40µl/min) or rUII at 6pmol.min^{-1}.100g bwt^{-1} for 1h, followed by a 30min saline washout period. Basal urine flow rate (UV), sodium excretion rate ($U_{Na}V$) and fractional sodium excretion (FE_{Na}) were lower (P<0.001) in SHR than WKY. Infusion of rUII did not affect WKY; however SHR responded with significant reductions in glomerular filtration rate (GFR), UV and $U_{Na}V$ during the washout period (Table 1). FE_{Na} was comparable between vehicle and rUII treated groups in both WKY and SHR (Table 1). These data show that rUII induces an anti-diuresis and anti-natriuresis through a reduction in GFR in young SHR but not WKY rats. In contrast to adult SHR, in which rUII influences both glomerular and tubular function, rUII only appeared to act at the glomerulus in young SHR. These results suggest that, in addition to a role in established hypertension, UII may contribute to greater sodium and water retention during the development of hypertension.

	WKY		SHR	
	Vehicle (n=6)	rUII (n=7)	Vehicle (n=6)	rUII (n=7)
GFR (ml.min^{-1}.100g bwt^{-1})	0.6±0.1	0.5±0.1	0.7±0.1	0.4±0.1**
UV (µl.min^{-1}.100g bwt^{-1})	33.5±5.5	23.8±5.3	25.8±4.4	10.6±1.1**
$U_{Na}V$ (µmol.min^{-1}.100g bwt^{-1})	4.6±0.6	3.7±0.8	4.7±0.7	1.9±0.3**
FE_{Na} (%)	5.7±0.5	7.8±2.2	5.0±0.5	4.7±1.4

Table 1. GFR, UV, $U_{Na}V$ and FE_{Na} during the final 15 mins of washout period in WKY and SHR treated with vehicle or rUII. ** P<0.01 compared to vehicle-treated equivalent group.

P205

Hyaluronan is synthesised by glomerular endothelial cells *in vitro* and contributes to the glomerular endothelial cell glycocalyx

Rebecca Foster[1], Anurag Singh[1], Gavin Welsh[1], Robert Steadman[2], Peter Mathieson[1], Simon Satchell[1]

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Hyaluronic acid (HA) is a high molecular weight polysaccharide which contributes to the luminal endothelial cell sugar coating, or glycocalyx, of the microvasculature and restricts macromolecular protein passage (Henry et al, 1999). We have reported the expression of glycocalyx components by glomerular endothelial cells (GEnC) and have evidence that the GEnC glycocalyx contributes functionally to the glomerular filtration barrier GFB) (Singh et al, 2008). In addition, hyaluronidase infusion reduces the GEnC glycoclayx thickness in mice (Jeansson et al, 2005) and HA metabolism is involved in the development of diabetes (Nieuwdorp et al, 2007). We aim to investigate the role of HA in the GEnC glycocalyx.

Human conditionally immortalised (ci)GEnC were grown on coverslips or in a 96 well plate, washed and treated with a range of doses of hyaluronidase (HYAL) in serum free media or left untreated in serum free media for 1hr at 37 ºC. HYAL was removed and cells were washed, then fixed or left for a further 30hr in serum free/serum containing media, then fixed. HA and zonnula occludins-1 (ZO-1) were detected separately by immunofluorescence using an HA binding protein (HABP) and anti-ZO-1. Cells on coverslips were imaged using a fluorescent microscope and the fluorescent intensity of the HABP in the 96 well plate was measured by excitation at 490nm and emission at 520nm on a fluorescent plate reader.

Immunofluorescence imaging demonstrated that HYAL appeared to remove HA in a dose dependent manner, starting as low as 500ng/ml. At this concentration the ZO-1 junctional distribution was not affected and only became disturbed at 500mg/ml HYAL, suggesting an effect on cell-cell junctions. Measurement of fluorescent intensity demonstrated that after 25μg/ml HYAL treatment (background), incubation in serum free medium for 30hr increased the HABP signal (171±18% increase to background) to a similar degree as untreated cells (215±44% increase to background), but significantly more so when allowed to recover in the presence of serum (358±23% increase to background) (One Way ANOVA, $p < 0.001$).

In conclusion we have demonstrated that HA forms a component of the ciGEnC glycocalyx and that ciGEnC can synthesise HA. Further endothelial barrier studies need to be conducted to demonstrate whether HA contributes to the function of the GFB.

Poster Session

Wednesday 22 April

13:00 – 14:00

AKI & Miscellaneous

Moderator Dr Jeremy Hughes

P206

SOCS knockdown differentially attenuates IL-1β induced cell death cascades in human osteoblastic cells.

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The suppressors of cytokine signalling (SOCS) are a family of inducible proteins that limit cellular responses to growth factors and cytokines, but their function in bone is still poorly understood. Here a gene knockdown (KD) strategy was adopted to determine if SOCS have a role in IL-1β induced cellular injury. MG-63 cells were pre-incubated with SOCS1, SOCS3, CIS or non-targeting control siRNA. Cultures were then subjected to the presence or absence of IL-1β (100 IU/mL) for 24 h before apoptosis, necrosis and STAT3 activity were determined. As anticipated, IL-1β greatly elevated caspase-3 activity in the control (C) group [nM AMC/min/mg protein, ±SD, n=3]. C 103.8±9.8, C+IL-1β 195.7±11.9 (P<0.0005). SOCS KD significantly reduced caspase-3 activity in all groups, SOCS1-KD 56.7±3.3, SOCS1-KD+IL-1β 74.6±7.4 (P<0.0002 v C+IL-1β), SOCS3-KD 55.1±5.1 SOCS3-KD+IL-1β 60.6±7.0 (P<0.0001 v C+IL-1β), CIS-KD 45.5±3.1, CIS-KD+IL-1β 91.8±5.5 (P<0.0002 v C+IL-1β). IL-1β treatment also greatly elevated the degree of necrotic injury in the C group [% cytotoxicity, ±SD, n=3]. C 12.7±1.5, C+IL-1β 23.2±0.5 (P<0.0005). However whilst SOCS KD reduced the cytotoxicity in the SOCS1-KD and CIS-KD treatment groups SOCS3 KD afforded no protection from IL-1β induced cytotoxicity. SOCS1-KD 4.1±0.4, SOCS1-KD+IL-1β 11.3±1.0 (P<0.00005 v C+IL-1β), SOCS3-KD 5.7±0.2 SOCS3-KD+IL-1β 22.2±2.6 (P=0.58 v C+IL-1β), CIS-KD 12.7±0.4, CIS-KD+IL-1β 15.5±1.3 (P<0.001 v C+IL-1β). Downstream effects of IL-Iβ was evident from STAT3 activation (absorbance/mg protein) in the C groups, C 0.37±0.02, C+IL-1β 0.56±0.03 (P<0.001) but interestingly CIS-KD prevented IL-Iβ induced activation, CIS-KD 0.31±0.01, CIS-KD+IL-1β 0.34±0.06 (P<0.005 v C+IL-1β) whilst SOCS3-KD significantly elevated IL-Iβ induced STAT3 activity, SOCS3-KD 0.41±0.04 SOCS3-KD+IL-1β 0.88±0.1 (P<0.01 v C+IL-1β). STAT3 activity was similar in the SOCS1-KD group to C values, SOCS1-KD 0.34±0.08, SOCS1-KD+IL-1β 0.57±0.02 (P=0.52 v C+IL-1β). Collectively these results indicate that IL-Iβ induced cell death is mediated differentially by SOCS proteins dependent on the type of cell death involved. Whereas SOCS1, SOCS3 and CIS are all involved in the apoptotic cascade, suggestive of a linear pathway, IL-Iβ induced necrosis appears to be independent of SOCS3.

P207

The Effect of Mycophenolic Acid on erythropoiesis in UT-7 cells and murine bone marrow

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INTRODUCTION: Mycophenolic Acid (MPA) is the active metabolite of Mycophenolic Mofetil (MMF). MMF inhibits lymphocyte proliferation through inhibition of inosine monophosphate dehydrogenase (IMPDH). This inhibition depletes cells of guanosine triphosphate (GTP). Some studies suggest that MMF may also be associated with anaemia, but the mechanism is not understood. The aim of this work was to assess the effect of MPA on erythopoiesis, and possible mechanisms, in vitro.

METHODS: UT-7 cells were treated with erythropoietin (EPO) 1 unit/1 x 10^4 cells; MPA ; GTP and Caspase-inhibitors [DEVD,Z-DCB]. Cells were incubated for 48 to 72 hours. Proliferation (MTS) and caspase assays were then performed. Murine bone marrow cells were acquired from mouse femur. They were cultured in Methocult Media (± EPO). The bone marrow cells were treated with MPA and GTP. The cultures were incubated for 14 days. Blast forming units-erythroid (BFU-e) was counted under light microscopy.

RESULTS: MPA significantly reduces proliferation of UT-7 cells in a dose dependant manner (measured in absorbance at 490nM): EPO: 0.64 ± 0.03 vs. EPO/MPA 0.01μM - 0.63 ± 0.029,p=0.77; EPO/MPA 0.1μM - 0.68 ± 0.027,p=0.37; EPO/MPA 1μM - 0.64 ± 0.019,p=0.92; EPO/MPA 10μM - 0.41 ± 0.014, p <0.001, EPO/MPA 100μM – 0.32 ± 0.015, p<0.001].UT-7 cells treated with EPO/MPA show a significant rise in caspase activity (195.4 vs. 861 nM AMC/mg/ml, p=0.02). Inhibition of proliferation is not reversed by the addition of GTP or caspase-inhibitors.

MPA also significantly reduces the number of BFU-e formed in a dose-dependant manner (measured in colonies/well): EPO - 6.17 ± 0.68 vs. EPO/MPA 0.0001μM – 2.75 ± 0.57, p=0.009; EPO/MPA 0.001μM - 2 ± 0.41, p<0.001; EPO/MPA 0.001μM, 1.75 ± 0.28, p< 0.001. This effect is not reversed by the addition of GTP.

CONCLUSION: MPA inhibits erythropoiesis in both an immortalised cell line and primary bone marrow cells. Inhibition does not appear to be via an apoptotic pathway and may be through inhibition of proliferation.

P208

Transfusion of Stored Leucodepleted Red Blood Cells Interacts with Cardiopulmonary Bypass to Amplify Post Cardiac Surgery Acute Kidney Injury.

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Introduction - Acute kidney injury (AKI) post cardiac surgery is associated with mortality rates approaching 20% and clinical outcomes have improved little over the past two decades. Clinical studies have demonstrated associations between allogenic red blood cell (RBC) transfusion and AKI in patients undergoing cardiac surgery, however causality has not been established and doubts remain as to the potential toxicity of RBC transfusion. The aim of this study was to determine whether transfusion has a causal effect on the development of AKI in a large animal experimental model of post cardiopulmonary bypass (CPB) AKI with significant homology to that which occurs in cardiac surgery patients.

Method - We evaluated serial functional and biochemical measures of AKI in adult landrace pigs (50-70kg, n=26) randomised to the following groups: A. Sham Procedure, B. 2.5 hours of CPB, C. Sham procedure plus RBC transfusion D, 2.5 hours of CPB plus RBC Transfusion. Perfusion pressure, central venous filling pressure and hydration were standardised. All pigs were recovered for 24 hours prior to nephrectomy and histological assessment of tubular damage, inflammation and endothelial activation.

Results - CPB elicited AKI manifest by an 18% reduction in glomerular filtration rate (mean difference 27.9 (95% CI 6.2-49.5) ml/min, p=0.016) as determined by Cr51 EDTA clearance, a 27% reduction in creatinine clearance (mean difference 44.6 (95% CI 6.3-82.9) ml/min, p=0.026), a 68% reduction in free water clearance (mean difference 52.5 (95% CI 10.6-94.3) ml/min p=0.018) and a 66% reduction in fractional sodium excretion (mean difference 3.2 (95% CI 0.8-5.6)%, p=0.012) when compared to Sham Procedure at 24 hours. These changes are similar to those reported in clinical studies. Transfused pigs received 1000mls (4 units) of cross-matched allogenic leucodepleted RBC stored in SAG-M preservative for 42 days. Accumulation of toxic metabolites within the supernatant as well as cellular changes showed considerable homology to those measured in SAG-M stored human RBC units. RBC transfusion did not elicit AKI in pigs undergoing sham procedures. However, RBC transfusion interacted with CPB resulting in more severe AKI compared to CPB alone as well as to all other groups. Transfusion plus CPB was associated with a 25% reduction in creatinine clearance (mean difference 56.4 (95% CI 0.1-112.7) ml/min, p=0.050) and a 6-fold increase in the urinary microalbumin/ creatinine ratio (mean difference 1.2 (95% CI 0.03-2.36) mg/mmol, p=0.045) when compared to CPB alone.

Conclusion - RBC transfusion interacts with CPB to elicit severe AKI. Modification of stored RBC prior to transfusion may reduce the incidence of clinically significant AKI post cardiac surgery. This study underlines the value of large animal models of AKI.

P209

Functional, Morphological And Cytochemical Changes In A Large Animal Recovery Model Of Post Cardiopulmonary Bypass Acute Kidney Injury.

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Objective

Acute kidney injury (AKI) post cardiac surgery is associated with mortality rates approaching 20% and outcomes have improved little over the past two decades. The development of effective treatments is hindered by the poor homology between rodent models, the mainstay of research into AKI, and that which occurs in humans. The aim of this study was to characterise post cardiopulmonary bypass (CPB) AKI in an animal model with potentially greater homology to cardiac surgery patients.

Methods

Adult White-Landrace pigs (50-70kg, n=16) were randomised in a 1:1 ratio to either 2.5 hours of cardiopulmonary bypass or sham procedure. Perfusion pressure, central venous filling pressure and hydration were standardised. Endpoints included serial functional and biochemical measures of AKI. All pigs were recovered for 24 hours prior to nephrectomy and histological assessment of tubular damage, inflammation and endothelial activation.

Results

Baseline measures of porcine renal function were within normal ranges for adult humans and similar between groups. CPB was associated with a 18% reduction in glomerular filtration rate (mean difference 27.9 (95% CI 6.2-49.5) ml/min, p=0.016) as determined by Cr51 EDTA clearance, a 27% reduction in creatinine clearance (mean difference 44.6 (95% CI 6.3-82.9) ml/min, p=0.026), a 68% reduction in free water clearance (mean difference 52.5 (95% CI 10.6-94.3) ml/min p=0.018) and a 66% reduction in fractional sodium excretion (mean difference 3.2 (95% CI 0.8-5.6)%, p=0.012) when compared to controls at 24 hours. These changes are similar to those reported in clinical studies evaluating the effects of CPB on renal function. CPB was also associated with an 86% increase in intrarenal levels of the vasoconstrictor adenosine (mean difference 0.079 (95% CI 0.025-0.132) nmol/mg protein, p=0.007). There was a modest increase in urinary protein:creatinine ratio post CPB, however this did not reach statistical significance (mean difference 268.93 (95% CI -70.9-608.8) mg/mmol, p=0.11). CPB resulted in significant changes in renal tubular morphology with marked renal tubular dilatation, tubular epithelial necrosis, accumulation of cell debris within the tubular lumen, and a moderate inflammatory cell infiltrate. Immunocytochemical staining demonstrated that AKI was associated with endothelial injury, as evidenced by reduced dBA lectin staining, and endothelial activation, as demonstrated by increased endothelin-1 and VCAM staining.

Conclusions

This novel porcine model of post-CPB AKI links functional, biochemical and histological measures of kidney injury and demonstrates significant homology to AKI in cardiac surgical patients. We propose that this model be explored as a platform for the development of novel renoprotective strategies in cardiac surgery. Endothelial activation may represent a therapeutic target in the prevention of AKI.

P210

Lymphocyte deficient SCID mice are protected against ischaemia reperfusion injury

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Introduction: The role of the adaptive immune system in modulating sensitivity to renal ischaemia reperfusion injury (IRI) remains controversial. Whilst animals lacking either B or T lymphocytes have been reported to be resistant to IRI, the more profoundly lymphocyte deficient RAG-/- animal has generated conflicting data in IRI. We sought to characterise the impact of a lack of B and T lymphocytes by studying renal IRI in SCID mice.

Methods: IRI was induced in Balb/c mice and SCID mice (on the Balb/c genetic background) by 20min clamping of the left renal pedicle with right nephrectomy (n=8-10/group). Blood and kidneys were collected 24 hrs post IRI. Circulating leukocyte numbers were assessed by flow cytometry. Viable & necrotic tubules in the outer medulla were counted on H&E tissue sections. Gr1 and F4/80 antibodies were used for immunohistochemical detection of neutrophils (PMN) and macrophages (MΦ).

Results: Flow cytometry confirmed that SCID mice exhibited complete absence of B & T lymphocytes. Interestingly, SCID mice exhibited reduced numbers of circulating monocytes ($6.4\pm0.5x10^5$ vs $2.3\pm0.8x10^5$ cells/mL; Balb/c vs SCID; $p<0.01$) and PMN ($2.1\pm0.1x10^6$vs $0.5\pm0.2x10^6$ cells/mL; Balb/c vs SCID; $p<0.0001$). There was no difference in numbers of resident renal F4/80+ MΦ between strains.

SCID mice had preserved renal function compared to control Balb/c mice (serum Creatinine 94±16vs 140±14μmol/L; $p<0.05$). The kidneys of SCID mice showed structural protection, with less necrosis of outer medullary tubules (30±1% vs 56±4% necrotic tubules; $p<0.01$). Despite a 4-fold difference in circulating PMN numbers, there was no difference in PMN infiltration (44±17 vs 35±15 PMN/hpf; SCID vs Balb/c). MΦ numbers were the same in each group (7.3±0.9 vs 9.3±0.7 MΦ/hpf SCID vs Balb/c). Increasing duration of ischaemia and intraoperative heating resulted in augmented IRI in both groups and an eventual loss of the protected phenotype.

Conclusion: Lymphocyte deficient SCID mice exhibit comparable PMN recruitment but reduced structural injury and renal dysfunction following sub-maximal renal IRI thereby supporting an injurious role for lymphocytes in ischaemic renal injury.

P211

Sodium nitrite inhibits apoptosis in PTECs and protects against renal Ischaemia/Reperfusion (I/R) injury in the rat

Shoab Memon, Julius Kieswich, David Allen, Steven Harwood, Nimesh Patel, Iftikhar Khan, Martin Raftery, Christoph Thiemermann, Muhammad Yaqoob

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Our previous study showed that topical application of sodium nitrite directly to the kidney prevents ischaemia/reperfusion injury in the rat following conversion to nitric oxide by xanthine oxidoreductase. Intravenous injection of sodium nitrite also ameliorates cardiac injury following myocardial infarction. In the present study we examined the role of sodium nitrite on apoptosis in renal proximal tubular epithelial cells (HK-2) as well as I/R injury in the rat kidney after dietary administration sodium nitrite. PTECs were cultured for 24 h in growth medium with or without foetal calf serum (serum deprived) in the presence or absence of sodium nitrite (50 – 500 nM). The cells were scraped and whole cell lysates prepared using modified RIPA buffer. Caspase-3 activity was measured on lysates using a fluorescent peptide substrate (DEVD-AMC). Results are expressed as nmol AMC/mg/min and are mean±SD. Caspase-3 activity was significantly increased in cells that were serum deprived when compared with controls (serum deprived = 208.5±65.3; control = 30.2±20.3, n=3, $P<0.05$) whereas sodium nitrite (100 nM) attenuated this increase (serum deprived plus nitrite = 95.1±33.4, n=3, $P<0.05$). Although 100 nM sodium nitrite was optimal for this effect there was significant reduction in caspase activity at 50 nM. To further test this hypothesis in vivo, we carried out a pilot study in which male Wistar rats were divided into three groups; sham operated rats, rats subjected to ischaemia/reperfusion of the kidney (I/R group) and I/R plus pre-treatment with sodium nitrite (50 mg/L in drinking water for 7 days). There was a significant reduction in renal injury in rats given sodium nitrite prior to I/R when compared with those subjected to I/R alone (serum creatinine μmol/L, mean±SD; I/R = 226±70 compared with I/R plus nitrite = 88±29; n=4, P<0.05). Taken together, our data show that sodium nitrite attenuates the increase in apoptosis in serum deprived PTECs and can prevent renal I/R injury in the rat. These interesting findings may have important clinical implications.

Poster Session

Tuesday 21 April

11:30 – 12:30

Diabetes & Vascular Biology

Moderator Prof Bruce Hendry

P212

Thioredoxin interacting protein and aldose reductase gene regulation in patients with type 1 diabetes mellitus

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INTRODUCTION: We investigated the role of thioredoxin interacting protein (TXNIP) and aldose reductase (AR) in the development of diabetic nephropathy in patients with type 1 diabetes mellitus (T1DM) by looking at the DNA binding activity of the Carbohydrate Response Element Binding Protein (ChREBP) on the promoter region of the genes of interest. Glucose and its metabolites can exert direct effects on gene expression. ChREBP is a glucose responsive transcription factor which of the response element is present in the promoter region of both TXNIP and AR genes. Both of these genes have been indicated in the development of diabetic nephropathy. We expected to see increased DNA binding of ChREBP in the PBMCs of patients with nephropathy in comparison to those without complications or normal controls.

METHODS: 28 Caucasoid patients with T1DM were recruited from the Diabetic Clinic, Derriford Hospital, Plymouth. 17 patients had diabetic nephropathy (nephropaths) and 11 had no microvascular complications after 20 years of diabetes (uncomplicated). 19 normal healthy individuals were used as controls. PBMCs extracted from blood were cultured for 5 days in normal (5mM) or high (31mM) D-glucose, and nuclear protein was extracted. Gel shift assay was employed to study the DNA binding activity of ChREBP to the TXNIP and AR promoters in the different patient groups.

Results: The results show that in the presence of high glucose there is a significant increase in DNA binding of ChREBP to the TXNIP promoter in PBMCs from nephropaths compared to the uncomplicated (1.36 ± 0.44 vs. 1.09 ± 0.25, $p = 0.05$). A similar trend can be seen in case of the AR gene (nephropaths vs. uncomplicated 1.48 ± 0.51 vs. 1.19 ± 0.29, $p = 0.08$). A significant increase was also seen in nephropaths versus normal controls for TXNIP (1.36 ± 0.44 vs. 1.05 ± 0.31, $p = 0.02$) and AR (1.47 ± 0.51 vs. 1.1 ± 0.27, $p = 0.02$), respectively. There was also a significant positive correlation between increased DNA binding to the AR and TXNIP genes ($r=0.675$, $P< 0.05$) across all patients studied.

CONCLUSION: An increase in DNA binding of ChREBP to the promoters of the genes of interest was evident in nephropaths in comparison to patients without complications or normal controls. These results suggest that the regulation by glucose of TXNIP and AR gene expression may be implicated in the pathogenesis of diabetic nephropathy.

P213

Apoptosis and accelerated calcification in dialysis vessels – an overwhelming of adaptive changes induced by chronic mineral dysregulation in CKD

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Background Early vascular calcification in chronic kidney disease (CKD) occurs in response to dysregulated calcium (Ca) and phosphate (P) metabolism and is characterized by vascular smooth muscle cell (VSMC) attrition and damage, particularly in patients on dialysis.

Aims To explore the mechanisms of Ca and P induced vascular calcification, we developed an *ex vivo* model of intact human vessel cultures, comparing vessels from pre-dialysis (n = 10) and dialysis (n = 24) patients with healthy age-matched controls (n = 6). None of the patients had diabetes or uncontrolled hypertension.

Results On exposure to elevated levels of extracellular Ca and/or P mimicking uraemic conditions, vessels from healthy controls did not accumulate Ca even on prolonged exposure in serum free conditions, whereas pre-dialysis and dialysis vessels showed an increased Ca load confirmed by von kossa staining. In all in vitro conditions, dialysis vessels had a significantly higher Ca load than pre-dialysis vessels ($p=0.007$). At equivalent CaxP products, Ca showed greater potency in inducing calcification ($p<0.0001$). Dialysis vessels exposed to increased Ca and P showed an ~50% reduction in cell numbers from VSMC apoptosis, whereas pre-dialysis and control vessels showed no cell loss ($p<0.001$). Calcification was reduced when apoptosis was inhibited by the pan-caspase inhibitor ZVAD ($p=0.04$).

Alkaline phosphatase (ALK), a marker of osteogenic differentiation, was increased on exposure to increased P whereas co-treatment with Ca and P reduced ALK levels. Levamisole, an inhibitor of ALK activity, caused an ~ 50% decrease ($p = 0.03$) in ALK levels, but there was no corresponding reduction in the Ca load ($p = 0.62$).

Calcification in dialysis vessels was associated with increased annexin VI and Fetuin-A levels, both markers of vesicle release. Electron microscopy confirmed that dialysis vessels showed extensive calcification in extracellular vesicles. However, vesicles and extracellular calcification were not evident in healthy control vessels, instead intracellular mitochondrial calcification was observed.

Conclusion In response to mineral dysregulation, and in particular, raised extracellular Ca in the presence of even modestly increased P, VSMCs undergo an adaptive phenotypic change and extrude Ca via vesicle release. This may enable short-term survival but ultimately results in extracellular matrix calcification. Transient bouts of hypercalcemia in dialysis may be highly inductive for vascular calcification particularly after prolonged exposure to high P, when adaptive responses are overwhelmed and VSMC apoptosis results.

P214

High glucose affects the expression of angiogenic regulators, including components of the VEGF-C system, in cultured human glomerular cell lines.

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The early stage of diabetic nephropathy (DN) is characterised by microalbuminuria (MA); the best predictor for overt disease. The mechanism of MA is not well understood, but it is associated with endothelial dysfunction and glomerular angiogenesis. We have previously described the importance of the VEGF family in glomerular cell-cell communication. Here we use focused PCR arrays to investigate the role of VEGFs, and other angiogenic regulators, in the glomerular cell response to high glucose,

Conditionally immortalised glomerular endothelial cells (ciGEnC) and podocytes (ciPod), developed in our laboratory, were cultured in high glucose media (25.5mmol D-glucose) for either 2h or 168h -alongside normal glucose (5.5mmol) controls. RNA extraction was performed using the TRIzol method and converted to cDNA using a commercially available kit. Expression of angiogenic regulators and response to high glucose was determined using two commercial real time PCR arrays: RT^2 Profiler™ PCR Arrays (SABiosciences) and TaqMan® Low Density qPCR Arrays ('TLDA', Applied Biosystems).

TLDA proved to be most cost effective on a per gene analysis basis. Although there was variability in the expression of angiogenic regulators in response to high glucose in both cell lines, the following regulators showed consistent changes. In ciGEnC, VEGF receptor 3 showed an increase in expression at 2h exposure to high glucose, followed by a decrease in expression at 168h exposure. In ciPod, VEGFR3 expression was reduced at both time points in each cell line. Expression of the chemokine CXCL10 was found to be reduced in both cell lines at each time point. In ciPod, there was a reduction in expression of VEGF-C, particularly at 2h. The arrays allowed other regulators which may be of potential interest to be identified. These include VEGF-D, plasminogen, TGFα and tenomodulin.

Future work will confirm these changes, by qRT-PCR and Western Blotting, and will investigate their biological importance. These results build on our previous observations and suggest that reduced glomerular VEGF-C signalling may be important in the pathophysiology of early diabetic nephropathy.

P215

FGF23 inhibits inflammation-induced calcification *in vitro* in human vascular smooth muscle cells

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Vascular calcification in patients with chronic kidney disease (CKD) is related to both chronic inflammation and hyperphosphataemia, and it correlates strongly with morbidity and mortality. Phosphatonins like fibroblast growth factor-23 (FGF-23) are humoral regulators of phosphate metabolism that can reduce circulating phosphate levels by decreasing gut absorption and increasing renal excretion (in part by suppressing 1α-hydroxylase activity); thereby countering potentially harmful effects of chronic phosphate overload. We hypothesised that FGF-23 may also prevent development of vascular calcification enhanced by inflammation.

Human vascular smooth muscle cells (VSMCs) from coronary arteries were cultured in standard growth medium. Experiments were carried out in an established calcification medium (M199 containing 6% of foetal calf serum, 2.7mM calcium (Ca) and 2mM phosphate (Pi)) or control medium (M199 containing 1.8mM Ca and 1mM Pi) for 7 days, in the absence or presence of lipopolysaccharide (LPS; 10µg/ml). Calcium deposition was determined by Alizarin Red S staining and quantitated by total calcium measurement. Expression of osteogenic calcification markers was examined by real-time RT-PCR.

Compared with control medium, calcification medium increased calcium deposition by cultured VSMC (10.96±2.84 vs 0.084±0.025µg/µg cell protein, $p<0.001$); LPS enhanced this calcification. Induction of an inflammatory response by LPS was confirmed by an increase in IL-6 mRNA expression. FGF23 (1ng/ml) inhibited VSMC calcification in the absence or presence of LPS, as indicated by Alizarin Red S staining. While LPS increased expression of bone Gla Protein (BGP) mRNA, a classic osteogenic calcification marker, FGF23 had no effect, suggesting that FGF23 inhibits VSMC calcification by a mechanism that is independent of osteogenic differentiation.

FGF23 reduces calcium deposition by VSMCs exposed to high calcium and phosphate concentrations, and in the presence of inflammation. These data highlight the therapeutic potential of phosphatonins in vascular disease, especially in a setting of chronic inflammation.

P216

Podocalyxin Excretion in the Urine of Patients with Diabetic Nephropathy

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Aim: The aim was to investigate the presence of Podocalyxin (Podxl) in the urine of patients with and without Diabetic Nephropathy (DN).

Background: Podxl is an integral membrane protein that is expressed in glomerular podocytes. It is thought to play an important role in maintaining the integrity of the slit diaphragm, and studies show that loss of slit diaphragm integrity has been implicated in the development of proteinuria.

Subjects: 116 Caucasian subjects were studied. Subjects with type 1 diabetes mellitus (T1D) were classified according to their microvascular complications. Uncomplicated (n=18) Short Duration (n=11) Nephropathy (n=24) and Retinopathy/Neuropathy (n=20). Non-diabetic normal controls (n=35) and non-diabetic proteinurics were also studied.

Methods: A freshly voided urine sample was obtained from all subjects. Supernatant and sediment samples were collected after centrifugation. The samples were probed for the presence of Podxl using immunoblotting and the results were statistically analysed using chi square and one-way ANOVA to determine differences between the groups. The samples were also probed for WT1, a podocyte specific marker.

Results: There was a highly significant difference between the numbers of subjects positive for Podxl in the urine supernatant in the DN and uncomplicated groups ($p<0.001$) and the DN and short duration (SD) groups ($p<0.01$), and also a significant difference between the normal controls (NC) and uncomplicated groups ($p<0.05$). In the sediment samples there was a significant difference in the number of positive samples between DN and SD/uncomplicated groups ($p<0.05$). There was no correlation between level of Podxl and age of subject, duration of T1D, serum creatinine or eGFR, but there was a significant difference in the mean level of Podxl present in DN and uncomplicated groups ($p<0.05$). The presence of WT1 was found only in DN and non-diabetic proteinuric samples.

Conclusion: Podxl can be detected in DN and normal healthy controls. The origin of the Podxl in the urine of patients with T1D is still to be resolved. Podxl excretion may ultimately provide an insight into the pathogenesis of DN.

P217

Increased expression of the calcium-sensing receptor and inhibition of calcification in human vascular smooth muscle cells cultured under cyclic strain

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Progressive arterial calcification is a major cause of cardiovascular mortality in patients with chronic kidney disease (CKD). Vascular smooth muscle cells (SMC) were shown to play a key role in the pathogenesis of arterial calcification. Here we aimed to investigate the role of SMC phenotype, pro-inflammatory factors and pulsatile strain in the development and progression of vascular calcification and calcium-sensing receptor (CaSR) expression.

Human aortic SMC (HAoSMC) were incubated with 5 mM β-glycerophosphate and 20 ng/ml TNF-α for up to 4 weeks. Cells were harvested and analysed for α-actin (SMC marker) and CaSR protein expression using Western blot and stained with alizarin red to assess the degree of calcification. In addition, cells were cultured under a cyclic biaxial strain (7% stretch, 30 cycles/min) using Flexcell apparatus on collagen I coated dishes for up to 14 days. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test.

We observed a significant decrease in smooth muscle α-actin expression in HAoSMC (by 35% ($p<0.05$) after 2 weeks and by 60% ($p<0.01$) after 4 weeks of incubation). It was accompanied by a 45% decline in CaSR protein expression ($p<0.05$). SMC α-actin expression decreased further after 4 week treatment with β-glycerophosphate (by 79%, $p<0.05$) and TNF-α (by 65%, $p<0.05$). No further changes in CaSR protein expression were observed. Alizarin red staining showed larger areas of calcification in β-glycerophosphate- and TNF-α - treated cultures than in control cells after 4 weeks of incubation, however, the observed increase was not significant. When HAoSMC were cultured under cyclic strain a significant up-regulation of α-actin expression by day 7 and 10 (by up to 23%, $p<0.05$) compared to control static cultures was found. CaSR expression in strained cells was also increased by 45% by day 14 ($p<0.05$). Importantly, alizarin red staining of 7 and 14 day cultures revealed significantly smaller areas of calcification in strained cells compared to control static cultures ($p<0.05$).

Our data indicate that long-term culture of HAoSMC lead to a phenotypic change towards a calcification-promoting phenotype that was enhanced in an inflammatory environment and accompanied by reduced CaSR expression. Importantly, HAoSMC cultured under cyclic strain maintained their phenotype and showed significantly less pronounced calcification along with an increased CaSR expression. This provides further evidence supporting a key role of the CaSR in the regulation of vascular SMC calcification.

Poster Session

Thursday 23 April

13:30 – 14:30

Anaemia

Moderator Dr Iain MacDougall

P218

Reticulocytosis may be predictive of erythropoietin resistance in a haemodialysis programme.

Marina Loucaidou, Seema Singh, Margaret Nevin, Shruthi Konda, David Taube, Neill Duncan, Thomas Cairns

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Introduction: Positive haemolytic screens have previously been associated with erythropoietin resistance in the context of chloramine-contaminated water.

Method: We performed haemolysis screening in a satellite haemodialysis unit following an observation of falling haemoglobin and rising erythropoietin requirements in the absence of evidence of water contamination.

Results: 60 patients receive maintenance haemodialysis at the West Middlesex satellite renal unit. We observed an unexplained falling trend in our monthly haemoglobins with a rise in the erythropoietin requirement. This was in the absence of any positive microbiological or chemical water results that were undertaken both routinely and indeed more extensively in association with the water authority once the trend was identified. We performed prospective haemolytic screens on all patients before and after replacement of the water treatment components in addition to our prospective analysis of haemoglobins, erythropoietin doses, ferritin levels and CRPs.

We present data from 3 months prior to 6 months following component change. There was a sustainable increase in haemoglobin from 11.6g/dL to 12.5g/dL ($p=0.0008$ student's paired t-test) and a continuing fall in erythropoietin dose from a mean Darbepoietin dose of 50.2 mcgs to 43.6 mcgs ($p=0.014$). The same trend was observed in the Darbepoietin dose adjusted for average body mass (0.77mcgs/Kg vs 0.67mcs/Kg, $p=0.058$) and the average body mass and haemoglobin adjusted dose (0.069mcgs/Kg/g/dL vs 0.056mcgs/Kg/g/dL, $p=0.005$).

Haemolytic screens were also undertaken before and after the water treatment component change. There was no evidence of overt haemolysis as judged by reticulocyte count (absolute or percentage), haptoglobin count, LDH or bilirubin. However, the reticulocyte count was significantly higher before than after the change (77.35 [1.98%] vs 60.49 [1.48%], $p=0.00006$) confirming increased bone marrow activity. We observed no difference in the ferritin or CRP levels. The unit had a stable kt/v of 1.8-1.9 pre and post change.

Conclusion: We report the importance of water treatment component replacement to mean haemoglobin levels and erythropoietin doses. In addition we observed that reticulocytosis is indicative and may be predictive of erythropoietin resistance even in the absence of overt haemolysis. We plan to prospectively analyse this parameter in our entire haemodialysis population with the intention of incorporating it to our prospective monthly quality data analysis for an earlier detection of erythropoietin resistance.

P219

Erythropoietin therapy leads to a reduction in plasma hepcidin in chronic kidney disease

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BACKGROUND

The hepatic hormone hepcidin prevents iron overload by inhibiting iron absorption and transport, but its increase in inflammatory states restricts iron available for erythropoiesis contributing to the anaemia of chronic disease. Levels are also high in renal failure, preventing the absorption of dietary iron, and possibly underlying erythropoietin resistance. However, using our recently developed immunoassay to measure circulating hepcidin in haemodialysis patients, we found that high erythropoietin requirements were associated with low, rather than high, hepcidin levels.

METHODS

Using our novel immunoassay, plasma hepcidin was measured in stable chronic kidney disease patients with moderate anaemia, before and after starting treatment with intravenous iron or erythropoietin.

RESULTS

Following a single intravenous dose of 200mg iron sucrose in 4 patients, hepcidin was markedly increased (59.3+/-18.6 vs 18.1+/-9.6ng/ml, p=0.047). In 7 patients hepcidin levels were significantly reduced after a single dose of 20mcg darbepoitein alfa (60.7+/-6.0 vs 71.0+/-4.7ng/ml, p=0.045) remaining at the lower level after several weeks of continued therapy (60.0+/-7.2ng/ml). There were no concurrent changes in iron indices, or in circulating levels of the putative hepcidin regulator GDF15 (growth differentiation factor 15).

CONCLUSION

Erythropoietin therapy leads to a reduction in circulating hepcidin. The resulting improvement in iron transport may be an important component of its efficacy in renal anaemia. Studies characterising this effect in healthy controls are planned.

P220

Conversion to CERA in haemodialysis patients receiving low doses of darbepoetin

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CERA (Mircera) is an erythropoiesis stimulating agent, with a half life six times longer than darbepoetin alfa (Aranesp). The manufacturer suggests conversion to a monthly dose of 120 mcg CERA for patients receiving <40 mcg/week darbepoetin. We introduced CERA in a satellite unit where the majority of patients were receiving low doses of darbepoetin. Due to concern that the suggested conversion could lead to undesired increases in haemoglobin, a modified conversion protocol, allowing lower doses, was implemented.

Patients receiving <40 mcg/week darbepoetin were converted to CERA according to a protocol based on the current darbepoetin dose and the mean dose over the last 6 months. The trend in Hb was also considered if Hb was outside the desired range. Hb, ferritin and RCH were monitored monthly. CERA dose changes were made at intervals of no less than two months using a predictive algorithm. Routine treatment with IV iron was maintained.

Data for 25 patients was audited six months after conversion to CERA. At conversion, two patients received no CERA, 17 received 50 mcg/month and six received 100 mcg/month. Nine patients required no dose changes during the six months after conversion, eight had one dose change and eight had two changes. After six months, 13 patients were on the same dose as at conversion, seven were on higher and five were on lower doses. There were no statistically significant changes in average Hb, ferritin, RCH, ESA dose or IV iron use during the audit period. The mean Hb at six months was 11.6 ± 1.1 g/dl (compared to 11.7 ± 1.4 g/dl prior to conversion) and the mean CERA dose was 74 ± 60 mcg/month (median 50 mcg/month).

Our audit suggests that patients treated with <40 mcg/week darbepoetin can be safely converted to CERA at lower doses than that suggested by the manufacturer. A 1:1 conversion of the monthly dose appears to be appropriate for stable patients.

P221

Renal function and haemoglobin in the year prior to starting RRT: differences between early and late presentation. A multi-centre study of 3,233 patients from the UK Renal Registry.

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Background

There are few studies on the association between late presentation and rate of deterioration in renal function or haemoglobin (Hb) during the 12 months prior to starting renal replacement therapy (RRT). We analysed the rate of decline in eGFR and the severity of anaemia by time from first renal presentation.

Methods

All incident ERF patients at 9 UK centres between 2001-2006 were included. The UK Registry extracted data electronically from renal IT systems at time points 0, 1, 2, 3, 4, 5, 6 and 12 months prior to ESRD. The 4-v MDRD eGFR was used. Rate of eGFR decline was calculated using a least-square analysis. Mean Hb was calculated using a mixed linear model. Analyses were adjusted for age, gender, ethnicity and primary renal disease. Late presentation is defined as being under the care of a renal physician for less than 3 months prior to initiation of RRT

Results

The adjusted rate of decline of eGFR (ml/min/1.73m^2/year) was 4.2 in the timely presentation group (>12m pre-ESRD), compared with 10.6 in the late presentation group (<3m) (p<0.0001)

There was no difference in eGFR at time of commencing RRT between the two groups.

The adjusted mean Hb over the 12 months pre-ESRD was 10.9g/dl for the timely presentation group and 9.8g/dl for the late presentation group (p<0.0001)

Conclusion

Patients who present to renal services within 3 months of commencing RRT have a faster rate of decline in renal function and a lower mean haemoglobin even after adjusting for age, gender, ethnicity and primary renal disease.

Figure 1. eGFR pre-RRT by time since first renal review

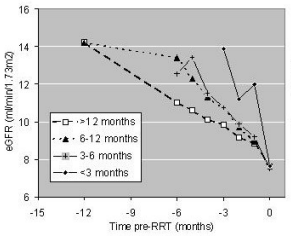
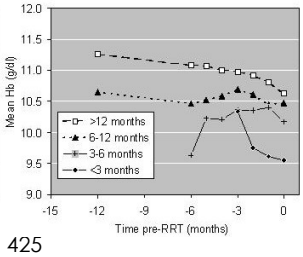


Figure 2. Hb pre-RRT by time since first renal review



British Transplantation Society

Poster Session

Wednesday 22 April

13:00 – 14:00

Infection

Moderator Dr Rachel Hilton

P222

A retrospective longitudinal study of nephrourological outcomes in BK virus positive renal transplant recipients

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Introduction: BK virus is a polyoma virus which may reactivate with or without clinical nephropathy following renal transplantation. Experimental/clinical evidence supports the hypothesis that the virus reactivates from cells of the donor kidney urothelium. Viral reactivation and inflammation within the urothelium of the donor ureter has the potential to affect healing of the anastomosis with the recipient urinary tract or ureteric vascularity. This study addresses the hypothesis that BK viraemia may have an effect on ureteric function and the development of strictures.

Methods: Clinical and demographic data from 140 consecutive patients over 2 years, undergoing renal transplantation were compiled using the prospective unit database (PROTON) supplemented by clinical and laboratory record review. All patients were screened for BK viraemia by PCR. The incidence of radiological hydronephrosis and clinically significant hydronephrosis (defined by requirement for nephrostomy +/- further surgical/radiological procedure) was compared between the group of patients manifesting BK viraemia in the year following transplant and the group with no viraemia. Statistical significance was assessed with the Fisher exact probability test.

Results: There was no significant difference in the demographic make up of the 2 groups and specifically no difference in donor/recipient age, cold ischaemic time or the use of stents. 1 case was excluded due to early transplant nephrectomy. 36 of 139 patients developed detectable viraemia. None manifested biopsy proven BK nephropathy. The incidence of radiological hydronephrosis was 16.7% in the BK viraemic group and 3 % in the no viraemia group ($p=0.01$). The incidence of clinically significant hydronephrosis was 10% in the BK viraemic group versus 1% in the no viraemia group ($p=0.04$).

Conclusion: BK viraemia, without nephropathy, was associated with both radiological and clinically significant hydronephrosis. Further studies are needed to evaluate any pathological role in transplant ureteric stricture development.

P223

Incidence and Risk factors for CMV following renal transplantation despite valganciclovir prophylaxis.

Jaisi Sinha, Agiris Asderakis

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Introduction: Cytomegalovirus continues to be a serious clinical problem for patient's receiving solid organ transplantation leading to morbidity and mortality of recipients and having a detrimental effect on graft survival. One of the methods to reduce its impact is the usage of prophylactic antiviral agents in the immediate period following transplantation.

Aim: The incidence of CMV infection and its impact in renal transplant recipients receiving valganciclovir prophylaxis for 3 months post transplant. In addition to study any risk factor for CMV infection.**Patients and methods:** From January 2005 to January 2008 351 patients received a renal or simultaneous kidney pancreas transplant. 70% of the patients received a triple maintenance immunosuppressive regime with tacrolimus, mycophenolate and prednisolone. 55% received anti IL-2 induction (simulect) and 19% received ATG as part of induction treatment. Steroids were not used in kidney pancreas transplants and were withdrawn at 3 months if no rejection had occurred in the rest of the patients.

Patients received CMV prophylaxis in the form of oral Valganciclovir for 3 months post transplant with dose adjustment according to renal function. Patients received prophylaxis if they were considered at risk of CMV infection:

a. recipients of CMV positive donor kidney
b. Positive recipients of negative donor kidneys if they received anti IL-2 induction.
c. Recipients who received ATG induction irrespective of status.

Results: Median recipient age was 46 years and median donor age was 49 years. The mean HLA mismatches were 2.48, (median 3, sd 1.48). 58.4% (205) of all patients received CMV prophylaxis according to the indications described above. However 28 patients (13.7%), developed CMV infection in this cohort of patients, 3 during the period of prophylaxis and 25 following completion of the 3-month regime. In addition 3 patients had CMV infection out of the146 that did not receive CMV prophylaxis. Univariate and regression analysis for risk factors of developing CMV infection revealed that donor age ($p=0.006$) and donor and recipient pretransplant CMV status ($p=0.0001$), but not recipient age, HLA mismatches, or use of polyclonal antibody as induction were risk factors for developing CMV infection. The donor age effect was partly explained by its association with seropositive CMV status (Mann Whitney $p=0.0004$). The average time to development of CMV infection was 166 days (median 125 days, sd 134.7 d) following transplantation. All patients responded to intravenous ganciclovir treatment and additional three months of prophylaxis without infection recurrence. There was no difference in the renal function as manifested by serum creatinine at one year between patients who developed CMV infection and CMV free patients (167 vs 148, $p=0.59$). **Conclusion:** Over 13% of kidney and pancreas transplant recipients get CMV disease despite 3 months valganciclovir prophylaxis but without any obvious adverse effect to kidney function at 1 year post transplant. ATG induction does not seem to confer any additional risk to CMV infection.

P224

Prevalence of CMV, JC and BK viruses in renal transplant recipients receiving induction with Alemtuzumab or basiliximab; Interim analysis from SALAMI study

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Infections after renal transplantation are associated with increased morbidity and mortality. Clinically significant infections with human Polyoma viruses are unique to renal transplant recipients. We compare prevalence of Human Polyoma viruses (BK and JC) and cytomegalovirus (CMV) in the two arms of SALAMI study (Steroid Avoidance in Leeds with Alemtuzumab or MMF Immunosuppression) at 12 months follow up.

SALAMI is a comparative, open label, randomised and prospective trial of tacrolimus based steroid avoidance in renal transplantation with either alemtuzumab induction followed by tacrolimus monotherapy (ALEM GROUP) or basiliximab induction with tacrolimus and mycophenolate mofetil (CONTROL GROUP). This is an equivalence study with no anticipated difference in major endpoints between the two arms.

Blood and urine of study population were tested by Polymerase Chain Reaction (PCR) at 0 month (post transplant), 6 months and 12 months for BKV, JCV and CMV. Data was analysed with Pearson's Chi square test.

No statistically significant difference was noted in the prevalence of BKV, JCV or CMV at the time of renal transplant or 6 and 12 months post transplant. Number of JC viruria was more in ALEM group than Control group at 6 months post transplant (3/24 vs 0/17) but it did not achieve statistical significance (p 0.1).

We conclude that Induction with Alemtuzumab followed by Tacrolimus monotherapy in renal transplantation is safe and not associated with increased risk of viral infections in the first post-transplant year.

P225

The outcome of patients who develop *Clostridium Difficile* infection following solid organ transplantation: a single centre experience.

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Manchester Royal Infirmary, Manchester, United Kingdom

Background: *Clostridium Difficile* (*C. Diff*) is a gram-positive, anaerobic, spore-forming, rod-shaped bacterium responsible for most cases of hospital-acquired infective diarrhoea. It is a very contagious organism, easily spread via direct contact. Immunocompromised transplant patients may be particularly vulnerable to this infection and may have a worse outcome.

Aim: The aim of this study was to find out the natural history of patients who develop *C .Diff*. within the first year following solid organ transplantation.

Method: All patients who develop *C .Diff* are notified to the Microbiology Department. We identified all transplant patients who developed *C. Diff* within the first year of transplantation between 2004- 2007. We then reviewed these patients' notes to identify when they acquired this infection and the natural history and complications that occurred.

Results: Between 2004-2008 we performed 682 transplants: 433 deceased donor kidneys, 143 live donor kidneys, 18 pancreas only transplants and 88 simultaneous kidney and pancreas transplants. Of those 25 patients developed *C Diff*. The median age for this group was 46. All patients had standard induction prophylactic antibiotics and immunosuppression. Only 5 patients were on a course of prescribed antibiotics at the time they developed *C Diff*. No single common antibiotic was identified. 2 patients developed fulminant colitis requiring urgent subtotal colectomy and ileostomy. Hospital stay was markedly increased at 15 days compared to 11 days for the general transplant population. When comparing first deceased kidney transplant the outcome of patient and graft survival at one year was worse for those who acquired *C.Diff.* (84% and 73% respectively) compared to the overall unit's results (95% and 94% respectively).

Conclusion: In our study 3.6% of transplant patients acquired *C.Diff* infection.

We did not identify any common antibiotic or patient risk factor which increased the risk of acquiring *C .Diff* infection. These patients had a markedly increased hospital stay, complication rate and poorer graft and patient survival.

P226

Infection – a significant clinical and economic burden following renal transplantation

Muhammad Shahed Ahmed, A Mohiuddin, A Bakran

Royal Liverpool University Hospital, Liverpool, United Kingdom

Introduction: Infectious complications are known to be the cause of significant morbidity and mortality after renal transplantation. Steroids are known to increase infection risk and hence we have audited the infection outcome of our steroid minimalisation immunosuppression policy. We present an audit of infection rate and outcome for patient and graft in our unit.

Methods: Admissions to the transplant unit were analysed prospectively over a 12 month period. Reasons for admission were documented, and, if due to infection, aetiology established, whether renal function was affected, as well as mortality. Immunosuppression consisted of basiliximab induction with tacrolimus/MMF maintenance, although iv steroids were used for acute rejection and oral steroids after repeated rejection episodes.

Results: A total of 183 patients (107 male, 76 female; mean age 47.55 ± SD 14.9 yrs) had 331 admissions over the 12 months. 21 % (69 episodes in 54 patients) of admissions, and the commonest cause, were attributable to infection. 13.3 % patients who were admitted for reasons other than infection experienced an infection during their admission. 40% of newly transplanted patients experienced an infection before discharge. 61.5% of all infective episodes resulted from a UTI and 10% had septicaemia. CMV syndrome was treated in 8 patients. 63 % patients experienced deterioration in kidney function due to infection (AKIN criteria). 78 % had full recovery of function but 16 % patients only had partial recovery, 1 patient needed to start long-term dialysis and 2 patients died. Length of stay was 15 days for patients with infection and 6 days for those without. Despite our intention to avoid long-term oral steroids, 50% of patients with infection had been commenced on oral prednisolone for clinical reasons

Conclusion: Bacterial infections were the predominant cause of admission post-transplantation with significant serious consequences in a minority of patients. Despite our intention-to-treat steroid sparing protocol, a significant number of patients ended up on steroids Peri/post-operative UTI remains a challenging problem. There may be a case for antimicrobial prophylaxis to reduce the burden of infection in patients, with its increased admission rate and economic costs as has previously been suggested.

[1] Reference: [1]Fox et al (Am J Med 1990, 89: 255-274).

P227

CMV mismatch and acute rejection in renal transplantation

Mark J Salji[1], Vasilis Kosmoliaptsis[3], Davide Prezzi[3], Ken G Smith[2,4], Menna R Clatworthy[2,4]

[1]University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [2]University of Cambridge Dept of Medicine, Cambridge, United Kingdom, [3]Addenbrookes Hospital Dept of Surgery, Cambridge, United Kingdom, [4]Cambridge Institute for Medical Research, Cambridge, United Kingdom

Introduction: Cytomegalovirus (CMV) is one of the major post-transplant infections. Previous studies have shown that CMV seronegative recipients (R-) receiving a renal allograft from a CMV seropositive donor (D+) have worse patient and allograft survival than those who avoid primary CMV infection. We wished to determine the effect of CMV serostatus on the incidence of biopsy-proven acute rejection (BPAR) and delayed graft function (DGF).

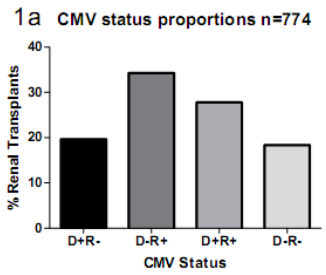
Methods: Data were collected on donor and recipient CMV serostatus, DGF(defined as need for dialysis in the first week post-transplantation), and BPAR in all renal transplants performed at a single UK centre from 1998-2008 (n=774).

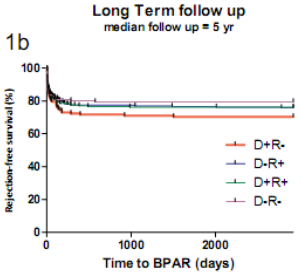
Results: Donor and recipient CMV serostatus are shown in Figure 1a. 20% of transplants were D+R-. The overall frequency of DGF and BPAR are shown in table 1. DGF was not higher in the D+R- group. BPAR at 1 year was highest in the D+R- group (29.6%) and lowest in the D-R- group (20.4%, Table 1, Figure 1b/c). In the D+R- group, the incidence of BPAR increased at around 100 days (Figure 1c). This corresponds to the time at which CMV prophylaxis is stopped and suggests that these rejection episodes may be triggered by primary CMV infection.

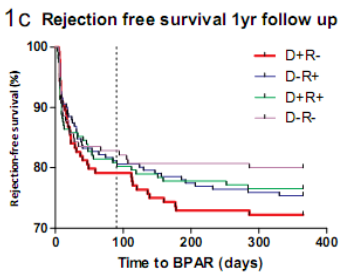
Conclusions: These data suggest that BPAR is increased in D+R- transplants and that CMV prophylaxis may delay acute rejection in this group.

Table 1

CMV serostatus	%DGF	% BPAR (at 1yr)	% of BPAR Mild ACR	% of BPAR Mod/Sev ACR	% BPAR Humoral/Mixed
D+R- (n=152)	25.0%	29.6%	42.2%	48.8%	8.9%
D-R+ (n=265)	30.7%	24.2%	51.5%	34.4%	14.1%
D+R+(n=215)	29.3%	23.7%	47.1%	33.3%	19.6%
D-R- (n=142)	19.0%	20.4%	41.4%	55.2%	3.4%







Poster Session

Thursday 23 April

13:30 – 14:30

Immunosuppression 2

Moderator Dr Adam Maclean

P228

Thrombocytopenia after Alemtuzumab induction in kidney transplantation

Ka Kit Edmond Chan, Anisha Tanna, Rawya Charif, Tom Cairns, Neill Duncan, Jack Galliford, Nicky Kumar, Adam McLean, Andy Palmer, David Taube

West London Renal and Transplant Centre, London, United Kingdom

Idiopathic thrombocytopenia [ITP] is a rare and serious complication of Alemtuzumab therapy. Despite this, there are few reports of ITP and no systematic studies of platelet counts following Alemtuzumab induction in renal transplantation.

In this study, we report our experience of Alemtuzumab induction [30mg iv] with Tacrolimus monotherapy [target level: 5-8 ng/mL] and thrombocytopenia in 340 kidney transplant recipients [m:204, f:136; mean age 46.9±12.87 years]. Mean follow up is 19.8±14.03 months.

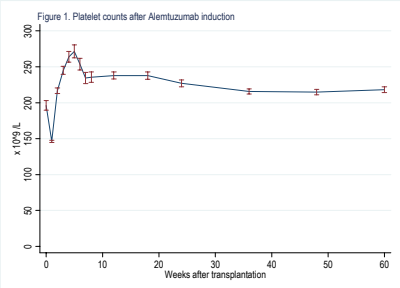
Cumulative patient and censored allograft survival are 97.2% and 94.8% at 3 years.

Figure 1 shows that the mean platelet counts in this group of patients drop significantly but transiently in the first post transplant week.

3/340 patients [1.0%, 0.045 episodes per 100 patient months, 95% ci 0.0092-0.1305] developed life threatening thrombocytopenia [platelet count < 20 x 10^9 / L] and after appropriate haematological investigation were found to have ITP. 2/3 patients presented with epistaxis. There was no other significant haemorrhage.

All 3 patients received oral prednisolone, IVIG [2g/kg] and Rituximab. 2/3 patients responded after 1 course of treatment; whilst the third patient required 2 further courses of IVIG and Rituximab. No patients were splenectomised.

This study shows that transient, mild thrombocytopenia occurs immediately after Alemtuzumab induction and that ITP is rare and reversible with conventional therapy.



P229

Steroid Sparing Immunosuppressive Regimes Reduce The Incidence Of New Onset Diabetes Mellitus After Renal Transplantation

Christopher Lawrence, Ka Kit Edmond Chan, Jack Galliford, Dawn Goodall, Rawya Charif, Nicky Kumar, Adam McLean, Andy Palmer, David Taube

West London Renal and Transplant Centre, London, United Kingdom

New onset diabetes after transplantation [NODAT] is a significant clinical problem associated with a higher incidence of death with a functioning graft [DwG], cardiovascular complications and obesity. There are few published studies describing the incidence, timing and causes of NODAT in patients receiving steroid sparing regimes.

388 non diabetic patients [229 m, 159f; mean age: 45.4±13.01 years] transplanted in our centre between November 2002 and July 2008 entered the study. All patients received an immunosuppressive protocol consisting of monoclonal antibody induction [Alemtuzumab 30mg or Daclizumab 2mg/kg], our steroid sparing regime [500mg methyl prednisolone iv pre operatively, followed by 60mg prednisolone days 0-3 and 30mg days 4-7, then stopped] and Tacrolimus alone or with Mycophenolate Mofetil. Steroids were only reintroduced if the patients developed rejection

None of these patients were diabetic at the time of transplantation and NODAT was defined as the need for oral hypoglycaemics or insulin post transplant.

Only 34/388 [8.8%] patients developed NODAT during a mean follow up period of 26.9±17.9 months. Cumulative NODAT free survival is 93.7%, 88.7% and 87.6% at 1, 3 and 5 years.

5 year cumulative patient and censored allograft survival in the NODAT group are 96.49% and 100% respectively, and 97.00% and 93.62% in patients not developing NODAT [no NODAT, p=ns]. Allograft function and the incidence of rejection was the same in both groups. Pre transplant HbA1c and random glucose levels were also similar in both groups.

Univariate analysis showed that NODAT was significantly more common in South Asians, older recipients and those patients started on steroids for rejection. Immediate pre transplant mean body weight was significantly higher in the patients who subsequently developed NODAT. [80.2kg vs 72.1kg in non NODATs; p=0.01].

This study shows that our steroid sparing regime is associated with a very low cumulative incidence of NODAT and occurs in patients from South Asia, those with a higher body mass and who received steroids for rejection.

P230

Tacrolimus weaning is not necessary after Alemtuzumab induction in live related renal transplantation

Ka Kit Edmond Chan, Jack Galliford, Rawya Charif, Terry Cook, Gary Chusney, Dawn Goodall, Candice Roufosse, Adam McLean, David Taube

West London Renal and Transplant Centre, London, United Kingdom

Calcineurin inhibitor [CNI] nephrotoxicity is a major concern and has been used as a rationale for Tacrolimus [Tac] weaning after successful live donor renal transplantation with Alemtuzumab induction. In this study we report our experience of Alemtuzumab induction with Tac monotherapy in live related transplants [LRD] in whom Tac treatment has been maintained and not weaned.

191 sequential live donor kidney recipients [80m: 111f, mean age 45.8±12.9 years received Alemtuzumab induction [30mg iv immediately post operatively] low dose Tac [0.1mg/kg/day, target level 5-8 ng/ml] and 7 days of oral steroids. Tac dose was only changed to maintain these levels.

Rejection was diagnosed by allograft biopsy. Cellular rejection was treated with iv methyl prednisone [0.5g x 3], the introduction of oral steroids and Mycophenolate Mofetil. Antibody mediated rejection was similarly managed with the addition of plasma exchange and ivIg [2g/kg] if severe or steroid unresponsive.

Mean follow up is 20.1±14.1 months. 3 year patient and allograft survival is 100% and 93.3% respectively. Allograft function [MDRD eGFR] at 1, 2 and 3 years is 54.7+14.4, 54.5+15.8 and 51.5+15.4 ml/min/1.73m^2,]

Rejection free survival at 12, 24 and 36 months is 84.4%, 80.7% and 74.0% respectively.

93 patients underwent 197 transplant biopsies for allograft dysfunction. Only 8/197 [4.1%] biopsies showed evidence of calcineurin inhibitor toxicity.

7/191 [3.6%] patients were found to have CNI toxicity. Cumulative CNI toxicity free survival is 95.1% at 3 years.

This study shows that the outcomes of live donor transplantation with Alemtuzumab induction and Tac without weaning are excellent. CNI induced allograft dysfunction is rare.

There is however a continuing incidence, albeit small, risk of rejection implying that Tac weaning in this group of patients may be hazardous.

P231

Cost-effectiveness of Thymoglobuline® versus basiliximab induction therapy in renal transplant recipients in the United Kingdom

Samantha Gillard[1], Curtis Moore[2], Adam Stay[2]

[1]Abacus International, Bicester, Oxfordshire, United Kingdom, [2]Genzyme Ltd, Oxford, United Kingdom

Objective: To assess the cost-effectiveness of induction therapy with Thymoglobuline® versus basiliximab for the prevention of rejection in renal transplant recipients perceived to be at increased risk of acute rejection.

Methodology: A cost-utility analysis was conducted from the perspective of the UK National Health Service (NHS). A decision-tree analytical model covers the first year post-transplant and is based on clinical outcomes from a clinical study comparing Thymoglobuline® and basiliximab in renal transplant recipients at increased risk of acute rejection (Brennan et al., 2006). The model considers biopsy confirmed acute rejection (BCAR), graft loss, delayed graft function and patient and graft survival over a one year period. Adverse events that differed significantly between the two treatment groups were also addressed in the model. Previously published utility scores were used for patients with functioning renal transplants and for those patients on dialysis.

Results: The mean incremental cost associated with induction therapy was £1,445. Thymoglobuline® is associated with significantly fewer episodes of BCAR and steroid-resistant BCAR, resulting in cost savings of approximately £1,000 and £1,415, respectively. The total one year treatment cost associated with Thymoglobuline induction therapy was £10,956 per patient compared to £12,803 per patient treated with basiliximab; a cost saving of £2,207 per patient. Thymoglobuline® induction therapy was associated with an incremental 0.0085 quality-adjusted life years and therefore was the dominant strategy relative to basiliximab that is it is less costly and more beneficial. The results are driven predominantly by the lower BCAR rates associated with Thymoglobuline®.

Conclusion: Thymoglobuline® induction therapy is pharmacoeconomically dominant relative to induction therapy with basiliximab.

P232

The Effect of Thymoglobulin (ATG) Induction to Post Transplant Albumin Levels

Phil Stevens, Adel Ilham, Rafael Chavez, Argiris Asderakis

Transplant Unit, University Hospital of Wales, Cardiff, United Kingdom

Background: ATG induction is used in transplantation to reduce rejection rate and allow minimisation of calcineurin inhibitors or steroid avoidance. We have shown excellent short / long term results using ATG induction in transplantation in Donor after Cardiac Death (DCD) and in pancreas transplantation (SPK/PAK).

Aim: Investigate the effect of ATG induction to albumin levels post-transplant.

Patient and Methods: Patients were transplanted over a 2 year period. Albumin was measured at day 2 post transplant and preoperatively and the ratio of those values was obtained as a percentage (*alb ratio2* = alb d2 / alb preop x100). Univariate and regression analysis was performed to identify factors for alb drop.

Results: 32 BSD and 44 DCD transplant recipients were included. 39 patients received ATG whereas 37 did not. Median pre-operative albumin for all patients was 40.0 g/L (95% CI 39.0 to 41.0g/L). The *alb ratio2* in patients who received ATG was 67% as opposed to 75% in patients who did not (p=0.035). Univariate analysis showed that the *alb ratio2* was dependent on the use of ATG (relative difference in *alb ratio2* of 9.5% in the non ATG vs. the ATG group, 95% CI 1.4-18%, p=0.023), the preoperative albumin (p<0.001), but not the donor, the recipient age, or CIT.

BSD recipients who did not receive ATG had *alb ratio2* 80% compared to 81 % of DCD patients who did not receive ATG and 67% of DCD recipients who received ATG (p=0.06). Interestingly the proportional drop in creatinine on day 2 was inversely correlated to the *alb ratio2 (p=0.01 correlation coefficient=-0.2), as well as the CIT (p=0.001),* without being correlated with the use of ATG (p=0.15).

Conclusion: There is a drop in post-transplant albumin following ATG. This drop is affected by recipient factors and marginally by the source of the transplant performed. It remains to be seen if this drop is a marker of any effect of ATG mediated by the significant release of cytokines seen following its administration.

P233

Complement inhibition in acute antibody-mediated rejection, preliminary experience with eculizumab

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

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

Patients undergoing antibody-incompatible transplantation (AIT) are at risk of antibody mediated rejection (AMR). Complement activation, via the membrane attack complex C5b-9, is thought to play a major part in the rejection process. A complement factor C5 inhibitor – eculizumab – has recently become available, and has potential benefit in AMR.

Patient 1 was a 33year old man who received a 2nd renal transplant from his father. Pre-treatment non-AHG cytotoxic crossmatch was +ve at titre 1:16 (donor specific antibodies (DSA) HLA A2, DR9, DR53, DQ9) and ABO (A1 to B). Post-operative course was complicated with oligo-anuria and AMR partially unresponsive to anti-thymocye globulin (ATG) and plasmapheresis. Both HLA and ABO antibody levels rose markedly above pre-treatment levels. He was treated with two doses of eculizumab. Urine output increased dramatically after the drug was given, and he is currently well at 4 months with serum creatinine 250 umol/l.

Patient 2 was a 29 year old man who received a 4th renal transplant from his mother. After his third transplant he experienced a serious thrombotic microangiopathy with coma, so immunosuppression was calcineurin inhibitor-free. Pre-treatment flow crossmatch was +ve (DSA HLA A2, B51, Cw14, DR15, DR51, DQ6). Two days post-transplantation his serum creatinine rose and a renal biopsy was suggestive of AMR. He was treated with eculizumab, but despite this a subsequent biopsy showed marked rejection, and ATG was given. Rejection resolved, but he experienced a CMV infection at 14 days, and subsequently an eosinophilic infiltrate of the graft that responded to steroids, lymphocoele, pneumonia, and urine infection with bacteraemia. He is well with serum creatinine at 3 months of 203 umol/l.

In summary, the availability of an inhibitor of the complement arm of the immune system is potentially an important addition to treatment modalities. Eculizumab did prevent the progression of rejection in one case. Further use of the drug requires careful monitoring for infection.

P234

Alemtuzumab (Campath-1H) Induced Coagulopathy and Catastrophic Postoperative Bleeding after Kidney & Simultaneous Pancreas/Kidney Transplantation

Shahid farid[1], Paul Goldsmith[1], Julie Barwick[1], Chas Newstead[1], Richard Baker[1], G Sen[2], BC Jacques[2], Krishna Menon[1], Niaz Ahmad[1]

[1]St James University Hospital, Leeds, United Kingdom, [2]The Freeman Hospital, Newcastle, United Kingdom

Introduction

There exists little literature highlighting Alemtuzumab associated coagulopathy in kidney transplantation. We highlight and describe the case of two patients from two major UK centres who underwent live related kidney transplantation and simultaneous pancreas/kidney transplantation (SPK) and suffered marked coagulopathy and postoperative bleeding in which Alemtuzumab (Campath) was used as induction immunosuppression before surgery.

The rare reports available in current literature highlight a similar clinical course as in both our patients, involving deranged intrinsic and extrinsic coagulation pathway parameters, repeated re-exploration for bleeding and significant requirements for blood products. The coagulopathy resolved within 48-72 hours but had important associated morbidity in patients. The precise mechanism of this observation remains to be fully explained but may involve the interaction and activation of the endothelium leading to an alteration in coagulation and fibrinolysis as a direct effect or due to secondary cytokine release. We postulate a synergistic pathway involving the surgical stress response, ischeamia – reperfusion injury and release of mediators resulting in a coagulopathic state.

Conclusion

An awareness of this potential complication is important to all who are using Alemtuzumab induction therapy and highlights the need for close heamatological monitoring when using this agent. Further research into etiological mechanism(s) is warranted.

Poster Session

Wednesday 22 April

13:00 – 14:00

ABOi/HLAi

Moderator Prof David Taube

P235

Plasma exchange versus antibody specific immunoabsorption for antibody removal prior to ABO and HLA incompatible transplantation

Nizam Mamode, David Curran, Lisa Burnapp, John Scoble, Geoff Koffman, Francis Calder

Guys and St Thomas Hospital, London, United Kingdom

A variety of preconditioning regimes exist for antibody removal prior to ABO (ABOi) or HLA (HLAi) incompatible transplantation and evidence for efficacy is uncertain. We compared complication rates when specific immunoabsorption (IA) or plasma exchange (Pex) were used preoperatively for antibody removal.

29 patients (15 females, mean age 51 years) underwent antibody incompatible transplantation (18 ABOi, 9 HLAi 2 both). 24 were given rituximab, 375 mg/m^2 1 month prior to transplantation, and all were given basiliximab, tacrolimus, mmf and prednisolone. 19 patients had IvIgG preoperatively.

At mean (s.e.) follow-up of 372 (64) days, graft survival was 90% and mean (s.e) serum creatinine was 128 (7.5) umol/l. 3 graft failures were due to CAN, acute aortic occlusion and early thrombosis, all in the HLAi group. 1 patient died from a CVA with a functioning graft.

10 patients had specific IA using carbohydrate columns (9 Glycorex, 1 Therasorb), 17 patients had plasma exchange and 2 had anti-CD20 therapy alone. 7 patients undergoing Pex required preoperative clotting factors, whilst none of the IA patients did so. Major complications and acute rejection rates are shown below:

	IA	Pex
Major perioperative complications	1 (pulmonary oedema)	7 (2 periop MI, 2 coagulopathy, 2 DGF, 1 thrombosis) p=ns
Acute rejection	5	4 p=ns

Although not statistically significant, the lower complication rate after IA suggests that this may be the optimum method for antibody removal, particularly when titres are high. Further study of perioperative coagulopathy following antibody removal is warranted.

P236

Transplant glomerulopathy after HLA antibody incompatible transplantation – preliminary experience

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

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

Transplant glomerulopathy (TG) may be a chronic manifestation of antibody-mediated injury after HLA antibody-incompatible (HLAi) transplantation. It is generally regarded as carrying a poor prognosis, and there is concern that it may limit the longer term outcomes after HLAi transplantation.

Between 2003-2008, 67 patients received HLAi transplants in our centre. Six patients had renal biopsies that showed TG. These were performed at 3, 3, 16, 24, 34 and 41 months after transplantation. This represented 2/59 (3.4%) patients at risk at 3 months, and 5/27 (18.5%) at 24 months.

Mean creatinine at presentation with TG was 196 (range 158-237) umol/l, and protein-creatinine ratio_(PCR) was 293 (range 36-696) mg/mmol, and the most recent mean creatinine was 236 (range 161-347) and PCR 179 (range 110-561). Treatment consisted of blood pressure therapy in all cases, and increase in immunosuppression in 5 cases. One case had immunosuppression reduced because of multiple infections. Three patients have had courses of plasmapheresis. No graft has yet failed, though one patient has slowly reducing renal function, and the follow up since renal biopsy is short (mean 10.2 months, range 3-22).

Development of TG was associated with donor specific antibody (DSA) levels pre-transplant. In patients at risk at 24 months post transplant, TG was present in 2/7 (28.6%) patients whose pre-treatment cytotoxic crossmatch (XM) was +ve, compared with 2/12 (16.7%) with flow cytometric (FC) XM +ve, and 1/8 (12.5%) with FC -ve. Four cases had DSA against HLA Class 1 only, and have stabilised function with current low DSA levels. The other two cases, including the one with declining graft function, have ongoing production of high levels of DSA against HLA Class 2.

In summary, the risk of TG was associated with time after transplantation, and the pre-treatment level of donor specific HLA antibody. Although the number of cases is small, it is possible that TG associated with HLA Class 1 DSA that modulate may carry a better prognosis than when it is caused by HLA Class 2 with ongoing high level production.

P237

ABOi renal transplantation – our unit's experience

Argiris Asderakis[1], Adel Ilham[1], Frances Boyns[2], Walters Robert[2], Rees Tracey[2], Ann Marsden[1], Rhian Cooke[1], Rommel Ravanan[1]

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

Introduction: Clinical protocols enabling successful blood group incompatible [ABOi] renal transplantation have been established in centres outside and more recently within the UK. We present our unit's ABOi program experience which commenced on 01/04/08.

Methods: ABO antibodies were estimated using DiaMed gel cards. A clinical protocol governing all aspects of ABOi renal transplantation from patient selection extending to care for 90 days after transplantation was drawn up and accepted by relevant stakeholders. Immunosuppression consisted of Rituximab on day-30, Simulect at induction with Tacrolimus, MMF and Prednisolone as maintenance immunosuppression. DFPP was used to remove ABO antibodies with an aim to achieve an AHG/IgG titre of <1:8 on day 0.

Results:

	1	2	3	4
Age / Sex	28 / M	58 / M	39 / M	46/F
PRD Pre-Tx RRT	Alport's CAPD	GN HD	HUS Pre-dialysis	GN HD
Donor type	A2	A1	B	A1
Recipient type	O	O	O	O
Initial titre	1:16	1:128	1:4	1:128
Titre at Tx	1:4	1:4	1:4	1:4
Number / litres of DFPP	4 sessions / 21 litres	7 sessions / 50 litres	0	7 sessions / 49 litres
Creatinine at 1 week[□mol/l]	131	145	103	145
Creatinine at 1 month	156	98	101	138
Current creatinine	147 at 8 months	103 at 6 months	83 at 4 months	107 at 6 weeks

Adverse events to date include one episode each of late rejection [at 7 months] and post-operative bleeding requiring blood transfusion & re-exploration.

Conclusion: Safe and successful ABOi renal transplantation was achieved in our unit with a protocol that is in line with national/international experience. For suitable patients, ABOi renal transplantation should routinely be offered as a renal replacement therapy option.

P238

ABO Incompatible live donor kidney transplantation in patients with splenectomy and non-spenectomy using with Rituximab

Atsushi Aikawa, Takeshi Kawamura, Jiro Takasu, Yujiro Aoki, Takeo Yanagisawa, Tomomi Hadano, Hiroyuki Nakano, Ken Sakai, Sonoo Mizuiri

Toho University, Tokyo, Japan

Aim The aim of this study is to compare outcomes of ABO incompatible live donor kidney transplantations (ABOIKTx) between patients with splenectomy and those without splenectomy using with rituximab.

Patients and Methods We have had 102 ABOIKTx since May 1989. Plasmapheresis and exchange were performed as preconditioning to reduce anti-donor blood group antibody IgG (ADBGAB) to x 16 before Tx. Immunosuppression consisted of cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil (MMF) and steroid with or without basiliximab. Recently we have introduced rituximab to avoid splenectomy in 10 patients. Rituximab was given 5 days and one day before Tx. The titers of ADBGAB were serially measured and the outcomes of ABOIKTx were compared between 92 patients with splenectomy (SP+) and 10 patients without splenectomy(SP-). CD20 positive cells were measured in Sp- group until 1 year post-Tx.

Results The maximum titers of ADBGAB IgG post-Tx were lower in SP- group significantly compared with SP+ group (x19.8±19.0 vs. x85.6±133.0; $p<0.0001$). CD20 positive cells were not detected in Sp- group from 2 days to 1 year post-Tx. Thirteen of 92 patients in SP+ group and 2 of 10 patients in SP- group were second Txs. Sixteen in SP+ group and 6 in SP- group were donated from wife or husband. Incidence of acute vascular rejection was 17/92 in SP+ group, compared with 1/10 in Sp- group. However one patient with acute vascular rejection had a splenectomy because the rejection was not controlled with steroid pulse and rituximab. Another one patient had recurrent membranous proliferative glomerulonephritis in the allograft. Graft survival rates in patients in SP+ group (n=92) were 94% at 1-year, 83% at 5-year and 63% at 10-year. Graft survival rates in SP+ group (n=50) from 1997 to 2004 were 100% at 5-year and 95% at 10-year. All ten patients in SP- group have so far survived and all grafts have kept functioning since August 2006.

Conclusion Rituximab and MMF despite of non splenectomy in ABOIKTx, were appeared to be useful for suppression of ADBGAB production and avoid acute vascular rejection. Short-term outcomes of ABOIKTx in SP- group are good although long-term outcomes of ABOIKTx were also excellent in recent Sp+ group from 1997.

P239

ABO incompatible live donor transplantation using Alemtuzumab and Tacrolimus monotherapy

Jack Galliford, Rawya Charif, Kakit Chan, Marina Loucaidou, Tom Cairns, Terry Cook, Adam McLean, Candice Roufosse, Anthony Dorling, Anthony Warrens, Vassilios Papalois, David Taube

Imperial College Kidney and Transplant Institute, London, United Kingdom

Most groups performing successful ABO incompatible [ABOiLD] renal transplantation use complex and expensive regimes with Rituximab [RTX], triple-drug combinations of steroids, calcineurin inhibitors and anti-proliferative agents.

We have previously reported that it is possible to successfully perform ABOiLD transplantation without steroids using RTX and Daclizumab[DAC], Tacrolimus [Tac] and Mycophenolate Mofetil [MMF].

Alemtuzumab is a potent cytotoxic antibody directed against the CD52 antigen which is expressed on T and B cells and therefore may also be effective in ABOiLD transplantation.

14 patients [9m, 5f; age 51.6 ± 10.8 yrs] received ABOiLD transplants [12 LURD and 2 LRD]. Mean follow up is 6.8±3.5months. Alemtuzumab [30mg iv] was administered at the start of plasmapheresis with Tac [target level 8–11 ng/ml]. 100mg/kg ivIg was given after each plasmapheresis until blood group IgG titre $\leq$ 1/4. Post transplant, patients received a further dose of Alemtuzumab [20mg iv] and prednisolone for 1 week [60mgs, day 0-4; 30mgs, days 5-7 and then stopped]. Tac monotherapy was continued. Rejection episodes were classified according to Banff 2007 criteria.

Patient and graft survival at 9 months is 100%. Mean allograft function [MDRD eGFR] is 54.6$\pm$6.8, 49.4$\pm$2.9, 47.8$\pm$5.6, and 55.3$\pm$7.6 mls/min/1.73m^2 at 1, 3, 6 and 9 months. There have been only 3 episodes of acute rejection. Two were T cell mediated and occurred at 12 and 146 days. One, at day 23, was antibody mediated and associated with de novo donor specific anti-HLA antibodies. All rejection episodes have been successfully reversed. Other adverse events include one patient with NODAT and one non-fatal pulmonary embolism.

There have been no significant infections or malignancies.

These data are comparable with our previous experience of steroid sparing ABOiLD transplantation using RTX, DAC, Tac, and MMF.

This short term study shows that ABOiLD transplantation can be safely, cheaply and successfully performed using a simple Alemtuzumab induction and Tac monotherapy regime.

P240

HLA antibody incompatible transplantation using Rituximab induction therapy and Therasorb antibody absorption.

Nicholas Torpey[1], Vaughan Carter[2], Martin Howell[2], David Rix[1], Naeem Soomro[1], David Talbot[1]

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Techniques for HLA antibody incompatible renal transplantation are used increasingly to allow live donation despite pre-formed donor-specific anti-HLA antibodies detectable in recipient serum. Here we describe 20 HLA antibody incompatible transplants performed in a single centre between 2006 and 2008.

In 7 recipients donor-specific anti-HLA antibodies (DSA) were detectable but cross-match testing by flow cytometry (FC) and complement dependent cytotoxicity (CDC) was negative. Immunosuppression comprised IL2R antibody induction, tacrolimus (TAC), mycophenolate mofetil (MMF) and prednisolone maintenance therapy but no antibody removal. There were no episodes of antibody-mediated rejection (AMR), and no differences in post-transplant course when compared to DSA-negative LD transplants.

In 13 patients DSA were present leading to a positive cross match (5 CDC+ and 8 FC+ but CDC-). Immunosuppression comprised Rituximab (either 375mg/m^2 or 1000mg) 1 month prior to transplantation, antibody removal (the number of pre-transplant treatments dependent on DSA titre, and 3 post-transplant treatments), IVIG, a further dose of Rituximab on the day of transplantation, and TAC, MMF and prednisolone maintenance therapy. There were only 2 episodes of C4d+ AMR, but 9 patients received Thymoglobulin, either because of delayed graft function or steroid resistant cell-mediated rejection. 3 grafts were lost (1 technical failure, 1 HUS without AMR, and 1 resistant cell-mediated rejection with BK virus nephropathy). The mean serum creatinine of the remaining 10 patients is 120μmol/L. Based on this experience our protocol has changed to include a single dose of Rituximab 30 days pre-transplant and T-cell depleting antibody induction therapy.

The 3 patients with the highest DSA titres received antibody removal therapy using the Therasorb immunoabsorption system. DSA were effectively removed, the procedure well tolerated and free of the adverse effects of plasma exchange.

P241

Therasorb immunoabsorption in HLA antibody incompatible transplantation

Jonathan Murray, Evelyn Watson, Caroline Scuffell, David Talbot, Nicholas Torpey

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Techniques for HLA antibody incompatible renal transplantation are used increasingly to allow live donation despite pre-formed donor-specific anti-HLA antibodies. Pre-transplant antibody removal is required in many patients, most commonly using plasma exchange (PEX). Here we describe the use of immunoglobulin specific immunoabsorption (IA).

Patients and methods

7 patients undergoing HLA incompatible transplantation were studied. 3 patients, all with positive CDC cross matches, received IA and 5 patients (2 CDC+ and 3 CDC- but with positive cross matches by flow cytometry) received PEX (1 CDC+ patient received both treatments). The case notes of all patients were reviewed, and FBC, coagulation, serum calcium, HLA antibody titres, and requirement for FFP recorded.

Results

The mean number of IA treatments was 11.3 (range 10-12), and PEX treatments 7.0 (4-11) on alternate days. The majority were pre-transplant, but all patients received 3 elective post-transplant treatments. The mean serum fibrinogen and PT before therapy were 3.9g/L (range 3.2-5.2) and 11.8 seconds (11-13). During IA treatment there was no change (3.8g/L and 11.7 seconds), but during PEX fibrinogen fell to 1.5g/L (0.6-2.2) and PT increased to 13.6 (12-15.2). All PEX but no IA patients required FFP prior to transplantation. There was no difference in FBC or serum calcium, and HLA antibody titre was reduced sufficiently to allow transplantation in all patients. 1 graft was lost in the PEX group due to bleeding. All 3 patients undergoing IA, but none receiving PEX, experienced C4d+ rejection.

Conclusion

Prolonged IA is safe and well tolerated, but probably no more effective than PEX in preventing antibody-mediated rejection.

P242

Soluble CD27 in Antibody Incompatible Transplantation

Rizwan Hamer[1,4], Laura Roche[3], Daniel Zehnder[1,4], Nithya Krishnan[1], Andrea Harmer[3], David Briggs[2], David Smillie[3], Guerman Molostvov[4], Rob Higgins[1]

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Introduction

CD27, a transmembrane glycoprotein, is a member of the TNF receptor superfamily and is preferentially expressed by natural killer cells, T cells and memory B cells. Activation of these cells results in cleavage of a 28-32 kilodalton soluble molecule (sCD27) into the circulation. Low levels of sCD27 are found in healthy individuals and has been used a disease marker of acute and chronic B cell malignancy. One previous study suggested a rise in sCD27 levels with rejection episodes. We sought to investigate sCD27 levels in patients undergoing HLA antibody-incompatible transplantation (AIT). Normal values are 215 ±57 U/ml.

Methods

We retrospectively analysed serum samples from 32 patients who had received (AIT). sCD27 was measured by ELISA on samples that had been stored at various time points including: Prior to starting treatment with plasmapheresis (as part of the AIT protocol), pre-transplantation, post-surgery, at onset of rise and at peak HLA antibody titres post-transplant, at onset and resolution of rejection and several weeks post-transplant.

Results

14/38 patients had an episode of antibody-mediated rejection (AMR). Mean pre-treatment levels was 567.18 U/ml (SEM ± 54.03) in rejectors and 661.32 U/ml (SEM ± 75.26) in non-rejectors (p=NS). There was a significant drop following surgery in rejectors (90.98 U/ml; $p<0.0005$) and in non-rejectors (87.35 U/ml; $p<0.0005$). There was no further rise in sCD27 levels with antibody re-synthesis in either group. No difference was seen between rejectors and non-rejectors.

Discussion

We report for the first time sCD27 levels in patients undergoing AIT. Highly sensitised patients with ESRF had higher values than normal individuals. Levels appeared to fall immediately after receipt of a renal transplant. Despite re-synthesis of donor specific antibodies following transplantation – to values higher than pre-transplant levels in some patients - there was no concomitant rise in sCD27 values. Larger studies will be needed to confirm these findings.

P243

sCD30 in HLA and ABO antibody incompatible renal transplantation

Nicos Kessaris[1], Pankaj Chandak[2], Robert Vaughan[2], Geoff Koffman[2], Nizam Mamode[2]

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Aim: To investigate sCD30 level before and after antibody incompatible renal transplantation. A high level of pre-transplant serum sCD30 in patients undergoing antibody compatible renal transplantation has been shown to be a risk factor for acute as well as chronic rejection.

Methods: The pre and post-transplant serum samples of 5 patients who underwent HLA-Incompatible and 3 who had ABO-Incompatible transplantation in a single unit were retrieved and analysed for sCD30 using ELISA. Pre-transplant sCD30 levels were also compared with those of 22 antibody compatible renal transplants.

Results: HLA-Incompatible group: There was a reduction in sCD30 after plasmapheresis. This was maintained over the first 6 months. Pre-transplantation sCD30 level was higher in the 2 patients that had rejection (mean 25.2U/ml) when compared with the other 3 patients (mean 6.7U/ml) in the same group but this difference was not significant (p=0.1). The creatinine of the 2 patients with rejection was also higher at 2 months (mean 241mmol/L) when compared with the 3 patients who had no rejection (mean 123mmol/L) but again this was not significant (p=0.1) when compared with pre-transplantation sCD30 level.

ABO-Incompatible group: Pre-transplantation sCD30 levels were higher in this group when compared with the HLA incompatible group. This may be a reflection of the process of ABO antibody removal, which was using Glycorex columns instead of plasmapheresis. There was no correlation between pre-transplant sCD30 and creatinine at two months as well as pre-transplant sCD30 and rejection at one year. The patient who rejected in this group had a higher sCD30 level at 6 months than the other two patients (172.5 U/ml versus 50 U/ml and 7.5 U/ml respectively). HLA and ABO compatible group: Pre-transplantation sCD30 level in this group did not correlate with creatinine (p=0.845), graft failure (p=0.464) or rejection rate (p=0.393) at one year. Pre-transplant sCD30 levels were significantly lower in the HLA antibody incompatible group (p<0.001) when compared with those of 22 antibody compatible renal transplant patients.

Conclusions: Even though the group samples were small, there was a trend between pre-transplant sCD30 and post-transplant creatinine as well as pre-transplant sCD30 and rejection in the HLA incompatible group.

Poster Session

Thursday 23 April

13:30 – 14:30

Immunosuppression 3

Moderator Mr Neil Parrott

P244

B cell depletion at induction increases acute cellular rejection

Menna Clatworthy[1], Chris Watson[2], Gemma Plotnek[1], Vicky Bardsley[3], Afzal Chaudhry[1], Andrew Bradley[2], Ken Smith[1]

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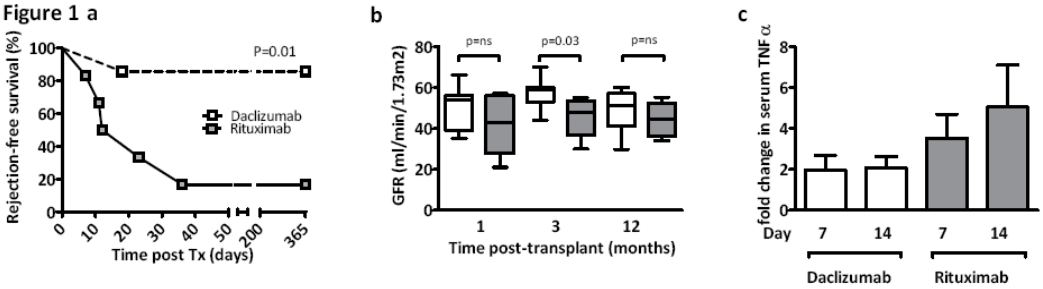
Introduction: In renal transplantation, acute cellular rejection (ACR) has been viewed as a T cell-dependent process but B cells are required for alloantibody production and may also play other roles, including alloantigen presentation to T cells. There are no published data on the use of B cell depletion at induction in non-sensitised patients in renal transplantation. Rituximab is a B cell-depleting, chimeric monoclonal antibody that binds CD20. We undertook a randomized controlled trial comparing the efficacy of rituximab to an anti-CD25 monoclonal antibody as induction therapy in renal transplantation. The study aimed to enlist 120 patients but was suspended following recruitment of the first 13 patients due to an excess incidence of ACR in the rituximab group.

Methods: 13 consecutive patients undergoing renal transplantation were randomised to receive rituximab (n=6, 10mg/kg IV day 0 and 7) or daclizumab (n=7, 1mg/kg IV day 0 and 7) at induction, followed by maintenance immunosuppression with tacrolimus (0.075mg/kg bd, target levels 8-15ng/ml) and mycophenolate mofetil (1g bd). Oral corticosteroids were not used.

Results: Five of the six patients (83%) who received rituximab experienced an episode of biopsy-proven acute rejection in the first three months post-transplant, compared to one of seven patients (14%) in the daclizumab arm (Figure 1a, p=0.01). Allograft function at 12 months was similar in both groups (figure1b).

Conclusions: Our results indicate that B cell depletion during the peri-transplant period appears to increase the risk of early acute cellular rejection. One possible explanation for this is that pro-inflammatory cytokine release associated with B cell depletion might prime antigen-presenting cells. Some patients treated with rituximab had elevated levels of proinflammatory cytokines (figure1c).

Figure 1 a



P245

The Withdrawal of Calcineurin Inhibitors Results in Improved Kidney Graft Function but an Increase in Acute Rejection Rates. A Meta-analysis of RCTs

Neil Russell[1,2], Andrew Bradley[1], Peter Morris[2]

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Introduction: The nephrotoxicity of calcineurin inhibitors (CNI) can result in decreased kidney graft function and may ultimately impact on long term graft survival. This has lead to the introduction of new immunosuppression protocols that reduce exposure to CNIs. Such protocols include the withdrawal of the CNI at a designated time point after transplantation. **Methods:** Detailed literature searches of the Medline, Embase and Cochrane databases were performed. RCTs that met the inclusion criteria were identified. The primary outcome of the meta-analysis was renal graft function. Secondary outcomes were acute rejection rates, patient and graft survival, BP, lipid profile and incidence of post transplant diabetes. Confidence intervals (CI) were set at 95%. **Results:** A total of 29 articles reporting on 16 trials including 2037 patients met the inclusion criteria. Creatinine was significantly improved with CNI withdrawal at 6 months (4 trials, 844 patients (pt), WMD -13.0µmol/l, CI -21.2 to -4.8), and at 12 months (7 trials, 1403 pt, WMD -11.8, CI -18.6 to -5.1). GFR was also improved with CNI withdrawal at 6 months (3 trials, 417 pt, WMD 6.1 ml/min, CI 4.2 to 9.7) and at 12 months (7 trials, 1201 pt, WMD 5.4, CI 3.5 to 7.4). Acute rejection was increased in the CNI withdrawal protocols at 12 months (11 trials, 1600 pt, RR 1.53, CI 1.3 to 1.9), and at 2 years (3 trials, 674 pt, RR 1.9, CI 1.4 to 2.7). There was no significant difference seen in graft or patient survival with the longest follow up being 5 years. No difference was seen in blood pressure or diabetes with withdrawal of CNI but both cholesterol (8 trials, 1117 pt, WMD 0.5mmol/l, CI 0.3 to 0.6) and lipids (6 trials, 1017 pt, WMD 0.3mmol/l, CI 0.2 to 0.5) were increased. **Conclusion:** Withdrawing CNIs results in better kidney graft function but an increased acute rejection.

P246

Sirolimus conversion post-renal transplantation – 5 year follow up data

Menna Clatworthy[1], Vicky Bradley[2], Elizabeth Wallin[1], Brian Camilleri[3], Paul Williams[3], J.Andrew Bradley[4], Chris Watson[4]

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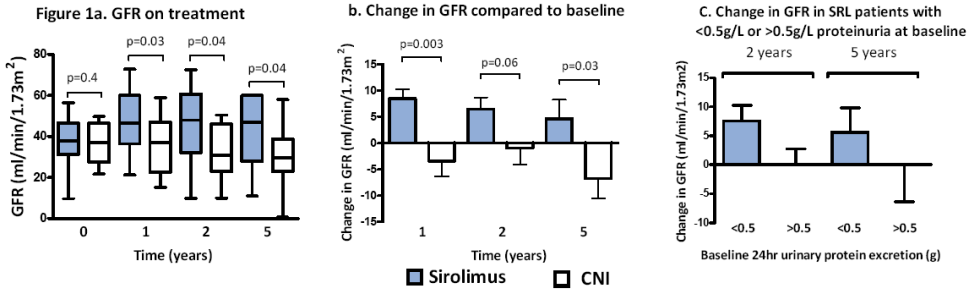
Introduction: Following renal transplantation, maintenance immunosuppression with calcineurin inhibitors (CNIs) is associated with nephrotoxicity and a decline in graft function. We aimed to assess whether conversion from a CNI-based regimen to a sirolimus-based regimen would reduce long-term renal dysfunction.

Methods: A single-centre randomised controlled trial was performed in which 40 renal transplant recipients (6 months-8 years post-transplant) were randomly assigned to continue on CNIs or to switch to sirolimus. The primary outcome was change in GFR at 12 months, which showed an improvement in sirolimus-treated patients (+12.9ml/min/1.74m^2, p<0.001)[1]. Here we report the 5 year follow-up data.

Results: 12/19 patients in the sirolimus arm remained on the drug, 11/19 patients in the CNI arm remained on the drug. There was no significant difference in patient survival or death adjusted allograft survival at 5 years between the sirolimus and CNI groups (89% versus 94%, p=0.96 and 94% versus 80% respectively (p=0.60). Mean GFR at conversion was 37.8 in sirolimus group and 36.1ml/ min/1.74m^2 in the CNI group. At 5 years, allograft function was significantly better in sirolimus-treated patients compared with controls (mean GFR 43.1 versus 30.9ml/min/1.73m^2 respectively p=0.03, figure1a). Patients who remained on sirolimus had an overall improvement in GFR whilst those on CNIs had a decline in GFR (figure1b). Patients with baseline proteinuria>0.5g/24hours had less improvement in GFR following conversion to sirolimus than those with less proteinuria (figure 1c).

Conclusions: Our study confirms that sirolimus conversion can lead to a long-term improvement in allograft function.



1. Am J Transplant 2005;5:2496-2503

P247

Conversion to Rapamycin in Clinical Practice; is it worth the fuss?

Argiris Asderakis, Mohamed Ilham, Rafael Chavez

Cardiff Transplant Unit, Cardiff, United Kingdom

Introduction: Conversion to rapamycin is performed to avoid calcineurin nephrotoxicity and despite recent evidence is still plagued with considerable controversy.

Aim, Patients and Methods: Study the indications and outcome of all patients *converted to rapamycin* from 4 weeks to 16 months, during an 18 months period, outside of a trial setting in a busy transplant centre. During this period 18 patients were converted to rapamycin from tacrolimus, 2 from AEB and in 2 patients rapamycin was added to tacrolimus. All patients had proteinuria less than 500 mg/day and had a recent biopsy that excluded rejection. Patients converted because of a previous tumour were excluded from the study. Median follow up was 12 months.

Results: 22 patients were converted for the following indications: 11 for slow decline of kidney function, 5 for 'failure to thrive', 2 for BK virus, 2 for ongoing rejection as add on and 2 conversions from AEB in trial patients.

Median conversion time was 4.7 months, median creatinine was 164 μm/l (range 121-297 μm/l), and median creatinine clearance at conversion was 37.4 ml/min.

The 6-month creatinine change was -29.8 μm/l (95% CI 9.2 -50.3 μm/l, p=0.007) and the 6 and 12-month change in creatinine clearance was +4.9 ml/min (p=0.02) and +6.7 ml/min respectively. Three patients (13.6%) were withdrawn from rapamycin (one with liquid form due to rejection, 1 where it was add on, and 1 for late sterile pneumonitis). There were 8 patients where creatinine clearance at conversion was less than 40 ml/min. Among them creatinine increased in 1 patient and dropped 50-110 μm/l in 7 patients. No patient was converted back for proteinuria. The 2 patients with BK viraemia had improvement in the kidney function and their BK virus PCR titer in the blood significantly dropped. Apart from the case of pneumonitis and 1 case of oral ulcer, which improved within 3 weeks, there were not any other significant adverse events.

Conclusion: In clinical practice, early *selective* conversion to rapamycin *for clear indications* (following a biopsy that excludes acute rejection) is associated with an improvement in creatinine and creatinine clearance. The results of this retrospective study do not necessarily predict what would have happened to another less selective cohort of kidney transplant recipients.

P248

Sirolimus after alemtuzemab induction: 3 year results of a prospective pilot study

Andrew Sutherland, Miguel Zilvetti, Jens Brockmann, Mary Simmonds, Sally Ruse, Andrea Devaney, Anand Muthasamy, Debarata Roy, Sanjay Sinha, Paul Harden, Anil Vaidya, Chris Darby, Peter Friend

Oxford Transplant Centre, Oxford, United Kingdom

***Background**:* The avoidance of long-term therapy with calcineurin-inhibitors is seen as a means of reducing the incidence of chronic allograft dysfunction. The use of mTOR inhibitors might achieve this, but sirolimus is difficult to use *de novo* because of side-effects and higher rejection rates. Our previous attempts to combine alemtuzemab with sirolimus were associated with unacceptable side effects. We have, therefore, investigated a modified strategy, avoiding early sirolimus exposure. Here we report the three year follow-up of this prospective pilot study in kidney transplantation.

***Methods**:* 30 patients were prospectively recruited to this single arm, open label trial. 15 patents received kidneys from non-heart-beating donors and 15 from heart-beating-donors. Immunosuppression comprised: induction with 2 doses of alemtuzemab; a 6-month period of tacrolimus and MMF; conversion to sirolimus and MMF; low-dose sirolimus monotherapy at 12 months. Outcome measures, including patient and graft survival, renal function, episodes of rejection, infection, and malignancy, were recorded for 3 years.

Results: All patients had immediate graft function. The 3-year patient survival was 90% with one peri-operative death due to myocardial infarction, one death due to PTLD 4 months post-operatively, and one death 2 years post transplant from a community-acquired pneumonia. All deaths occurred with functioning grafts. In the first six months there were 2 rejections, and no rejection in the second 6 months. However, of the first 17 patients to be reduced to sirolimus monotherapy at 12 months, three developed (reversible) acute rejection (17.6%). Therefore, for the remaining patients, MMF was continued at very low dose (250mg bd) from 12 months - there were no further rejections. In the surviving 27 patients, graft survival was 100% at 3 years, with a mean creatinine of 137.5 +/- 60.6 (SD) and estimated creatinine clearance of 64.0 +/- 23.4 (SD). Infectious complications were within the expected range but there was a higher than expected incidence of PTLD 3/30 (10%). At 3 years, 85% of patients are maintained on steroid and CNI-free immunosuppression.

Conclusions: A 6-month initial treatment with tacrolimus enables conversion to low dose sirolimus and MMF without the side effects seen in earlier protocols and with a low rejection rate. Withdrawal of MMF at 12 months was associated with rejection, which was avoided by maintaining very low-dose MMF in conjunction with sirolimus. The use of alemtuzemab and sirolimus in this way enables reliable and tolerable long-term immunosuppression without the chronic toxicity associated with calcineurin inhibitors or the side-effects of steroids.

P249

Sirolimus Conversion to achieve calcineurin-inhibitor-free, steroid-free Immunosuppression

Raman Dhanda, Judith Welham, Deyna Owais, Amita Singh, Mathew Howse, Abdel Hammad, Ali Bakran, Ajay Kumar Sharma

Transplant Unit, Royal Liverpool University Hospital, Liverpool, United Kingdom

Background:

Significant reductions in acute rejection (AR) of renal allograft were achieved after calcineurin-inhibitors (CNI) but it did not get translated into improvement in long term outcome. Steroid-free regimen would minimise metabolic complications. But the conversion to CNI free steroid –free regimen would entail the risk of graft loss due to AR.

Patients & Methods:

Indications for conversion to sirolimus plus mycophenolate mofetil (myfortic) and steroids (n=103): gout n=1, paranoid delusions n=2, hyperacute rejection n=1, cancer n=7, biopsy proven CAN n = 12, biopsy proven CNI toxicity/ischemia n=10, fall in creatinine clearance n=64, ATN n=4.

Results:

At 6 months following successful conversion 71% patients were steroid-free.

Group 1: Successful conversion, n=61; Group 2: Converted back to previous immunosuppression due to complications, n=20; Group 3: Failed, n=22

Group 1: Mean creatinine before conversion was 246µmol/L vs after conversion of 195µmol/L. p <0.05. Mean proteinuria before conversion was0.8 gm/day vs after conversion of 0.9gm/day, p=n.s.

Group 2: Mean creatinine before conversion was 318µmol/L vs after conversion of 216µmol/L, p=n.s. Mean proteinuria before conversion was 0.7gm/day vs after conversion of 1.5gm/day.P <0.05. Two patients developed AR, though completely reversible.

Group 3: Mean proteinuria before conversion was 1.9 gm/day vs after conversion of 3.2 gm/day. p <0.05.

Markers of Failure

Proteinuria >1 gm/day, 66% failed conversion.

Creatinine >300: 62% failed conversion

MMF ≥ 1.5 gm 80%, failed conversion

MMF ≥1.5 gm + Sirolimus >5 mg/day 90% failed conversion.

Conclusions

Sirolimus based immunosuppression is worth considering in patients with chronic graft nephropathy. Serum creatinine >200 µmol/L and proteinuria >0.8 gm/day is a contraindication to conversion.

P250

Earlier induction of cyclosporine for GVHD prevention in stem cell transplantation results with better engraftment, higher chronic GVHD and better survival.

Michael Shapira, Liliane Drey, Igor Resnick, Benjamin Gesundheit, Reuven Or

Department of Bone Marrow Transplantation & Cancer Immunotherapy, Hadassah – Hebrew University Medical Center, Jerusalem, Israel

Introduction: cyclosporine (CSA) is the backbone of GVHD prophylaxis. It is established that CSA levels in the 1st weeks after transplant are critical for the rate and severity of GVHD. Initially, we gave CSA starting on day -1 in all our protocols. However, 7 years ago, we have changed CSA initiation in most of our protocols to day -4 in order to have stable, controlled therapeutic blood levels of CSA prior to transplant. Patients and methods: the records of 1798 patients were analyzed. Out of them, we identified 2 groups of patients that received T-cell repleted grafts in which CSA was used for GVHD prevention, starting on days -1 or -4 (n=219 and 261 respectively). The guidelines for CSA cessation and DLI were uniform in both groups. Results: the groups were equal for age (p=0.83), sex (p=0.58), donor type (p=0.54), matching (p=0.98), disease (p=0.25) and disease status (p=0.42). The median time to ANC engraftment was 16 and 15 days in the CSA -1 and -4 groups respectively with a trend toward better engraftment with CSA -4 (figure 1A, P=0.07). However, platelet engraftment was significantly better with CSA -4, with a median of 14 and 12 days in the CSA -1 and -4 groups respectively (p=0.0005). One hundred and twelve and 138 patients developed aGVHD of any grade, respectively. Out of them 54% and 44% had severe aGVHD (p=0.45). The median time to aGVHD was similar, with a median of 29 and 28.5 days in the CSA -1 and -4 groups respectively (p=0.54). However, 64 and 102 patients developed cGVHD in the CSA -1 and -4 groups respectively (p=0.0002. Hazard ratio 0.5893, 95% CI 0.3693 to 0.7328). Of these patients, 46.8% and 40.2% of the patients had extensive cGVHD (p=0.70), respectively. The mortality in the groups was higher in the CSA -1 group (148/219 (67.6%) and 132/261 (50.5%). Shown in figure 2B, p=0.074. Hazard ratio 1.2370, 95% CI 0.9792 to 1.5828). Additionally, despite lower GVHD rate, GVHD associated death occurred more frequently in the CSA -1 group then the CSA -4 group (41/148 and 17/132 patients, p=0.02). Conclusion: we conclude that initiating CSA on day -4 improves engraftment, conversely increases the risk for cGVHD of any grade (possibly through prevention of tolerance), but reduces the risk of GVHD associated death and improves overall survival.

Poster Session

Wednesday 22 April

13:00 – 14:00

Kidney - Clinical 1

Moderator Mr Niaz Ahmed

P251

Renal Transplant Recipient Magnetic Resonance Angiography (MRA) of the Aorta and Iliacs: Correlation between Pre-operative Findings and Post-Transplant Outcomes

Michelle Luna, Christoph Juli, Steven Moser, David Taube, Vassilios Papalois

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Introduction: MRA is employed in many renal transplant centres as a pre-operative tool to assess aortic and iliac vasculature of potential recipients. Little or no clinical evidence exists to demonstrate any impact that MRA-detected findings such as atheroma, stenosis, tortuosity, thrombus or post-stenotic dilatation may have on transplant outcomes.

Methods: We conducted a study of all patients undergoing MRA prior to renal transplantation in our Centre over a 27-month period, from November 1st, 2005 to January 31st, 2008. MRA scans were anonymised and independently reviewed by two Consultant Radiologists. Findings for atheroma, tortuosity, thrombus and post-stenotic dilatation were recorded as being either present or absent; degree of stenosis was graded and scored on a scale of 0-3.

Results: Amongst 70 cases identified, there was a concordance level of 100% between the two reviewers. 19 individual pathologies were detected, across 16 of the original 70 scans, and these were assessed for correlation with transplant outcomes (patient and graft survival, acute tubular necrosis, polar graft infarction, transplant renal artery stenosis and new or worsened peripheral vascular disease). There was no correlation between the presence of 1 or more MRA findings and adverse transplant outcome, both when assessed individually and collectively. Analysis was also performed in a reverse fashion comparing the various individual (and collective) adverse outcomes against each radiological finding as well as the overall presence or absence of a radiological finding, also failing to yield any association.

Conclusions: Our study demonstrated that vascular pathology detected on pre-operative recipient MRA bears no correlation with adverse transplant outcomes, and thus, although it can certainly be useful in planning the operation, MRA should not be used to negatively influence or in any way preclude the decision to transplant.

P252

Reducing cold ischaemic time; assessing the effect of local and national initiatives at a single renal transplant centre

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Introduction : Cold ischaemic time (CIT) is an important modifiable risk factor for renal transplant survival. CIT is influenced by local and national factors. This study investigated the effect of individual changes at both a national and local level on CIT. Local changes included: loss of routine access to emergency theatre associated with a hot/cold surgical split on 2 different hospital sites and the introduction of a sample transit form that audits the timing of sample transit from the clinical area to the tissue typing laboratory. The national factor was the introduction of pre-emptive offering of renal allografts.

Methods: The effect of these changes on the mean time of (1) transit of blood/ spleen sample from clinical area to laboratory (2) perfusion of kidney to receipt of organ at the transplant centre (3) crossmatch result to start of operation ; were investigated

Results:

	Time interval	
	Before change	**After change**
Transit of specimen	44minutes	23 minutes
Perfusion to receipt of organ	8 hours	4 hours 42 minutes
Crossmatch to start of op.	2 hrs 48 minutes	3 hrs 50 minutes
CIT	19 hours 16 minutes	16 hours 36 minutes

Since the introduction of a hot/cold split at our Trust, the time taken from obtaining the crossmatch result to start of operation has significantly increased. However, the introduction of a Sample Transit Form has reduced the transit time of biological samples within the Trust. Furthermore, pre-emptive offering has reduced the time between kidney perfusion and receipt of organ at our centre. Overall, the CIT has been reduced significantly.

Conclusion: Although the introduction of a hot/cold surgical split has resulted in a delay in assessing theatre, other local and national initiatives have resulted in an overall reduction in the CIT in kidney transplantation at our centre.

P253

Should random glucose plasma measurement be abandoned in favour of oral glucose tolerance tests in the potential transplant recipient?

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Background: New Onset Diabetes After Transplantation (NODAT) is a common complication of renal transplantation associated with decreased graft and patient survival. In accordance with BTS guidelines potential recipients in our unit are screened for diabetes using random plasma glucose measurement. The World Health Organisation's (WHO) gold standard for the diagnosis of diabetes is the Oral Glucose Tolerance Test (OGTT). Other studies have calculated the sensitivity and specificity of random glucose and fasting glucose measurement to be 14.6% and 97.6% and 58.4% and 78.2%, respectively.

Patients and Methods: All non-diabetic patients on the living donor waiting list at North Bristol NHS Trust are approached to enter a prospective longitudinal study aiming to identify risk factors for NODAT. 12 potential recipients on the living donor waiting list have so far undergone a pre-transplant OGTT. The OGTT consists of a 75g glucose load after a 12 hour fast with glucose plasma measurement at zero and 120 minutes.

Results: Of the 12 patients studied so far, four patients were shown to have impaired glucose tolerance and one to be diabetic in the presence of normal random plasma glucose measurement and HbA_{1c}.

Discussion: Interpretation of the literature regarding NODAT is difficult due to different diagnostic criteria being used to define the clinical entity. Our findings endorse the weakness of random glucose as a screening tool for diabetes in potential renal recipients and we therefore propose that it be abandoned in favour of the OGTT. This would facilitate accurate monitoring and surveillance of impaired glucose tolerance or diabetes and help determine the true incidence of NODAT.

P254

Pre-emptive Renal Transplantation at Nottingham Renal Transplant Unit– barriers to success

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Background: Despite clear advantages of pre-emptive renal transplantation there are wide variations in referral practices amongst units. Pre-emptive transplantation accounted for 3.4 % of established renal failure patients in 2006. There are a number of barriers to pre-emptive transplantation which include practical dilemmas such as late referral and delayed transplant centre evaluation and ethical dilemmas amongst some physicians. In the last 3 years there has been a 3% increase in overall pre-emptive renal transplantation in the UK.

Aim: To identify characteristics of CKD patients on the pre-emptive renal transplant list and practices pertaining to referrals.

Methods: We performed a retrospective analysis of pre-emptive renal transplantation carried out at Nottingham Renal transplant unit last five years (n=37). We analysed demographic characteristics of pre-emptive renal transplant recipients and cross-sectional analyses of the prevalent CKD population to make comparisons between two cohorts. We excluded patients with an eGFR >20 ml/min/1.73m2 or age over 70 years (205/501patients were included). We used the UNOS threshold for pre-emptive listing (eGFR ≤20ml/min) and compared our data with BTS national datasets. Workup for transplantation is done by nephrologists and suitable patients are referred to the surgeons.

Results: All pre-emptive renal transplant recipients were Caucasian, 2/37 patients had diabetes, 62 % were male gender (23 versus 14), majority young 23/37 aged ≤ 20 and majority were from transplanting centre (33/37). Transplant activity was comparable to national average, however live donor pre-emptive transplants accounted for 25% compared to national average of 31%. Of the CKD cohort 106/205 had eGFR ≤ 15 and majority of the CKD patients on the list had eGFR ≤ 15 (16/18). The majority of CKD patients on the list were Caucasian (88 %) and aged between 40-50 years whilst patients over 65 accounted for only 1.5 % (1/66). Overall 9% of CKD patients were on the pre-emptive waiting list (18/205), another 9 % were waiting to see a transplant surgeon and 10 % were being worked up by physicians. In 19% of cases there was no documentation of a plan for listing. Out of 73 patients with diabetes only 3 (4%) were on the list including 2 on SPK. They were all Type 1 though the majority of the CKD cohort with diabetes had Type 2 (66%).

Conclusions: Patients who had pre-emptive transplant were younger, more male, all Caucasians and mainly from transplanting centre. 9% of Predialysis patients were listed at Nottingham. Though there are no national recommendations, we believe about 20-30% of CKD patients will be eligible for pre-emptive transplant listing considering patient numbers currently on the work up pathway. At our centre there have been theatre capacity issues affecting the live donor programme. We feel further work needs to be done regarding threshold for listing and investigation in to other barriers.

P255

Pelvic Vascular Calcification in Renal Patients Awaiting Transplantation – Controllable Risk Factors a West of Scotland Perspective

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Vascular disease is common in patients awaiting and receiving renal transplants, potentially leading to significant peri-operative complications, reduced transplant function and graft survival. Initially in the transplant assessment phase, pelvic calcification is assessed via a pelvic x-ray. After which if significant vascular disease is observed a CT Angiography is requested. The purpose of this study was to ascertain if there any controllable risk factors in the incidence of moderate to severe vascular calcification in our pre-transplant population.

Potential renal transplant patients with 1 or more risk factors for vascular disease were included in the study n=145. Risk factors included diabetes mellitus, hypertension, hyperparathyroidism, smoking history, other vascular disease, and previous transplant. Of those with risk factors 80/145 (55%) have no significant vascular calcification whilst 65/145 (45%) have moderate to severe vascular calcification of the external iliacs as judged by an independent radiologist.

The most significant potentially controllable independent predictor for moderate to severe calcification as found by logistic regression is of duration of dialysis (OR: 1.1/month p=0.002). Two other significant findings related to external iliac calcification are of the initial calcium phosphate product pre dialysis (p=0.01) and the difference between the calcium phosphate product pre dialysis and at the time of x-ray (p= 0.02). The risk factors associated with vascular calcification included vascular disease at other sites (p=0.007) and diabetes mellitus (p=0.05). There also appeared to be an association between the centre of dialysis and the number of patients with vascular calcification.

Our results suggest that the duration of dialysis and the calcium phosphate product pre-dialysis has a bearing on the amount of pelvic vascular calcification. Therefore these factors should be monitored and manipulated. With the hope that pelvic vascular calcification will be reduced, prolonging graft survival in our renal transplant population.

P256

Transplantation in Adults with Primary Hyperoxaluria: Experience with 5 cases.

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Introduction The incidence of primary Hyperoxaluria with End Stage Renal Failure (ESRF) in Europe remains around 1:120 000, with almost all patients developing (80%) ESRF by the third decade. Primary Hyperoxaluria type 1 (PH1) is an autosomal recessive metabolic disorder caused by deficiency of the alanine-glyoxylate aminotransferase whilst Primary Hyperoxaluria type 2 (PH2) is caused by a defective D-glycerate dehydrogenase. Kidney transplantation alone is associated with a high rate of recurrence and in many cases early graft loss. Liver transplantation offers the possibility of correcting the metabolic defect. Transplantation is a definitive therapeutic option but requires critical timing.

Methods A retrospective review of five cases of Primary Hyperoxaluria managed at a major renal unit was performed. The cases were evaluated with a focus on presentation, symptoms, dialysis, transplantation, recurrence of disease and retransplantation as outcome measures.

Results The 5 patients had a mean age of 32.2 years (range 28-40) at time of first transplantation. The female to male ratio was 3:2. The common presenting symptoms were urolithiasis (4), nephrocalcinosis (3), recurrent urinary tract infections (2) and uraemia (1). There was a significant delay in diagnosis in 2 patients. One was diagnosed after a first kidney transplant and another after a second kidney transplant. They all had signs of impending renal failure (2) or ESRF (3) at diagnosis. 4 patients had PH1 and one male had PH2. All patients were on haemodialysis before transplantation. 2 patients had previous native nephrectomy (one unilateral and one bilateral). 3 patients had kidney only transplants (one live donor, 2 deceased donor) and 2 had segmental liver followed by delayed kidney transplantation. All 3 kidney alone (100%) have failed, the first at 3 weeks (oxalate nephrocalcinosis and urolithiasis) the second at 9 years (recurrent urolithiasis) and the third at 13 years (chronic allograft nephropathy). It is of interest that the final patient had a planned month of intensive daily haemodialysis before live donor kidney transplantation. Out of these three patients, one is now awaiting a live donor transplant, one underwent kidney alone retransplantation (failed 5 years later) and one had a combined deceased donor liver and kidney transplantation (remains well at 4 years). The 2 segmental liver sequential kidney transplant recipients remain well at 1 year and 3 years.

Conclusions Primary Hyperoxaluria though rare should be considered in calculus ESRF and continues to be a management challenge. Isolated deceased donor kidney transplantation invariably fails. Combined liver-kidney transplantation may be a better choice as the primary transplant procedure although living donor kidney transplantation after intensive dialysis is an option. The indication and timing for pre-emptive liver or liver followed by delayed kidney transplantation remains a matter of debate.

P257

Charlson Comorbidity Index - a simple clinical tool to determine suitability for the renal transplant waiting list

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Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Background

Various comorbidity scores have been used in renal dialysis patients, but their applicability in the renal transplant population has not been validated.

Aim

The aim of this study was to evaluate the use of Charlson Comorbidity Index (CCI) as a predictive tool to determine whether patients are suitable for the renal transplant waiting list.

Material and Methods

1530 patients assessed for transplantation in 13 transplant centres across the United Kingdom were included in this prospective multi-centre study. Demographic and comorbidity data were prospectively collected over a one year period from October 2006 to September 2007. Charlson Comorbidity Index was calculated for every patient. Listing data was updated on the 31st December 2008. Cox Regression and logistic regression analysis were used for analysis.

Results

45% patients in the study had at least one comorbid condition. The median CCI of the cohort was 4 (2-12, range). 98% of patients between 18-34 years had a CCI of 2-4 as opposed to a CCI of >5 in all patients over 65 years of age. There was, however, no significant difference in the CCI score between males and females ($p=0.12$) or based on patient's ethnicity ($p=0.81$). 92% of patients with diabetes in the study had a CCI score of 5 or more. Patients who were placed on the waiting list had significantly lower CCI compared to those who were not listed ($p<0.0001$). A CCI score of 5 and above was significantly associated with reduced chances of access to the waiting list. (CCI 5-8, HR=0.68, CI=0.6-0.7; CCI ≥9, HR=0.3, CI=0.1-0.8). On multivariate analysis Asian ethnicity, CCI and transplant centre were independent predictors of access to the waiting list. With an increase in CCI score by 1, the chances of listing at one year after assessment are reduced by 12%.

Conclusion

Charlson Comorbidity Index is a simple clinical tool to quantify patient comorbidity and can be used to determine if a patient is suitable for the waiting list.

P258

Pre-emptive assessment and renal transplantation in the United Kingdom

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Background: Pre-emptive transplantation offers patients the best outcome, avoiding the ill effects of dialysis.

Aim: The study investigated the pre-emptive assessment and subsequent renal transplantation practice in the United Kingdom.

Methods: Demographic, comorbidity, listing and transplant data for all patients assessed for transplantation in 13 centres in the United Kingdom were collected prospectively between 01.10.2006 and 30.09.2007. The Charlson Comorbidity Index (CCI) was calculated for each patient. The listing and transplantation status was updated on 31.12.2008.

Results: 632 (41.3%) patients were assessed pre-emptively with significant variations between centres ($p<0.001$, $\chi 2$ test). The median age of patients assessed pre-emptively was 51 years (17-77 years). 27% patients were in the 55-64 years age group. The median Charlson Comorbidity Index (CCI) was 4 (2-11, range), with significant variations ($p<0.0001$ χ^2 test) between centres. 470 patients (75%) have been placed on the list by the end of study follow-up, whilst in the remainder, the reason for not listing included: too early for transplantation, excessive comorbidity, high BMI, patient refusal or compliance issues.

161 patients (34%) have been transplanted by 31st of December 2008. 64 (40%) received a cadaveric kidney and 97 (60%) received a living donor transplant. 39% of the transplanted patients were never placed on the waiting list and all received a living donor kidney. These patients were transplanted sooner compared to those who have been placed on the waiting list (9 mo vs. 12 mo, $p=0.003$), but had comparable Charlson Comorbidity Index scores. The time from assessment to listing was shorter for the patients who eventually received a cadaveric kidney compared to living donor recipients (3 mo vs. 4.4 mo, $p=0.01$).

Conclusion: There are significant centre variations with regards to pre-emptive assessment and transplantation practice in the UK. Some patients are simultaneously considered for a cadaveric or living donor transplant, whilst others are only offered a living donor option.

Poster Session

Thursday 23 April

13:30 – 14:30

Preservation

Moderator Prof Steve Wigmore

P259

An Ex-Vivo Model For Hypothermic Pulsatile Perfusion Of Porcine Pancreata

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Introduction: Hypothermic machine perfusion (HMP) is a well established preservation method for kidneys that allows better preservation over longer periods and pre-transplant assessment of graft viability. HMP has only sporadically been used for pancreatic grafts. The aim of this study was to establish a HMP model for porcine pancreas perfusion.

Methods: 15 porcine pancreata were obtained from an animal source unit. Each organ was subjected to 25 minutes of warm ischemia and 2.5 hours of cold ischemia before undergoing meticulous bench work preparation and perfusion via an aortic segment on the RM3 perfusion machine with University of Wisconsin solution. Perfusion variables (temperature-°C, systolic perfusion pressure-mmHg, flow volume-ml/min, resistance-mmHg/ml/min) were recorded every 30 minutes and perfusate samples were collected every 15 minutes for measuring amylase as an indicator of tissue damage. Histological sections were assessed pre- and post-perfusion for each pancreas using a semiquantitative scoring scale: acinar cell necrosis (0-4), islet cell necrosis (0-3), inflammation (0-3) and oedema (0-3).

Results: HMP time was set at 315 minutes and all grafts were maintained at 4°C-10°C. The results were as follows (range, mean $\pm$ SD): systolic perfusion pressures were 5-13 mmHg (9.61 $\pm$ 3.25) during the first 60 minutes (priming) and 15-23 mmHg (21.07 $\pm$ 4.261) during the maintenance period of perfusion. Target flow volumes reached 141-152 ml/min (147.6 $\pm$ 8.969) at 60 pulses per min. Intra-pancreatic resistance decreased throughout priming to 0.03-0.09 mmHg/ml/min (0.083 $\pm$ 0.042) and remained unchanged till completion of perfusion. Pancreatic weight increase varied from 3.2% to 18.3% (13.36 $\pm$ 4.961). Perfusate amylase (IU/L) was significantly reduced at the end of HMP (22488 $\pm$ 17034 vs 1457.5 $\pm$ 631.07, p=0.04). There was a significant post-perfusion reduction in islet and acinar cell necrosis (p=0.001 and p=0.01 respectively).

Conclusions: We have developed a model of machine perfusion for porcine pancreata which is simple, reliable and protects graft viability. This model can be used in further studies aiming to improve the quality of pancreas preservation, assessing viability and improving the condition of borderline pancreatic grafts.

P260

The safety and efficacy of normothermic preservation in an experimental autotransplant model of non heart-beating donor kidneys

Sarah Hosgood[1], Adam Barlow[1], Phillip Yates[1], Maarten Snoeijs[2], Ernest van Heurn[2], Michael Nicholson[1]

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Introduction

The addition a short period of Normothermic Preservation (NP) after hypothermic storage may improve the graft function of non-heart-beating-donor (NHBD) kidneys. This study assessed the safety and efficacy of NP in a porcine autotransplant model.

Methods

Kidneys were subjected to 30min of warm ischemia then preserved by hypothermic machine perfusion (HMP) for a total period of 22h or 20h HMP followed by 2h of NP using autologous blood. Kidneys were then re-implanted, a contralateral nephrectomy performed and renal function measured over 10 days.

Results

During HMP intra-renal resistance fell to a similar level in both the HMP and NP groups (0.46 ± 0.11, 0.45 ± 0.19mmHg/min; P =0.522). During NP kidneys demonstrated a sustained low level of renal function (Table 1). Post-transplant, 4/6 animals survived in the NP group compared to 5/6 in the HMP group (P=1.00). Creatinine (Cr) levels fell below 250µmol/L in the four surviving animals in the NP group compared to 2/5 of the HMP group. There was no significant difference in the level of peak Cr [(HMP) 1736 ± 866, (NP) 1553 ± 516µmol/L; P=>0.05].

	60 minute	120 minute
Intra-renal resistance (mmHg/min)	1.04 ± 0.27	1.09 ± 0.23
O_2 Consumption (ml/min/g)	31.77 ± 12.02	28.30 ± 6.76
Cr Clearance (µmol/L;ml/min/100g)	2.23 ± 2.35	2.26 ± 1.88

Table 1. Mean functional parameters during NP

Conclusion

A period of NP staged at the end of the renal preservation period in NHBD kidneys did not improve early post-transplant function but did not have any adverse effects. NP could prove to be a useful technique to predetermine graft function and allow pre-transplant modification of organs.

P261

Non heart-beating porcine pancreas preservation prior to islet isolation: a comparison of the two layered method and pulsatile machine perfusion.

Dan Ridgway[1], Michael Nicholson[1], Rachel Kimber[1], Sue Swift[1], Steve White[2]

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Pancreas and islet cell transplantation are treatment modalities which restore islet mass and offer a potential cure for diabetes. Each requires efficient preservation of the donor pancreas in order to maximise graft function. The detailed sequelae of pulsatile machine perfusive preservation (PMP) in porcine pancreatic preservation has not been established. This study investigates the effects of PMP, and compares PMP to two-layer method (TLM) and static cold storage (CS) preservation in a pre-clinical non heartbeating donor porcine model.

PMP resulted in significantly lower islet yields compared to CS (mean 1250 *vs* 3280 IEQ/g pancreas), and significantly increased gradient contamination compared to both CS and TLM pancreata (mean amylase content 36% *vs* 22% and 25% respectively). There were increases in the ADP:ATP ratio as the duration of preservation increased in all groups. Moreover TLM showed significantly higher tissue ADP:ATP ratios compared to CS and TLM after 4 hours of preservation (mean difference 0.85 and 1.03 respectively).

PMP is a means of preserving the NHBD pancreas which results in lower islet yields and a high degree of gradient contamination compared to conventional methods. This may arise from bioenergetic preservation injuries manifesting as an increased tissue ADP:ATP ratio.

P262

Improved preservation of non heart-beating-donor pancreases prior to islet isolation using portal venous oxygen persufflation

Mettu Reddy[1,3], Aimee Kibondo[3], Ali Aldibbiat[2], Susan Stamp[2], Brian Shenton[2], James Shaw[2], Noel Carter[3], Anne Cunningham[3], David Talbot[1,3]

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Introduction: Pancreases from non-heart-beating-donors (NHBD) are not routinely used for islet transplantation due to low islet yield. We investigate the effect of preservation with portal venous oxygen persufflation (PVOP) on the islet yield, islet in-vitro function and reperfusion injury in an experimental NHBD rat pancreas model

Methods: Pancreases were retrieved from male Wistar rats (350-450g) after 35 minutes of warm ischaemia. In one set of experiments, pancreases were preserved at 4◦C for 5 hours by either simple cold storage in UW solution (Group SCS) or underwent PVOP with 100% oxygen (10-15mmHg) through the portal vein (Group PVOP). All pancreases underwent islet isolation by standard technique. Islet yield and in-vitro function (static glucose stimulated insulin secretion test) were compared between the two preservation groups. In another set of experiments, retrieved pancreases were preserved overnight (16 hours) by static cold storage or PVOP. The pancreases then underwent warm oxygenated reperfusion for one hour in Krebs-Henseleit buffer. Portal venous effluent was collected during reperfusion at timed intervals for measurement of amylase/lipase, lactate, pyruvate and glycerol. Biopsies at end of reperfusion were snap frozen and homogenized. Tissue lysates underwent estimation of products of lipid peroxidation by TBARS assay.

Results: Within the two preservation groups, the purified islet count and IEQ of VOP (265±93,708±394) was better than SCS (175±73,322±140) ($p<0.05$). Islets from PVOP had better viability (79±4% vs. 74±5%), lesser fragmentation and higher percentage of functioning islets i.e. stimulation index >1 (7/8 vs 4/8). After warm reperfusion, there was no significant difference in lipid peroxidation, effluent amylase &lipase levels and effluent glycerol & lactate-pyruvate ratios between the two preservation groups.

Conclusions: Preservation with PVOP improved the number and quality of islets when compared to SCS. Prolonged preservation with PVOP does not increase the extent of reperfusion injury in the pancreas.

P263

Normothermic perfusion can be used to predict the viability of porcine livers

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Aim: To evaluate whether parameters measured during normothermic preservation can predict the post-transplant viability of donor livers.

Background: The shortage of donors requires the transplantation of more marginal donor organs but conventional cold preservation does not allow reliable assessment of viability prior to transplantation. Therefore, many such organs, particularly from non-heart-beating donors (NHBD), are not transplanted because of concern regarding viability. Normothermic preservation allows the measurement of organ function during preservation and may enable assessment of viability such that a reliable decision can be made before committing a patient to transplantation.

Methods: Porcine heart-beating-donor (HBD) livers (n=7) and NHBD livers subjected to 40 minutes (NHBD40, n=6) and 60 minutes (NHBD60, N=4) of warm ischaemia were preserved for 20 hours by normothermic preservation and transplanted. All pigs in the NHBD 60 group died of liver failure in contrast to none in the HBD and NHBD40 groups. Hence HBD and NHBD 40 groups were deemed 'successful' groups and the NHBD 60 group 'unsuccessful'. Parameters measured during normothermic perfusion were analysed and compared between successful and unsuccessful groups as potential markers to predict post-transplant liver viability.

Results: The following parameters were highly predictive of post-transplant outcome within four hours of starting normothermic perfusion: Rate of bile production (P=0.003); maintenance of acid-base homeostasis in the perfusate (base excess, P=0.02); markers of cellular injury (ALT P=0.015, AST P=0.01,LDH P=0.006, hyaluronic acid P=0.006); perfusion flow dynamics (portal pressure P=0.006, portal-hepatic venous resistance P=0.006).

Conclusions: The post-transplant viability of NHBD livers can be predicted by measurement of biochemical, and haemodynamic parameters during normothermic preservation. This could allow the safe transplantation of many marginal donor organs currently not utilised.

P264

A simplified circuit design for oxygenated sanguinous perfusion of the non-heart-beating donor liver, kidney and pancreas

Christopher Ray[1], Aditya Kanwar[1], Soroush Sohrabi[1], Alex Navarro[1], M S Noormohamed[2], Stephen Ray[1], Susan Stamp[2], Noel Carter[3], Brian Shenton[2], Anne Cunningham[3], John Hayden-Smith[1], Steve White[1], David Talbot[1]

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Aim To re-animate the retrieved organs from a porcine non-heart-beating donor model to simulate transplant and to assess viability

Methods We designed a novel circuit that can be quickly adapted for normo-thermic sanguinous perfusion of the liver, kidney or pancreas.

A closed system was employed, thereby negating the need for a reservoir, and as such simplifying both the design and operation of the circuit.

Pulsatile flow was delivered to the organs at physiological rates. Pressure changes were recorded as markers of vascular resistance and organ health. The organs were perfused with a mixture of whole blood and AQIX RS-I solution in a ratio of 1:5 respectively, with the addition of heparin.

The organ sat in a purpose-sized container, with venous effluent drained from the base of this via a filter. The organ receptacle was housed in incubated water.

The blood perfusion mixture was oxygenated with a paediatric Medlite 2800 oxygenator, in which an integral heat exchange chamber allows temperature control.

After use, the circuit was rapidly exchanged and re-primed with fresh perfusion fluid. Simple changes in connectors and exclusion of the second organ inflow limb, allowed varying sized organ vessels to be quickly changed.

Sampling ports were used to collect blood for ABG analysis. Microdialysis catheters were inserted into the organs to capture real-time markers of ischaemia.

Results In a comparison of ECMO versus cooling in a porcine Maastricht category II NHBD model, oxygen consumption was found to be markedly higher in the cold preserved organs compared with ECMO. Initial results suggest this is a marker of organ damage.

Conclusion The circuit is a simple and reproducible design that allows sanguinous organ re-animation and viability testing.

Poster Session

Wednesday 22 April

13:00 – 14:00

Immunosuppression 1

Moderator Mr Rafael Chavez

P265

Health-Related Quality Of Life Maintained Despite Increase In Mycophenolic Acid (MPA) Dose Following Conversion From Mycophenolate Mofetil (MMF) To Enteric-Coated Mycophenolate Sodium (EC-MPS): A Randomized, Multicenter Trial In Kidney Transplant Recipients

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Introduction: Poor tolerability frequently leads to MMF dose reduction or discontinuation, adversely affecting efficacy, while gastrointestinal (GI) side effects negatively affect quality of life (QoL). Conversion to EC-MPS may permit increased dosing but QoL should be preserved. **Methods:** In a prospective trial at 19 UK centers, MMF-treated maintenance kidney transplant recipients experiencing GI complications, or who had previously required MMF dose reduction due to GI events, were randomized to continue MMF or convert to EC-MPS (week 1). At week 3, MPA dose was adjusted in both groups to achieve the highest tolerated dose. Patients were followed to week 13 i.e. 12 weeks post-randomization. Symptom burden and GI-specific health-related QoL were assessed at weeks 1 and 12 using The Gastrointestinal Symptom Rating Scale (GSRS) and the Gastrointestinal Quality of Life Index (GIQLI), respectively. The SF-36 health survey was used to assess global well-being. **Results:** The intent-to-treat population included 68 EC-MPS and 61 MMF patients. Groups were well-matched other than more EC-MPS patients <65 years old. Significantly more patients randomized to EC-MPS than MMF were receiving an increased MPA dose (i.e. an increase of EC-MPS ≥180mg/day or MMF ≥250mg/day) at week 13 vs. baseline: EC-MPS 47.1%, MMF 16.4%; p<0.001. At week 3, there was a significantly greater improvement from baseline with EC-MPS vs. MMF for GSRS total score (-0.50 vs. -0.07, p=0.004) and GIQLI total score (8.9 vs. 1.9, p=0.037). At week 13, following MPA dose adjustments, the change from baseline was not significantly different between groups (GSRS -0.49 vs. -0.22, n.s.; GIQLI 8.2 vs. 4.3, n.s.; EC-MPS and MMF, respectively). The improvement in SF-36 physical composite score was also greater in the EC-MPS cohort vs. MMF at week 3 (1.93 vs. -0.45, p=0.045), and was similar at week 13 (2.56 vs. 0.58, n.s.). The change in SF-36 mental composite score did not differ significantly between groups at either timepoint. **Conclusions:** Despite almost threefold more EC-MPS patients achieving an MPA dose increase than MMF-treated patients, all health-related QoL measures were similar in the EC-MPS and MMF groups at 12 weeks post-randomization.

P266

Incidence of new onset diabetes mellitus in de novo renal transplant recipients treated with enteric-coated mycophenolate sodium in combination with reduced or standard tacrolimus target levels: Results of a 6-month randomized study

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This study was designed to investigate the safety and efficacy of *myfortic*® (enteric-coated mycophenolate sodium; EC-MPS) in combination with tacrolimus (tac) and addressed the possibility to preserve renal function by reducing exposure to tac while keeping the efficacy level. **Methods:** In a 6-month, multicentre, randomised trial, de novo renal transplant patients (n=292) were randomized (1:1) to one of two regimens, all receiving basiliximab, EC-MPS 720 mg twice daily and corticosteroids (CS): Group A was treated with reduced tac (target trough levels of 5-9 ng/mL, first 3 months, and 3-6 ng/mL, subsequent 3 months), Group B with standard-dose tac (10-15 ng/mL followed by 8-12 ng/mL). Primary endpoint was Glomerular Filtration Rate (GFR) at 6 months calculated using the Nankivell formula. Here, the incidences of new onset diabetes mellitus (NODM) are presented. **Results:** Baseline patient characteristics of the treatment groups were similar. The mean daily dose of EC-MPS was comparable between Group A and B (1296mg and 1325mg, respectively), and cumulative steroids were also similar (3033mg and 3020mg, respectively). The incidence of NODM, assessed by means of oral glucose tolerance testing and/or fasting glucose measurements or by the need for the use of hypoglycemic treatment, was significantly lower in the reduced-dose tac group than in the standard-dose tac group (17% vs. 30%; p=0.016); 11% and 17% patients respectively, received hypoglycemic treatment for a minimum period of 14 consecutive days (ns). The overall safety profile was comparable between treatment groups. **Conclusions:** Results from this study showed a clinically important lower incidence of NODM in patients receiving EC-MPS with reduced tac levels as compared to those with standard tac levels.

P267

Initial Experience with Advagraf in Renal Transplantation.

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Introduction: Advagraf is the new modified release version of tacrolimus (tac) which requires once daily dosing as compared to the traditional Prograf twice daily dosing**.** We report the largest single centre UK experience using Advagraf in renal transplantation.

Methods: During the 13 month period to 31/10/2008, 134 renal transplants were carried out at our institution, of which 64 (48%) received Advagraf immunosuppression, together with anti-CD25 induction, an anti-proliferative (azathioprine or MMF) and corticosteroids.

Results: Dose adjustment based on blood levels takes longer (36 hours) than with Prograf (12 hours) and a learning experience on optimal dosing occurred. Advagraf was discontinued in 12(19%) of the 64 patients and discontinuation occurred mostly (9/12 patients) during the first 4 months of our experience with the drug. This was mostly in patients with delayed graft function (6/9 of the patients) where our standard practice is to halve the dose of calcineurin inhibitor and we were not sufficiently confident during our early experience to adjust the dose of Advagraf. Advagraf was also discontinued because of failure to swallow tablets (one patient), failure to absorb the drug due to severe diabetic gastroparesis (one patient) and neurological side-effects (two patients). Two patients developed graft dysfunction attributed to calcineurin inhibitor toxicity on biopsy and had Advagraf stopped.

Of the remaining 52 patients receiving Advagraf, three had the Advagraf treatment temporarily stopped but then recommenced.

Thirteen (25%) of the 52 patients had 17 episodes of rejection (15 biopsy proven) within the first 6 months. Currently graft survival is 98%.

Conclusion: Our experience with Advagraf is generally favourable. It has the advantage of once daily dosing and provides a satisfactory alternative to Prograf.

P268

A 6-month interim analysis to compare viral kinetics and liver function in steroid-treated and steroid-free cohorts in calcineurin inhibitor (CNI)-treated patients included in the REFINE trial.

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REFINE is a 12-month treatment, 24-month follow up multicentre, randomised, open-label trial which compares the incidence of stage ≥2 hepatic fibrosis in adult patients transplanted for hepatitis C cirrhosis and receiving either cyclosporine micro-emulsion (CsA-ME) or tacrolimus (tac). At study start, centres opted to treat all randomised patients with either an adjunct immunosuppressive regimen with steroids (Cohort A) or IL-2R antagonists + MPA without steroids (Cohort B). Key exclusion criteria were multiorgan transplant recipients, HBV/HIV co-infected patients, and serum creatinine ≥2.0 mg/dL prior to transplantation. A total of 303 liver transplant recipients have been randomised to the treatment groups, CsA-ME or tac. This abstract includes data from a planned interim analysis, comparing six-month data for cohorts A and B with regards to viral kinetics, liver function tests, and treatment failure. In order to maintain the integrity of the study, results by treatment group were not revealed during data analysis, thus each cohort includes patients on either CNI. Results: 177 eligible patients treated for 6 months, 131 in cohort A and 46 in cohort B were included. Demographics were comparable. The majority of donors were deceased, heart beating (86% vs. 94%). Overall, the results of baseline liver biochemistry were comparable in both cohorts. After start of treatment, albumin was consistently higher in Cohort B ($p<0.05$ at Day 2, Month 1, 2, 3 and 6), but there were no consistent, sustained significant differences in SGPT, SGOT and bilirubin. Viral kinetics data were not available for all patients, and HCV RNA was lower in Cohort B only at Month 1 ($p<0.01$). The incidence of treated acute rejection was 16% in both cohorts. Graft loss or death was 7% in Cohort A vs. 11% in Cohort B. The overall incidences of adverse events and serious adverse events were comparable between cohorts. Conclusions: Liver function tests were comparable in HCV-positive liver transplant recipients treated with CNIs in combination with steroids or as part of a steroid-free regimen with IL-2R antagonists plus MPA. Efficacy and safety profiles were similar in both cohorts.

P269

Hypogammaglobulinemia and bronchiectasis in mycophenolate mofetil treated renal transplant recipients single centre experience

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INTRODUCTION AND AIMS: Mycophenolate Mofetil (MMF) is a relatively new immunosuppressant has made a significant impact on the management of solid-organ transplantation and in the treatment of autoimmune conditions such as Systemic Lupus Erythematosus. In general, hypogammaglobulinemia predisposes to recurrent infections primarily localized to the upper and lower airways. Chronic recurrent pulmonary infection and hypogammaglobulinemia is a known risk factor for bronchiectasis in children and adults. The aim of our study was to determine the incidence of hypogammaglobulinemia and bronchiectasis in renal transplant recipients receiving MMF.

METHODS: We performed a retrospective analysis of all renal transplant patients in our units who were on MMF. We identified 289 transplant patients on MMF. We collected demographic, clinical, radiological and laboratory data from case notes and electronic medical records. Imaging examined included chest radiographs and computerised tomography scans. Laboratory data included creatinine levels, serum immunoglobulin levels, C-reactive protein, full blood count and alpha-1-antitrypsin level.

RESULTS: 23 patients (8%) were identified to have recurrent severe chest infection (more than 2 episodes) after introduction of MMF. Respiratory symptoms started at a range of 12 to 96 months after start of MMF treatment. Pulmonary lesions fulfilled clinical, radiographic and computerised tomographic criteria for bronchiectasis in 6 patients (2 % total). All the 6 patients with bronchiectasis had low serum IgG levels. Patient E did not receive MMF following the first transplant and interestingly experienced pulmonary complaints 12 months after the introduction of MMF with his second transplant. Alpha-1-antitrypsin level was also found to be low at 0.74 g/L (ref range 1.1-2). 2 Patients received parenteral immunoglobulin replacement and MMF was stopped in all cases.

CONCLUSIONS: These cases would suggest that assessment of immunoglobulin levels pre-transplant and infrequent but regular monitoring post transplantation would be prudent clinical practice in all patients being maintained on MMF, with consideration given to dose or drug alteration in the context of sustained hypogammaglobulinemia in a similar manner to the established clinical response in the context of MMF and leukopenia.

P270

Does dosing based on actual body weight lead to high initial tacrolimus levels in overweight renal transplant recipients? – a retrospective analysis of a single centre's experience

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Background: It has been suggested through observations in practice that dosing tacrolimus according to actual body weight (ABW) in overweight renal transplant recipients may result in a high first trough plasma concentration level. The latter has been associated with an increased risk of post-transplant diabetes mellitus. **Aim:** To explore the relationship between weight of renal transplant recipients (which dictates the initial tacrolimus doses) and first trough tacrolimus level (FK level). **Methods:** A single centre retrospective analysis was conducted using data gathered from patients' medical notes and electronic laboratory records. The primary objectives were to examine the relationship (if any) between first FK level and:(1) ABW; (2) body mass index (BMI); (3) percentage weight above ideal body weight (IBW) using multivariate regression analysis. Patients were analysed according to the induction they received: "daclizumab" or "alemtuzumab" as this determined their tacro-limus regime and target FK level range. Within these groups they were split into non-overweight and over-weight defined as BMI>25kg/m^2 for comparative analyses. **Main results:** A total of 219 sets of patients' medical notes were reviewed, 168(77%) were excluded as per set criteria, which included having received five stable doses of tacrolimus initially amongst others - resulting in 50 patients in the final analyses. No statistically signi-ficant correlations were found between first FK levels and (1)ABW; (2)BMI; or (3)percent-age weight above IBW. Overweight patients were more likely to get a high first FK level however this was not statistically significant: daclizumab, 3 (75%) overweight patients vs. 5(50%) non-overweight patients; alemtuzumab 8(62%) over-weight patients vs.12(52%) non-overweight patients. Interestingly, the dose of tacrolimus at therapeutic levels did not differ between the groups regardless of their initial starting dose: daclizumab group mean daily dose 10.0mg in overweight patients vs. 9.5mg in non-over-weight patients (95% CI -3.13 – 4.13 p =.769); alemtuzumab group mean daily dose 6.09mg in overweight patients vs. 7.15mg in non-overweight patients (95% CI -3.33 – 1.20, p = .346). **Conclusion:** This study has found some interesting albeit statistically insignificant trends, suggesting that dosing of tacrolimus according to ABW may lead to high first trough tacrolimus levels in overweight patients. However, further studies involving larger sample sizes are needed.

P271

Is it time to develop a standardised protocol to manage immunosuppression in failed renal allograft patients on dialysis?

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Introduction. Current studies "suggest" immunosuppression (IS) in dialysis patients carries additional risk of infection and cardiovascular mortality. Withdrawing IS on the other hand is associated with the risk of rejection, loss of residual renal function, secondary adrenal insufficiency and potential adverse immunological effects affecting subsequent transplantation. Management of IS after renal allograft failure remains a topic of debate due to the lack of robust evidence presenting clinicians with a dilemma about the optimal method of tapering / withdrawing IS therapy in these patients.

Aims To observe the current IS burden in our prevalent dialysis patients with renal allograft failure.

Methods We performed a cross sectional audit. Data was collected from our renal database. Patient demographics, time on dialysis and IS regime was collected. Patients within 3 months of starting dialysis and patients with graft nephrectomy were excluded.

Results 60 patients (30 male) with a mean age of 53.6 years (28-74 years) were audited.13 patients were on peritoneal dialysis and 47 on haemodialysis. 4 patients had 2 previous transplants and 1 had 3 previous transplants. They had a functioning transplant for a median of 8 years (3 months -27 years). The median time on dialysis/IS post transplant failure was 27 months (6 -139 months). 65% were on combination IS therapy. Ciclosporin 100mg and prednisolone 5mg were the commonest combination therapy and ciclosporin 100mg was the commonest monotherapy. 9 pt's were on IS for more than 5 yrs.

Conclusion

Our audit has raised awareness of the burden of IS in our dialysis patients with failed renal transplant. This is the first step in the process of developing protocols to taper/ withdraw IS bearing in mind the cardiovascular and infection risks not to mention the pill burden, cost and side effects associated with IS.

Prospective studies are needed to determine the best method of tapering/withdrawing IS.

Poster Session

Thursday 23 April

13:30 – 14:30

Kidney - Clinical 2

Moderator Mr Jacob Akoh

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Post transplant renal artery stenosis – Does the source of kidney matter?

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Background: Transplant Renal Artery Stenosis (TRAS) is a well recognised vascular complication after renal transplantation. The incidence varies from 1% to 23%. The known risk factors are long cold ischemia time, deceased donor grafts and kidneys with multiple arteries.

Aim: Identify incidence of TRAS in all types of kidney transplantation in our unit and identify risk factors.

Materials and methods: 488 renal transplants were performed from 1 January 2002 to 31 December 2007. Patients with clinical suspicion for TRAS were radiologically investigated to confirm the diagnosis. Recipient age and sex, donor age and sex, cold ischemic time, diabetic status of recipients, source of kidney and number of renal arteries in patients with (TRAS) and without (no TRAS) renal artery stenosis were analysed.

Results: There were 308 male and 180 female recipients. 335 deceased donor (DD), 113 live donor (LD) and 40 donor after cardiac death (DCD) kidney grafts. The mean follow up was 42 months (range 10-83).

The mean age of the recipient was 45 years (17 -81) and 46 (23-66) (P = 0.82), donor age 49 years (23-72) and 46 (2-79) (P=0.45), Cold ischemic time 16 hours (3-27) and 14 hours (1-33) (P=NS), recipients with diabetes 3/16 and 60/472 (P=0.48) in the TRAS and no TRAS groups respectively. The overall incidence of TRAS was 3.2% (16/488). The incidence of TRAS in DCD grafts (12.5%, 5/40) was significantly higher compared to LD grafts (0.8%, 1/113, P=0.001) and DD grafts (2.9%, 10/335, P=0.004). There was no difference in the incidence of TRAS between DD and LD kidneys (P=0.82). The incidence of TRAS was also higher in kidneys with more than one artery compared to single artery (7.7% vs 2.2%, P=0.008). All patients with TRAS were successfully managed by interventional radiology with no loss of grafts following the procedure.

Conclusion: Transplanted kidneys from donors after cardiac death have higher incidence of renal artery stenosis compared to kidneys from other types of donors. The presence of multiple renal arteries represent, as expected, a risk factor for the development of renal artery stenosis following transplantation.

P273

Role of routine implantation biopsy in renal transplantation

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Background - Implantation biopsy has been reported to predict graft function. The accuracy of graft function prediction and the risks of the procedure in a clinical setting are unclear.

Aim - To evaluate the accuracy of implantation renal graft biopsy in predicting graft loss or poor graft function at one year and to evaluate the complications of the procedure in a single renal transplant unit.

Methods - 53 adult patients who had cadaveric kidney transplantation successively between March 2006 and October 2007 underwent implantation renal biopsy. Biopsies were taken using a trucut needle after re-perfusion. The biopsies were evaluated by a renal transplant pathologist for chronic renal pathology using the Banff criteria. The pathology findings were converted into a qualitative score (ranging from 0-3) for each of four aspects i.e. glomerulosclerosis, tubulo-interstitial fibrosis, arteriolar hyalinosis and arteriosclerosis. Total biopsy score (TB) was calculated from the sum of individual scores (maximum score12). Data regarding the outcome of the graft at the end of one year (graft loss or eGFR<30) was collected. The biopsy scores (individual scores and TB) of functioning and failed grafts were compared. Data pertaining to the complications of biopsy was also collected.

Results - 53 grafts were included in the study. Chronic graft changes were seen in 33 biopsies. Most had mild changes with median TB scores of 1 (inter-quartile range 1-3). At the end of one year, 3 grafts were lost. 4 functioning grafts had a eGFR <30. There was no difference in individual and total biopsy scores between functioning and failed grafts (Mann Whitney U, p=0.259). During this period four grafts had biopsy related complications. Two grafts developed AV fistulae, managed with angiography and coil embolisation (1 graft loss). Two grafts needed re-exploration for bleeding from the biopsy site. There were no biopsy related deaths.

Conclusions - Routine implantation graft biopsy was not helpful in predicting one year renal graft survival. This could be because significant chronic pathology was infrequent in our study. The procedure was also associated with significant complication rate.

P274

Ureteric complications after kidney transplantation: Influence of donor type

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Introduction: There has been a steady increase in the proportion of kidneys transplanted from live (mainly laparoscopic) donors (LD) and donors after cardiac death (NHB; non-heart beating), compared to donors after brain death (HB; heart beating). This study aimed to determine the impact of type of donor on the incidence and outcome of major urological complications (MUCs) after transplantation.

Methods: We studied 950 consecutive renal transplants performed in our centre since 1998, retrieving data from a prospective, cross-audited, computerised database and by case-note review. The patient cohort was divided into three groups according to the donor type (NHB n= 217, HB n=539 and LD n=194). A vesico-ureteric anastomosis over a double pigtail ureteric stent was performed in all transplants and ureteric stents were removed 4-6 weeks post-operatively.

Results: The incidence of MUCs in the three groups was similar: 3.2% (n=7) in the NHB group, compared to 2.2% (n=12) in the HB and 2.6% (n=5) in the LD groups (p=NS). Complications consisted of 21 cases of ureteric stenosis and 3 cases of urinary leak. There was no association with cold ischaemia time (mean 12.5±7.1 h) and no significant difference in delayed graft function rates between patients with and without MUCs. Patients with MUCs, within each group, had similar incidences of microbiology-proven urinary and CMV infections before presentation (overall 38% and 17% respectively). However, the incidence of acute rejection in patients with MUCs, although no different within each group, was overall 50% compared to 25% for patients without MUCs (p=0.0089). Management in all cases involved surgical implantation of the native ureter onto the transplant renal pelvis or proximal ureter, or re-implantation of the transplant ureter onto the bladder. 28 procedures were performed in total, with re-stenosis in 17.4% requiring re-operation. No grafts were lost as a direct consequence of MUCs or their treatment.

Conclusion: Transplantation of NHB kidneys is not associated with an increased incidence of major urological complications compared to transplantation of LD or HB kidneys. When complications do occur, they can be treated successfully by surgical re-implantation of the ureter, although a significant proportion requires re-operation.

P275

Native nephrectomy in transplant patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Introduction: Transplant patients with ADPKD may require native nephrectomy (NN) in either the pre or post transplant period for recurrent infection, loin pain, haematuria or suspected malignancy.

Methods: Retrospective review of our institution's transplant patient database and histopathology results for patients with ADPKD over the last 20 years.

Results: Between 1988 and 2008, 1712 patients underwent renal transplantation. Renal failure was due to ADPKD in 157 patients (9%) who received deceased (DDT n=114) or living (LDT n=41) donor kidneys. 27 ADPKD patients (17%) required bilateral NN, 10 (6%) pre- and 17 (11%) post-transplant at a mean of 49 months post transplant (range 5-204). Pre-transplant NN was more common with a LDT (8% v 6%) and post-transplant NN was more than twice as likely following DDT (13% v 5%). One patient with ADPKD and type 1 diabetes received a simultaneous pancreas kidney (SPK) transplant. Right NN was performed at the start of transplant surgery to make space for the pancreas.

Bilateral NN was by open (n=24) or hand assisted laparoscopy (n=1). The majority (23/25) of NN were for recurrent infection and pain. However, two patients (1.3%) presented with macroscopic haematuria 6 and 4 years post transplant and had renal cell carcinoma (RCC): a pT3b clear cell RCC and a bilateral pT1a papillary RCC, who concomitantly had a bladder transitional cell carcinoma (pTa G2). 4 small incidental tumours were found in the series: 2 chromophobe renal adenoma, a papillary microadenoma, and an oncocytoma.

Conclusions: The majority of ADPKD patients do not require NN and only 6% require NN prior to transplantation, although this may be more likely if a living donor transplant is planned. The only occasion where NN was required for space was in SPK. The main post transplant indication remains recurrent infection and pain. However, macroscopic haematuria in ADPKD patients should not be assumed to be due to benign disease and requires exclusion of urinary tract malignancy. Areas for future study relating to NN in ADPKD include optimal imaging of the native kidneys and comparisons of open and hand assisted laparoscopy for bilateral NN.

P276

Effect of donor age, obesity and complicated kidney graft vascular anatomy on live kidney donor and recipient outcomes.

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Introduction: The rapid development of live donor kidney transplantation is associated with an expansion of the donor acceptability criteria. Candidates previously excluded as high risk surgical patients or because their kidneys had complicated vascular anatomy are now increasingly considered as potential donors.

Aim: To study the effect of donor age, obesity and complicated kidney graft vascular anatomy on live kidney donor and recipient outcomes at a single Centre.

Methods: We conducted a retrospective case note analysis of 237 consecutive live donor kidney nephrectomies and transplants performed between November 2005 and November 2008 in our Centre. All donor nephrectomies were performed by a modified mini-open technique by two surgeons. Higher risk donors were considered who: were >60 years, had BMI >30, and their kidney vascular anatomy resulted in more than one arterial and/or venous anastomoses. Donor nephrectomy operative parameters (incision length, operative time, blood loss, warm ischaemia time), post-operative complications and length of hospital stay as well as recipient and kidney graft survival were analysed. Mean follow up is 18.3 months (range 1-37 months).

Results: 28 donors (12%) were > 60 years old (mean±SD: 44±12, range:21-75), 49 (21%) had a BMI> 30 (mean±SD: 26.4±5 range: 17.1-44.9.) and 27 (11%) kidneys required more than one arterial and/ or venous anastomoses. The comparison of donors >60 vs. < 60 years, BMI >30 vs. < 30 and kidneys requiring more than one vs. single arterial and venous anastomoses did not demonstrate a statistically significant difference for either the donor nephrectomy intra-operative parameters, post-operative complications and length of hospital stay or the recipient and kidney graft survival.

Conclusions: This study demonstrated that candidates who may have otherwise been excluded from live kidney donation on the basis of age, weight or difficult kidney vascular anatomy can safely undergo a donor nephrectomy combined with excellent post-transplant recipient and graft outcome.

P277

Operative Intervention for Autosomal Dominant Polycystic Kidney and Liver Disease: A UK Single Centre Experience

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Introduction:

This study presents a single centre's 5 year experience of laparoscopic kidney and liver deroofings in patients with autosomal dominant polycystic kidney and liver disease (APKD). Recent NICE guidance regarding laparoscopic deroofing of simple symptomatic renal cysts does not address whether this intervention is efficacious in patients with APKD.

Methods:

Eleven patients with APKD underwent a total of 17 laparoscopic interventions between September 2001 and November 2006 with a median follow up of 20 months (Minimum follow up of one year). Nine procedures involved laparoscopic deroofings of kidneys only. Four procedures solely de-roofed liver cysts (three on one patient). Four procedures involved simultaneous laparoscopic deroofings of kidney and liver cysts (in three patients). There were no conversions.

Results:

Some degree of symptomatic recurrence occurred in 55% of all patients by 12 months and 33% underwent a second laparoscopic deroofing.

39% of all laparoscopic de-roofings suffered from complications. Acute on chronic renal failure occurred in two patients; one of whom required ITU admission (due to acute renal failure induced narcosis). Other complications were persistent port site wound discharge (n=1), chest infection (n=1), pneumothorax (n=1), Pulmonary Oedema (n=1) and PD peritonitis (n=1).

Conclusions:

Laparoscopic de-roofings offers patients short to medium term relief from the intractable pain of polycystic disease. However, complications related to impaired renal function and laparoscopic surgery need to be considered as does the and high rate of symptom recurrence.

P278

Transversus abdominis plane (TAP) block for renal transplant surgery

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Transversus abdominis plane (TAP) block has been evaluated for pain relief following bowel surgery, caesarean section and for prostatectomy with favorable results. The neurovascular bundle of the anterior abdominal wall runs in the plane between the internal oblique and the transversus abdominis muscles, and can be easily visualized on ultrasound imaging. The ultrasound-guided TAP block technique was described by Hebbard in 2007, but no record of its use in renal transplantation has been documented since. Our aim was to investigate the use of TAP block in patients undergoing renal transplantation.

10 successive patients were anaesthetised for renal transplantation using a standard technique. TAP block was then performed under ultrasound guidance using a high frequency 5-13 MHz linear array probe (Sonosite Micromaxx®). The transducer was placed transverse to the abdominal wall in the mid-axillary line between the lower costal margin and iliac crest. An 80 mm needle (Pajunk, Germany) was inserted into the TAP where 20 ml of 0.5% l-bupivacaine was injected.

Postoperative pain relief consisted of regular paracetamol (1g IV every 6 hours) and a patient controlled analgesia (PCA) pump that was set to deliver 0.5 mg of morphine on demand with a lockout period of 10 minutes. Haemodynamic variables and pain scoring using a visual analogue scale (score 0-10: 0 = no pain, 10 = maximum pain) were recorded hourly for the first 24 hours**.** Data from 10 controls matched for age and sex was retrospectively collected from case notes for comparison. Mean morphine requirement during the first 24 hours was 10.5mg in the TAP group versus 29 mg in the control group. ($P<0.0001$).

Efficacious TAP block provides anaesthesia from T10-L1. We have demonstrated a reduction in opioid use following renal transplantation subsequent to such a block. We postulate that this may reduce the frequency of side effects associated with opioid use, such as nausea, bowel dysfunction and drowsiness. Any such effect would be particularly advantageous in patients with renal impairment, in whom the metabolites of many opioids are prone to accumulation. We hope to investigate this effect prospectively, to provide data on the frequency of opioid-associated side effects, length of stay and return to pre-morbid function in patients who have received TAP blockade during renal transplantation.

We recommend that TAP blocks should be incorporated as part of the analgesia regimen for surgery where a muscle cutting incision is anticipated. TAP blocks under ultrasound guidance are easy to perform, provide consistent analgesia and have displayed an exceptionally good safety profile.

P279

Renal transplantation after endovascular repair of abdominal aortic aneurysm: a single centre experience

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INTRODUCTION: Endovascular aneurysm repair (EVAR) is an effective modality of treatment for abdominal aortic aneurysm (AAA), particularly in patients with renal disease, because of advantages over the standard open procedure, including lower morbidity, shorter operative time and shorter hospital stay. There is paucity of data in the transplant literature on RT after EVAR. A Medline search showed two case reports on renal transplantation (RT) after EVAR, including the one from our institution. In this context, we present the outcomes of our two cases of successful RT following EVAR and discuss intra- and post-operative issues pertinent to the subject.

METHODS: Case 1: A 54-year-old male with end-stage renal failure secondary to membranous nephropathy, was treated successfully with EVAR for an 5.7 cm diameter AAA using an endovascular bifurcated stent graft, where the distal ends extended to the bifurcation of the common iliac arteries. He underwent a deceased donor RT 2 years after EVAR where renal vessels were anastomosed to the recipient external iliac (EI) vessels. A medial dissection occurred on the grossly atherosclerotic EI artery, which was repaired. The vascular anastomosis time was 60 minutes.

Case 2: A 64 year-old male with ESRD of unknown cause underwent DD RT 18 months after undergoing EVAR. He has undergone coronary angioplasty and repair of right popliteal aneurysm 1 year ago. The donor renal artery anastomosed to the left EIA just distal to existing aneurysm of the CIA. The vascular anastomosis time was 37 minutes.

RESULTS: Postoperatively, both transplants functioned immediately with progressive fall in the serum creatinine. Duplex and Mag3 scans showed well-perfused kidney with patent EI arteries. No dislodgement, migration, endoleak, dissection or thrombosis of the stent occurred. A follow-up computerised tomographic scan showed minor dissection of the EIA and normal renal allograft vessel in the first case 1 year after RT.

CONCLUSIONS: Current evidences show favourable outcomes of EVAR in normal population, in patients with renal diseases and in renal transplant recipients. Although the long-term outcomes of RT after EVAR remain unknown, from the experience of our two successful RTs, we endorse RT in renal failure patients who have undergone EVAR in the past.

Poster Session

Wednesday 22 April

13:00 – 14:00

Kidney - Clinical 3

Moderator Miss Laura Buist

P280

Renal Transplant Biopsies: The use of aviation principles for safe and adequate biopsy practice.

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INTRODUCTION: Renal transplant biopsy remains the gold standard assessment of parenchymal causes of graft dysfunction. In addition it can facilitate timely and appropriate management changes, improving graft survival. The procedure itself however is not without risk. We have devised a biopsy technique with a robust safety profile, the *glide path approach*, which derives from aviation principles. To date, no major complication has been reported since we instituted this technique for all diagnostic and protocol biopsies.

METHOD: The *glide path* approach to renal transplant biopsies (diagnostic and protocol) was introduced in our unit between September 2006 and January 2009. The *glide path* approach is based on the runway principle used in aviation to guide an airplane to earth. A disposable, spring-loaded, automated 16G biopsy needle was deployed under ultrasound guidance. The crux of the technique lies in maintaining constant needle visualisation. This is ensured if the needle tip and body remain within a finite curtain of ultrasound emitted by the probe. A specific protocol was employed for patients on anticoagulation therapy. The majority of biopsies were performed as day procedures. Patients were confined to bed rest for 6 hours with observation and repeat check ultrasounds.

RESULTS: A total 259 biopsies were performed on 201 patients comprising; 48 diagnostic,162 three month and 49 twelve month protocol biopsies. Patient participation was excellent with only one patient refusing biopsy. 2 complications were reported. 1 patient was admitted with gross haematuria requiring a transfusion of packed red cells and a urinary catheter/washout. The second patient developed a capsular haematoma, which was managed conservatively in the outpatients with routine ultrasound scans. No graft was lost. On average there were 18 glomeruli per core of biopsy tissue. 2/259 procedures were reported as missed biopsies and had to be repeated.

CONCLUSION: In recent years we have witnessed an expanding role for transplant biopsies. They have rapidly become an important management strategy. Therefore, it is imperative that a transplant unit has confidence in its biopsy technique. We have devised a procedure with a formidable safety profile, based on clear guiding principles.

P281

Is renal biopsy of intra-peritoneally placed kidney transplants associated with an excessive risk?

Mohamed Ilham[1], Ali Haque[1], Michael Prichard[1], David Griffiths[2,1], Argiris Asderakis[1]

[1]Cardiff Transplant Unit, Cardiff, United Kingdom, [2]Histopathology Department, Cardiff, United Kingdom

Introduction: Renal transplant biopsy is still required to allow adequate diagnosis of graft dysfunction. However it is not without its complications. Renal transplants are occasionally placed intra-peritoneally particularly in the context of simultaneous kidney pancreas transplantation (SPK). Biopsy form such kidneys is expected to be more challenging and fraught with more complications compared to biopsy from extra-peritoneally placed organs due to the absence of external tamponade.

Aim: Examine the safety and utility of kidney biopsies of intra-peritoneally placed renal (IPK) transplant in the setting of SPK.

Patients and Results: All renal transplant biopsies of IPK were performed under ultrasound guidance using an 18 gauge automated biopsy needle. Biopsies were evaluated by light microscopy for adequacy and further cores were taken if required for adequate pathological evaluation. Patients had bed rest six hours post biopsy with regular observation. If a patient was on warfarin or heparin it was stopped beforehand. However, low dose aspirin was not stopped. All patients had their coagulation profile evaluated before biopsy.

From 1/2005 to 10/2008, 43 biopsies of IPK were performed in 20 patients out of 41 with SPK. All biopsies had adequate material for pathological diagnosis. 24 biopsies revealed rejection, while 19 biopsies revealed other pathological diagnoses (ATN, CNI toxicity). One patient suffered from bleeding that required exploration and 4 patients received blood transfusion (2 of them though because they had a low Hb prior to the IPK biopsy). There were minor episodes of post biopsy haematuria early following the procedure but none was associated with clots in the urine or required catheterisation for retention.

Conclusion: Renal transplant biopsy of intra-peritoneally placed adult kidneys in the context of SPK provides valuable information to aid diagnosis and management of patients, and it is safe, therefore it should not be avoided. However it should be dealt with more cautiously than biopsies from extra-peritoneally placed kidneys.

P282

Urine NGAL Levels are not Reflective of Organ Injury in Kidney Transplant Recipients with Residual Native Renal Function.

Declan de Freitas, Beatrice Coupes, Paul Brenchley, Michael Picton

Manchester Royal Infirmary, Manchester, United Kingdom

Urinary neutrophil gelatinase-associated lipocalin has been identified as an early marker of acute kidney injury and is reported to be predictive of delayed graft function following kidney transplantation. We are conducting a single centre placebo controlled study examining the effects of high dose erythropoietin prior to reperfusion in kidney recipients of deceased donors with cardiac death or extended criteria. Pre-op urine and plasma were collected from patients (n=11) with residual renal function for biomarker quantification. NGAL levels were measured by ELISA and expressed as ng/mg creatinine (Cr).

Residual urine output ranged from <100mls/day to >2000mls/day and was inversely correlated with urine NGAL (uNGAL) levels ($r = -0.6$, $p=0.046$). Age, sex and renal failure aetiology had no effect on uNGAL levels, which ranged from 0-8748 ng/mgCr, with a mean of 3498 ± 847ng/mgCr prior to transplantation. Plasma NGAL (pNGAL) ranged from 345-3303ng/ml with a mean of 1032 ± 239.4 ng/ml. Pre-op pNGAL levels directly correlated with pre-op uNGAL levels ($r = 0.66$, $p = 0.029$). Delayed graft function (DGF), defined as the need for haemodialysis post transplantation, occurred in 6/11 patients and did not correlate with pre-op or 24hr post-op urine or plasma NGAL levels.

uNGAL measurements post transplantation are confounded in patients with native urine output and it is therefore difficult to define the relationship with allograft injury and prediction of the need for dialysis. Finally, high NGAL levels did not appear to confer protection on the allograft.

P283

Area under the curve serum creatinine 7 days post transplant determines graft outcome in live donor kidney transplantation.

Sarah Hosgood, Adam Barlow, Yasha Johari, Joshua Elias, Michael Nicholson

University hospitals of Leicester, Leicester, United Kingdom

Introduction

Live kidney donation is considered the best mode of treatment for patients with end stage renal failure. However, there is a degree of variability in graft function in the immediate post transplant phase that may influence graft outcome. We investigated whether the calculation of Area under the curve serum creatinine (AUC Cr) in the first 7 days post transplant could predict graft outcome in live donor kidney transplantation.

Methods

One hundred and ninety two live donor renal transplants performed between October 1998 and October 2007 were retrospectively analysed. AUC Cr was calculated and the recipients divided into two groups (AUC Cr <2000:n=106 and AUC Cr >2000: n=86). The spearman rank correlation model was used to determine factors that influenced AUC Cr and correlate AUC Cr with one year graft function.

Results

The mean values of AUC Cr were (<2000 group;1479 ± 347 and >2000 group; 2718 ± 790 µmol/L.day). Serum creatinine levels were significantly higher in the >2000 group at 12 months post transplant (179 ± 146.1 vs 124 ± 36.2µmol/L; P = 0.0001) and eGFR significantly lower (47 ± 15.0 vs 53.9 ± 14.6; P = 0.004).

AUC Cr significantly correlated with 12 month serum creatinine levels (Correlation coefficient 0.478; P = 0.0001). Independent variables that correlated with AUC Cr were donor gender, donor Isotope GFR, cold ischaemic time and recipients that were on dialysis prior to transplantation.

Conclusion

The simple calculation of AUC Cr levels 7 days post transplant is a valuable and reliable means to assess acute graft function in live donor kidney transplantation. It predicts poorer graft function at 12 months which is known to influence long-term graft survival. This study also highlights the need for careful donor selection, reduction of cold ischaemic time and the benefits of pre-emptive transplantation.

P284

Delayed graft function is only harmful if associated with rejection and this effect is predominant in the first year after renal transplantation

Aravind Cherukuri, Seerapani Gopaluni, James Tattersall, Chas Newstead, Andrew Lewington, Magdi Attia, Krishna Menon, Niaz Ahmad

St James's University Hospital NHS, Leeds, United Kingdom

There is conflicting evidence for the influence of delayed graft function (DGF) on long term graft outcomes in renal transplantation. In this study we analyse the impact of DGF both with and without acute rejection on long term graft survival.

696 consecutive renal transplants performed and followed-up in a single centre between January 1988 and December 2006 were analysed. Patients with DGF underwent transplant biopsy between day 7 and 10 post op. Patients were divided into four groups; Group-1 DGF-/rejection-; Group-2 DGF+/rejection-; Group-3 DGF+/rejection+; and Group-4 DGF-/rejection+. A multivariate Cox proportional hazards model was used to study actuarial 5 year death censored graft survival in these four groups. The outcome was adjusted for recipient age, gender, HLA mismatches, donor age, donor-type and graft number. 622 grafts which survived more than 12 months were analysed separately to eliminate the early effects of DGF/rejection within the first year and study the longer term impact. In the primary analysis (Fig-1), DGF with acute rejection had a significant impact on death censored graft survival (RR=4.3, 95%CI=2.5-7.6, p<0.001). DGF without rejection has no effect on early graft survival. Analysis of the grafts surviving more than a year (Figure-2) shows that this effect diminishes considerably if the graft survives one year (RR=1.9, 95% CI= 0.6-5.8, p=0.3).

We conclude that in this population DGF does not exert any major influence on graft survival unless associated with acute rejection. DGF with rejection is associated with a significant negative impact on one year graft outcome but if the graft survives the first year then the effect is less important.

Figure-1:

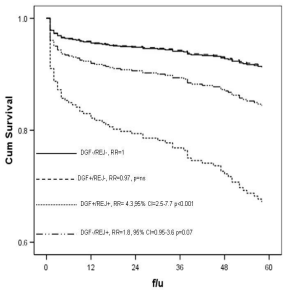
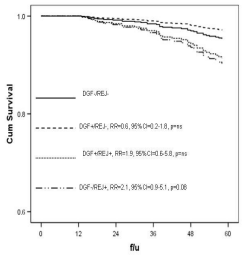


Figure-2:



P285

What effect do pre-transplant risk factors have on Delayed Graft Function (DGF)?

Aravind Cherukuri, James Tattersall, Seerapani Gopaluni, Chas Newstead, Andrew Lewington, Niaz Ahmad, Richard Baker

St James's University Hospital NHS, Leeds, United Kingdom

Although various parameters have been strongly associated with DGF, the role of various pre-transplant vascular risk factors is unknown. Here we analyse the role of various factors related to pre-transplant dialysis care in a cohort of 229 patients who were transplanted and followed up in a single centre from 1999 to 2007.
Potential dialysis-related factors including type of dialysis, mean of all systolic and diastolic blood pressures, haemoglobin, albumin, calcium, phosphate, calcium-phosphate product and PTH for the year prior to transplantation were studied along with any preceding history of vascular disease, adjusted for the effect of recipient age, gender, HLA-DR mismatch, cold ischemia time, h/o diabetes, duration of dialysis, donor age and type of donation using multivariate binary logistic regression analysis.
The summary of the analysis is tabulated. Patients on PD prior to transplantation had a significantly lower risk of DGF. Low systolic and diastolic blood pressures are associated with an increased risk of DGF. In particular patients in the highest tertile of both systolic and diastolic BP groups had significantly less DGF.
We conclude that HD and lower dialysis blood pressures are significant risk factors for DGF in our study population. It is possible that patients in the low blood pressure groups are at a risk of intra-operative hypotension and increased ischemia-reperfusion injury. This might highlight a group who would benefit from intervention and merits further study.

FACTOR	RR FOR DGF	95%CI	P-VALUE
PD vs. Haemodialysis	0.3	0.1-0.8	0.01
Systolic BP- SBP	0.97	0.95-0.99	0.01
SBP- highest vs. lowest tertile	0.4	0.2-0.9	0.04
Diastolic BP-DBP	0.9	0.88-0.97	0.001
DBP- highest vs. lowest tertile	0.3	0.1-0.7	0.004
Haemoglobin	0.9	0.7-1.3	NS
Calcium	2.3	0.3-22	NS
Phosphate	1.03	0.4-2.9	NS
PTH	0.99	0.97-1.01	NS
Calcium Phosphate product	1.1	0.7-1.6	NS
Vascular history prior to Tx	1.4	0.7-2.9	NS
Albumin	0.98	0.9-1.1	NS

P286

Upper endoscopy for kidney transplant patients, single centre experience

Gabor Telkes[1], Antal Peter[1], Zsolt Tulassay[2], Argiris Asderakis[3]

[1]Semmelweis University, Transplantation and Surgical Department, Budapest, Hungary, [2]Semmelweis University, II. Internal Medicine Clinic, Research Group of Hungarian Academy of Sciences,, Budapest, Hungary, [3]University Hospital of Wales, Cardiff, United Kingdom

Introduction: Upper gastrointestinal complications have historically resulted in considerable morbidity and mortality to solid organ transplant recipients.

Aim: Summarize the largest endoscopic database for kidney transplanted recipients.

Materials and methods: In a large transplant unit, 2135 kidney transplants were carried out between 1994 and 2007. At that period, 672 upper endoscopies were performed for 543 of those patients with significant gastrointestinal complains. 56,9% were male, with a mean age of 49,5 years (16-78). All patients got ulcer prophylaxis long term following transplantation. During the endoscopy, biopsies were taken from the duodenum, antrum, corpus, and processed for histology, and cytomegalovirus (CMV) DNA-PCR.

Results: The main indications for endoscopy were pain in 46.2% of cases, dyspepsia in 23.2% and bleeding in 18.4%. Macroscopic findings included inflammation in 46.7%, oesophagitis in 24.7%, ulcer in 16.9%, and erosions in 14.8% of cases. The presence of Helicobacter pylori (H.p) was verified by histology in 20.9% of cases, less than the 49% found by serology in the uraemic population ($p<0.0001$). Its presence was independent from the presence of erosions and ulcers. 29% of patients were examined in the first posttransplant year, when 45.7% of all ulcers developed. CMV-DNA was found in 53,4% of endoscopies performed. Its presence was independent from erosions, ulcers and positivity for H.p.

Using logistic regression it was found that the use of mycophenolate increased the risk of erosions by 1.8 fold (95% CI, 1.02 to 3.29, $p=0.043$), and the risk of cytomegalovirus by 2.3 fold (95% CI 1.34-3.79, $p=0.0021$).

Conclusions: More than 25% of all kidney recipients required upper endoscopy in their “posttransplant journey”. The rate of clinically significant endoscopic findings was 84% and frequency of ulcer disease was 17%, both figures significantly higher than the ones found in the general population that required endoscopy ($p<0.0001$). The most vulnerable period is the first year. The use of mycophenolate mofetil had an independent role on gastrointestinal complications, while H.p. and CMV were not associated with any specific endoscopic findings. Adopting a low threshold for endoscopy in a specialised centre revealed very frequent abnormalities that required medical intervention.

Poster Session

Thursday 23 April

13:30 – 14:30

Kidney - Clinical 4

Moderator Mr Andrew Ready

P287

Commercial overseas kidney transplantation is associated with poor outcome compared with standard practice in the country of transplantation

Seika Kalsoom[1], Farah Fiaz[1], Saeed Akthar[2], Nithya Krishnan[3], Paul Cockwell[4], Indy Dasgupta[1]

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Indo Asian (IA) patients with ESRF often travel abroad for commercial kidney transplantation. We have already reported poor outcomes of such transplantation in a cohort from West Midlands (Renal Association 2008). We hypothesised that the poor results seen in this group is not representative of the baseline outcomes of these centres. To address this hypothesis we have compared outcomes of kidney transplantation between live kidney transplantation into native patients in one major centre in Pakistan and IA patients from the West Midlands that had kidney transplantation in Pakistan over a similar period of time.

There were 109 patients in the 'native' cohort that had live donor kidney transplantation at Shifa International Hospital, Islamabad between 2001 and 2008, mean recipient age was 46 years (17 – 75), and 71% were male. Eighty five (78%) of the donors were live related and the others were unrelated. Of the 40 patients that had overseas kidney transplantation from West Midlands between 1996 and 2006, twenty two patients of British-Pakistani origin had their transplants done in Pakistan. Mean recipient age was 49 years (24 – 87) and 70% were male. Ten patients (45%) were on the UK transplant waiting list. All transplants were live unrelated.

One year graft survival in the native cohort was 92.7% and in the overseas cohort was 86.4 % ($p = 0.02$). One year patient survival was also significantly better in the native group compared with the overseas group at 94.6% and 82% respectively ($p = 0.009$). The composite one year graft and patient survival was also significantly better in the native transplant group at 87.2% compared to 68.2% in the overseas transplant group ($p = 0.007$).

This study confirms that native patients undergoing live kidney transplantation in Pakistan fare significantly better than transplant tourists from the West Midlands. Although there are differences in factors confounding outcomes between the two groups and comparison may not be absolutely valid, the results of this study emphasises that commercial overseas kidney transplantation is associated with poor outcome compared with standard practice in the country of transplantation, and any patient considering this treatment should be made aware of these differences in outcome.

P288

Transplant tourism from the UK, what is the outcome?

Trevor Gount[1], Heather Lumgair[3], Nishani Jayasooriya[3], Chandni Ondhia[3], Thuraisingham Raj[1], Puliatti Carmelo[1], Kessaris Nicos[2], Mamode Nizam[3], Cacciola Roberto[1]

[1]Royal London Hospital, London, United Kingdom, [2]St George Hospital, London, United Kingdom, [3]Guy's Hospital, London, United Kingdom

Background. An increasing number of patients attending renal transplant assessment clinics ask advice regarding live donor renal transplantation performed outside the UK. There is a lack of data regarding outcome of living related and unrelated renal transplants from patients who travel from the UK to other countries recognised as common destination of transplant tourists. In this study we reviewed the outcome of patients from three units who received a renal transplant outside the UK.

Methods. We retrospectively reviewed our database from three different renal transplant units and identified 58 consecutive patients who received a renal transplant abroad. Five had cadaveric transplants and were excluded from the analysis. Fifty-three were from living donors; nine related and 44 unrelated. We used as a control group 40 patients who received a living donor renal transplant in our units and were matched by year of transplant and age of recipient at time of transplantation. We analysed patients and graft survival at 1 year.

Results. Fifty-two patients who received a living donor transplant abroad were Asian and only one Caucasian; in the control group 70% were Caucasian. Median age was 40 in the group transplanted abroad and 39 in the control group. In the group who received a renal transplant abroad there were 9 deaths; one year patient survival was 83%. Three deaths were secondary to septicaemia and multi-organ failure, in 4 cases the cause of death was uncertain and in 2 cases death occurred peri-operatively. Patient survival in the control group was 100%.

Nine patients lost the graft in the first year; death censored one year graft survival was 79.5%. While in the control group one year graft survival was 98%. The main cause of graft failure was rejection followed by technical failure.

Also, four patients developed hepatitis B or C following unrelated renal transplant abroad.

Conclusion. Transplant tourism is ethically unacceptable and paid donation is illegal. However a large number of UK resident patients are transplanted abroad. The results of this series are worse than those from our units and national data. Data collection proved to be challenging and some patients may have been missing. Nationally collected data will facilitate analysis. This study may offer a useful tool for counselling patients wishing to travel abroad for a renal transplant.

P289

A simple Kidney Risk Score (KRS) and Mortality Risk Score (MRS) for renal transplant recipients

Xiang He[1], Jason Moore[2], Xiang Liu[1], Shazia Shabir[2], Paul Cockwell[2], Mark Little[2], Simon Ball[2], Nicholas Inston[2], Atholl Johnston[1], Richard Borrows[2]

[1]Barts and The London School of Medicine and Dentistry, London, United Kingdom, [2]University Hospital Birmingham, Birmingham, United Kingdom

Although risk factors for allograft failure and mortality in kidney transplant recipients are well described, no practical risk scores that could be used for prognostication exist. The purpose of this study was to develop and test a kidney risk score (KRS) and a mortality risk score (MRS) for kidney transplant recipients.

Prospectively collected data from 2763 prevalent adult (age ≥ 18 years) renal transplant recipients enrolled into the LOTESS (Long Term Efficacy and Safety Surveillance) study were analysed. Cox model hazard ratios for significant variables associated with graft failure and mortality were used to construct simple scoring systems. Performance characteristics (discrimination [concordance statistic], calibration [Hosmer-Lameshow goodness of fit] and risk reclassification [net reclassification improvement]) of the scores were assessed in an independent test cohort (n=829).

Both scores displayed good discrimination and calibration for risk prediction (c-statistic>0.75 for both; Hosmer-Lemeshow p-value>0.7 for both). In addition, the KRS enabled significant risk reclassification when assessed against estimated glomerular filtration rate in isolation (net reclassification improvement: 19.6%; $p<0.05$). Conversely, the MRS was not superior to recipient age in isolation (net reclassification improvement: 1.02%; p=NS).

The KRS represents a potentially useful tool for risk stratification in kidney transplant recipients; further study is warranted to confirm its utility in different populations and clinical scenarios. A prognostic tool for assessing mortality risk in kidney transplant recipients remains elusive.

P290

Impact of comorbidity on mortality following renal transplantation: comparative clinical utility of seven scoring systems

Jason Moore[1], Xiang Liu[2], Xiang He[2], Shazia Shabir[1], Simon Ball[1], Paul Cockwell[1], Nicholas Inston[1], Mark Little[1], Richard Borrows[1], Atholl Johnston[2]

[1]University Hospital Birmingham, Birmingham, United Kingdom, [2]Barts and The London School of Medicine and Dentistry, London, United Kingdom

Despite the increased comorbid burden associated with chronic kidney disease, few data exist on comorbidity scoring systems as they apply to renal transplant recipients. This study assessed and compared the performance of seven established comorbidity scores in predicting mortality following kidney transplantation, and accounted for the variable inclusion of recipient age within such indices.

De novo adult renal transplant recipients (n=2033) from the LOTESS (Long Term Efficacy and Safety Surveillance) database were analysed. The outcome measure of interest was mortality. Separate models were built, investigating the association between mortality and each studied comorbidity index: Recipient Risk Score (RRS); Charlson Comorbidity Index (CCI); Age adjusted CCI (ACCI); Modified End Stage Renal Disease CCI (MECCI); Foley Score (FS); Wright-Khan Index (W-KI); Davies Index (DI).

Age-stratified Cox analyses demonstrated the RRS-based model displayed best fit. Analysis of scores not containing age as a component (CCI, MECCI, DI), revealed age was independently associated with mortality; the addition of age to the model improved the fit. Receiver operating characteristic (ROC) curve analysis demonstrated the RRS to have greatest predictive utility (5 year mortality c-statistic: 0.787).

Recipient comorbidity is an important predictor of renal transplant recipient survival. Of the currently available comorbidity scores, RRS demonstrated greatest utility. This has implications for deceased donor organ allocation policy, research in transplanted and wait-listed populations, and the management of individual patients.

P291

Regulatory T Cells and Lymphoid Subsets in Recipients of Long Term Kidney Transplants with Good Function on Minimal Immunosuppression

Zareen Goburdhun, John Girdlestone, Sally Hamour, Mark Harber, Cristina Navarrete, Colin Brown

NHS Blood and Transplant, London, United Kingdom

Regulatory T Cells and Lymphoid Subsets in Recipients of Long Term Kidney Transplants with Good Function on Minimal Immunosuppression

Immunological tolerance is a desired transplant outcome to achieve optimal lifespan of the patient and allograft without chronic rejection or use of immunosuppressive drugs. T Regulatory cells (Tregs) have been shown to be involved in immune regulation and may represent a potential therapy to improve long-term graft outcome. To determine if increased circulating Treg numbers correlate with longer graft survival, we have investigated a cohort of 18 renal recipients who have retained their transplants beyond the average survival period (mean of 23 yrs) while on minimal immuno-suppression (Aza/Pred). Using 4 colour flow cytometry, we analysed the proportions of Treg and other lymphoid subsets in the renal cohort and a control population (19 healthy blood donors).

Results: Significantly lower percentages of Tregs were found in the patient group compared to the controls as defined by three criteria: CD3+4+25hi127lo; CD3+4+25hiFoxP3+; CD3+4+25hi152+. NK (CD56+) cells were also significantly lower in the patients.

Conclusions: Contrary to expectations, the frequencies of Tregs and NK cells in the peripheral blood of patients were significantly reduced in comparison to healthy controls. It will be of interest to analyse the suppressive capabilities of the Tregs in patients, and to determine the significance of low circulating numbers of Treg and NK for renal graft survival.

P292

Factors Effecting Erectile Dysfunction in Renal Transplant Patients

Seerapani Gopaluni, Aravind Cherukuri, Andrea Parker, Charles Newstead, Andrew Lewington, Richard Baker

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Erectile dysfunction (ED) is reported to be highly prevalent in renal transplant recipients (RTR). We studied the prevalence of ED in our male transplant population and the impact of various factors on ED.

Data on ED and on the exercising habits (divided into three groups: 1-no exercise, 2-moderate exercise, 3-ample exercise) of 491 RTR was collected by a single investigator, who was blinded for the results of this study. Recipient age, age of the graft, GFR at the time of clinic, systolic and diastolic blood pressures, smoking history, diabetic status, steroid therapy and cholesterol levels were also analysed and adjusted for.

ED was reported in 10.8% of the 491 RTR. Age of the graft (RR: 1.053, p=0.006) Ex-smoker status (RR: 1.955, p=0.035), steroid therapy (RR: 3.562, p=0.008) and age of the patient (RR: 1.042, p=0.001) were found to adversely affect sexual life in the univariate analysis. Diabetes interestingly was found not to be significant in this study population. Not surprisingly, ample exercise (RR: 0.347, p=0.005) was found to be advantageous. Recipient age (RR: 1.04, p=0.009) and ample exercise (RR: 0.425, p=0.029) showed significant independent effect. Even though steroid usage is associated with an increased risk (RR: 2.6, p=0.07), statistical significance is not achieved. Although ample exercise seems to be beneficial for ED, this in fact may represent the population with reasonably good peripheral vasculature and thus with good exercise capacity. Given the proven relationship between ED and peripheral vascular disease this result should be interpreted with caution.

Factor (Univariate Analysis)	RR	p value
Age of the patient	1.042	0.001
Ex-smoker status	1.955	0.035
Steroid therapy	3.562	0.008
Age of the graft	1.053	0.006

Factor (Multivariate Analysis)	RR	p Value
Age of the patient	1.04	0.009
Ample exercise	0.425	0.029

Adjusted for graft age, smoking status, steroid therpy.

P293

Analysis Of Vascular Risk Factors In Steroid And Steroid Avoidance Renal Transplant Groups: A Cross Sectional Study

Seerapani Gopaluni, Aravind Cherukuri, Andrea Parker, Charles Newstead, Andrew Lewington, Richard Baker

St.Jame's University Hospital, Leeds, West Yorkshire, United Kingdom

Long-term steroid usage in renal transplant recipients (RTR) has been associated with increased cardiovascular risk. We performed a cross-sectional analysis of various vascular risk factors present between two groups of RTR based on long term steroid usage. (Group-1: long-term steroids, Group-2: steroid avoidance).

Data from 714 RTR was collected by an independent investigator, when seen in well man clinic over a period of one year. Even though no significant differences in systolic and diastolic blood pressures between the two groups were identified, Group-1 needed more anti-hypertensives to achieve similar blood pressure control. There was no significant difference in the development of new onset of diabetes after transplantation (NODAT) between the two groups. The HbA1C levels were marginally higher in group-2 contrary to our belief. Mean cholesterol was marginally high in Group-1 and needed more statin usage. A similar pattern of smoking behaviour was seen in both the groups. Analysing the exercising trends, we found patients in Group-2 are physically more active. In conclusion, patients on steroid avoidance regime had better cardio-vascular risk profile when compared to patients on steroid based regimes in this population.

Factor	Group 1	Group 2	p-value
Age	50.52	47.39	0.034
Systolic BP mmHg	139	138	0.5
Diastolic BP mmHg	79	78	0.17
No of anti-hypertensives	1.9	1.3	<0.001
Total Cholesterol (mean)	4.43	4.1	0.001
Diabetes	11.3%(n=548)	10.4%(n=164)	0.085
NODAT	7.4%(n=548)	9.1%(n=164)	0.085
HbA1C (mean)	5.7	6	0.124
Exercise- none	27.5% (n=363)	24.4%(n=123)	0.08
Exercise-Moderate	38% (n=363)	30%(n=123)	0.08
Exercise- Ample	34.5%(n=363)	45.6%(n=123)	0.08
Smoking status-Ex	26%(n=548)	26%(n=166)	0.86
Smoking status-Current	13%(n=548)	11%(n=166)	0.86
Statins	78%(n=546)	59%(n=164)	<0.001

P294

Transplant referral pattern from a single UK renal centre.

Muhammad Naeem Raza[1], Evans Diane[2], Debbie Godferie[3], Lynette Puddicombe[1], Coralie Bingham[1], Richard D'Souza[1]

[1]Royal Devon & Exeter Hospital, Exeter, UK, [2]Southmead Hospital, Bristol, UK, [3]Derriford Hospital, Plymouth, UK

Introduction: Renal transplantation is the best form of RRT for patients with ESRD with improved survival compared to long-term dialysis. Preemptive transplantation of kidneys from living donors without the previous need for dialysis is associated with longer allograft survival than transplantation performed after the start of dialysis. The Renal Association endorses as a good practice guideline to refer patients 6 months in advance of requiring dialysis.

Aim & Objective: To identify the referral pattern for renal transplantation in ESRD patients including preemptive transplant referrals in our unit over a 12 month period (January to December 2007).

Methods: All the renal transplant referrals made in 12 months to two transplant centres in the region were identified and their notes reviewed. Patients were divided into a preemptive and non-preemptive referral group (referral >6M in advance of requiring dialysis). Data was updated for number of transplants in December 2008.

Results: A total of 52 patients were referred to two transplant centres, including 35 M, 17 F with a median age of 51yrs (21-73). This included 20(38%) preemptive and 32(62%) non preemptive (23 HD, 9 PD) referrals. The commonest underlying diagnosis was glomerulonephritis in 20(38%), ADPKD in 7(13%) and diabetes mellitus in 5(10%) cases.

In the non preemptive referral group the median time on dialysis before transplant referral was 257 days (37-2184) and from referral to transplant centre assessment was 54 days (16-872). The median time from referral to transplantation was 322 days (133-958) and a total of 13 (42%) patients in this group were transplanted (7 HBD, 4 NHBD, 3 LKD).

In the preemptive group the median time from referral to requiring dialysis was 377 (185-622) days and from referral to transplant centre assessment 52(15-689) days. The median time from referral to transplantation was 417(180-525) days. A total of 9(45%) patients were transplanted, 8 preemptively (I HBD, 2NHB, 4LKD, 2SPK); 7 later required dialysis. Median creatinine and eGFR at the time of referral for those transplanted were 383 μmol /L (309-334) and 13 mls/min (8-14) respectively vs 646 μmol/L (366-714) and eGFR 8.5 mls/min (7-12) in those who subsequently required dialysis.

From the remaining 30(58%) non-transplanted patients, 21 were active on the transplant list, 4 considered unfit by transplant centre (3 later died), one dead and 5 still not listed.

Conclusions: A high percentage of our patients were referred preemptively for transplantation. Patients referred with a median eGFR of 13 mls/min were most likely to be pre-emptively transplanted.

Poster Session

Wednesday 22 April

13:00 – 14:00

Post-Transplant Medical Complications 1

Moderator Dr Colin Short

P295

Is it possible to predict who will develop New Onset Diabetes After Transplantation (NODAT) in renal recipients using epidemiological data alone?

S. J. Robinson[1], S. M. Eckoldt[1], R.C. Andrews[2], R.M. Smith[1]

[1]North Bristol NHS Trust, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom

Background: NODAT is an important complication of renal transplantation that is associated with decreased graft and patient survival. This audit aimed to identify epidemiological risk factors for the development of NODAT in our renal transplant population.

Patients and Methods: A retrospective study of 306 patients included all consecutive patients with end-stage renal disease who underwent a kidney transplant from September 2004 to October 2007 at our unit was carried out. Data was drawn from the hospital's electronic database.

Results: The mean follow-up time of the patients was 365 days. The incidence of NODAT was 15.4% with the mean time following transplant to development of NODAT being 48 days, with a median of 34 days and a range of 11 to 156 days. Diabetes resolved in 22 of the 42 recipients, 12 within 3 months of diagnosis.

The only independent risk factor associated with the development of NODAT identified by this audit was age at transplant. Although Autosomal Dominant Polycystic Kidney Disease was shown to be associated with development of NODAT on univariate analysis, this association was not an independent risk factor on multivariate analysis. There was no difference in graft survival between recipients who developed NODAT and those who did not.

Discussion

NODAT is a common, early complication of renal transplantation in our unit. Approximately half the cases resolve before one year. Age was the only independent risk factor for the development of NODAT in this population.

P296

Who should follow-up New Onset Diabetes After Transplantation? The experience of a single centre discussed.

S.J. Robinson[1], S.M. Eckoldt[1], R.C. Andrews[2], R.M. Smith[1]

[1]North Bristol NHS Trust, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom

Background: In our unit New Onset Diabetes After Transplantation (NODAT) is a common, early complication of renal transplantation with apparent resolution in over half of those who develop the complication. Resolution of NODAT is defined as a return to normal random glucose measurements following cessation of hypoglycaemic agents. When this happens routine life-long post-transplant follow up is resumed with no review from a diabetologist.

Patients and Methods: A retrospective study of 306 patients including all consecutive patients with end-stage renal disease who underwent a kidney transplant from September 2004 to October 2007 at North Bristol NHS Trust, identified 42 patients with NODAT. 22 patients were demonstrated to have returned to normal random glucose measurements off hypoglycaemic treatment. This cohort were offered an Oral Glucose Tolerance Test (OGTT).

Results: 3 of the 22 patients with resolved NODAT had died. 2 declined the invitation for the OGTT. 6 did not reply. Hence, 11 OGTTs were performed. 3 OGTTs were normal, 3 revealed impaired glucose tolerance (IGT) and 5 showed on going diabetes.

Discussion: This audit has shown that 8 of 11 patients thought to have recovered from NODAT still have abnormal glucose handling demonstrated by OGTT. IGT is associated with ongoing cardiovascular morbidity and mortality. Large prospective randomized studies in the IGT population have shown a survival benefit with exercise and hypoglycaemic therapy. The involvement of a diabetologist and implementation of the Type 2 diabetes pathway should confer a similar advantage to the post-transplant diabetic population.

P297

Does a family history of diabetes increase the risk of developing New Onset Diabetes After Transplantation? (NODAT)

S.J. Robinson[1], R.L. Clissold[1], S.E. Eckoldt[1], R.C. Andrews[2], R.M. Smith[1]

[1]North Bristol NHS Trust, Bristol, United Kingdom, [2]University of Bristol, Bristol, United Kingdom

Background: The cumulative incidence of NODAT in our renal transplant population is 15.4%. Broadly speaking NODAT falls into the Type 2 category of diabetes where family history is an established risk factor. Within the literature there is conflicting evidence regarding the importance of family history as a risk factor for NODAT.

Patients and Methods: Family history (FH) data was collected by a nephrologist in a follow-up transplant clinic. A proforma was attached to the notes of patients already identified in a previous audit of 306 consecutive transplants. The NODAT status had been established using random glucose measurement with manual cross reference for hypoglycaemic therapy. The proforma was completed during the consultation; patients missed in clinic were phoned by one of the authors.

Results: For 29 (10.9%) of 267 non-diabetic recipients there was no data available. The distribution of missing data was shown to be random within the group who developed NODAT and those who did not (Pearson Chi square = 3.785, p = 0.151). The missing data included 14 deceased patients. Of the 238 recipients interviewed, 63 (27%) had a family history of diabetes. 15 of 37 (41%) patients with NODAT interviewed had a family history (Chi-square = 4.456, p = 0.035).

Discussion: This audit revealed an association between family history of diabetes and development of NODAT. This is consistent with expectation since strong familial clustering is seen in Type 2 diabetes. Ongoing studies will collect this data prospectively establishing whether this preliminary observation is validated in the cohort of patients transplanted over the next 2 years.

P298

Renal Allograft Dysfunction after Parathyroidectomy

Raj Rajaganeshan, Alex Cho, Mohemmad Shahid Ahmad, Amita Singh, Raman Dhanda, Mathew Howse, Ajay Kumar Sharma

Transplant Unit Royal Liverpool University Hospital, Liverpool, United Kingdom

Background

Parathyroidectomy has been shown to deteriorate allograft function. This study was performed to assess if deterioration in renal function was affected by the timing of the parathyroidectomy, i.e. performed prior to renal transplantation (Group 1) versus those who had this operation after renal transplantation (Group 2).

Methods

In the period 1987-2007, 57 patients were identified from the transplant database who had renal transplant as well as parathyroidectomy at Royal Liverpool University Hospital. Serum calcium, creatinine, parathyroid hormone levels were retrieved and analysed using SPSS version 12.0.

Results

Higher degree of deterioration in renal function was observed in Group 1 patients compared to those in Group 2, though the difference was not statistically significant. In Group 2, five patients showed a serious worsening of graft function following parathyroidectomy requiring maintenance dialysis within a year. In retrospective these patients had higher base-line creatinine. When patients in group 2 were sub-divided into high and low creatinine groups, there was a statisitically significant difference in the rate of change of creatinine (Mann Whitney U test p=0.03) between the high creatinine group (mean 82, 95% CI: 57.2-106.4) and low creatinine group(mean 40, 95% CI: 8.5-80.4).

Conclusion

Although parathyroidectomy is necessary if medical treatment of renal hyperparathyroidism is not effective, yet it poses a risk for impairing graft function. By identifying patients who are at high risk of developing renal impairment, the graft function of such patients may be prolonged.

P299

The synergistic adverse effect of abnormal renal function and glucose metabolism on post transplant patient survival

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Introduction

A major challenge in the field of renal transplantation is to prolong patient survival and graft survival. Previous studies have demonstrated that renal function at 1 year is a major determinant of long term patient and graft survival. Similarly, the development of new onset diabetes after transplantation identifies patients at high risk of cardiovascular events and mortality. The aim of this study was to assess whether there was an additive effect of impaired renal function and elevated glucose levels at 1 year post transplant on patient mortality.

Methods

Consecutive renal transplants from a single centre over a 10 year period were analysed using multivariate logistic regression modelling the risk of patient mortality stratified by GFR status and impaired fasting glucose levels.

Results

Data were available on 307 patients with fasting glucose and GFR measurements at 1 year post transplant. Overall 37% (n=114) had a GFR of less than 40mL/minute and of these 24% (n=27) had fasting glucose levels greater than 7 mmol/L. After adjusting for age, sex and donor factors patients with fasting glucose greater than 7 mmol/L and a GFR less than 40mL/minute had a mortality odds ratio of 5.47 ($p<0.01$) compared to those with glucose levels less than 5.6 mmol/l and a GFR greater than 40 mL/minute.

Discussion

This study confirms previous findings of the impact of GFR on mortality. In the transplant population we have demonstrated that the development of impaired fasting glucose is associated with a 35% increase risk of mortality and the development of new onset diabetes associated with a 2-fold increased risk. Our study further suggests that there is a negative synergistic effect of deteriorating renal function and progressive impaired glucose regulations on patient survival. This study suggests that therapeutic strategies that could both improve GFR at one year and the incidence of diabetes might be expected to improve long term patient survival.

P300

Bone mineral disorder following successful kidney transplantation: data from the UK Renal Registry (UKRR)

Lynsey Webb[1], Thomas Ben[2], Anna Casula[3], David Ansell[3], Charlie Tomson[1,3], Fergus Caskey[1]

[1]The Richard Bright Renal Unit, Southmead Hospital, Bristol, United Kingdom, [2]1st Department of Medicine, University of Debrecen Medical School, Debrecen, Hungary, [3]Renal Association UK Renal Registry (UKRR), Southmead Hospital, Bristol, United Kingdom

Background

The effect of successful kidney transplantation (KTx) on the calcium (Ca), phosphate (PO4) and parathyroid hormone (PTH) abnormalities associated with chronic kidney disease (CKD) has not been studied in large series. This study examines the prevalence of bone mineral disorder abnormalities from 3 months to 20 years post kidney transplantation.

Patients and Methods

Two cohorts were studied – an incident cohort (all patients receiving a KTx in centres reporting to the UK Renal Registry between 1997 and 2005) and a prevalent cohort (all patients alive with a functioning KTx in those centres on the 31st Dec 2006). Data on Ca, PO4 and PTH at 3, 6 and 12 months post transplant came from the incident cohort; data at 3, 5, 10 and 20 years post transplant came from the prevalent cohort. As well as the normal ranges, KDOQI CKD stage specific ranges for Ca, PO4 and PTH were studied. Patients with missing Ca and PO4 data and PTH data were excluded from the CaPO4 and PTH analyses, respectively.

Results

Amongst the 6,739 incident patients and 8,225 prevalent patients, data completeness ranged from 83-94% for the CaPO4 to 24-42% for the PTH analyses at the different time points. Due to the sample size, patients excluded due to missing data differed statistically (but not clinically) for most demographic characteristics. At 3 months, 3 years and 20 years post KTx, high Ca (>2.6 mmol/l) was observed in 20%, 7% and 6% of patients, low PO4 (<0.85 mmol/l) in 44%, 20% and 13% of patients and high PTH (CKD stage 3 >7.7 pmol/l, stage 4 >12.1 pmol/l, stage 5 >32.0 pmol/l) in 65%, 62% and 64% of patients.

Discussion

Although disorders of Ca and PO4 improve markedly following transplantation, a significant proportion of patients continue to have bone mineral disorder abnormalities – a recognised non-traditional cardiovascular risk factor. The high rate of persistent hyperparathyroidism observed in this nationally representative cohort of patients requires further study.

Poster Session

Thursday 23 April

13:30 – 14:30

Malignancy

Moderator Dr Paul Harden

P301

Post Transplant Lymphoproliferative Disorder Outcomes In Adult Renal Transplant Recipients

Muir Morton, Maria Marko, Kate Ryan, Michael Picton

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Post transplant lymphoproliferative disorder (PTLD) is a serious condition affecting 1-2% adult renal transplant recipients. This study aims to contribute to knowledge of the disease with a view to improving patient outcomes. 58 cases of PTLD, presenting over 30 years in 4012 transplants, at a single UK centre serving a population of 4 million, are reviewed.

Patients were identified from the pathology database. Medical notes, histological and radiological reports were obtained for each case. Mean age at diagnosis was 47 years and time from transplantation to diagnosis 72 months (1-211).

Survival	**1 year**	**5 year**
Patient Overall	36/53 (68%)	16/38 (42%)
Graft Overall	31/49 (63%)	12/37 (32%)
Monomorphic PTLD n=44 (76%)	26/39 (67%)	18/29 (62%)
Polymorphic PTLD n=9 (16%)	5/8 (63%)	3/6 (50%)
Early PTLD n=4 (7%)	3/4 (75%)	2/3 (67%)
Early Presentation n=13 (22%)	3/11 (27%)	3/11 (27%)
Late Presentation n=45 (78%)	31/40 (78%)	12/27 (44%)

A PTLD prognostic index score (0-3) (PIS) using age, LDH and performance score was applied to 21 patients. Patients who died had higher index scores at diagnosis. 5/21 died, all PIS >2. 14/16 survivors had PIS <2. Overall survival is poor across all histological classifications. Early onset disease has poor outcomes. The PTLD specific prognostic index appears useful in predicting high risk patients. Development of blood and tissue markers to guide treatment are needed.

P302

Development of early malignant disease in a multicentre, randomised study comparing conversion from Calcineurin inhibitors (CNIs) to Sirolimus in renal allograft recipients.

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This study recruited patients from renal units, 21 in UK and one in Dublin primarily to assess the impact of the conversion of immunosuppression from CNIs to sirolimus (Rapamune) in renal transplant recipients with eGFR 30-80 ml/min.

190 patients initially receiving CNIs (CsA, 60.6%, tacrolimus, 39,4%) were randomised (2 : 3) to continue standard therapy (N=74) or to stop CNIs (N=116) and receive a single dose of 12mg of sirolimus followed by 4mg a day, subsequent doses were adjusted to target trough level 8-16 ng/ml. Data is presented as an intention to treat analysis.

Patients were on average 4.95 ±2.4 (mean ±SD) and 4.83 ±3.0 years post transplantation before they entered the study.

There was a significant difference in the drop out rate of 14.9% for the standard and 34.5% for the conversion group (p=0.003).

By month 12, there were two episodes of acute rejection in each group (p=NS), graft survival was 94 and >99% (p=NS).

eGFR (MDRD) was not significantly different at one year from baseline for the standard treatment group 35.0 ±16.7 compared to the conversion group 37.3 ± 13.6.

During the first year after randomization, 7 (9.5%) patients in the standard treatment group and 2 (1.7%) in the conversion group experienced new malignancies (p=0.029).

In conclusion, this immunosuppressive strategy of conversion from CNI to sirolimus did not demonstrate a significant difference in eGFR, preliminary observations suggest a clinically important effect of sirolimus in reducing the rate of malignant disease.

P303

Outcome of renal transplant recipients with Post Transplant Lymphoproliferative Disorder at Nottingham Renal Transplant Unit- 20 year's experience

Sunil Daga, Linda Evans, Gavin McHaffie, Catherine Byrne

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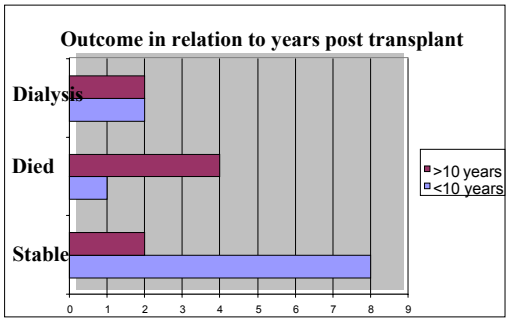
Introduction: Post-transplant Lymphoproliferative disorders are more common in renal transplant recipient (21%) than in the general population (5%). The incidence of PTLD in renal transplant recipients is of the order of 1- 2.3%. Risk factors include duration/intensity of immunosuppressants and EBV seropositivity.

Aim: To systemically look in to outcomes of renal recipients diagnosed with PTLD and identify factors affecting the outcomes.

Method: We retrospectively analysed cases over the last 20 years in our centre. 19 cases were identified from 741 renal transplant recipients. Analyses were carried out on demographic data (age, ethnicity & gender), variation in presentation, cumulative treatment doses and outcome. The cumulative doses of immunosuppressants were calculated as gram per month unit.

Results: The overall incidence of PTLD was 2.5 %. All patients were Caucasians. The time interval to diagnosis of PTLD ranged from less than 1 year to 20 years (mean 8.8 years) and cumulative dose varied widely with patients on low dosage also developing PTLD. 79 % of patients had extra nodal disease; the majority having GI / intra-abdominal disease (63%). Patients presenting acutely had GI & CNS involvement whilst those presenting chronically had lung, allograft & other intra-abdominal & nodal involvement. Data for EBV at diagnosis was poor (63% completed) but in those who were screened, all were positive. Treatment with rituximab had some advantage over reduction of immunosuppressants alone

(62% versus 50% patients had table kidney function) and fewer patients reached end stage requiring dialysis (13 % versus 25%). In our cohort 25% died, 16 % lost their transplant whilst 58% had stable renal function. 5% had acute rejection following reduction in immunosuppressants. Outcome was better in patients diagnosed within 10 years of transplantation (9% died versus 50 %). The site of involvement did not appear to influence the outcome.



Conclusion: Incidence is comparable with international data. Our data suggests survival advantage in Rituximab treated patients compared to reduction of IS alone. Outcomes were worse in patients with PTLD diagnosed after 10 years.

P304

Is the risk of transmission of intracranial malignancy overestimated? A UK Study.

Rebecca Roberts[1], Karen Wright[2], David Greenberg[2], Claire Hamilton[3], David Collett[3], Andrew Bradley[1], Christopher Watson[1]

[1]University of Cambridge Dept of Surgery, Cambridge, United Kingdom, [2]ECRIC on behalf of the UK Association of Cancer Registries, Cambridge, United Kingdom, [3]NHS Blood and Transplant, Bristol, United Kingdom

Background.

Anecdotal case reports and registry data show the potential for transmission of donor CNS malignancy, and the Council of Europe guidelines advise against the use of such donors, in particular high grade gliomas such as Glioblastoma Multiforme. We examined the UK data concerning transmission of primary intracranial malignancy from the donor to the recipient.

Methods

Data from the National Transplant Database at UKT were merged with data held by the cancer registries of England, Wales and Northern Ireland to identify all donors with current or previous intracranial malignancy. The recipients of organs from these donors were then identified at UKT and the names searched by the cancer registries to identify any post transplant malignancy in the recipient.

Results

From 1/1/95 to 31/12/01 there were 5936 for whom an NHS number or postcode was recorded so that they could be matched with cancer registry data. From these, 194 donors were identified by the cancer registries as having a past or current (at time of death) primary intracranial malignancy. These tumours included 23 glioblastomas, 9 medulloblastomas, 34 malignant gliomas and 44 astrocytomas. Fuller characterisation of the donor tumours, together with obtaining information regarding donor surgery and radiotherapy, is currently underway. Organs from these 194 donors were transplanted into 411 recipients, 26 of whom were subsequently notified as developing a malignancy within at least 2 years of transplant. Of these 26 malignancies 10 were tumours identified in the explanted liver immediately post transplant (9 hepatomas & a cholangiocarcinoma); 8 were skin cancers (inc melanoma) and 7 were lymphoproliferative disorders.

There was no incidence of transmission of any primary intracranial malignancy.

Conclusion

These data suggest all such donors may be used, but the recipients should be warned of the potential risk of transmission.

Current evidence suggests judicious use of donors with intracranial malignancy is safe.

P305

Giant Angiomyxiod Tumour in a Renal Allograft: A diagnostic dilemma

Sanjay Mehra, Bence Forgacs, Sarah Heap, Helen Denley, Hany Riad, Neil Parrott, Titus Augustine, Babatunde Campbell

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We report a case of a giant tumour in a failed transplant kidney presenting as an abdominal mass twelve years after transplantation.

A forty four year old gentleman with primary disease of Glomerulonephritis underwent a deceased donor renal transplant (mismatch 1:1:0) from a 32 year old male donor. He was immunosupressed with Neoral and Prednisolone. He had two episodes of steroid responsive rejection with full recovery of serum creatinine. The transplant failed after 8 years in 2004 and he was commenced on haemodialysis in 2005.

The paired kidney from same donor failed 5 years after transplantation and histology of transplant nephrectomy specimen showed chronic allograft nephropathy.

The patient was noted to have a protruding abdomen at a consultation for vascular access in January 2008. Examination of abdomen revealed a large, firm mass arising from the pelvis and extending up to supra umbilical region. An abdominal CT scan showed a mass measuring 14x 18x 21cm. It appeared to be arising from the left transplant kidney, encasing the iliac vessels but with a well defined capsule. It was thought to be benign. Initially, the gentleman declined surgical intervention as the swelling was asymptomatic. He consented for excision of the mass 9 months later because of pressure symptoms. An initial embolisation of the renal artery to decrease blood loss was performed prior to surgery. The mass was excised completely in two stages from the iliac vessels with an uneventful postoperative course.

The histopathologic appearance of the tumour has been discussed at three different UK centres and a final concensus of an angiomyxiod soft tissue tumour has been made. It is a tumour which is difficult to classify but has at least a potential to recur. The patient is well with no signs of recurrence at 4 months follow up. He will be seen six monthly onwards.

The incidence of neoplasia in transplant patients is much higher than in the general population. Most tumours occurring in transplanted kidneys are malignant. The incidence of renal cell carcinomas in transplanted kidneys is between 0.145 – 0.32% in reported series. (Cincinnati Transplant tumour registry, etc). The only benign tumour reported in a graft is an angiomyolipoma.

This is our first experience of a giant benign tumour completely replacing the renal allograft and presenting as a large abdominal mass. We believe this is the first case of its kind to be reported.

P306

Risk factors for Post-Transplantation Malignancy in Heart, Lung and Heart-Lung Transplant Recipients Reported by UNOS 1988-2006

Cara Baker, Andrew Brett, Alireza Jahromi, Mohammed Morsy, Iain MacPhee, Jiri Fronek, Nicos Kessaris

St George's Hospital, London, United Kingdom

AIM: To investigate the risk factors for development of post-transplant malignancy in heart (H), lung (L) and heart-lung (HL) transplant recipients.

METHODS: United Network for Organ Sharing and Organ Procurement and Transplantation Network data* as of 25/02/2008 was used. Age, gender, ethnicity, ABO match, history of pre-transplant malignancy, type of malignancy, years between transplant and cancer diagnosis and immunosuppressant used were analysed. Odds ratio (OR) or relative risk (RR) was calculated.

RESULTS: Of 40903 H, 15168 L and 934 HL recipients, 17.1%, 11.6% and 10.6%, respectively, developed malignancy post-transplantation. Diagnosis was >6 years after transplant in 51% H, 24% L and 47% HL cases. Skin cancer was the most common diagnosis. Age >50y (OR 2.7, 1.8, 1.9), Caucasian ethnicity (OR 3.4, 2.5, 1.6), previous cancer (OR H 1.3, L 1.3), immunosuppression with cyclosporine (RR 1.4, 1.3, 1.2), ATG (RR 1.6, 1.9, 1.6), OKT3 (RR H 1.4, L 1.2), steroid (RR L 1.9, HL 1.3) and azathioprine (RR 1.8, 1.6, 1.3) were associated with increased risk of cancer. Afrocarribean ethnicity (OR 0.3, 0.4, 0.1) and immunosuppression with tacrolimus (RR H 0.4, L 0.7), sirolimus (RR H 0.6, L 0.4), and mycophenolate mofetil (RR 0.5, 0.7, 0.6) were associated with reduced risk.

CONCLUSION: Age ≥50years, Caucasian ethnicity, certain immunosuppression medications and history of pre-transplant malignancy had increased risk of post-transplant malignancy in heart, lung and heart-lung transplant recipients from 1988-2006. This supports the need for close follow up and screening of transplant recipients.

*Supported by Health Resources & Services Administration contract 234-2005-370011C. The content is the author's responsibility alone.

P307

Risk factors for Post-Transplantation Malignancy in Small Intestine Transplant Recipients Reported by UNOS 1988-2006

Cara Baker, Mei Nortley, Mohammed Morsy, Iain MacPhee, Jiri Fronek, Nicos Kessaris

St George's Hospital, London, United Kingdom

AIM: To investigate the risk factors for development of post-transplant malignancy in small intestine transplant recipients.

METHODS: United Network for Organ Sharing and Organ Procurement and Transplantation Network data* as of 25/02/2008 was used. Age, gender, ethnicity, history of pre-transplant malignancy, type of malignancy, years between transplant and cancer diagnosis and immunosuppressant used were analysed. Odds ratio (OR) or relative risk (RR) was calculated.

RESULTS: Of 1320 recipients (669 male, 651 female), 5.8% developed malignancy post-transplantation. Diagnosis was within 3 years of transplantation in 73% of cases and after 6 years in 13%. While most cancer types were not reported, of those reported, lymphoma and oropharyngeal malignancies were the most common. Female recipients had higher risk than male (OR 1.5). 60% recipients were <18y, and 72% of malignancies occurred in this group. Caucasian ethnicity (OR 1.2), previous cancer (OR 3.5), immunosuppression with cyclosporine (RR 1.1), OKT3 (RR 2.5), steroid (RR1.6), azathioprine (RR 3.2) and tacrolimus (RR 1.2) were associated with increased risk of cancer. Immunosuppression with sirolimus (RR 0.5) and daclizumab (RR 0.7) were associated with reduced risk.

CONCLUSION: Female recipients, Caucasian ethnicity, certain immunosuppressants and history of pre-transplant malignancy had increased risk of post-transplant malignancy in small intestine transplant recipients from 1988-2006. This supports the need for close follow up and screening of transplant recipients.

*Supported by Health Resources & Services Administration contract 234-2005-370011C. The content is the author's responsibility alone.

P308

High numbers of FOXP3+ T Cells and poor lymphocyte proliferation identifies patients at high risk of developing squamous cell cancer after renal transplantation.

Robert Carroll[1,2], Paul Harden[2], David Segundo Arribas[1], Taane Clark[3], Kathryn Wood[1]

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Organ Transplant Recipients (OTR) are up to 200 times more likely to develop cutaneous squamous cell cancer (SCC) than the general population. Increased risk is associated with age and duration of immunosuppression. In the general population $FOXP3^+$ T cells are a sign of poor prognosis in cancer. We therefore assessed the relationship of $FOXP3^+$ T cells and SCC in Kidney Transplant Recipients (KTRs).

In a case-control study subjects were matched for age, sex and duration of immunosuppression. 60 KTRs with at least 1 SCC were matched to 50 KTRs without SCC. Using multi-parameter flow cytometry, peripheral blood lymphocyte (PBL) populations were assessed. PBL were also stimulated with phytohaemagluttinin in vitro and proliferation assessed by thymidine incorporation. Using conditional logistic regression; demographic, immunosuppressive and immunological factors were assessed to determine which factors associated independently with history of SCC (see table).

Multivariate analysis: risk of SCC			
	OR	95% CI	P value
Absolute number of FOXP3+ cells	1.12	1.06-1.18	<0.001
PHA stimulation <10000 counts per min	5.61	1.82-17.3	0.003
Per 10% increase in CD8+ CD28- T cells	1.2	1.02-1.40	0.025
Per 10% increase in CD8+ Central memory T cells	0.53	0.31-0.93	0.026

Poor lymphocyte proliferation was partly explained by the proportion of CD8+ CD28- T cells in peripheral circulation. Immunosuppressive regimen was retrospectively assessed post-transplantation; steroid cessation occurred in 34 (68%) of the no SCC group compared to 26 (43%) in the SCC group (Fishers exact test; p=0.013). There were no other significant differences in immunosuppressive load between the two groups.

Although there are multiple confounding factors affecting immune profiles we have defined multiple immunological parameters that independently define risk of developing SCC. Prospective and laboratory investigator blinded studies are ongoing to determine the translational potential of these assays.

Poster Session

Wednesday 22 April

13:00 – 14:00

Ischaemia Reperfusion Injury

Moderator Mr Stephen McNally

P309

Effect of Ischemia-reperfusion and Anti-Thymocyte Globulin on the perioperative cytokine profile in clinical renal transplantation.

Manimaran Ranganathan[1], Edward Frances[2], Edvardo Chavez[2], Robert Walters[2], Argiris Asderakis[1], Rafael Chavez[1]

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Background: Ischemia reperfusion Injury (IRI) is a potential cause of delayed graft function and primary non-function of solid organ transplants. Cytokines are among the main mediators of inflammation, acting through a complex network. Blood cytokine levels can be affected by administration of immunosuppressive antibodies that act directly on white blood cells, such as Anti-Thymocyte Globulin (ATG). In this study we assessed the effect of reperfusion and the first dose ATG on blood cytokine levels during perioperative period in clinical renal transplantation.

Materials and Methods: Peripheral blood from 20 adult renal transplant recipients was collected at four time-points; i.e: at induction of anaesthesia, just before reperfusion of the graft, 1 hour after reperfusion and 24 hours after reperfusion. 27 different cytokines were measured in those serum samples by Luminex based Bioplex suspension array method. Patients were divided into 3 groups according to the source of the graft: Live Donor (LD) (n=4), Deceased Donor (DD) (n=8) and Donor following Cardiac Death (DCD) graft group (n=8). DCD recipients received an initial dose of 1.25 mg/kg of ATG in intravenous infusion over 4 hours, following induction of anaesthesia.

Results and Discussion: In LD and DD groups, there were no major changes in cytokine concentrations at any time point. In DCD group, there were increased levels of cytokines 1 hour after initiation of ATG infusion, before reperfusion of the graft. Pro-inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-α and IFN-γ were elevated (p=0.02, 0.06, 0.05, 0.05 and 0.02 respectively) as compared to their induction sample. Interestingly the anti inflammatory cytokine-IL-10 was also elevated (p=0.02). Raised levels of cytokines were already observed before reperfusion of the grafts in DCD renal transplants without an obvious physiological effect on intra-operative vital parameters.

Conclusion: We conclude that the first dose ATG infusion in clinical renal transplantation is associated with significant elevation of both pro and anti inflammatory cytokines without any obvious immediate physiological changes. Reperfusion by itself had no apparent impact on the perioperative cytokine profile as shown by the LD and DD groups.

P310

Inactivation of Lactate Dehydrogenase by Hydrogen Peroxide: Implications for *in vitro* Models Mimicking Free Radical Injury.

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Lactate dehydrogenase (LDH) is a constitutively expressed cytosolic enzyme released into the supernatant following damage to the cell membrane. Spectrophotometric measurement of LDH activity is used to measure cell cytotoxicity in response to injurious stimuli, and hydrogen peroxide is frequently used in vitro to produce free radical damage.
We used H_2O_2 in an in vitro model mimicking free radical injury in renal cells, and assessed necrosis by measuring LDH in the supernatant. We postulate that there is a deleterious interaction between LDH and H_2O_2 which is affected by temperature and medium. We therefore investigated :-

1. Renal tubular epithelial cells (HK-2) exposed to increasing concentrations of H_2O_2 (0.03 - 2mM) in UW solution at 4ºC. Measured LDH (Roche) was inversely proportional to H_2O_2 concentration.

2. Increasing amounts of pure LDH (Sigma) from 1.25U/ml to 20U/ml in UW solution and in culture medium incubated at 37C and at 4C for 4 hrs. Significantly reduced levels of LDH were detected in UW at 4C and 37C at every concentration ($p<0.003$, ANOVA).

3. Pure LDH from 1.25U/ml to 20U/ml was incubated in UW for 4 hrs with increasing concentrations of H_2O_2. LDH activity was significantly reduced in a dose dependent manner ($p<0.05$, ANOVA with Tukey's multiple comparison test).

We concluded that H_2O_2 (partially) inactivated or destroyed LDH in solution, in a concentration dependent manner. We would therefore urge caution with interpretation of results when H_2O_2 and LDH are co-incubated.

P311

Effects of inducible nitric oxide synthase on renal blood flow and function in a model of non-heartbeating transplantation

Phillip Yates, Sarah Hosgood, Michael Nicholson

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Background:

There is an increasing reliance on marginal organs from non-heartbeating (NHB) donors. Inhibition of ischaemic reperfusion injury (IRI) may improve graft outcomes in NHB donors. The role of nitric oxide (NO) in the generation of IRI is pivotal. Following ischaemic injury there is an upregulation of inducible nitric oxide synthase (iNOS). NO maybe generated from the endothelium of the injured kidney or infiltrating leukocytes. The protein 1400W is a highly specific inhibitor of iNOS. Our group has previously described a porcine, blood perfusion model of NHB transplant reperfusion.

Methods:

Kidneys were randomized into four groups. Group one (control) kidneys were perfused with whole blood (WB) (n=6), group two with leukocyte-depleted blood (LDB) (n=6), group three whole-blood+1400W, and group four LDB+1400W.

Renal blood flow parameters were recorded. Analysis of serum and urine samples was performed hourly. Statistical analysis was performed.

Results:

Parameter	WB	LDB	WB+1400W	LDB+1400W	P-value
AUC Cr (µmol/L.h)	2327±154	1907±364	2189±104	3062±227	0.01
AUC CrCl (ml/min/100g.h)	0.96±0.32	4.5±2.7	2.37±0.97	0.29±0.49	0.004
AUC RBF (ml/min/100g.h)	270±87	574±151	274±143	61±37	0.002
AUC IRR (mmHg/min.hr)	13.4±7	6.9±4	17.8±8.5	57.5±10	0.002

Area under curve (AUC), Creatinine (Cr), Creatinine Clearance (CrCl), Renal Blood Flow (RBF), Intrarenal Resistance (IRR)

Conclusion:

These results demonstrate that inhibition of iNOS at reperfusion has a deleterious effect on intial intrarenal resistance. iNOS expression is thus necessary to maintain RBF in the immediate post-reperfusion period.

P312

The effect of leukocyte depletion on reperfusion injury in a model of non heart beating kidney transplantation

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Background: The need for donor kidneys far outstrips the availability of organs. For this reason there is an increasing reliance on marginal organs such as those from non-heartbeating donors. Non-heartbeating (NHB) kidneys are at increased risk of delayed graft function and reduced long-term graft survival. Amelioration of ischaemic reperfusion injury (IRI) may improve graft outcomes in NHB donors. Our group has previously described a porcine, normothermic whole-blood perfusion model of NHB transplant reperfusion. White cells have been implicated in the generation of IRI in renal transplantation. The aim of this study was to assess the effect of white cells on the reperfusion injury in NHB kidneys.

Methods: Kidneys retrieved from slaughter-house pigs were exposed to 25 minutes warm ischaemia and cold-stored for 18 hours. Kidneys were randomized into two groups. In group one kidneys were perfused with whole blood (n=6) and in the second group with leukocyte-depleted blood (LDB) (n=6). Renal blood flow and perfusion pressure were recorded. Biochemical analysis of serum and urine samples was performed hourly. Tissue samples were taken for histological analysis. Statistical analysis was performed.

Results: Results demonstrated that renal blood flow, intra-renal resistance, urine output and creatinine clearance were significantly better in the LDB group than controls.

Parameter	WB	LDB	p-value
AUC Cr (µmol/L.h)	2327 ± 154.1	1907 ± 364.7	0.032
AUC Cr Cl (ml/min/100g.h)	0.96 ± 0.3	4.5 ± 2.7	0.016
AUC RBF (ml/min/100g.h)	270.3 ± 86.7	574.4 ± 151.0	0.002
AUC IRR (mmHg/min.h)	13.39 ± 7.3	6.86 ± 4.0	0.009

Area under curve (AUC), Creatinine (Cr), Creatinine Clearance (CrCl), Renal Blood Flow (RBF), Intrarenal Resistance (IRR)

Conclusions:

Perfusion with LDB improves initial perfusion of NHB kidneys and improves immediate post-ischaemic renal function. These results indicate that modulation of white cell populations in NHB donor transplantation has the potential to improve immediate graft function and ameliorate IRI.

P313

Mitochondrial protection by oxygenated perfusion after warm ischaemia

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INTRODUCTION: We have previously shown that oxygenated perfusion at physiological temperature resuscitates non-heart-beating-donor (NHBD) livers after warm ischaemic injury. The mechanism of the benefit conferred by oxygenated perfusion remains unclear. Mitochondria play a central role in hepatic ischaemia-reperfusion injury. We have examined mitochondrial functional changes during ischaemia-reperfusion in NHBD livers and the relationship of these with hepatocellular injury.

METHODS: Porcine livers were retrieved after cardiac arrest and divided into three groups: Group 1 (Control, n=5) no warm ischaemic injury; Group 2 (n= 5) 60 minutes of warm ischaemia; Group 3 (n= 5) 60 minutes of warm ischaemia followed by *in-situ* oxygenated perfusion. All livers were then cooled (60 minutes) during the bench work and then connected to an oxygenated normothermic extracorporeal perfusion circuit for 24 hours for assessment of function. Mitochondria were isolated from sequential liver biopsies and analysed for: ATP content; mitochondrial function (respiratory control ratio (RCR); cytochrome *c* release; caspase activation and mitochondrial level of superoxide dismutase. The perfusate was analysed for serum transaminase and base deficit. Bile production was measured. Apoptotic and necrotic changes were examined by TUNEL and haematoxylin staining respectively.

RESULTS: Group 1 livers maintained normal mitochondrial function during cold preservation and subsequent reperfusion with minimal hepatocellular damage.

In Group 2 livers, cellular ATP levels reduced significantly during 60 minutes of warm ischaemia ($p<0.01$), with minimal change in mitochondrial function. However, subsequent cold preservation produced a significant decline in mitochondrial function (RCR 3.9±0.4 vs. 2.4±0.2 $p<0.001$) with parallel decline in mitochondrial ATP level ($p= 0.001$). Mitochondrial injury was associated with cytochrome *c* release, caspase activation and increased hepatocellular injury as evidenced by raised transaminase release ($p<0.05$). In Group 3 livers, in situ oxygenated perfusion improved mitochondrial RCR ($p<0.05$) and ATP levels significantly ($p< 0.01$). This effect was maintained throughout the perfusion period with greater functional recovery with bile production ($p<0.05$) compared to Group 2.

CONCLUSIONS: These data suggest that mitochondria sustain progressive damage during sequential warm and cold ischaemia followed by reperfusion, leading to cell death in NHBD livers. *In-situ* oxygenated perfusion immediately following warm ischaemia confers mitochondrial resilience to ischaemia-reperfusion injury and may have therapeutic benefits in NHBD transplantation.

P314

The physiological effects of hydrogen sulphide on ischemia reperfusion injury in non heart beating donor kidneys.

Sarah Hosgood, Phillip Yates, Michael Nicholson

University Hospitals of Leicester, Leicester, United Kingdom

Introduction

Therapies to alleviate ischemia reperfusion (I/R) injury and improve graft function have an important role in kidney transplantation. This study used a porcine model of non heart beating donor (NHBD) kidneys to investigate the effects of hydrogen sulphide on I/R injury.

Methods

Porcine kidneys were subjected to 25 minutes of warm ischemia and 18 hours of cold storage. They were then reperfused *ex vivo* with oxygenated autologous blood to assess renal function for a period of 3 hours. Kidneys were randomised into 4 groups: (n = 4) Control, 1mM, 0.5mM and 0.1mM hydrogen sulphide. Hydrogen sulphide was infused for 10 minutes before and after reperfusion.

Results

1mM and 0.5mM hydrogen sulphide significantly improved the renal blood flow and lowered intra-renal resistance ($P =< 0.05$). Serum creatinine (Cr) fall and Creatinine clearance (CrCL) were significantly improved with the treatment of 0.5mM and 1mM hydrogen sulphide. (Area under the curve (AUC) Cr µmol/L.h; control 2257 ± 152.1, 1mM 1549 ± 286.6, 0.5mM 1647 ± 310.1, 0.1mM 1812 ± 328.7; $P = 0.013$) (AUC CrCl ml/min/100g.h; control 1.5 ± 1.5 1mM 5.2 ± 2.35, 0.5mM 7.57 ± 6.33, 0.1mM 5.57 ± 2.87;$P =0.04$).

Conclusion

This study provides new evidence of the physiological role of hydrogen sulphide in porcine kidneys. Hydrogen sulphide improved renal blood flow and ameliorated the renal dysfunction associated with ischaemic damage. It therefore has potential as a new therapy against I/R injury in NHBD kidney transplantation.

Poster Session

Thursday 23 April

13:30 – 14:30

Post-Transplant Medical Complications 2

Moderator Dr Andrew Lewington

P315

Correlation between insulin resistance indices and insulin sensitivity in non-diabetic renal transplant recipients maintained on tacrolimus treatment

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

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Introduction. Insulin resistance is common post-transplantation and combines with declining insulin secretion to cause new-onset diabetes after transplantation. It is also implicated in the pathophysiology of the metabolic syndrome. Insulin resistance indices have been validated in non-diabetic renal transplant recipients on ciclosporin treatment. Similar validation has not been obtained in transplant recipients on tacrolimus, which is more diabetogenic. This study aimed to validate various insulin resistance indices against insulin sensitivity in non-diabetic renal transplant recipients maintained on tacrolimus.

Methods. Fasting insulin, fasting glucose:insulin ratio, homeostatic model assessment (HOMA) index, quantitative insulin sensitivity check index (QUICKI) and McAuleys index were assessed for correlation against insulin sensitivity as derived by mathematical minimal model analysis from an intravenous glucose tolerance test (IVGTT). Pearson or Spearmans correlation was used for parametric and non-parametric analysis respectively. A p value < 0.05 was considered statistically significant.

Results. All insulin resistance indices analyzed in this study failed to correlate significantly with insulin sensitivity as derived from the IVGTT: fasting insulin ($r = -0.033$, p = NS), fasting glucose:insulin ratio ($r = 0.018$, p = NS), HOMA ($r = -0.065$, p = NS), QUICKI ($r = 0.057$, p = NS) and McAuleys index ($r = 0.009$, p = NS). All indexes correlated significantly with each other index (all $p < 0.001$). Insulin sensitivity was found to correlate with pulse pressure ($r = -0.41$, $p = 0.015$), HDL cholesterol ($r = 0.35$, $p = 0.039$), CRP ($r = -0.42$, $p = 0.011$) and HbA1c ($r = -0.37$, $p = 0.029$).

Conclusions. We have demonstrated poor correlation between various surrogate estimates of insulin resistance, previously validated in non-diabetic ciclosporin treated renal transplant recipients, in non-diabetic renal transplant recipients maintained on tacrolimus as a primary immunosuppressant. Further work is required to find a validated simple tool to estimate insulin resistance in these patients.

P316

HbA1c is independently associated with early pathophysiological parameters indicative of worsening glycaemic metabolism post-transplantation

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

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Introduction. Hyperglycaemia is common post-transplantation. The hyperbolic equilibrium between first-phase insulin secretion (FPIS) and insulin sensitivity (IS) is termed the disposition index (DI). In the context of insulin resistance, declining FPIS reflects the first stage of new onset diabetes after transplantation (NODAT) as the DI is lowered. Early identification of these defects is desirable as considerable physiological dysfunction of these glycaemic parameters can exist before the onset of hyperglycaemia. HbA1c has been found to detect subclinical NODAT better than fasting glucose. We conducted multivariate analysis to determine which simple glycaemic variables could be utilized as surrogate markers of declining glycaemia post-transplantation.

Methods. FPIS, IS and DI were calculated by minimal model analysis from intravenous glucose tolerance tests. Second-phase insulin secretion (SPIS) was calculated from the meal tolerance test. 40 of both tests were conducted in non-diabetic, tacrolimus treated renal transplant recipients with additional clinical/biochemical analysis. Linear regression model was used for univariate analysis and statistically significant variables entered into a multivariate model for analysis. A p value < 0.05 was considered significant.

Results. HbA1c independently correlated with first phase insulin secretion ($R = 0.106$, $p = 0.049$), insulin sensitivity ($R = 0.136$, $p = 0.029$) and disposition index ($R = 0.201$, $p = 0.006$). Fasting glucose and insulin correlated with second phase insulin secretion alone (fasting glucose, $R = 0.165$, $p = 0.015$; insulin, $R = 0.311$, $p = 0.001$). From all clinical/biochemical variables tested, only HbA1c was independently associated with all components of the glycaemic hyperbolic equilibrium.

Conclusion. HbA1c independently correlates with FPIS, IS and DI. Fasting glucose and insulin only correlate with SPIS. As declining FPIS is the first quantifiable defect of glucose metabolism in the context of insulin resistance, the association with HbA1c suggests it may be a valuable marker to monitor for glycaemic abnormalities post-transplantation.

P317

Disorders of mineral and bone metabolism are associated with reduced patient survival following kidney transplantation

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The long-term impact of chronic kidney disease related mineral and bone disorder (CKD-MBD) and arterial stiffness following kidney transplantation has not been defined. We studied the association of serum phosphate and calcium levels, and surrogate measures of arterial stiffness, determined by both arterial augmentation index (AIx) and the timing of the return of the reflected arterial wave (Tr), with long term kidney transplant recipient and allograft survival.

270 prevalent adult (≥18 years) renal transplant recipients (mean 81±69 months post transplantation) were prospectively studied, with a subsequent median follow up of 88 months. Detailed demographic, clinical and laboratory data, in addition to both peripheral and central non-invasive pressure measurements were recorded. Cox regression and Kaplan-Meier survival analysis were used to determine the association of candidate variables with patient and graft survival.

Higher serum phosphate and calcium concentrations were associated with reduced patient survival following adjustment for other covariates ($p<0.001$ and $p=0.04$ respectively). Every 1mmol/L increase in serum phosphate and serum calcium resulted in a 7-fold and a 7.6-fold increase in the risk of death respectively. Serum phosphate and calcium were associated with death-censored graft loss on univariable ($p<0.001$ and $p=0.02$ respectively), but not multivariable analysis. AIx and Tr were not associated with mortality or graft loss.

This is the first report to demonstrate that higher serum phosphate levels are associated with increased mortality in kidney transplant recipients. It highlights the need for randomised trials assessing current interventions available for improving phosphate control following renal transplantation.

P318

Management of Hyperparathyroidism in renal transplant patients

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Background

Parathyroidectomy(PTH) has been shown to deteriorate graft function in patients who have had a renal transplant. We wanted to see if the deterioration in renal function was affected by the timing of the PTH, i.e prior to renal transplant compared to patients who had the renal transplant first.

Methods

Patients who underwent PTH and renal transplant between 1987 and 2007 were identified from the transplant database at the Royal Liverpool University Hospital. Fifty seven patients were identified. Serum calcium, creatinine, parathyroid hormone levels were retrieved and analysed using SPSS version 12.0.

Results

Increased deterioration in renal function was observed in patients who underwent PTH post renal transplant compared to having PTH first, but the difference was not found to be statistically significant. Of the patients who had a renal transplant first, five patients showed a significant worsening of graft function following parathyroidectomy and needed dialysis within a year. These patients were found to have a high creatinine. When patients who had a renal transplant first were divided into high and low creatinine groups, there was a statistically significant difference in the rate of change of creatinine (Mann Whitney U test p=0.03) between the high creatinine group (mean 82, 95% CI: 57.2-106.4) and low creatinine group(mean 40, 95% CI: 8.5-80.4).

Conclusion

Parathyroidectomy is an efficient way to treat hyperparathyroidism, but represents a risk for impairing graft function. By identifying patients who are at high risk of developing renal impairment and considering medical therapies first, the graft function of patients with decreased renal function may be prolonged.

P319

The incidence, nature and risk factors for stroke following renal transplantation

Michelle Willicombe, Nicky Kumar, Ka kit Chan, Adam McLean, Neill Duncan, David Taube

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There are few reports describing the nature, incidence and outcome of stroke following renal transplantation in the modern era of immunosuppression.

637 patients [385m, 252f, mean age 43.6 ± 14.5 years] transplanted between 2000 and 2007 receiving our monoclonal antibody induction, steroid sparing [steroids for the first week post transplant] and tacrolimus based regime were included in this study

580 patients received a kidney alone and 57 patients received a simultaneous kidney and pancreas transplant [SPK]. 139/637 [21.8%] patients were diabetic nephropaths. Stroke was defined as a neurological event with associated CT and or MR findings.

36 /637 [5.6%] patients had strokes. 34/36 [94.4%] patients had cerebral infarcts and only 2 patients had cerebral haemorrhages. Stroke was significantly [$p < 0.003$] more common in the patients with SPKs [9/57 (15.8%)] when compared with patients with kidney transplants alone [27/580 (4.7%)

The mean age of the patients at the time of the stroke was 51.4 ± 12.9 years.

Cumulative risk of stroke post transplant at 1, 3, 5 years was 2.2%, 4.6% and 12.5% respectively. Patient survival at 1, 3 and 5 years in the stroke group was 94.2%, 94.2% and 90.0% respectively. Censored allograft survival was 100% at 1 and 3 years and 90.8% at 5 years. The results were not significantly different from patients who did not have strokes. Only 1/636 patients died as a result of stroke.

Multivariate analysis [Cox Regression] shows that age and diabetes were associated with a higher risk of stroke [$p<0.05$]. Pre-emptive transplantation and male gender were associated with a lower risk of stroke [$p<0.05$]. Blood pressure was no different in the stroke group from the non-stroke group. We found that an acute rejection episode was significantly associated with stroke, 11/36 patients had rejection prior to their stroke [$p<0.05$].

This study shows that stroke is a rare complication of modern transplantation, is more frequent in diabetics, SPK recipients and patients who have had an acute rejection episode. It is associated with a low mortality and is mainly due to cerebral infarction rather than haemorrhage.

P320

Persistent hyperparathyroidism following renal transplantation can be treated safely and effectively with cinacalcet

Michelle Willicombe, Henry Boardman, Nilesh Pareek, Ka kit Chan, Neill Duncan, David Taube

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Although cinacalcet (CT) is widely used to treat hyperparathyroidism in patients with end stage renal failure, pre and post the initiation of dialysis, there are few reports of its use following renal transplantation. This study reports the largest single use of this agent in stable renal transplant recipients.

The records of 745 patients receiving a tacrolimus based and steroid sparing protocol were analysed. 25/745 [3.4%] patients [13m,12f; mean age 48.1 ±10.9 yrs] are currently receiving cinacalcet for persistent hyperparathyroidism. 14/25 patients received CT pre-transplantation and all had CT stopped at time of transplantation as part of our protocol. The mean PTH at time of transplant was 86 ± 54.1 pmol/l.

All patients developed hypercalcaemia [corrected Ca > 2.6 mmol/l] post transplant [mean time to hypercalcaemia was 27 ± 67days] with a mean serum calcium and phosphate at the start of CT, 2.8 ±0.2 and 0.7 ±0.2 mmol/l respectively. Mean PTH level was 76.4 ±38.6pmol/l and the mean creatinine was 125 ±35 µmol/l. Patient follow up is 2.89 ± 2.0 years. Mean dose of CT is 58.8 ± 28 mg/day with an average annual cost [BNF list price] of £3226.52.

Patient and allograft survival was 100%. There was no significant difference in allograft function or rejection episodes between those patients receiving CT compared with the other recipients. 14/25 patients had biopsies post CT therapy and 3/14 showed evidence of tubular calcification. There was a significant fall in PTH post CT introduction [17.1 ±8.3 pmol/l, $p<0.001$] and serum calcium [2.44 ± 0.2 mmol/l, $p<0.001$]. There was no change in phosphate levels [0.079 ±.02, $p=0.58$]. There was no significant change in plasma creatinine during the first month of CT therapy and no patients had a renal biopsy during this time for allograft dysfunction. No patients had to have CT withdrawn due to side effects.

This study shows that a small but significant proportion of our transplant patients are receiving CT for persistent hyperparathyroidism. CT is effective and not associated with allograft dysfunction or significant side effects. CT is expensive and it may be more effective to consider subtotal parathyroidectomy for these patients pre-transplantation.

Poster Session

Wednesday 22 April

13:00 – 14:00

Basic Science 1

Moderator Dr Julian Pratt

P321

An Assessment of an Indirect Allorecognition Model of Cardiac Allograft Vasculopathy

Batool Hariri, Ying Xu, Ann Mc Cormack, Marlene Rose

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Background Chronic allograft vasculopathy (CAV) remains the major obstacle to long-term cardiac allograft survival. The purpose of this study was to identify new markers of CAV and humoral rejection, utilizing a single MHC class I-disparate rat model of CAV. Here we have assessed the features of atherosclerotic lesions posttransplant, determined the relative contribution of antibody and T cells and endothelial cell attrition and presence of biomarkers in this model. **Methods** Prior to transplant, PVG.R8 and PVG.RT1^{u} rat recipients were thymectomised and treated with anti-CD8 monoclonal antibody. PVG.RT1^{u} donor hearts were heterotopically transplanted into allogeneic (PVG.R8) or syngeneic (PVG.RT1^{u}) recipients. Donor hearts were removed at 2,4 and 8 weeks and quantitated morphometrically for lesion development, presence of smooth muscle cells (SMC), leukocytic infiltration, biomarkers, CD31 and C4d. The biomarkers were PI3K, Bcl-2 and caspase-3 for antibody-mediated rejection, NF-κB for T cell activation and HIF-1α, Hsp25 p38-MAPK and Bax for stress responses. **Results** All allografts showed chronic rejection including presence of SMCs in the intima of occluded vessels. Elastin-positive vessels showed a mean luminal occlusion of 6±3.5% (syngeniec) and 29±6% and 58±2% for allogeneic transplants 4 and 8 weeks posttransplant, respectively. Flow cytometry revealed depletion of CD8^{+} T cells in thymectomised animals compared to non-treated rats of the same strain and age (4.5-2.4% vs 23%) and presence of alloantibody. There was significantly more T cells in allografts with CAV compared with syngeneic grafts (P<0.01), however, the majority of CD4-positive cells infiltrating allografts were macrophages (>70 CD11b vs 24.7 TCR+ve at 4 weeks; 22.5 CD11b vs 8.5 TCR +ve 8 weeks). There was extensive capillary C4d deposition in the myocardium of allografts, compared to no C4d in syngeneic grafts. There was no difference in numbers of CD31-positive endothelial cells in allogeneic and syngeneic grafts at 4 weeks posttransplant. Hsp25 was more abundantly expressed in the myocytes of allogeneic transplants compared with syngeneic transplants. No other biomarkers were detected. **Conclusion** We have verified that this strain combination develops CAV with features similar to clinical humoral rejection (predominance of macrophages and capillary C4d). The upregulation of Hsp25 may reflect hypoxic injury. This is a suitable model to explore new biomarkers of antibody mediated CAV.

P322

Human memory T cell responses to allogeneic dendritic cells are effectively costimulated by both CD80 and CD86.

David Game, Anthony Dorling

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Introduction: With the widespread use of therapeutic lymphodepletion strategies in autoimmune disease and transplantation, the role of memory T cells in harmful immune responses is increasingly recognised. It has been shown previously, using transfected fibroblasts, that memory T cells are effectively costimulated by CD80 but take a negative signal from CD86. Differential CD80 and CD86 expression could therefore be an attractive method of switching off memory T cell responses.

Aim: To test whether differential expression of CD80 and CD86 on human dendritic cells influences memory T cell responses.

Method: Mature dendritic cells were cultured from monocytes with IL4 and Gm-CSF for 5 days and LPS for the final 24 hours as previously described. High expression of CD80, CD86 and HLA-DR was measured by flow cytometry. Allogeneic naïve (CD3+CD45RA) and memory (CD3+CD45RO) T cells were purified using bead selection. Mixed lymphocyte cultures were devised with and without blocking antibodies for CD80 or CD86. Cell proliferation was measured by thymidine incorporation.

Results: Flow cytometry consistently demonstrated that expression of CD86 and HLA-DR was dramatically increased by LPS and CD80 less so (figure 1). When CD86 was blocked, cell proliferation was almost abolished for both naïve and memory T cell populations. Conversely when CD80 was blocked there was only a slight reduction in T cell proliferation: no differential response was seen for naïve versus memory cells. Similar results were found for IFNγ secretion.

Conclusion: Unlike transfected fibroblasts, mature human dendritic cells, which express high levels of CD86, predominantly costimulate naive and memory cells by CD86. These results suggest that, on their own, manipulation of CD80 and CD86 expression by DCs will not be a useful intervention in the selective inhibition of memory T cell responses. We have not excluded a role for other costimulatory molecules on memory cell – DC interactions.

P323

The functional effect of platelet endothelial cell adhesion molecule (PECAM-1/CD31) gene polymorphism

Rajesh Sivaprakasam, Eleanor Bolton, Vasilis Kosmoliaptsis, Andrew Bradley, Craig Taylor, Reyna Goodman

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Introduction: Platelet endothelial cell adhesion molecule-1 (PECAM-1) plays an important role in leukocyte-endothelial cell diapedesis. Single nucleotide polymorphisms of PECAM-1 encoding amino acid substitutions at positions 98 (leucine /valine [L/V]), 536 (serine/asparagine [S/N]) and 643 (arginine/glycine [R/G]) results in two common haplotypes (LSR and VNG), and we previously identified a correlation between donor heterozygosity for PECAM-1 genotype and increased incidence of acute graft-versus-host disease following haematopoietic stem cell transplantation. In this study, we have investigated the functional role of PECAM-1 genotype on leukocyte diapedesis.

Methods: We examined the interactions between peripheral blood (monocytes & neutrophils) and activated human umbilical vein endothelial cell monolayers with and without shear stress *in vitro*. We also determined the role of stereochemical properties of amino acid substitution at position 98 using the Modeler6v2 programme to address the observed effect of PECAM-1 heterozygosity.

Results: There was a significant increase in firm adhesion of heterozygous monocytes ($P<0.0002$) and neutrophils ($P<0.0001$), accompanied by an increase in PECAM-1 dependent transmigration across endothelium ($P<0.0001$). The modelling studies demonstrated that the superimposed orientation of domain-1 relative to the axis of domains-2 and -3 differed markedly between the two molecules.

Conclusion: This is the first observation of the functional effect of PECAM-1 heterozygous genotype on the stages of leukocyte diapedesis. The structural modelling of PECAM-1 suggests a conformational change in the protein resulting in the homodimer formation and may differentially alter the leukocyte-endothelial cell interaction.

P324

Effect of different glycolipid ligands and accessory molecule blockade on NKT cell activation: Potential pathways to reinforce transplantation tolerance?

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Natural Killer T (NKT) cells are a recently identified subset of T cells characterised by rapid cytokine secretion in response to glycolipid ligands. The effect of such rapid activation in transplantation remains unclear, and the effect of monoclonal antibody (mAb) treatment on *In vivo* NKT cell function remains unknown.

We determined the *in vivo* effect of mAbs used in experimental tolerance induction on NKT cell function (anti-CD4 mAb YTS177 and anti-CD154 mAb MR1). The specific invariant NKT cell ligand, αGalCer increased spleen NKT cell numbers 3-fold. However, this was inhibited by pre-treatment with both mAb, although mAb treatment did not affect expression of NKT activation markers induced by αGalCer. However, MR1 inhibited secretion of the Th1 cytokines IFN-γ, IL-1, IL-2, and TNF-α by 50-80% at multiple early time points (6h $p=0.002$, 12h $p=0.07$, 24h $p=0.003$) whilst augmenting IL-10 secretion 3-fold after 12 hours, $p= 0.02$. In contrast, YTS177 did not alter αGalCer induced cytokine production.

We further polarised NKT cell cytokine production using novel NKT glycolipid ligands OCH and C-Glycoside, which bias NKT cells toward Th2 and Th1 cytokines, respectively. Using these ligands, mAb pre-treatment reduced NKT number 3-5 fold following treatment with C-Glycoside, but not with OCH. Similarly, mAb treatment only affected expression of NKT activation markers induced by C-Glycoside activation, but not OCH. Thus in addition to polarising NKT cell cytokine secretion, glycolipids ligands have different effects on NKT cell activation in the presence of mAb.

Our findings indicate that NKT cell responses can be manipulated by mAb treatment and activation with different glycolipids ligands. We postulate that this ability to alter NKT cell phenotype and bias an early Th1 or Th2 cytokine secretion has important consequences for subsequent immune activation after transplantation, and may facilitate tolerance induction. These studies are currently underway in the laboratory.

P325

Expression and Regulation of Chemokine Scavenger D6 During Cardiac Allograft Rejection

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Background: Chemokines control the influx of leukocytes into rejecting allografts. As well as signalling receptors, chemokines also bind to non-signalling decoy receptors that are thought to have scavenging properties. The decoy receptor D6 binds and internalises at least 12 proinflammatory chemokines. There are currently no studies examining the expression of D6 during allograft rejection.

Methods: 16 cardiac allograft biopsies were stained for D6 and chemokine expression. Expression of D6 in leukocyte cell lines in response to cytokine treatment was examined by Western blotting and immunofluorescence. D6-mediated chemokine scavenging was determined by incubating cells with chemokine for 3 hours; supernatants were collected and ELISA performed to quantify the residual chemokine.

Results: D6 expression showed a positive correlation with increasing severity of rejection ($p<0.05$). D6 expression was localised to graft infiltrating leukocytes. *In vitro* staining detected some expression of D6 in resting monocytes. The transplant-associated cytokines IFN-γ and TGF-β were applied to THP1-monocyes in order to identify a possible regulator of D6; 10ng/ml TGF-beta caused a strong upregulation of D6. The functional consequences of enhanced D6 expression were examined by *in vitro* chemokine scavenging assay; cells treated with TGF-beta were significantly more efficient at scavenging the chemokine CCL5 (60%, $p<0.01$).

Conclusions: This study describes the first examination of the decoy chemokine receptor D6 during human allograft rejection. We present the novel observation of TGF-beta as a cytokine able to control D6 expression and speculate this may provide a pathway to regulate inflammation.

P326

Complement synthesis by human glomerular endothelial cells

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Introduction The complement system has an integral role in the pathogenesis of antibody mediated rejection (AMR) in renal transplant recipients. Previously we found no evidence of systemic activation of the classical, alternative or mannose-binding lectin complement pathway during episodes of AMR, suggesting a local process may be involved. Local synthesis by renal endothelial cells of complement factors, in particular C3, has been implicated as a possible source. Given that peritubular capillary C4d is a hallmark of AMR, we sought to demonstrate C4 production by microvascular endothelial and, in particular, glomerular endothelial cells.

Methods Human microvascular endothelial cells (HMEC-1) and conditionally immortalised glomerular endothelial cells (ciGEnC) were cultured under laboratory conditions to 80% confluence. These were stimulated with TNF-α (10ng/nl), LPS (5mcg/ml) and IFN-γ (1000U/ml) for 12, 24 and 48 hours.

Results Western blot analysis of HMEC-1 lysates showed C4 synthesis on stimulation (maximally by LPS). Unstimulated cells did not appear to synthesize C4. A similar pattern for C3 was observed.

Western blot of cytokine-stimulated ciGEnC confirmed C3 and C4 production. Although all cytokines enhanced complement synthesis, unlike in HMEC-1, IFN-γ had the major stimulatory effect on ciGEnC. Synthesis was more at 24 hours than at 12 hours but longer stimulation did not increase synthesis further. Unstimulated cells did not show complement production. Complement synthesis was knocked down by transfection with small interfering RNA, confirming the observation of synthesis by endothelial cells.

Confocal microscopy of both cell lines showed the presence of intracellular C4 and C3 protein expression.

Discussion We have shown, for the first time, C4 synthesis by glomerular endothelial cells and confirmed previously demonstrated C3 and C4 production by other endothelial cell lines. IFN-γ appeared to have the maximum stimulatory effect for C4 synthesis. These findings suggest the possibility of locally synthesised C4 having a role in complement driven AMR – this may have therapeutic implications. More studies, including in-vivo experiments are required to better characterise our findings.

P327

Thiopurine S-Methyltransferase gene polymorphism in renal transplant recipients with post transplant malignancy

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Azathioprine/thiopurine drugs are widely used agents which inhibit *de novo purine synthesis* for immunosuppressive and anticancerous effects. Significant numbers of renal transplant recipients have received azathioprine treatment for long term post transplant immunosuppression. Life long immunosuppression affects post-transplant malignancies in organ transplant recipients. Azathioprine is metabolised to 6 - Thioguanine Nucleotides (6-TGN) by Thiopurine S-Methyltransferase (TPMT) enzyme. TPMT*3A (G460A and A719G), TPMT*3B (G460A), TPMT*3C (A719G), TPMT*2 (G238C) account for 80-95% mutant alleles in Caucasians. TPMT genotype may influence post-transplant malignancies, although this has not been studied in renal transplant recipients. This has been highlighted previously in published literature for brain tumour with leukaemia, colonic cancer in inflammatory bowel disease and nodular regenerative hyperplasia with liver transplant treated with thiopurine drugs. The aim of our study was to determine whether the presence of TPMT polymorphism can predict post-transplant malignancies particularly skin cancer in renal transplant patients.

253 patients were found to have developed post-transplant malignancy following renal transplantation in years from 1970 till 2000. 90 DNA samples were analysed from this group. 126 individuals on azathioprine therapy without post-transplant malignancy and 99 samples from patients with basal cell carcinoma (BCC) in general population were analysed. TPMT genotype was defined by Polymerase Chain Reaction (PCR) - Restriction Fragment Length Polymorphism (RFLP) analysis for common TPTMT variants.

A total of 10 out of 90 individuals had variant TPMT alleles. Two of these 10 individuals were on azathioprine therapy. 20 (22.2%) patients with post-transplant malignancy were identified to have received azathioprine therapy. 12 (60%) out of these 20 patients had skin malignancy. Two (10.0%) individuals with malignancy and azathioprine therapy had variant alleles compared to a total of 8 (11.4%) individuals without azathioprine therapy and malignancy. 15.0% on azathioprine without malignancy had variant TPMT allele. The frequency of variant TPMT allele was slightly higher in renal transplant group compared to non-renal general population group with BCC. However, there was no significant difference in frequency of variant TPMT allele between renal transplant group with BCC and general population with BCC ($p=1.00$). Interestingly no variant allele was identified in azathioprine treated patients with BCC.

There is a negative correlation between TPMT genotype and post-transplant malignancy particularly skin malignancy. TPMT polymorphism with resultant azathioprine toxicity at an earlier stage may reduce long-term exposure to azathioprine and prevent from post-transplant malignancy in renal transplant recipients. Larger studies in future will explore further whether lower frequency of TPMT polymorphism in general population with BCC increases the risk of skin cancer.

P328

Biological Ageing: A novel determinant of organ function post transplant

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Older and marginal donors are used to meet the shortfall in organs for renal transplantation. Post transplant function from these donors is often poorer than chronologically younger donors. Some organs, however, function adequately. We hypothesised that such organs are biologically younger than poorer performing ones. We tested this in pre-implantation human renal biopsies (n=75) by measuring the expression of the biological ageing marker CDKN2A, by Real Time PCR, and analysing it for associations with organ function post transplant (serum creatinine (SC) levels).

Increased CDKN2A levels were observed in organs from older donors ($p=0.014$), indicating elevated levels of biological ageing. Linear regression analyses indicated an association for SC with CDKN2A levels ($p=0.001$) and donor age ($p=0.004$) at 6 months post transplant. The combination of both accounted for 24.6% of the observed variability in SC ($p=0.001$). When patients were categorised by donor sex, the association for SC with donor age and CDKN2A was lost in patients receiving male organs. However in patients receiving female organs, CDKN2A expression accounted for 46.9% ($p<0.001$) and donor age 32.2 % ($p=0.001$) of the variability in 6 months SC levels. The combination of these factors was the most significant contributor as they accounted for 62.2% of variability.

Donor age contributes significantly to organ function post transplant, this study suggests that variability in organ function is also determined by biological age. Our data indicate that the most powerful predictor for renal function post transplant is chronological age combined with biological age. Interestingly we demonstrate a significant difference in the role that both these parameters play in influencing post transplant function in male and female donated organs. Elevated levels of CDKN2A are associated with increasing biological age and in female organs this corresponded to poorer organ function post transplant. This however, was not observed for male organs and perhaps suggests that there are gender specific mechanisms or markers of biological aging. This study highlights that allograft biological age is a novel prognostic determinant of renal transplant outcome.

Poster Session

Thursday 23 April

13:30 – 14:30

Live Donation 2

Moderator Ms Lisa Burnapp

P329

Attitudes Of Healthcare Professionals And Patients Towards Live Donor Kidney Transplantation

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Introduction: The rapid development of live donor kidney transplantation (LDKT) programmes has intensified the debate regarding the acceptability of certain categories of donors as well as the potential commercialisation of LDKT.

We surveyed the views regarding those issues of medical and nursing staff involved in the care of patients with end-stage renal failure as well as of patients on dialysis, recipients of kidney transplants (deceased or live donor) and live kidney donors.

Methods: The participants were recruited in a tertiary renal and transplant centre and were invited to complete an anonymous questionnaire.

Results: 432 participants completed the questionnaire; 165 (38.2%) were healthcare professionals and 267 (61.8%) were patients. Live related donation was considered as acceptable by 94% (parent to child), 92% (sibling to sibling) and 79.4% (child to parent) of all participants. Unrelated donation was considered acceptable by 91% and non-directed donation (between strangers) by 57.4% of participants. 87.3% of participants were willing, if needed, to donate a kidney to their children, 82.2% to their siblings, 59.5% to their parents, 74.8% to a non-blood related relative or friend and 14.8% to a stranger. Participants answered that, if they had renal failure, they were prepared to accept a kidney from a parent (78.5%), a sibling (78.7%), their children (57.2%), a non-blood related relative or friend (81%) or a stranger (53%). For live related and unrelated transplantation, participants thought that the donor: should have no financial reward (29.4%), should be compensated for expenses only (61.1%), should receive a direct financial reward (9.3%). For non-directed donation, 23.6%, 56.3% and 19.9% were in support of no reward, compensation only and direct financial reward respectively. Healthcare professionals were more in favour compared to patients for sibling to sibling ($p=0.0009$), child to parent ($p<0.0001$) and non-blood related donation ($p=0.03$) while patients were more in favour of non-directed donation ($p=0.02$). Healthcare professionals would more readily donate to a parent ($p=0.03$), a sibling ($p<0.0001$), a child ($p=0.002$) and to a non-blood related relative or friend ($p=0.02$) and would also be more willing to accept a kidney from a parent ($p=0.005$), a sibling ($p=0.0004$) and a child ($p<0.0001$).

Discussion: In our study live related and unrelated kidney donation were widely accepted (with some reluctance for child to parent donation although less so among healthcare professionals). Over half of the participants considered non-directed donation as acceptable with patients more in support. 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 regulations and monitoring.

P330

Live Kidney Donation: Attitudes Towards Donor Approach, Motives And Factors Promoting Donation

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Introduction: There is a variety of views regarding the initiation of the process for LDKT, the motives of the donor and the appropriate ways to promote LDKT.

We surveyed the views regarding those issues of medical and nursing staff involved in the care of patients with end-stage renal failure as well as of patients on dialysis, recipients of kidney transplants (deceased or live donor) and live kidney donors.

Methods: The participants were recruited in a tertiary renal and transplant centre and were invited to complete an anonymous questionnaire.

Results: 432 participants completed the questionnaire; 165 (38.2%) were healthcare professionals and 267 (61.8%) were patients. Most of participants (37.7%) suggested that the first approach to a potential donor should be made by the potential recipient while 24.3% advocated that the transplant team should make this approach. Participants believed that the most important motives of a kidney donor are relief from the recipient's improved health after the transplant (85.4%) and altruism (81.7%). 11.8% stated that financial rewards are an important motive. 88.2% of participants believed that proper long-term medical follow-up of the donor is the most important factor that can promote LDKT. The most important sources of information regarding LDKT were considered to be multi-disciplinary transplant teams (81.2%), printed publications (78.9%) and General Practitioners (78.5%). Healthcare professionals were more supportive compared to patients of the concept that relief from the recipient's improved health is a vey important motive for the donor ($p=0.01$). Also healthcare professionals considered patient's associations as a very important source of information for LDKT compared to patients ($p=0.001$).

Discussion: In our study participants generally preferred a direct approach of the donor by the recipient and they saw the relief from the recipient's improved health as a very strong motive for donation. Proper donor follow up was considered to be paramount for further developing LDKT. Traditional sources of information were also considered to be very valuable in promoting LDKT compared to modern media while healthcare professionals also put a lot of weight on the patient's initiatives as well.

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Live Kidney Donation: Attitudes Towards Organisation And Risk

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Introduction: Live donor kidney transplantation (LDKT) is widely accepted but the pathway to surgery, the post-operative follow up and the perceived and acceptable risk are under debate.

We surveyed the views regarding those issues of medical and nursing staff involved in the care of patients with end-stage renal failure as well as of patients on dialysis, recipients of kidney transplants (deceased or live donor) and live kidney donors.

Methods: The participants were recruited in a tertiary renal and transplant centre and were invited to complete an anonymous questionnaire.

Results: 432 participants completed the questionnaire; 165 (38.2%) were healthcare professionals and 267 (61.8%) were patients. Most perceived the risk for the donor as negligible or very small (64%). Almost half of the participants (48.4%) suggested that a potential donor should be given up to 3 months to re-consider the decision to donate and only 0.02% suggested that this period should be extended to 1 year. The participants were almost equally divided whether family consensus of the donor's and recipient's families is necessary (46.5%) or not (45.3%) in order to proceed with LDKT. 50.7% of participants advocated that individuals with marginal health problems and 65.3 % that elderly donors should be accepted to donate if they were well informed and prepared to take the risk. 71.5% suggested that patients appreciate more LDKT after even a short period on dialysis. 59.8% of participants thought that the post-operative management of donor and recipient should take place on the same ward next to each other. 44.4% answered that the postoperative follow-up for the donor should last up to 1 year and 39.1% more than a year while 83.8% believed that the donor follow up should include medical condition and quality of life. Finally, healthcare professionals were less keen compared to patients to accept as donors individuals with marginal health problems ($p<0.0001$).

Discussion: In our study participants were generally supportive of the idea of the potential donor having a period of time to reconsider donation. More than half of participants were in favour of accepting donors with marginal health problems or elderly donors although healthcare professionals were less supportive of this concept compared to patients. Participants believed that pre-emptive transplantation may result in lack of appreciation of LDKT on behalf of the recipient while most participants supported a complete follow up of the donor including quality of life.

P332

Socioeconomic status, ethnicity and access to living kidney donor transplantation in England and Wales

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Background: The association between socioeconomic status (SES) and its contribution to the ethnic differences in access to living kidney donor (LKD) transplantation in England and Wales is not known.

Methods: Patients aged 18-70 years (n= 12282) starting RRT (1997- 2004) in centres linked to the UK Renal Registry with complete data on covariates and no malignancies were included. Townsend index used as proxy for individual level SES with patients divided into population quintiles (Townsend quintile (TQ) 5 most deprived). Multivariable logistic regression was used to study the association between SES and access to LKD transplant in White patients (n=10487), controlling for patient factors (age, gender, cause of renal failure, year of start of RRT) and centre. Associations between ethnicity (White, Black, South Asians) and access to LKD transplant was examined controlling for above factors and Townsend index. Median time to LKD transplant was compared between SES and ethnic groups using the Kruskal Wallis test amongst those who received LKD transplant.

Results: In a fully adjusted model, patients living in the most deprived areas had reduced access to LKD transplant: Hazard ratio (HR) for TQ 5 is 0.40 (95 %CI 0.33, 0.49, trend $p < 0.0001$). SES gradients were more pronounced amongst males (interaction test $p = 0.03$) and in centres that were performing more LKD transplants (interaction test $p<0.0001$). Compared to Whites, Blacks (HR 0.40, 95%CI 0.21, 0.73) and South Asians (HR 0.66, 95%CI 0.45, 0.96) had relatively less access to LKD transplant even after controlling for SES and centre. The lower odds of LKD transplant amongst non-Whites was seen only amongst those aged <50 years (interaction test $p <0.0001$). Sensitivity analyses including only those who survived three years or more from start of RRT yielded similar results suggesting comorbidity does not explain reduced access to LKD transplant for deprived patients and non-Whites. Amongst those who received a LKD transplant, the median time to transplant was longer for deprived patients (TQ 5: 387.5 days; TQ 1 268 days, $p = 0.06$), and for Blacks (580 days), South Asians (539 days) compared to Whites (300 days, $p=0.0004$).

Conclusions: Access to LKD transplant was lower for socially deprived patients, Blacks and South Asians. Further studies are needed to examine if these differences are due to patient (clinical, social factors) and/or health care related barriers that may be amenable to intervention.

P333

Potential donors who do not proceed on the living kidney donation program –can early disappointment be avoided?

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Aim - Examine the reasons why potential donors do not proceed - attempt to improve the referral pathway and reduce the number of unsuitable candidates receiving medical review.

Background - An individual coming forward as a potential donor is an emotional time for both the potential donor and recipient. At our unit all potential donors who come forward on the living kidney program are seen by a transplant coordinator in a dedicated clinic. Assessment of suitability is a multistage process and the individual may be declined or leave the process at one of three stages. UK Transplant does not record any information regarding declined donors although guidelines are in place to guide the process.

Patients and Methods - We retrospectively analysed prospectively collected data on all referrals for potential living donors for adult and paediatric recipients at our unit from 1st January 2000 to 31st December 2008.

Results - 618 potential living kidney donors were seen over the 9 year period, 357 (58%) did not proceed. 36 (6%) and 180 (29%) of potential donors are declined at Stage 0 and 1 respectively. The most common reason for not proceeding was kidney disease at screening; 22 (6%) with 14 (4%) declined due to low GFR.

Conclusions - Non-proceeders represent over half the work-load of living kidney donor transplant coordinators. Most potential donors are declined at stage zero / one before medical review and thus reducing burden in clinics.

P334

Impaired graft function following live donor renal transplantation is associated with pre-operative use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers (ACEi/ARB).

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Background: Live donor transplantation (LDTx) is carried out electively in a controlled environment with minimal cold ischaemic time; serum creatinine as a marker of graft function should fall dramatically over the first days post transplantation. Delayed graft function (DGF) has been shown to affect long term graft survival adversely. ACE inhibitors and angiotensin receptor blockers lower blood pressure but are associated with increased activity of renin, angiotensin I (ACEi) and angiotensin II (ARB). In recipients treated with ACEi/ARB, transplantation of a kidney with normal ACE activity and (unblocked) AT 1 receptors may expose the transplanted kidney to high local levels of angiotensin I and angiotensin II causing intense vasoconstriction that may affect graft function post operatively.

We observed DGF in two patients on ACEi/ARB following uncomplicated LDTx. We therefore sought to determine whether serum creatinine, falls more slowly in LDTx recipients on an ACEi/ARB pre-operatively.

Method: The computerised records and case notes of all patients who received a LDTx between January 2001 and August 2008 were reviewed. Patient demographics, the time of transplantation, whether the patient was on an ACEi/ARB pre-operatively and daily serum creatinine for 7 days post-operatively were recorded. Impaired graft function post transplant was defined as a <75% fall in serum creatinine at day 3. Renal transplant biopsy and urine culture results were reviewed. Statistical analysis was performed using SPSS.

Results: Between January 2001 and August 2008, there were 128 live renal transplant recipients; 18 of whom were transplanted in other centres. Of the remaining 110 patients, 2 lost their grafts in the immediate post operative period and a further 14 were excluded on the basis of renal transplant biopsy proven acute rejection (n=11), calcineurin inhibitor toxicity (n=1) or urinary sepsis (n=1). The remaining 94 patients had a median age of 33.5 years (range 16.8-72.4 years); 56% (n=53) were male and 43% (n=40) were on an ACEi/ARB. 57% (n=54) had a fall in serum creatinine of <75% at day 3 post operatively. Of these 54% (n=29) were on an ACEi/ARB. Patients on an ACEi/ARB pre- transplant were more likely to have impaired graft function with a fall in serum creatinine of <75% at day 3 post operatively (p=0.035). In addition there was a significant difference in the mean serum creatinine at day 3 between those on an ACEi/ARB and those who were not (p=0.011). 2 patients required haemodialysis following transplantation; both of whom were on an ACEi/ARB.

Conclusion: Live renal transplant recipients who are on either an ACEi/ARB pre-operatively are more likely to have impaired graft function in the absence of other explanations. This may have implications for graft survival in the longer term. LDTx is carried out electively in a controlled environment and therefore we should stop ACEi/ARB in those scheduled to undergo LDTx. The same mechanism is likely to influence function following cadaveric transplantation.

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Patient defined success one year after live donor kidney transplantation: a study of patient reported outcomes (PROMS)

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This is a pilot study aiming to establish individual donor and recipient expectations and evaluate whether these are met following transplantation. Do the PROMS differ from those of the transplant team?

An opportunistic sample of 18 donors and 17 recipients, due to undergo living-donor kidney transplantation, underwent structured interview to explore their expectations and experiences, and completed the Hospital Anxiety and Depression Scale (HADS) and SF-36 Quality of Life questionnaires before, 3 months post-transplant and 1 year post-transplant. Quantitative (based on 5 point Likert scales), qualitative and aggregate data were collected. Differences were assessed using Mann-Whitney and Wilcoxon tests.

Donor and recipient minimum acceptable graft survival was low (4.6 and 8.6 pre-transplant and 1.68 and 4.3 at 1 year respectively). 100% of participants agreed that their transplant was successful, despite 50% of recipients experiencing episodes of rejection. 75% of donors report emotional benefits 3 months post-transplant. Expectations for their own health and happiness were exceeded at 1 year (Mean scores: 3.3v3.2 & 4.1v3.9). Donor HADS scores at 1 year (1.3) improved to below the pre-transplant (2.0) and 3 month levels (2.6). Donors rated their own recovery and care lower than recipients rated theirs (3.9 and 4.2 v 4.2 and 4.7). 40% of recipients and 33.3% donors expressed qualitative concerns regarding donor support. For recipients, pre-operative expectations of improved health, less pain and more happiness were exceeded one year post-transplant (4.6v4.2, 3.7v3.5, 4.3v4.0). However they were more tired (4.1v4.5), less able to work (3.8v4.2) and socialise (4.1v4.3) than expected. HADS scores and SF-36 scores showed progressive improvement from pre-transplant and 3 month levels.

In conclusion, recipient recovery exceeds their expectations. Donors make full recoveries both physically and emotionally with many reporting benefits having donated. But there is some concern over their early support and care. Patient reported outcome measures differ in some domains from outcome measures of the transplant team and expectations are exceeded.

P336

A single program experience of increasing living donation kidney transplants.

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The lack of increase in deceased donor transplants has mandated units to optimise their living donor programs. In 2003 the living donor program serving 3 sister units aspired to increase its living donor rate compared to deceased donor transplants from below 40% to the 50% then achieved overall in the USA. A program of continuous improvement (PDSA) cycles was instituted. Ideas to improve the service were gained from the USA and also generated internally. The program included improved donor information, streamlined donor assessment, laparoscopic donation and the introduction of an ABO incompatible transplant program. This was matched by incremental sustained and sustainable changes in resource in areas such as staffing and theatre capacity. These changes were matched by changes in national governance standards.

	‘98	‘99	‘00	‘01	‘02	‘03	‘04	‘05	‘06	‘07	‘08
DD	71	69	79	87	74	58	74	49	54	49	61
LD-t	18	26	31	23	26	34	42	42	60	68	96
LD-u	5	4	9	6	10	14	14	12	21	22	42
New	0	0	0	0	0	0	0	2	3	4	20

The table shows: deceased donor transplants (excluding kidney-pancreas transplants) **DD**; Living donor transplant total **LDt**; Living unrelated donor transplants **LDu**; ABO incompatible, HLA desensitisation, altruistic donation and paired donor exchange transplants **New**. This shows that the increase in living donor transplant rates in an individual program are the result of local initiatives, national initiatives and a change in the proportion of transplants from groups which were not numerically important in 1998. In the same period the program has achieved a pre-emptive living donor transplant rate of over 50%. In the present financial and governance environment it is possible to increase living donor transplantation to rates over 60%.

P337

^{51}Cr-EDTA GFR Measured in 619 healthy prospective renal transplant donors – the effect of age and gender

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The measurement of GFR is fundamental to the detection and monitoring of many chronic renal diseases. Accurate GFR estimation allows definition of chronic kidney disease (CKD), need for dialysis, transplantation, and also, the safe donation of a kidney from a living donor to a recipient. In our department such potential donors are thoroughly assessed, according to BTS guidelines. One such assessment is GFR measurement using ^{51}Cr-EDTA plasma clearance. There are conflicting reports in the literature about the relationship between age and GFR in this healthy" population of prospective donors.

From 1991 to 2008 619 healthy carefully-screened prospective renal transplant donors were studied. GFR was measured using ^{51}Cr-EDTA plasma clearance. GFR was estimated using the slope intercept, with corrections for body surface area and the fast exponential curve (British Nuclear Medicine Society). The CV for this technique is approximately 10%.

The relationship between gender, age and GFR was then examined using best-fit curve analysis. First the relationship between eGFR and age was studied using scatter plot and Pearson's correlation coefficient. Then fractional polynomials were fitted to describe the relationship.

Our 619 patients consisted of 304 females and 315 males aged between 18 and 74 years. The range of values was between 41 and 163 ml.min-1/1.73m^2. The mean GFR was 97.6 ml.min-1/1.73m2 (3SF) and the standard deviation of results was 15.6 ml.min-1/1.73m^2. There was no gender difference in BSA-corrected GFR. The relationship between eGFR and age was studied using scatter plot and Pearson's correlation coefficient ($r = -0.4$, $p < 0.001$). Then fractional polynomials were fitted to describe the relationship: fractional polynomial of degree 1 fitted the relationship best. This relationship is non-linear and this can be best described using a fractional polynomial model of degree 1 (eGFR=98.42 - 0.6199 Age^2), see Fig.

This is the largest reported ^{51}Cr-EDTA clearance study reported in the literature, with 619 carefully screened potential donors covering the age range 18 - 74. A novel relationship between age and GFR was found, which will help to inform GFR in health and refine decisions about safe renal donation in the future.

Poster Session

Wednesday 22 April

13:00 – 14:00

Paediatrics

Moderator Mr Geoff Koffman

P338

Successful Outcome of Paediatric En Bloc Kidney Transplantation from the Youngest Non-Heart Beating Donor in the United Kingdom

Shahid Farid, Paul Goldsmith, Jayne Fisher, Sally Feather, Eric Finlay, Magdy Attia, Niaz Ahmad

St James University Hospital, Leeds, United Kingdom

Introduction: The practice of transplanting pediatric en bloc cadaver kidneys is not universally accepted and experience in paediatric recipients is minimal. We describe the successful outcome of kidney transplantation from the first paediatric en bloc non-heart beating donor into a paediatric recipient in the United Kingdom.

The donor was 2 years old, 12 kg male child (Maastricht category III), who died secondary to drowning. Only kidneys were accepted for transplantation and were retrieved *en bloc* with aorta and vena cava. The recipient was a 15-year-old female weighing 40kg, with end-stage renal failure secondary to familial nephritis.

We describe our technique of graft preparation and implant technique and compare to the previously described Newcastle technique [1]. Warm ischaemia time was 32 minutes and cold ischaemia time 11 hours. Postoperative ultrasound showed good perfusion of both kidneys. Primary function was observed and the postoperative recovery uneventful. The patient remains well to date and three-month creatinine was 84μmmol/L (0.95mg/dl).

Conclusion: This is the youngest reported paediatric NHB donor in the United Kingdom and the first case of transplantation of paediatric enbloc kidneys into a paediatric recipient in Europe with successful outcome.

1]. M.F.A. El-Sheikh, M.A. Gok, P.E. Buckley, N. Soomro, B.C. Jacques, D.M. Manas, and D. Talbot. En Bloc Pediatric Into Adult Recipients: The Newcastle Experience. Trans Proc 2003; 35: 786-88

P339

The Impact of Size Mismatched Renal Transplantation on Postoperative Haemodynamic Parameters in Low Weight Paediatric Recipients.

Paul Goldsmith[1], Daniel Ridgway[1], Sonal Asthana[1], Sally Feather[2], Kaye Tyreman[2], Krishna Menon[1], Stephen Pollard[1], Niaz Ahmad[1]

[1]Department of Organ Transplantation, St James's University Hospital, Leeds, United Kingdom, [2]Paediatric Nephrology, St James's University Hospital, Leeds, United Kingdom

Objectives: Renal transplantation in low weight children conventionally requires a graft well matched to recipient size. The low rate of organ donation from paediatric donors has prompted interest in the use of adult sized grafts. Such transplants are challenging and potentially complicated by graft hypoperfusion. It is imperative that graft perfusion is maintained using an adequate intravascular volume and perfusion pressure. This study examined the perioperative changes in haemodynamic parameters of recipients of size matched and mismatched renal transplants.

Methods All paediatric transplants in low-weight recipients (<20kg) were included in this study. Recipients were stratified into two groups comprising ‘high’ and ‘low’ donor: recipient weight ratios based on the median value. Primary outcomes were systolic blood pressure (SBP) at reperfusion, one hour post perfusion and on day 1; central venous pressure (CVP) at reperfusion and 1 hour post perfusion; and recipient body weight on the first three post-operative days. Secondary outcomes were volumes of infused fluid and the need for ionotropic/vasopressor therapy in the first 48 hours.

Results: Twenty-three recipients weight less than 20kg. 12 patients had ‘low’ donor: recipient weight ratios and 11 ‘high’ ratios about the median value (4). haemodynamic parameters were comparable in each group.

Conclusion: Low weight paediatric recipients of renal allografts have comparable post-operative cardiovascular parameters irrespective of graft size. Furthermore, the requirements for fluid and vasoactive therapy is equivalent to maintain such parameters.

P340

Donor: Recipient Size Discrepancy in Paediatric Renal Transplantation - Comparable Outcomes Using Size Mismatched Donors.

Paul Goldsmith[1], Daniel Ridgway[1], Sonal Asthana[1], Maggie Fitzpatrick[2], Eric Finley[2], Magdy Attia[1], Stephen Pollard[1], Niaz Ahmad[1]

[1]Department of Organ Transplantation, St James's University Hospital, Leeds, United Kingdom, [2]Paediatric Nephrology, St James's University Hospital, Leeds, United Kingdom

Objectives: Outcomes of paediatric renal transplantation are unfavourable compared to adults. Small children are particularly disadvantaged from a lack of donors matched for size. Transplantation of adult kidneys into paediatric recipients is technically difficult and associated with complications such as longer warm ischaemic times, abdominal compartment syndrome and graft hypoperfusion. Hence we sought to study outcomes in small paediatric recipients of large and small grafts.

Methods: All paediatric transplants in low-weight recipients (<20kg) were included in this study. Recipients were stratified into two groups comprising 'high' and 'low' donor: recipient weight ratios based on the median value. Primary outcomes were rates of primary non function (PNF), delayed graft function (DGF), acute rejection (AR) and 1 year graft survival. Secondary outcomes were serum creatinine and body weight. Statistical analysis comprised Student t test for comparison of ordinal data means, Chi squared for categorical data and a 5% level of statistical significance.

Results: Twenty three transplants were performed in recipients <20kg. 22 were implanted in extraperitoneal positions. 12 patients had 'low' donor: recipient weight ratios and 11 'high' ratios about the median value (4). There was no significant difference in rates of the primary outcomes; though 1 graft was lost at 2 months in the low ratio group. Secondary outcomes were comparable between groups.

Conclusion: Donor:recipient weight ratio does not impact on rates of PNF, DGF, AR and 1 year graft survival. Size mismatched grafts from large donors have comparable outcomes to conventional size matched grafts in small (<20kg) paediatric recipients.

P341

Non-Adherance and clinical outcome of kidney transplantation in recipients aged <23 years: a single centre experience

Ben Corteville[1], Steven van Laecke[1], Paul Harden[2]

[1]Faculty of Medicine, University Hospital of Gent, Gent, Belgium, [2]Oxford Transplant Centre, Oxford, United Kingdom

Non-adherence is a major contributor to renal allograft failure in teenagers and young adults. Transition from paediatric to adult healthcare systems poses a particularly high risk of non-adherence resulting in graft loss rates up to 40% within 2 years of transfer. We aimed to study the outcome of all patients transplanted <23 years of age in a single large adult transplant centre and impact of previous transition from paediatric care. Non-adherence was explored using a variety of clinical markers including clinic attendance rates; immunosuppressive drug level variability and frequency of late rejection episodes. Eligible patients were identified from the transplant centre electronic clinical database. Patient records were scrutinised for evidence and timing of rejection episodes; outpatient clinic attendance (good- missed < 1 clinic/year; fair- missed 1-3 clinics/yr and poor- missed > 3 clinics/yr); proportion of all sequential calcineurin-inhibitor levels outside the target range were analysed for each patient.

123(4.7%) of 2629 transplants managed at this centre between 1974 and 2008 were in recipients aged <23; complete records were available on 113 transplants in 104(84.6%) recipients for inclusion in this study (6.7% received > 1 transplant). 90.3% white; 7.9% asian and 1.8% black recipients; (61.9% male) with mean age at transplantation 19.3 (1-23) years. 79.6% transplants were performed in this centre; 20.4% were transferred from paediatric units. Late acute rejection (> 3 m post-transplant) occurred in 18.6% overall (26.4% aged < 20; 11.7% aged 20-23 $p<0.04$ Pearson Chi-Square) and was associated with an increased risk of allograft failure. Clinic attendance was good in 76.3%; fair in 12.4% and poor in 11.3%. Poor clinic attendance was associated with increased risk of late rejection (36.4% versus 8.1%; $p<0.001$). In recipients on calcineurin-inhibitors(CNI) with late rejection 45.5% of drug levels were in the centre-specific therapeutic range compared to 57.4% of levels in non-rejecters ($p=0.019$). Mean transplant survival 3759 days in recipients > 20 yrs (3453 < 20 yrs); 3602 days transplanted in centre (3667 transferred from paediatric unit; p=NS);

We found a high prevalence of late rejection in young adult recipients associated with poor clinic attendance rates and out of range CNI drug levels. However we found no difference in allograft survival between patients transplanted in a paediatric or adult centre.

P342

Evolution Of Post Transplant Lymphoproliferative Disorder Management In Pediatric Liver Transplant Recipients. A Single Centre Experience.

A Verma, PT Cherian, Z Ahmadinejad, D Hadzic, A Baker, G Mieli-Vergani, N Heaton, M Rela, S Height, Anil Dhawan

Kings College Hospital, London, United Kingdom

Aims: The aims of this study were to review the incidence, clinical presentation, histological patterns, different therapeutic modalities, and outcome of PTLD in the pediatric liver transplant recipients (PLTR) in our institution.

Methods: A retrospective analysis was done for 24 cases of PTLD diagnosed on histology between June 1990 and December 2007 in 658 PLTR.

Results: The incidence of PTLD was 3.7%. The median age at diagnosis of PTLD was 57 months (Range 16-152) with median interval for PTLD presentation from liver transplant was 112.5 weeks (Range 13-404). Clinical manifestations were gastrointestinal in 16 patients, neurological in 2, and neck pain and lump in 2. Lymph node enlargement was observed in 20 patients, splenomegaly in 17, fever in 15 and hepatomegaly in 13. Primary immunosuppression was cyclosporine in 13 patients and tacrolimus in 9.

Histopathologic findings were high-grade lymphoma for 9 patients and polymorphic PTLD for 6. In-situ hybridization for EBV was positive in 18 of 21 cases. Pretransplant EBV serology was negative in 14 patients.

Initial therapy for 21 patients was reduction of immunosuppression (RDI). Nine patients received rituximab, but only three responded. Fourteen children underwent chemotherapy of whom 2 responded. Four patients had surgical removal of the lesions. Twelve patients received an acyclovir antiviral agent. One patient died before any intervention. Two patients had improvement with RDI along with surgery. Six (27.3%) patients died during the follow up period with PTLD being the predominant cause in 4.

Conclusion: The treatment of PTLD continues to evolve because of the availability of newer agents. The efficacy of rituximab as sole agent in the treatment of PTLD remains to be proved.

Key words: post transplant lymphoproliferative disorder, pediatric liver transplant, rituximab.

P343

Incidence of Infectious Complications and Their Effect on Outcome in Children With and Without Liver Transplantation for Acute Liver Failure.

G Godbole, PT Cherian, A Dhawan, N Shanmugam, M Rela, N Heaton, A Verma

Kings College Hospital, London, United Kingdom

Aim: We sought to determine the incidence of IC and their effect on outcome in children with ALF and in children who received liver transplantation (LT).

Methods: Retrospective review of the case records of children presenting with ALF. All patients had surveillance of cultures from all sterile body fluids every week or more often if clinically indicated. All received antibiotic & antifungal prophylaxis and high dose acyclovir in neonates. Biochemical parameters of liver dysfunction, renal dysfunction, duration of hospital stay and patient outcome were compared between patients with IC and non-infectious groups overall and in children with LT

Results: 145 children (69 male), median (range) age of 4.22 (1 day-16 yrs) years were studied. The aetiology of ALF included paracetamol overdose in 26 patients (18%), viral infections in 18 (13%), metabolic causes in 13 (9%), indeterminate in 42(29%), autoimmune in & neonatal hemochromatosis in 8 (5 % each) and others in 30 (21 %). 47/145 patients had proven IC (32%). 18 episodes of bacteraemia were observed in 13 patients, the most common organism was *Enterococci spp*. LRTI was seen in 12 patients and most common *Pseudomonas spp.* UTI was also seen in 12; Other infections included gastroenteritis (5), intrabdominal infections (5), wound infections (3) and line site infections (3) . IC occurred in patients after a median (range) duration of 14 days (0-54 days) of admission. 8 (5%) had IC at admission. Median (range) duration of hospital stay in patients with IC 35(4-201) days was significantly higher than those without IC 11 (1-14) day, $p < 0.0001$. The duration of ventilation was also significantly higher in the group with IC (10 days) as compared to non-infectious group (5 days); $p<0.01$. Overall mortality was 16% (23) of which 5% (8) were from IC group, 10% (15) from non infectious group. The cause of death was culture proven sepsis in 6, clinical suspicion of sepsis/SIRS in 11, multi organ failure in 5 and graft failure in one. 45% (21) in IC group had LT compared with only 26% (26) in non infectious group ($p<0.03$). Patients with IC and underwent LT had a longer duration of hospital stay and ventilation ($p< 0.03$) as compared to those transplanted without IC, 4 days.

Conclusions- Culture proven sepsis was not associated with increased mortality in children who did or did not receive liver transplantation, however this group had prolonged duration of ventilation and hospital stay.

P344

Chronic kidney disease parameters among paediatric pre-emptive renal transplants and non pre–emptive renal transplants

Rajiv Sinha, Ahmed Saad, Stephen Marks

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Introduction: Pre-emptive renal transplantation (PRT) is the preferred modality for renal replacement therapy in children. Despite this, there are no studies comparing chronic kidney disease (CKD) parameters between PRT and non-pre-emptive renal transplant (NPRT) recipients.

Study design: This was a single centre cross-sectional study of renal transplant recipients with at least one year post-transplant follow-up. CKD parameters as per K/DOQI were compared between PRT and NPRT.

Results: Of 129 children (39 PRT and 90 NPRT); 54% (70) had Stage 3 33% (43) Stage 2 and 12% (15) Stage 4 CKD (with only one child Stage 1 CKD (NPRT). Post-transplant follow-up was 1.3 to 14.2 (median 4.2) years in PRT 1.2 to 17.7 (median 4.7) years in NPRT (p=0.5) with 36% and 51% living-related renal transplants in PRT and NPRT respectively (p=0.1). Despite similar baseline characteristics a significantly lower proportion of PRT (1, 2%) were in Stage 4 CKD in contrast to NPRT (14, 16%; p=0.03). CKD parameters ((hypertension, anaemia, hypocalcemia, hyperphosphatemia, hyperparathyroidism, hypoalbuminemeia, albuminuria and acidosis) were better among PRT with the incidence of hypertension and acidosis achieving statistically significant difference (p=0.02). Similarly uses of CKD medications (anti hypertensive, iron supplements, erythropoietin, 1 alfacalcidol, phosphate binders and bicarbonate supplement) were more common among NPRT. Among these anti hypertensive, iron supplements, erythropoietin and 1 alfacalcidol showed statistically significant difference (p= 0.03, 0.02, 0.01 and 0.04 respectively).

Conclusion: We did demonstrate better CKD parameters and lower use of CKD medications among PRT when compared with NPRT. This finding should act as an added impetus to paediatric PRT programs.

Poster Session

Thursday 23 April

13:30 – 14:30

NHBD

Moderator Mr Hany Riad

P345

Non heart beating kidney donors – How long is a reasonable time to wait for asystole?

Anusha Edwards, Abby Gill, Elaine Clarke, Najib Kadi, David Mitchell, Paul Lear, Barry Pentlow, Justin Morgan

North Bristol NHS Trust, Bristol, United Kingdom

Non-heart beating programmes funded by UKT have increased the number of kidneys available for transplantation. Our local programme has a 2-hour waiting time between withdrawal of treatment to asystole. If asystole is not achieved in this time, the kidneys are not retrieved.

In order to assess whether this 2-hour waiting time is appropriate records kept by coordinators of all donors/potential donors since the establishment of the programme were examined.

In the five-year period studied 67 patients had become non-heart beating kidney donors, with an average time to asystole of 15 minutes ranging from less than one minute to 98 minutes. One set of data was incomplete. 64 of the donors died within 60 minutes, with only 2 dying within the next hour. There had been 30 non-donors who did not proceed as asystole occurred beyond the 2-hour waiting period. In this group there were three sets of records not documenting time of asystole. In the remaining 27 cases the time to asystole ranged from 2 hours 5 minutes to more than six days. Only 2 patients proceeded to asystole in the following 3 hours, both within 2 ½ hours from withdrawal.

This retrospective study shows that a 2-hour waiting time for asystole is appropriate for the retrieval of kidneys from NHB donors. The implications of cutting the time to one hour would have been four less kidneys over the five-year period, whereas if we extended the time to 2 and a half hours, we would have retrieved four more kidneys.

P346

NHB kidney retrieval programmes in the UK. Are we all doing the same thing?

Anusha Edwards, Kay Hamilton, Justin Morgan

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In the UK, when programmes were established to retrieve organs from NHB donors each unit was allowed to develop its own protocols. We performed a questionnaire study to look at the differences in protocols between all the units in the UK retrieving kidneys from NHB donors.

100% response rate was achieved by contacting co-ordinators at all 17 units currently retrieving NHB kidneys. All units retrieved organs from controlled donors with one unit using organs from category 2 donors also. Most units, 13, had no exclusion criteria for NHB donors that differed from their cadaveric donors. The other four units had different upper age limits for donors in the two programmes. Only four units had a fixed upper age limit for NHB donors.

There was considerable variation amongst units regarding when they considered their start point for the wait for asystole began and how long they would wait. Most units consider the withdrawal of treatment as their start point and would wait between 90 minutes to five hours for asystole to occur. Other units had a target blood pressure/saturation measurement and so would wait a considerably shorter time. Eight units were pump perfusing the retrieved kidneys, with one unit performing viability testing.

All units perform a crossmatch, with nine units insisting that this is done on a new donor sample, rather than historical. There is also variation in organ allocation between units.

This questionnaire has demonstrated that there is considerable variation amongst the transplant units in the UK that are retrieving organs from NHB donors.

P347

Successful Double Kidney transplant from NHBD category 4 outside the BTS selection criteria. Is it time now to revise the non heart beating donor selection criteria?

Ahmed Elaffandi, Martin Raftery, Raj Thuraisingham, Roberto Cacciola, Carmelo Puliatti

Royal London Hospital, London, United Kingdom

Background: Kidneys transplanted from non-heart-beating donors (NHBD) are regarded as marginal or extended criteria grafts. The current non heart beating donor selection criteria (BTS) for kidney transplant excludes donor age >65 years, uncontrolled hypertension or complicated insulin dependent diabetes. We present here a novel way of utilising donors outside these criteria.

Case: A 56 year old male with idiopathic membranous nephropathy and nephrotic syndrome received dual kidney transplant. The donor (aged 77 and diabetic) suffered an intracranial haemorrhage. The transplant proceeded without a cross-match as the recipient was non-sensitised based in three monthly screening by luminex. He received ATG induction (total dose 6mg/Kg over 4 days) with a CNI free regimen in the first week. First warm ischaemia time was 17 min and cold ischaemia time for the first and second kidneys was 9 and 9.5 hours.

Results: The recipient had primary graft function without requirement for dialysis. The length of hospital stay was 8 days with an uneventful recovery and no surgical complications. Pre-perfusion biopsy showed 16% glomerular sclerosis, mild to moderate focal interstitial fibrosis, mild medial and intimal hypertrophy, mild focal tubular atrophy. Renogram on the 2nd postoperative day showed good perfusion of both grafts. Postoperative biopsy day 7 showed resolving ATN without evidence of rejection. Creatinine at 5 month is stabilised to 140 mmol/l.

Conclusion: We believe that using dual kidney transplant from non heart beating donors might extend the range of donor selection criteria in such settings. However, this has to be evaluated in a well designed controlled study.

P348

The Influence of Agonal Phase Characteristics on the Function of Kidneys Donated After Cardiac Death.

Alex Reid, Antonia Wells, Marian Ryan, J Andrew Bradley, Gavin Pettigrew

Department of Surgery, Cambridge, United Kingdom

INTRODUCTION

Kidney Donation after Cardiac Death (DCD) is now considered as important a source of organs as those from Donation after Brain Death (DBD), but concerns persist about how unfavourable circulatory and biochemical agonal phase parameters impact on graft function.

METHODS

We analysed 235 consecutive DCD referrals from 2004-8. Donors were scored (0-5) according to presence of 5 physiological variables after controlled withdrawal of lifesaving treatment (WLST): hypotension (SBP < 85 mmHg for > 30 mins), oliguria (< 30 ml/hr), hypoxia (SaO2 < 70% for > 30 mins or pO2 < 6 kPa), acidaemia (arterial pH < 7.30) and lactataemia (arterial lactate > 2.0 mmol/l). Transplant outcome was assessed by analysis of delayed graft function (DGF) and 3-month GFR

RESULTS

As the programme developed, annual referrals increased (32 in Yr1 to 91 in Yr4) with a concomitant increase in age of patients referred (median age 48 to 64) and donors (median age 41 to 58).

Of the 235 referrals, 131 (56%) were not pursued - mainly due to medical unsuitability (31%) and relative refusal (19%). Of the 104 patients (44%) who underwent WLST, 64 (27%) proceeded to donation and 40 (17%) did not. Of these that did not donate, 13 were abandoned because of unfavourable agonal characteristics and 23 due to time constraints. In the later study years, donors had more unfavourable agonal phase characteristics (1.59 yr 4 vs. 1.14 yr 1) suggesting donor selection criteria became less stringent with experience. Whereas in year one no donor scored > 2, by year four 7 of 22 (32%) donors scored > 2, including four donors with oliguria and documented acute renal impairment (Cr > 200 μmol/l).

Of 128 kidneys retrieved, 10 were not implanted (poor perfusion or chronic disease on biopsy) and 7 developed acute vascular thrombosis or never functioned. 3-month GFR in the remainder was 42.9 mL/min/1.73m^2, comparable with contemporaneous DBD kidneys (45.1). Surprisingly, there was no correlation between the agonal score and the development of either poor graft function (3-month GFR < 30) or DGF. Of the agonal phase physiological variables, only lactataemia was associated with DGF ($p<0.01$ Fishers Exact Test), but there was no correlation with 3-monthly GFR.

CONCLUSIONS

Only approximately 1/4 of referrals for DCD proceed to kidney retrieval. Our results suggest that this could be increased, without compromising results, by extending donor criteria and pursuing donation despite development of unfavourable agonal characteristics.

P349

Comparison of the Incidence of Delayed Graft Function in Heart Beating vs Non Heart Beating Donor Renal Transplants in a cohort of Manchester Royal Infirmary patients 2006/2007

Alex Jewkes, Mark Lammas, Faieza Qasim

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Introduction: As the demand for viable, transplantable kidneys increases, the use of Non Heart Beating Donors (NHBD, also known as deceased cardiac death, DCD) in renal transplantation has become increasingly common in the UK. Here at Manchester Royal Infirmary, in the past two years there has been a significant rise in the number of NHBD transplants performed. These kidneys would naturally be expected to give rise to an increased incidence of Delayed Graft Function (DGF) compared to Heart Beating (HBD or DBD, deceased brain death) and Living Donor (LD) transplantations. This assumption has been the case in the majority of reports in the literature. These reports have, however, suggested clinically acceptable outcomes. We decided to analyse the incidence of DGF in our own transplantations for the past two complete years to determine if the incidence and outcomes in our centre were in line with published data.

Method: Using our own Transplant database, all renal transplant recipients from the years 2006 and 2007 were identified, alongside whether the renal donor was a NHBD, HBD or LD. Using the patients' medical records, it was determined whether the transplant recipient experienced DGF. DGF was defined as the need for dialysis in the first week post transplantation. The incidence of DGF was then calculated individually for the NHBD, HBD and LD groups.

Results: From our pilot data, encompassing 152 patients in total, a significantly higher incidence of DGF was seen in NHBD transplantations compared to HBD and LD transplantations (62.5% vs 34.5% and 11.1% respectively). Further data analysis is ongoing.

Conclusions: Our initial results appear to be in line with the outcomes from more experienced centres with 2/3 of NHBD recipients developing DGF in cf 1/3 in HBD and 1/20 LD. Work is continuing to identify the role of individual factors in the development of DGF.

P350

Resisitive Indices as a measurement of short and long-term outcome in non-heartbeating renal transplant donors.

Paul Goldsmith[1], Dan Ridgway[1], Sheila Fraser[1], Charles Newstead[2], Krishna Menon[1], K. Rajendra Prasad[1], Niaz Ahmad[1]

[1]Organ Transplantation, St James's University Hospital, Leeds, West Yorkshire, United Kingdom, [2]Nephrology, St James's University Hospital, Leeds, West Yorkshire, United Kingdom

Aims

The increasing demand for renal transplantation, and reduction in cadaveric donor numbers, has prompted increased use of non-heartbeating donors (NHBD). Rates of delayed graft function (DGF) are 48-94% in NHBD and graft surveillance with Doppler ultrasound (USS) is used to monitor graft perfusion during periods of DGF. Ultrasonographic parameters such as the resistive index (RI) may usefully predict renal function and vascular complications. This study describes the role of early USS in monitoring grafts from NHBD with DGF.

Methods

From April 2002 to September 2005, 77 renal transplants were performed from NHBD. Four grafts had PNF and were excluded from further analysis; 44 grafts had DGF defined by a need for dialysis within the first week after transplantation (60%). All recipients had USS within 3 days of transplantation during which RI was measured. Multiple regression was used to correlate RI, donor parameters and graft outcomes.

Results

RI (mean 74%±8%) showed no correlation with early (Day 5) calculated glomerular filtration rate (eGFR) (β=-0.35;p=0.16) or eGFR 1 year after transplantation (β=0.61;p=0.92). RI showed no correlation with 1 year graft (β=0.33;p=0.16) or recipient survival (β=0.33;p=0.16). The only predictor of long-term graft function was donor age as increased donor age was negatively correlated with eGFR at 1 year (β=-0.78;p=0.04).

Conclusions

The use of early USS, and measurement of RI, does not reliably predict short or long term graft or recipient outcomes during DGF in recipients of NHBD renal transplants.

P351

Poor perfusion of retrieved kidneys from non-heart-beating donors – the impact of machine perfusion

Christopher Ray, Soroush Sohrabi, Aditya Kanwar, Alex Navarro, Susan Stamp, Brian Shenton, David Talbot

Liver/Renal Transplant Unit, Freeman Hospital, Newcastle-Upon-Tyne, United Kingdom

Aims

To highlight the efficiency of hypothermic machine perfusion in salvaging organs that would otherwise have been discarded.

Methods

A retrospective search of the units' non-heart-beating database was conducted. The donor records between January 2003 and January 2009 were searched for reports of kidneys appearing blue, mottled or ill-perfused at retrieval. Maastricht category II and III included.

The data for Newcastle viability testing was examined and the outcome of each organ traced, via the local database and hospital records. The primary end points were passing the viability testing, subsequent transplantation and success rate.

Results

There were 15 cases of kidneys reported as blue at retrieval. These were all subjected to Newcastle Viability testing. A perfusion flow index was calculated and GST samples measured at hourly intervals for 4 hours. 2 pairs of kidneys failed to pass viability testing. Of the 13 pairs that passed, 7 were successfully transplanted as dual transplants. The remaining 6 pairs were implanted as single grafts. Of these 12 single grafts, one patient died at one month with a functioning graft and one patient underwent transplant nephrectomy at 1 month secondary to renal vein thrombosis. The others transplants were all successful.

Conclusion

By perfusing the whole organ effectively, machine perfusion converts what would traditionally have been deemed marginal or unusable organs into successful transplants.

P352

Are there potential controlled non-heart beating organ donors in the emergency department ?

Murray Blackstock, David Ray, Dermot McKeown

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Introduction The continuing shortfall of organs for transplantation has increased the use of non-heart-beating organ donation (NHBD).[1]Patients in the emergency department after failed cardiopulmonary resuscitation have provided organs for donation.[2,3,]Patients who are potential controlled non-heart-beating organ donors are likely to have severe intracranial pathology but do not fulfil the criteria for brain stem death. Critical care is unlikely to be in their interest. We hypothesised that some patients intubated in the emergency department (ED) and assessed for, but not admitted to, critical care might be potential controlled non-heart-beating organ donors.

Patients and methods We retrospectively reviewed patients who had drug-assisted tracheal intubation performed in the ED of a large urban teaching hospital and identified those who were not admitted to a critical care area for continuing management. We reviewed the notes of these patients to ascertain diagnosis, management, outcome and potential exclusion criteria for controlled NHBD. NHBD was not an option in the ED during this period.

Results During the three year period 2004-6, 575 patients were anaesthetised and intubated urgently in the ED. Fifty patients were not admitted to critical care: 18 were extubated after their condition improved; 16 were extubated after emergency surgery; 1 died during surgery; 2 died during resuscitation in the ED; and 11 were extubated in the ED as admission to critical care was considered not appropriate. Four patients, all of whom had intracerebral haemorrhage with midline shift, had the potential for controlled NHBD; however two had co-morbidities that may have precluded donation. Therefore only two patients might have been missed as potential controlled non-heart-beating organ donors during the period of our review. Our results demonstrate that very few patients were extubated in the ED of our hospital and most of these did not meet criteria for controlled NHBD.

Discussion The low number of missed potential controlled non-heart-beating donors in our study may reflect a low threshold for tracheal intubation and admission to critical care in our hospital. The potential for controlled NHBD from the ED will depend on local critical care resources and admission policies.

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P353
An audit of sudden deaths in accident and emergency unit as an on-going review of potential NHBD donors

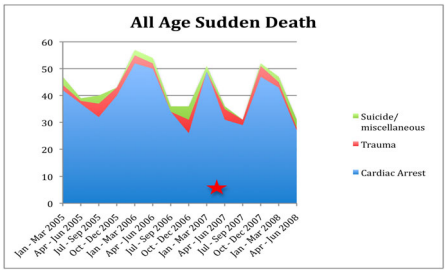
Christopher Ray, Aditya Kanwar, Soroush Sohrabi, Alex Navarro, Lynne Robson, Julie Wardle, Joyce Curwen, Claire O'Brien, Gordon Elder, David Talbot

Liver/Renal Transplant Unit, Freeman Hospital, Newcastle-Upon-Tyne, United Kingdom

Since 1998 the Newcastle renal transplant programme have actively recruited Maastricht category II donors principally from Newcastle Accident and Emergency departments, which initially were the Royal Victoria Infirmary and later Newcastle General hospital. This has provided about 10 donors per year. However over the last 18 months this number seems to have declined for no real reason. We were aware of publications from the Scottish cardiologists on the decline of acute coronary syndrome admissions, which was attributed to the smoking ban in public places and wondered if this could have any bearing on the declining number of donors.

Method The admission notes were reviewed for all sudden deaths that were brought to the Newcastle General Hospital Accident and Emergency unit.

Results



It is apparent that sudden deaths are a seasonal phenomenon, as are deaths from IHD. To claim that rates of ACS have fallen 10 months after a smoking ban may be somewhat premature. Particularly as the national figures suggest that there have been a decline in sudden deaths for some time; which predates the smoking ban. No information on smoking history was available from the sudden deaths; therefore the cardiologists claim that the non-smoking group is the main beneficiary remains to be determined.

Poster Session

Wednesday 22 April

13:00 – 14:00

Pancreas 1

Moderator Mr John Taylor

P354

Outcome of Pancreas Alone (PA) and Simultaneous Kidney Pancreas (SPK) Transplantation: A single centre experience.

M Jacob[1], G Sen[1], D Talbot[1], N Torpey[2], SA White[1], BC Jacques[1], J Shaw[3], DM Manas[1]

[1]HPB and Transplantation Unit, Freeman Hospital, Newcastle upon Tyne, United Kingdom, [2]Dept of Nephrology, Newcastle upon Tyne, United Kingdom, [3]Dept of Diabetology, Newcastle upon Tyne, United Kingdom

Introduction: SPK transplantation is now well-established as the treatment of choice for young diabetics with ESRF. The majority of SPK donors are younger (<50ys) with an average cold ischaemic time (CIT) less than that for kidney alone (KA) transplants. We have undertaken a review of our current practice in patients undergoing SPK/PA transplantation with specific reference to the renal function.

Methods: The records of 53 patients were retrospectively reviewed. The immunosuppression protocols, surgical techniques and outcomes (patients and grafts both pancreas and kidney) were assessed and compared to the national figures.

Results: A total of 53 pancreas transplants were performed over the last 8 yrs. Mean age was 40yrs and 50% of the recipients were females. 37% of patients were pre-dialysis. 75% of patients had basiliximab induction and 20% (last year) were induced with alemtuzumab and a steroid free immunosuppression regime. All 53 patients were maintained on Tacrolimus and MMF. 87% of the transplants were done as SPK's. 80% of the pancreatic grafts were enterically drained to a roux loop and the rest bladder drained. 44% of the kidneys in the SPK patients had delayed graft function(DGF) compared to a 24% DGF rate in the KA patients. 37% of patients were diagnosed with graft pancreatitis and/or pancreatic fistulae. The majority were treated conservatively. The re-laparotomy rate was 37%. The mean length of stay (LOS) was 32 days. 75% of SPK donors were under the age of 50ys and the CIT for SPK's was 13hrs compared to 19.5hrs for KA grafts. Patients who experienced KDGF had a longer LOS as the only consequence. The 1_year pancreas graft survival was 85% (95% confidence interval 64% to 88%), the 1_year kidney graft survival was 96% and the 1 year patient survival was 94% (95% confidence interval 80% to 97%). The survival figures were comparable to that published nationally.

Conclusion: SPK transplantation offers patients both short and long-term benefits, albeit at the cost of increased short term surgical morbidity. KDGF increases LOS but our audit failed to show any obvious cause for the high incidence of DGF our patients have experienced. This will require a meta-analysis.

P355

Is there a need for removal of the appendix at the time of pancreas transplantation?

John Asher, David Talbot, Jeremy French, Bryon Jaques, Derek Manas, Nicholas Torpey, Steve White

Freeman Hospital, Newcastle upon Tyne, United Kingdom

Introduction and Methods

Pancreas transplantation is a major intra-abdominal operation and in most cases all grafts are placed into the right iliac fossa. Since 2001 appendicectomy has been performed at the time of pancreas transplantation to reduce the risk of future appendicitis and the need for further surgery. All subsequent histology reports were reviewed.

Results

50 pancreas transplants were performed between 2001 and 2008 (42 SPK, 7 PAK, 1 PTA), of these, histology reports were available in 41. 10 (24%) were reported as normal. 19 (46%) were reported as showing fibrosis consistent with previous inflammation. 12 (29%) were found to have faecal material in the lumen of the appendix, of which one had an obstructing faecolith, and another two were reported as showing luminal distension with faeces. 3 (7%) were reported as showing lymphoid hyperplasia. There was also one unexpected finding of a 1.1mm carcinoid tumour in an otherwise normal appendix, one appendix with Enterobius worm infestation, and one appendix with focal endometriosis. There were no cases of acute appendicitis. No patients experienced a complication as a direct result of their appendicectomy.

Conclusion

A policy of appendicectomy at the time of pancreas transplantation appears to be justified.

P356

Pancreas retransplantation: challenging but justified.

Deep Malde, Afshin Tavakoli, Ravi Pararajasingham, Babatunde Campbell, Hany Riad, Neil Parrott, Titus Augustine

Manchester Royal Infirmary, Manchester, United Kingdom

Introduction.

There have been 31 pancreas retransplants in the U.K., forming a mere 3.7% of overall pancreases transplanted. The outcome of pancreas retransplantation continues to improve, with results comparable to primary pancreas transplants. As long-term patient survival rates for pancreas transplant recipients continue to improve, an increasing number of these recipients are presenting for re-transplantation after loss of the initial graft. We discuss our centre's experience.

Methods.

We present our initial experience of re-transplantation in eight diabetic recipients after loss of their first grafts from thrombosis (N=4) and rejection (N=4). From 2001 – 2008 eight deceased donor pancreas re-transplants were carried out (bladder drained in 2 and enteric drained in 6). During this time period, 26 primary pancreas after kidney (PAK), 128 simultaneous kidney and pancreas(SPK) and 7 pancreas transplant alone (PTA) were carried out. The results of pancreas retransplants were compared with primary SPK, PAK and PTA outcomes.

Results.

The average waiting time for retransplants was 32 months (range 4-61). 4 were after primary PAK, 2 after primary SPK and two after primary PTA. There was no patient mortality amongst this group but 5 patients (62.5%) underwent reoperation (6 procedures) due to complications, compared to 76 patients (47.2%) in primary transplants (151 procedures). 1 year graft survival rate (GSR) was 75 % for retransplants compared to 71% and 81% for primary pancreas only and SPK transplants respectively. Patient survival at one year was 100 % for retransplants and 97% and 90% for primary pancreas only and SPK respectively. Graft thrombosis rate was 25% for retransplants (2/8) compared to 10.9%, 23% and 14.3% for primary SPK, PAK and pancreas alone transplants.

Conclusion.

Retransplantation remains a technically formidable procedure with a higher incidence of graft thrombosis and acute rejection. Although our numbers are small, we believe that in selected patients, the therapeutic effects on secondary complications of diabetes justify pancreas retransplantation when the first graft is lost from technical or immunologic causes.

P357

Comparison of primary enteric (ED) with bladder drainage(BD) on short term patient morbidity and pancreatic graft survival

M JACOB[1], G SEN[1], SA WHITE[1], BC JAQUES[1], N TORPEY[2], J SHAW[3], D TALBOT[1], DM MANAS[1]

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Introduction: The optimum technique for management of pancreatic graft exocrine drainage is still a matter of considerable debate. It has been suggested that bladder drainage (BD) offers short term advantages over enteric drainage (ED) with decreased incidence of intra abdominal sepsis but at a cost of long term urological complications. The aim of this study was to assess the impact of the two techniques on perioperative morbidity and graft survival.

Methods: All patients receiving a pancreas transplantation between 1999 and 2008 were included in this study. Depending on the technique used to manage exocrine secretion patients were divided into enteric drainage or bladder drainage respectively.

Patients were assessed for demographics, perioperative, post operative factors and in hospital morbidity following pancreas transplantation. Patient and graft survivals were also compared. Logistic regression techniques were used for statistical analysis using Stata 8 soft ware.

Results:. A total of 53 patients underwent pancreas transplantation during this period of these 42 (80%) were enterically drained and 11 (20%) bladder. Mean age at transplantation were 40 years and 45 years respectively for ED and BD patients. 33% of ED patients were predialysis and this proportion was 56% for BD patients. 77% of BD patients had at least one episode of post transplant UTI compared to 55% for ED patients. The incidence of graft pancreatitis and intraabdominal collections were 32% and 34% for ED patients and 0% and 11% respectively for BD patients. Similarly the relaparotomy rates were also lower for BD patients (22% v/s 44%) . Patient and graft survival were 93% and 81% in the ED group and 100% and 91% in the BD group. None of the above findings were statistically significant.

Conclusion: We have noticed a trend towards lower post operative morbidity and also an increase in patient and graft survival however the differences did not reach statistical significance. This is probably due to the relative smaller number of patients in each group. A multi-centre, multivariable analysis might help in undersatnding the perceived differences.

P358

Role of Myocardial Perfusion Scintigraphy in predicting outcome after pancreas transplantation

Anand Sivaprakash Rathnasamy Muthusamy[1], Nancy Suh[1], April Stanley[1], Isabel Quiroga[2], Shirley Lockhart[1], Jens Brockmann[1,3], Sanjay Sinha[1], Anil Vaidya[1], Andrik Klucniks[4], Phil Mason[5], Oliver Ormerod[6], Peter Friend[1,3]

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Introduction: Diabetic patients have a high incidence of occult cardiac disease and pre-operative cardiac assessment is essential in pancreas transplantation. This study investigates the role of myocardial perfusion scintigraphy (MPS) in predicting the risk of post-transplant cardiac events (CE), defined as cardiac symptoms or signs with elevated troponin levels or cardiac death (CD).

Methods: The preoperative evaluation of 250 recipients (203 SPK, 39 PAK and 21 PTA) consisted either of MPS (n=204), coronary angiography (CA) (n=39) or stress echocardiography (n=7). Abnormal results were discussed with a cardiologist with a view to CA and revascularisation. Postoperative events have been reviewed with a median follow-up of 18months (range 1-81).

Results: 183 patients had normal MPS and 21 were abnormal (19 reversible ischemia, 2 left ventricular dysfunction). Of these, 18 subsequently underwent CA prior to revascularisation in 7 patients; the remaining 3 patients were optimised with medical therapy. There were a total of 5 cardiac deaths (CD, 2%), of which 4 were of patients evaluated by MPS. Three of 183 patients with negative MPS had a CE (1 CD), compared to 4 of 21 patients with a positive MPS (3 CD), an event rate of 1.6% (negative MPS) and 19% (positive MPS). The Relative Risk (RR) of CE following a positive (compared to negative) test was 11.62 (95% CI, 2.787 to 48.43; P = 0.0024, Odds Ratio14.12). None of the patients who had pre-transplant revascularisation (7 out of 18) had a CE. The RR of CD following a positive test was 26.14 (95% CI, 2.84 to 240.3; p=0.0036; OR 30.33). MPS showed acceptable sensitivity & specificity for CE (0.57 & 0.91) and CD (0.67 & 0.91).

Conclusion: In diabetic patients assessed for pancreas transplantation, a negative MPS is associated with low post-transplant CE and CD. Conversely, an abnormal MPS is associated with higher event rate of CE and CD. Thus, MPS is useful to clinicians in assessing the cardiac risk and the need for further investigations pre-transplant.

P359

Clinical Significance of Contamination of Organ Preservation Fluid in Pancreas Transplantation

Nancy Suh, Ian Bowler, Jens Brockmann, Anand Muthusamy, Sanjay Sinha, Anil Vaidya, Peter Friend

Oxford Transplant Centre, Oxford, United Kingdom

Purpose: Despite increasing success of pancreas transplantation, sepsis remains a significant cause of morbidity and mortality. Contamination of perfusion fluid used for organ procurement and preservation prior to transplantation is a potential source of sepsis in the recipient. The aim of this study is to determine the clinical significance of contamination of perfusion fluid in pancreas transplantation.

Method: A sample of organ preservation fluid (University of Wisconsin solution) is routinely sent for microbiological assessment at the commencement of back table dissection at our centre. Results of samples from January 2006 to December 2008 were analyzed retrospectively and correlated with subsequent infections in the first month after transplantation.

Result: 210 pancreas transplants, as part of simultaneous kidney-pancreas transplant (SPK n=155), pancreas transplant alone (PTA, n=22), pancreas after kidney transplants or (PAK, n=33) were performed in this period. Microbiological assessment was not performed on 25 patients. Of 185 samples processed, 101 (54.6%) showed evidence of contamination. A total of 134 organisms were cultured in 101 samples, the majority of which were of low virulence. 51 of the 134 organisms were coagulase-negative Staphylococcus. Pseudomonas was cultured in 25 samples and Candida species, in 15 samples.

Contamination of perfusate did not correlate with recipient sepsis in the early post operative period. 75 of 101 patients with contaminated perfusate did not experience localised or systemic sepsis in the post operative period. 12 of the 101 patients subsequently cultured the same organism post operatively in various specimens such as urine, blood, wound swabs and vascular catheter tips. In 11 of the 12 patients, the organism was coagulase negative Staphylococcus, but in one patient, Candida albicans was isolated from both the perfusate and from intra-abdominal collection.

Conclusions: This study highlights the importance of strict aseptic technique during organ procurement; the high rate of positive culture may reflect the fact that the bowel is stapled and transected in pancreas retrieval. It should be ensured that organisms of high virulence, as well as those commonly isolated in perfusate cultures, are covered with appropriate prophylactic antibiotics. Given that Candida species frequently contaminate perfusion fluid and is potentially life-threatening, monitoring for fungal contamination should continue. However, any benefit gained from routine bacterial culture of perfusion fluid is unclear.

P360

Value of Magnetic Resonance Angiography in Pancreas Transplantation

Nancy Suh, Anand Muthusamy, Alex Tzivanakis, Fergus Gleeson, Phil Boardman, Anil Vaidya, Sanjay Sinha, Jens Brockmann, Peter Friend

Oxford Transplant Centre, Oxford, United Kingdom

Purpose: The monitoring of pancreas graft perfusion and function is limited by the lack of a sensitive and accurate investigative tool to identify treatable complications before these become irreversible. The purpose of this study was to analyse the role of magnetic resonance angiography (MRA) in demonstrating vascular abnormalities following pancreas transplantation.

Methods: From June 2005 to June 2008, 176 pancreas transplants were performed. During this period, 110 MRA were performed on 76 pancreas transplant recipients, ranging from first post operative day to 31 months after transplantation. Retrospective analysis of the indications, MRA findings, further imaging and/or intervention was correlated with graft and patient outcomes.

Results: Indication for MRA was abnormal serum glucose level in 50% of our cohort. 36 studies (33%) revealed complications involving the pancreatic allograft vasculature. Of these studies, there were 22 arterial abnormalities and 6 venous abnormalities. Further 8 cases showed diffuse narrowing of the arterial vasculature recognised to be a feature of chronic vascular rejection. 57 (52%) studies did not show any abnormalities. Incidental renal allograft abnormalities were found in 3 studies, whilst 4 studies found intra-abdominal collections or graft pancreatitis. 6 (5%) studies were not diagnostic. 2 studies were abandoned due to patient refusal and 1 study was suboptimal and required a repeat study.

32 MRA were performed after initial discharge from hospital. In 22 cases, MRA was impaired glucose tolerance. Of 32 studies, there were 18 cases of vascular abnormalities. In particular, 9 studies showed arterial stenoses in 7 patients. Percutaneous angioplasty of arterial stenoses was performed in 5 of 7 patients. 4 patients currently have functioning grafts with normal glucose tolerance, whilst 1 graft was lost due to chronic rejection. 1 patient had no focal stenosis identified on angiography and the other patient is awaiting angioplasty.

Conclusion:

We have a low threshold to carry out MRA to investigate pancreas transplant recipients in whom there is concern about graft perfusion. This non invasive method has aided the diagnosis of a range of complications with a high level of accuracy and sensitivity.

Poster Session

Thursday 23 April

13:30 – 14:30

Pancreas 2

Moderator Mr Argiris Asderakis

P361

The Impact of Pancreas Only Transplantation on Existing Renal Function: Does it Deteriorate?

Sarah Heap, Bence Forgacs, Ravi Pararajasingam, Hany Riad, Tunde Campbell, Neil Parrott, Mike Picton, Colin Short, Titus Augustine, Afshin Tavakoli

The Renal & Pancreas Transplant Unit, Manchester Royal Infirmary, Manchester, United Kingdom

Introduction: The long-term effects of pancreas only transplantation on kidney function among transplanted patients is still debatable.

Aim: To examine trends in renal function and factors which may contribute during the first post transplant years.

Method: From June 2001 to December 2008 we performed 36 pancreas only transplants in 31 patients (28 PAK & 8 PTA). Clinical data was collected prospectively into an electronic database (Microsoft Excel).The glomerular filtration rate was estimated (eGFR) using MDRD calculation, similarly the serum creatinine at any time point (pre-transplant, one week, 1, 3, 6, 12 and 24 months) was evaluated. Several potential risk factors effecting renal function (type of drainage, surgical complications, etc.) were also analysed. Induction immunosuppression was the same in all patients.

Results: The median eGFR remained unchanged throughout (48, 56, 47, 47, 47, 47 and 48 at pre, 7, 30, 90,120, 360 and 720 days of operation respectively). The pattern was the same for median serum creatinine (138, 118, 136, 139, 138, 138 and 144) at above time points. Analysing PAK and PTA separately showed that: In PAK subgroup the median eGFR remained unchanged (44 and 48 at pre-operative and at 24 months respectively). This was mirrored in the functioning PAK group where the eGFR increased from 47 to 50. In the PTA group however there was a marked drop at one year (84 to 66) of overall PTAs compare to functioning PTAs which showed no changes in eGFR at one year (81 to 76). A large reduction of eGFR (>20%) was seen in 2 patients whom had received PAK (baseline eGFR of 26 and 42) and one PTA (baseline eGFR of 62). Bladder drainage, number of urinary tract infection (UTI), surgical complication were all analysed.

Summary: In our series the renal function does not deteriorate after solitary pancreas (PAK & PTA) transplantation. In the PTA subgroup only the loss of graft seems to be detrimental to native renal function (the number however is small). A large reduction in eGFR following pancreas transplantation was pronounced in patients with low base line eGFR. The type of ductile drainage and surgical morbidity and post operative UTI did not show any significant correlation.

P362

Safety of Steroid Withdrawal after Simultaneous Kidney Pancreas Transplant.

Cinzia Sammartino, Jonathon Olsburgh, Geoff Koffman, John Taylor

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Introduction. The results of steroid withdrawal in simultaneous kidney pancreas transplant recipients (SPK) under tacrolimus immunosuppression were analyzed.

Methods. 108 patients have received an SPK from 2003 to 2008. The mean age of patients at transplantation was 40 years (range: 15-58 years); 51 were female and 57 were male. The induction immunosuppressive treatment was Basiliximab, Tacrolimus, Prednisolone and Mycophenolate Mofetil (MMF). Prednisolone was targeted at 5 mg/day by 3 months. Steroid withdrawal at 1 mg/month started 6 months after last rejection episode.

Results. The median follow up was 605 days (range: 60-1918 days). 39 out of 108 patients have experienced one or more episodes of kidney rejection (36%), at a median post- transplant of 66 days (4 -983 days). 45 (42%) were steroid free at a median post- transplant of 397 days (275-1491 days). 38 (35%) were still on Prednisolone. Data on 22 patients (20%) incomplete for now, due to follow up in other units. Of 38 patients still on Prednisolone, 22 (56 %) have a short follow up of < 360 days. 2 patients died 55 and 125 days after transplant and 1 patient lost both transplants <30 days. Acute rejection after steroid withdrawal occurred in 1 patient with two episodes of acute cellular rejection of the kidney (Banff 4, type IA) 552 and 601 days after cessation of steroids and lost the kidney. 2 Prednisolone maintained patients had acute rejection, 1 kidney loss with cellular and vascular rejection (Banff 4, type IIA) 534 days after transplant and 1 pancreas loss with acute rejection 627 days after transplant.

Conclusion. These data suggests that steroid withdrawal can be safely accomplished in pancreas transplant recipients maintained on Tacrolimus and MMF long term immunosuppression. Steroid withdrawal is not associated with increased acute rejections and kidney and pancreas graft loss.

P363

Impact of HLA Matching on Acute Kidney Rejection after Simultaneous Pancreas and Kidney Transplantation

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Introduction. Simultaneous pancreas and kidney transplantation (SPK) has become the treatment of choice for type 1 diabetic patients with end-stage renal disease. The current analysis examines the impact of human leukocyte antigen (HLA) matching and particularly of HLA-DR on SPK.

Methods. This is a retrospective study of 108 SPK patients from 2003 to 2008. The mean age was 40 years (range: 15-58). 51 were female and 57 male. Immunosuppression with Simulect + Prednisolone + Tacrolimus + Mycophenolate Mofetil.

Results. Median follow up was 605 days (21-1918). The overall acute rejection incidence was 35%. The incidence of rejection by number of HLA mismatches (MM) was 41 % (n = 42 for HLA MM 0-3) vs 32 % (n = 66 for HLA MM 4-6). Losses to acute rejection were 1 kidney in the 0-3 MM group and 1 kidney and 1 pancreas in different patients in the 4-6 MM. The incidence of rejection by number of HLA-DR MM was 55 % (n = 14 for HLA-DR MM =0) vs 33 % (n = 48 for HLA-DR MM =1) vs 30 % (n = 46 for HLA-DR MM =2). The three graft losses to acute rejection were in the HLA-DR MM=1 group.

Conclusions. This analysis shows no effects of HLA matching on preventing acute kidney rejection and kidney and pancreas graft failure with the current follow-up. Additionally the HLA-DR 2 MM category had the lowest incidence of acute rejection. We see no reason not to continue doing HLA-DR MM=2 SPK transplants.

P364

A review of factors influencing early post-transplant events in simultaneous pancreas & kidney transplantation

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AIM: To identify the factors that influence early post-transplant events and the outcome after pancreas transplantation and to select modifiable factors in order to minimise adverse events.

METHODS: 108 pancreas transplants were performed in our unit between April 2000 and November 2008 (98 SPK, 7 PAK, and 2 PA). Immunosuppression was with tacrolimus, mycophenolate mofetil and prednisolone. After July 2004 all patients were also given basiliximab induction therapy (n=62). The outcome measures were overall pancreas and kidney graft survival at the time of analysis. We identified 36 donor and recipient related variables and assessed the correlation between these variables and the outcome.

FINDINGS: The mean recipient age was 40.6y (16-61) and 57% were male. The patients were followed for a mean of 52 months (1-103 months). Of the 98 SPK recipients, 8 kidneys failed (4 with a failed pancreas) and 19 pancreata failed (4 with a failed kidney). The risk of pancreas graft failure was increased when (1) the recipient waited longer than the mean of 230d (p=0.09), (2) the donor was older than the mean age of 30y (p=0.04), (3) transplantation from a donor who died following an intra-cerebral event (p=0.06). The risk of failure of either the kidney or the pancreas was increased when there was high HLA mismatching (122 or 222) (p=0.04). There were more out-of-region donor organs transplanted than local organs after Jul 2004 (19.4% v 43.5%, p=0.01) Pancreas graft survival was 5% higher and insulin independence at discharge was 10% higher after introduction of basiliximab despite the donor age increasing by a mean of 5 years and the waiting time increasing by a mean of 39 days.

CONCLUSION: In pancreas transplantation minimisation of waiting time should be a priority for the allocation process. Donor age and donor cause of death should be considered as risk factors informing patient selection. Highly HLA mismatched transplants should be carefully monitored with attention to immunosuppression.

P365

Body Mass Index, weight and insulin dose as selection criteria for islet transplantation recipients?

Stephanie M Eckoldt, Robert C Andrews, Isabelle Douek, Steven J Robinson, Richard M Smith

University of Bristol, Bristol, United Kingdom

Introduction: Selection criteria for islet transplantation include Body Mass Index (BMI), weight and Insulin Dose (ID) as clinical indicators of insulin resistance. Identification of patients with high levels of insulin resistance is essential as it is undesirable to transplant a small beta cell mass in the face of significant insulin resistance this mismatch being likely to impact on transplant outcome. There are few data comparing these surrogate markers to the gold standard assessment of insulin resistance (euglycaemic hyperinsulinaemic clamp) in patients with Type 1 Diabetes Mellitus (T1DM). We aimed to define the range of insulin resistance within this patient group as well as the validity of BMI, weight and insulin dose as measures for estimating insulin resistance.

Materials and Methods: We assessed insulin resistance in 15 patients with T1DM awaiting islet or pancreas transplantation using the euglycaemic hyperinsulinaemic clamp method. We then correlated glucose disposal rates (GDR) as estimated by the euglycaemic clamp to patient BMI, weight, insulin dose and daily insulin dose per kg.

Results: Patients demonstrated a wide range of insulin resistance with GDRs ranging from 149 $mg/m^2/min^{-1}$ to 325 $mg/m^2/min^{-1}$ comparable to the distribution of GDRs within a population of healthy subjects. We demonstrated no correlation between BMI and estimations of insulin sensitivity. Similarly when GDRs were plotted against both total insulin dose per day (ID/day) or weight adjusted insulin dose (ID/kg/day), no significant correlation was demonstrated.

Conclusions: Islet transplantation in the face of high levels of insulin resistance may mean patients are less likely to achieve the same quality of metabolic control or maintain insulin independence for as long as their insulin sensitive counterparts. Thus identification of patients with high levels of insulin resistance is clinically important in the context of clinical islet transplantation. Our data suggest that not all patients with Type 1 DM are insulin sensitive and that measured insulin sensitivity fails to correlate reliably with BMI, weight and insulin dose. Simple assessment of weight /BMI and insulin dose, although shown to be important for islet transplant success, are perhaps not good clinical indicators of insulin sensitivity in patients with Type 1 diabetes.

P366

Metabolic measures of graft function after pancreas transplantation

Stephanie M Eckoldt, Robert C Andrews, Steven J Robinson, Richard M Smith

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Introduction: At present there is no simple means of monitoring metabolic function after pancreas transplantation. Random or fasting glucose and HbA1c are all used. However, these measures may remain within the normal range despite significant changes in insulin resistance and beta cell mass. In many centres patients are stratified according to glucose tolerance determined by an oral glucose tolerance test (OGTT). These simple measures do not however interrogate beta cell function or beta cell mass and may be confounded by different levels of insulin resistance. We aim to determine a rate of beta cell decline as a measure of graft function post transplantation and adjust for individual variation in insulin resistance.

Materials and Methods: We performed metabolic assessments in 2 simultaneous pancreas and kidney patients, 2 pancreas alone and 2 pancreas after kidney transplant patients. Metabolic assessments included a frequently sampled 75g oral glucose tolerance test (OGTT), an arginine and intravenous glucose tolerance test (Arg IVGTT) to allow estimation of beta cell mass and a euglycaemic hyperinsulinaemic clamp study to estimate insulin sensitivity. The assessments were completed at 3 months post transplant in all patients and at 3 and 12 months after transplantation in 2 patients.

Results: On OGTT 4 patients exhibited normal glucose tolerance (NGT), 1 patient had impaired glucose tolerance (IGT) and 1 had diabetic glucose tolerance (DGT) at 3 months post transplant. In the 2 patients assessed at 12 months the response to a glucose load was equivalent to that seen at 3 months (1 NGT and 1 IGT) despite significant increases in both insulin sensitivity and acute insulin response to arginine and glucose.

Conclusions: Detailed assessment of glucose homeostasis reveals abnormalities in a significant proportion of patients receiving whole pancreas transplants. Recognition of these abnormalities may allow targeted interventions able to prolong graft function.

Poster Session

Thursday 23 April

13:30 – 14:30

Basic Science 2

Moderator Dr Wilson Wong

P367

1H-NMR Spectrometric Identification of Acute Rejection in Renal Transplantation

Paul Goldsmith[1], Hayley Fenton[2], Elizabeth Turner[2], Julie Fisher[2], Niaz Ahmad[1], K Raj Prasad[1]

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Aims

Acute rejection (AR) can effect up to 30% of renal transplants. Earlier diagnosis leads to improved outcomes. The current gold standard for diagnosis is invasive biopsy, which has associated morbidity and is not normally performed before day seven. We aim to identify a non-invasive plasma biomarker capable of diagnosing AR earlier using 1H-nuclear magnetic resonance (NMR) spectroscopy and chemometrics.

Methods

12 renal transplant patients, 7 with no rejection and 5 with AR had nine blood samples taken at separate time points. The blood was centrifuged and plasma separated and frozen until required. Subsequently the plasma was analysed Each spectrum was divided into regions of uniform separation and the areas in these regions measured. These data were then subjected to principal component analysis.

Results

Clear differentiation between AR and no rejection was seen in principal components 1 and 2 from day 1 post operation. The cause of the separation is the biomarkers which appear in the region 3.24-3.4ppm of the spectrum. The nature of the biomarkers remains to be confirmed.

Conclusions

These preliminary studies support the suggestion that 1H-NMR based metabolic profiling can provide an early non-invasive test for detection of acute rejection in renal transplantation.

P368

Cyclosporine-Induced Renal Allograft Fibrosis: A Role for Epithelial to Mesenchymal Transition (EMT)?

Watchara Pichitsiri, Sarah Jenkinson, Simi Ali, John Kirby

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Introduction: Since the introduction of cyclosporine A (CsA) in the early 1980's, the acute rejection rate has declined in parallel with a significant improvement of 1-year kidney allograft survival. However, chronic cyclosporine nephrotoxicity, which is characterized by tubular atrophy with interstitial fibrosis or striped fibrosis, has remained one of the main causes of late allograft loss. Previous studies have suggested that tubular epithelial cells can contribute to renal fibrosis through the induction of epithelial to mesenchymal transition (EMT) which may be mediated by enhanced production of TGFβ.

Aim: To determine the potential of CsA to induce EMT associated with chronic cyclosporine nephrotoxicity.

Methods: The renal tubular epithelial cell (REC) lines HK-2 and HKC-8 were treated with a range of concentrations of CsA (10ng/ml, 100ng/ml, 1ug/ml and 5ug/ml) or with 10ng/ml TGFβ1 for periods up to 72 hrs. The immunosuppressive effect of these concentrations of CsA on mitogen-induced T cell proliferation was demonstrated by measurement of ^{3}H-thymidine incorporation. The viability and proliferation of treated REC were assessed by flow cytometry and cell counting. The expression of the homotypic adhesion molecule E-cadherin and the fibroblast marker S100A4 were assessed by immunohistochemical (IHC) staining. Real-time PCR was performed to measure the expression of S100A4 and TGFβ1 mRNA. TGFβ activity was also assessed by reporter cell bioassays and ELISA.

Results: Immunosuppressive concentrations of CsA were not toxic for REC but decreased E-cadherin expression and increased the expression of immunoreactive S100A4; similar IHC results were observed after stimulation with TGFβ1. However, levels of mRNA encoding S100A4 were not altered by CsA. Furthermore, CsA did not increase production of either $TGF\beta_1$ mRNA or bioactive TGFβ by treated REC.

Conclusions: The data from this *in vitro* study suggest that CsA does not induce REC to secrete TGFβ, the most important mediator for EMT process. However, treatment of REC with CsA did enhance the expression of S100A4 and reduce E-cadherin suggesting induction of EMT. The failure to detect changes in S100A4 at the mRNA level may suggest post-transcriptional regulation of this stable, oligomeric and potentially secreted protein.

P369

Erythropoietin Modulates NGAL and IL-18 Gene Expression but not FABP1 Gene Expression

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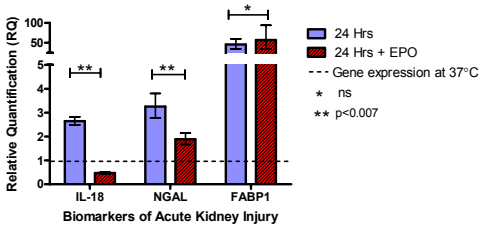
Neutrophil gelatinase-associated lipocalin (NGAL), IL-18 and fatty acid binding protein 1 (FABP1) have been identified as novel biomarkers of acute kidney injury (AKI). Erythropoietin (EPO) reduces inflammation and apoptosis in AKI. The aim of the study was to examine the effects of EPO on these biomarkers in an *in vitro* model. Primary renal proximal tubular epithelial cells were incubated in University of Wisconsin (UW) solution in 1% oxygen at 4°C for 2, 6, 16 and 24hrs, with or without EPO (50U/ml) following pre-incubation with EPO for 1 hour. Control cultures were incubated in complete medium at 37C. Gene expression was quantified using RT-PCR. Statistical analysis used a paired t test.

Significant up regulation of NGAL (p=0.003), IL-18 (p=0.01) and FABP-1 (p=0.015) occurred in response to cold hypoxic injury in UW solution at all time points (example 24hrs, see fig.). EPO treatment significantly down regulated NGAL (p=0.007) gene expression although it still remained significantly (p=0.003) above baseline. EPO treatment resulted in a decrease in IL-18 (p=0.005) gene expression, below levels seen at 37C but had no effect on FABP1 expression. The model promises to be a useful tool with which to interrogate the mechanism of EPO induced tissue protection.



P370

The effect of Mycophenolic acid on neutrophil function

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Introduction: Mycophenolate mofetil (MMF) is a common component of current immunosuppressive protocols following transplantation. Transplant recipients are known to have an increased susceptibility to bacterial infections, which suggests a defect in innate immunity. It has been previously shown that the active ingredient of MMF, mycophenolic acid (MPA), elicits a dose-dependent decrease in neutrophil Reactive Oxygen Species (ROS) production. However, little work to date has been undertaken to investigate the effect of MPA on neutrophil function.

Methods: Neutrophils were isolated from healthy controls and incubated in RPMI 1640 medium (+HEPES +10% pooled human AB serum) in the absence (control) or presence of MPA. Total neutrophil ROS production was determined by luminol-dependent chemiluminescence following stimulation. Extracellular ROS production was measured by isoluminol-dependent chemiluminescence or reduction of cytochrome c. The xanthine:xanthine oxidase reaction was utilised as a cell-free system for producing ROS. Apoptosis was assessed by morphology and neutrophil chemotaxis was measured using a modified Boyden chamber. An *S.aureus* killing assay was used to establish the killing capacity of neutrophils

Results: MPA elicits a dose-dependent decrease in neutrophil ROS production within 30 min (1-100 µg/mL, $p<0.05$). There was, however, no effect on neutrophil chemotaxis or apoptosis. Inhibition was rapid, occurring within 30s, and was both reversible and sustained over 6h. This effect was observed in cells stimulated by both fMLP and PMA, which activate the NADPH oxidase via different pathways, suggesting MPA mediates its effect downstream of NADPH oxidase activation. While MPA decreased cell-dependent cytochrome c reduction, it had no effect on cell-free xanthine:xanthine oxidase ROS production, suggesting that MPA exerts a direct cellular effect, rather than acting as a scavenger. Bacterial killing was decreased by 20% in the presence of MPA ($p<0.05$)

Conclusions: MPA remains one of the key immunosuppressive drugs used in transplant patients to prevent acute rejection. MPA has been shown to reduce ROS generation, which in turn leads to a decrease in the ability of these cells to kill bacteria. While the MPA-mediated decrease of neutrophil killing capacity is small, this may have a more profound effect upon development of bacterial infection following transplantation.

P371

Problems and their solutions in the establishment of Fisher to Lewis rat model of chronic allograftnephropathy: a single centre experience.

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Introduction: Chronic allograft nephropathy (CAN) is the leading cause of late renal transplant (RT) failure. RT between Fisher-to-Lewis (F-L) strains of rats leads to CAN, which is successfully established in our institute. Anatomical variations in the *donor* (D) such as multiple renal arteries, retroaortic renal veins (RV), multiple tributaries of the RVs, short RVs and discrepancies in sizes of the renal vessels between the D and *recipients* (R) made end-to-end anastomoses (EEA) impossible, leading to vascular complications and RT loss. Hypothermia, hypovolaemia, hypotension, over- of under-dosage of anaesthesia and analgesia, aspiration pneumonia, paraplegia in the D and R led to either intra- and post-operative deaths, inadequate clearance of blood in the D kidneys or necrosis of the transplanted kidneys. A detailed presentation of the *anatomical* and *physiological* problems encountered in D and R, experiments to identify the problems and measures taken to address them, will be made with supporting data.

Methods: Over a period of 3 years, male Lewis (N=150) and Fisher (N=22) rats were used in the model. Surgical techniques of RT employing cuff technique, EEA, aortic and inferior venacaval (IVC) conduits were evaluated. The anatomical problems described above were successfully overcome by using donor aortic (N=52) and IVC conduits (N=32), which allowed use of kidneys with multiple arteries and veins, simplified anastomoses, reduced anastomosis time (37 min), and preserved ureteric blood supply. Use of body heating mat with measurement of rectal temperature prevented hypothermia and its consequences. Continuous measurement of blood pressure (BP) through a cannula in the carotid artery and infusion through internal jugular vein at variable rates helped establish intra-operative fluid regimen (2mls IV bolus followed by 6mls/ hr continuous IV infusion) to maintain a stable BP. Administration of buprenorphine (50µg/ml) SC and isoflurane 1% in oxygen led to optimum maintenance and recovery.

Results and Conclusions: With the above regimens and changes in surgical techniques, normal homeostasis was achieved in D and R. The D kidney remained perfused until nephrectomy and perfused well in the recipients, led to development of CAN in the allografts (F-to-L) as evidenced by proteinuria, hypertension, progressive decline in the glomerular filtration rate and histological and electron microscopic changes, but with no such changes in the isografts (L-to-L).

P372

Increased excretion of urinary ε(γ-glutamyl)-lysine in the Fisher to Lewis rat model of chronic allograft nephropathy

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Introduction: The identification of urinary biomarkers may be an important step in the diagnosis and treatment of chronic allograft nephropathy (CAN), the leading cause of renal graft loss. The deposition of extracellular matrix in the transplanted kidney, may be induced by transglutaminase type 2 (TG2), an enzyme which generates inter & intra protein crosslinks through the formation of ε(γ-glutamyl)-lysine dipeptide bonds. Both the ε(γ-glutamyl)-lysine crosslink and TG2 protein are increased in animal and human kidney transplants developing CAN. The aim of the present study was to measure the total urinary excretion of the ε(γ-glutamyl)-lysine crosslink in the Fisher-to-Lewis (F-L) model of CAN.

Methods: Fisher (n=7) or Lewis rat kidneys (n=5) were transplanted into Lewis rats by end-to-side anastomosis employing aortic and inferior vena caval conduits under isoflurane anaesthesia. Urinary protein was exhaustively digested using a proteolytic enzyme cocktail. The ε(γ-glutamyl)-lysine dipeptide was fractionated on a Biochrom 30 amino acid analyser using cation exchange chromatography and derivitisation with ninhydrin. Peaks at 570nm were quantified using single point analysis.

Results: Lewis-to-Lewis (L-L) isografts were normotensive in the absence of either proteinuria or renal fibrosis. Total urinary ε(γ-glutamyl)-lysine excretion from L-L isografts was 3.4±0.2 μmol/24h (n=5) which remained unchanged for 4 months (2.7±0.5 μmol/24h). F-L allografts were hypertensive developing proteinuria and renal fibrosis. Total urinary ε(γ-glutamyl)-lysine excretion from F-L allografts was significantly higher at 7.4±0.5 μmol/24h (n=7, $p<0.05$) gradually increasing over 4 months to 18.4±5.9 μmol/24h ($p<0.05$), higher than L-L isografts by 7-fold. Total urinary ε(γ-glutamyl)-lysine excretion showed a positive linear correlation with urinary protein excretion ($r=0.8121$, $p<0.0001$).

Conclusion: The ε(γ-glutamyl)-lysine crosslink was detected in urine from L-L isografts. As far as we are aware, this is the first report of ε(γ-glutamyl) lysine measurements in the urine of any species. Total urinary ε(γ-glutamyl)-lysine excretion was higher in the F-L allograft, increasing with the development of proteinuria. The source of urinary proteins contributing to increased ε(γ-glutamyl)-lysine excretion is currently under investigation.

Johnson T et al. Transplantation 2004;77:1667-1675

P373

Increased pancreatic islet cell viability and insulin secretion after enzymatic digestion using EDTA as a collagenase inhibitor

Soroush Sohrabi[3,2], Brian Shenton[1], Susan Stamp[1], Noel Carter[2], Anne Cunningham[2], Bob Peaston[1], David Talbot[3,2]

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Introduction

Although pancreatic islet cell transplantation has promising results in short term as a novel method for treatment of diabetes, after 5 years only 10% of initial successful transplant recipients remaining insulin independent after five years. It has been suggested that the current islet isolation techniques are not islet friendly and cause damage to the islets that is not entirely reversible. These pre-damaged islets when transplanted in the recipient undergo immunological and non-immunological destruction leading to graft failure.

Material and methods

Cultured rat beta cells were exposed to collagenase and washed either with EDTA+ Human Albumin (HA) and HA alone followed by washing with cold HBSS. Beta cell apoptosis and death was analysed using flow cytometer and TMRE (Tetramethylrhodamine Ethyl Ester) and 7-AAD (7-aminoactinomycin D) staining. Islet insulin secretion was assessed using ELISA.

Results

Viable islet count (Non-apoptotic live islets) was significantly higher in the group of islets which were treated with EDTA + HA compared to HA alone ($p<0.05$). Insulin secretion in islets washed with EDTA+HA was significantly higher than islets washed with HA alone ($p<0.05$).

Discussion

Adding EDTA as a collagenase inhibitor to human albumin after digestion with collagenase increases islet cell viability and insulin secretion.

Poster Session

Wednesday 22 April

13:00 – 14:00

Extended Criteria Donors

Moderator Mr Justin Morgan

P374

"Extended Criteria Donor (ECD) kidneys: Should we be discarding more?"

Farhina Sayyed[1], Jonathon Ellis[1], Desley Neil[2], Jason Moore[1], Hari Krishnan[1], Ahmed Hamsho[1], Steve Mellor[1], Andrew Ready[1], Nick Inston[1]

[1]Queen Elizabeth University Hospital, Birmingham, United Kingdom, [2]Department of Pathology, University of Birmingham, Birmingham, United Kingdom

Kidney transplantation has been limited by the supply of donor organs which has led to increased use of extended criteria donors (ECD). These have been defined as any donor aged ≥ 60 years and any donor age 50-59 years with any two of the following: treated or untreated hypertension, CVA as cause of death, terminal serum creatinine >132.5µmol/L (>1.5 mg/dl)*(Sung RS et al.2008)*.Donors outside these criteria were classified as non-ECD donors.

Analysis of registry data in the US found that up to 40% of ECD organs were discarded predominantly based on biopsy or machine perfusion parameters.

The aim of this study was to analyze the number of ECD organs that were accepted in a large single centre in the UK and assess the rates of discard and reasons for this. In addition outcome of kidneys from ECD donors were compared with non-ECD donors.

Between Jan 2000 and January 2008 all accepted ECD (n=170) and non-ECD (n=444) kidneys were compared. Non Heart beating donors were excluded.

Recipient details for each group were comparable although recipient age was significantly higher in the ECD group (Mean Age ECD vs non ECD= 51.3 vs 45.7 years $p<0.05$). Machine perfusion was not performed on any of the kidneys accepted during this study period. Over this year period <1% kidneys were biopsied. None were discarded based on glomerulosclerosis or non-neoplastic findings.

Delayed graft function (DGF) was not significantly higher in the ECD group than non ECD group (44.7% vs 38.3%)(P=0.17). Serum creatinine (mean ± SD micomol/L) was higher in ECD then non ECD 199.7±126.8 vs 156.2 ± 98.7($p<0.01$) and 206.5 ± 137.7 vs 171.2±130.7 **(**$p<0.01$) at 3 months and 1 year respectively.

Graft loss in the first year was not significantly different (graft loss n=15 vs 32 for ECD vs non ECD; p=0.448; Mantel Cox) and 1 year graft survival being 91.2% in the ECD group and 92.5 % in the non ECD group.

Results from both ECD and non ECD kidneys were acceptable although long term data is required. In contrast to previous reports a low rate of discard occurred which may reflect different practices in organ selection.

P375

Changes in Donor Demographics over a Decade. The Experience of One UK Retrieval Centre.

Sarah Richards, Christopher Callaghan, Christopher Watson

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Introduction

The critical shortage of organs available for transplantation has lead to alternative strategies for increasing the donor pool including the use of expanded criteria donors. We compare changes in donor demographics over a ten-year period in one UK organ retrieval zone.

Methods

Donor data was collated retrospectively over two time periods: January 1996 - December 1997 and January 2006 -December 2007. Data was acquired from the Core Donor Data Form (D-CDD-TCO) produced by UK Transplant and filled in at the time of retrieval.

Results

Data collected was 99% and 97% complete for the two time periods respectively. The number of retrievals increased from 88 to 142. The average age of the donor was seen to increase from 40 to 46 years (p=0.01). The percentage of donors over 60 years of age increased from 8.0% to 21.1%. Donor cause of death was compared over the two time points. Trauma related injury fell from 27.3% to 21.6% in 1996-1997 and 2006-2007 respectively, whilst donors resulting from intra-cerebral bleeds rose from 53.4% to 59.7%. There was no statistical difference in the average creatinine at retrieval, with a mean of 88 and 92 (p=0.55) for the two time periods; however there was a small increase in donors with a creatinine of greater than 135 (10.2% and 12.7% respectively). Marginal donors over 50 years of age with either a history of hypertension and/or a creatinine >135 rose from 40.9% to 54.2%. Documented infection in donors (chest, urine, blood or other) was seen to rise from 29.5% to 45.5%, and the prevalence of inotrope use increased from 31.8% to 65.7%. Non-heart beating donors accounted for 27% of the cohort in 2006-2007.

Conclusions

This comparative study over a decade in our retrieval zone illustrates a change in donor demographics. Recent donors are likely to be older, non-trauma related deaths, have hypertension or elevated creatinine, sepsis, be on vasopressor support or be non-heart beating donors.

P376

The effects of a very prolonged cold ischaemia time on renal transplantation outcomes

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Organ Transplantation, St James's University Hospital, Leeds, West Yorkshire, United Kingdom

Aims

The increasing demand for renal transplantation, and reduced conventional donor pool, has increased use of marginal donors. Very prolonged cold ischaemic times (CIT) have hitherto precluded transplantation, and the outcomes in recipients of such grafts is not well established. Herein we describe the short and long term outcomes in recipients of renal transplants where CIT has exceeded 24 hours.

Methods

From January 1995 to September 2005, 101 renal transplants were performed using donors with CIT >24 hours. Duration of delayed graft function (DGF), graft and patient survival, and calculated estimates of GFR (abbreviated MDRD equation) were compared with recipients of grafts were CIT did not exceed 24 hours (n=942). Ordinal data were compared using student t test (SPSSv14). Data are expressed as means±SD using a 5% level of statistical significance.

Results

No statistical significance was seen between the two groups in DGF ($p=0.52$), graft survival (p-0.94) or days of recipient survival ($p=0.28$). eGFR was significant at 5 days ($p<0.001$), but became non-significant from 6 months onwards

Conclusions

Renal transplantation from donors with a very prolonged CIT (>24 hours) results in comparable durations of DGF, graft and recipient survival to conventional donors (CIT<24 hours). Though immediate eGFR is reduced where CIT is prolonged, eGR from 6 months to 5 years are comparable.

P377

The use of extended criteria donors: a single centre experience, 1 and 5 year follow up.

Susana Fernandez-Diaz[1], Jalal Sarker[2], John Taylor[1], Geoff Koffman[1], Nizam Mamode[1]

[1]Transplant Unit, Guy's Hospital, London, United Kingdom, [2]Division of Health and Social Care Research;GKT School of Medicine, Kings College, London, United Kingdom

The imbalance between demand for kidney transplantation and number of organs available has led to the use of "sub-optimal" donors. We assessed 1-yr and 5- yr outcome of transplantation in recipients who had marginal kidneys (MK) versus those who received standard kidneys (SK). **Methods:** 223 cadaveric kidney recipients, on whom complete data was available, transplanted between 2001 and 2003. Grafts were considered marginal if one or more of the following: donor age > 60 non-heart beating (NHBD) donors, cold ischaemia time (CIT) > 24 hrs, history of hypertension or diabetes. 1 yr follow up data was collected for all of them, 5 yr in only 113. End points were: Incidence of delayed graft function (DGF), 1 yr patient and graft survival (PS, GS), estimated glomerular filtration rate (eGFR) at 1 yr and rejection with number of episodes. Statistical tests included chi-squared, two-sample t-tests or Fisher's exact test. Regression models included stepwise logistic and stepwise linear regression. We reviewed 5 yr graft and patient survival and serum creatinine (SCr). **Results**: 99 (44.4%) were MKs. 124 (25.3%) were SKs. PS and GS were similar between MK and SK at 1-yr. MKs had significantly higher DGF than SKs (39.4% vs. 20.2%, p=0.002). MKs had lower eGFR than SKs (mean 40.1 vs. 46.6, p=0.003) and higher serum creatinine sCr (172.3 mmol/l vs. 143.4 mmol/l, p<0.001) after one year. Mean DGF for the standard and marginal kidneys was 5.5 days SD: 18.5 and 6.4 days SD: 11.7 respectively. Those with DGF, had higher sCr at 12 months (mean 184.3 DGF vs. 147.0 non-DGF, P<0.001) and lower eGFR (mean, 39.6 DGF versus 45.0 non-DGF, P=0.03). DGF was not related to rejection. CIT was not related to any one of the outcome measures. Donor sCr > 130 mmol/l was significantly related to DGF (p=0.005) after adjustment. After 5 yrs, only 113 patients remained under our care, the rest transferred out and follow up lost. Of those 113, 8 had lost their graft or died in the first year. Of the remaining 95, 7 had died at 5 years, 5 of them with a functioning graft. Out of these 7, only 2 had received MK.GS was similar for both groups (MK 92.5% vs. SK 96.3% p=0.7) **Conclusions:** MKs do not differ from standard kidneys in terms of graft survival and patient survival at 1 yr. MKs have significantly more DGF and worse function after 1 year. 5 year follow up does not show an impact in those grafts which survived after 1 year.

P378

En bloc vs singly implanted kidneys from young donors

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While kidney donation from younger donors is increasing, the optimal implantation strategy (either en bloc or singly) for these organs remains controversial. The current UK Kidney Allocation Scheme in operation since 2001 offers kidneys from donors aged four and under as en bloc pairs to a limited number of centres nationally rather than to specific patients via the national pool. The decision to implant en bloc or singly is made by the receiving centre.

In this centre we have transplanted six recipients with organs from four male heart-beating donors (age ≤ 4) during the period from 01/01/2005 to 01/01/2009. All recipients were given Campath at induction and maintained on tacrolimus and mycophenolate except that of the first recipient listed below who received basiliximab induction with tacrolimus, azathioprine and prednisolone for maintenance based on HLA mismatch and sensitisation. Median length of follow-up was 7 months. Donor and recipient demographics and outcomes are as follows:

Donor					Recipient						
age *months*	GFR*	weight *kg*	height *cm*	cause of death	Age *years*	sex	CIT†	serum creatinine‡ *1*	*3*	*5*	*12*
implanted en bloc											
24	209	12	90	Meningitis	28	M	16.7	126	112	121	115
16	195	12	80	hypoxic brain injury	35	F	10.5	245	116	90	
implanted singly											
43	112	18	106	Meningitis	39	F	23.8	98	88	78	
					39	M	20.2	140	126	137	
38	143	14	100	Smoke inhalation injury	37	M	26.5	166			
					30	M	13.5	206			

* GFR = glomerular filtration rate (ml/min/1.73 m2). † CIT = cold ischaemia time (hours). ‡ serum creatinine at 1, 3, 5 and 12 months

As shown, serum creatinine at 1 month is comparable between en bloc and singly implanted organs. The second recipient listed underwent ureteric reimplantation for anastomotic stricture at 5 weeks post-transplant. The 5th and 6th recipients suffered delayed graft function. Serum creatinine was 143 and 181 at last follow-up (2.5 months) respectively. There were no other complications.

These results demonstrate that good outcomes can be achieved from singly-implanted kidneys from donors aged 4 and under. It may be timely to incorporate other factors such as donor weight into the policy for allocation of organs from these donors so as to increase the number of transplants and improve equity in access to transplantation.

P379

Outcome of kidney transplants from older living donors

Habiba Nabti, Najib Kadi, Nicola Hamilton

Renal transplant Unit, Southmead, Bristol, United Kingdom

Aim Evaluate outcome of kidney transplants from older living donors (over 55) within a single transplant unit.

Background: With the ongoing shortage of kidney donors and subsequently longer waiting times for transplants, older living donors may provide a valuable source. There have always been concerns about outcome from this group of donors with regards to graft function because of their physiological decline in glomerular filtration rate and their increased susceptibility to surgical complications.

Patients and Methods

We retrospectively analysed prospectively collected data on all living kidney donors who were over 55 years at the time of the transplantation at our unit between 1993 and 2008.

Results

82 living kidney donations from donors aged over 55 years were performed over the 15 years period. The mean age of donors was 60.6 yrs (range 55-73), there were 46 males (56%) and 36 females (44%).

Analysis of the donors' relationship to recipients revealed that 59% were first degree relatives, 3% second degree, 35% were spousal and 3% were unrelated. Out of the eighty two donor nephrectomies, 14 were performed laparoscopically and 68 open and 81 were primary transplants with only one as a second transplant.

The mean age of recipients was 45+/- 15 (range 18-71) with 47 males and 35 females.

With regards to outcomes, graft function was measured using the recipients' mean estimated glomerular filtration rate (eGFR) at 30 days which was 48.2+/- 14.7 (n=79) and then at one year which was 49.3+/- 13 (n=59).There were no major postoperative complications and the older donors had similar surgical outcome when compared with younger donors.

Conclusion

Our study revealed good graft function for kidney transplants from older living donors (>55yrs) within our unit and therefore more older living donors should be considered, in view of the ongoing donor shortage.

Poster Session

Thursday 23 April

13:30 – 14:30

H&I

Moderator Mr John Smith

P380

Fluorescent bead based multiplex luminex assay for characterization of perioperative cytokine profile in renal transplantation.

Manimaran Ranganathan[1], Edward Frances[2], Edvardo Chavez[2], Robert Walters[2], Argiris Asderakis[1], Rafael Chavez[1]

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Background: In organ transplantation, there is evidence of involvement of cytokines in reperfusion Injury and organ rejection. Due to the low concentration of cytokines in the peripheral blood, their redundancy and pleiotrophic nature it is difficult to understand their role in this clinical situation. The purpose of this study is to describe the application of the fluorescent bead based multiplex Luminex assay for the characterisation of the perioperative cytokine profile from patients undergoing renal transplantation.

Material and methods: We collected peripheral blood from 20 adult renal transplant recipients during various time points (induction of anaesthesia, just before kidney reperfusion, 1 hour after reperfusion and 24 hours after reperfusion). We measured 27 different cytokines by Luminex - Bioplex suspension array method in each serum sample. (IL-1β, IL-1rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Eotaxin, FGF, G-CSF, GM-CSF, IFN γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, RANTES, TNFα- and VEGF). In luminex based multiplex sandwich assays, the percentage of Coefficient of Variation (CV) represents the level of precision and the CV of less than 10% indicates good level of precision.

Results: The % of CV was calculated for all the cytokines. Over all %CV was 8.4%. In this study, a recovery of 70% to 130% had been taken as acceptable for calculation, as per Bio rad principles of multiplex sandwich immunoassays. With this recovery rate, the total percentage of values within the range for calculation for each cytokine was calculated; most of the cytokine values were within the range, except in the cases of IL2, IL17, MCP-1, FGF, RANTES and GM-CSF whose values were predominately out of range for calculation. Perhaps that indicates that this method might not be the most appropriate for those cytokines. Overall 86% of the cytokine values were with in the range for calculation and the method we used is probably appropriate for all the rest of the cytokines measured.

Conclusion: Fluorescent bead based multiplex Luminex technology can be effectively used to measure the complex cytokine response in clinical settings such as renal transplantation, since it simultaneously measures multiple cytokines using a small serum sample.

P381

ABO-IgA levels may be important in HLA incompatible renal transplants.

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

[1]University Hospitals Coventry & Warwickshire NHS Trust, Coventry, United Kingdom, [2]National Blood Service, Birmingham, United Kingdom, [3]Clinical Science & Research Institute, Coventry, United Kingdom

In recent times, in solid organ transplantation, the non-HLA antibodies are thought to be responsible for both acute and chronic renal allograft outcomes. Non-HLA antibodies may occur as alloantibodies, autoantibodies or natural antibodies. The most ubiquitous antigens to which patients are sensitized are the blood group antigens. There has not been any study looking at blood group antibodies in patients undergoing HLAi transplantation.

We therefore analysed 30 patients (17 F: 13 M) who underwent HLAi renal transplant at our centre from September 2005 to September 2007. Out of whom 9 had no previous transplants; 19 had 1 and 2 had 2 or more. Pre-transplant, patients had 5 alternate day sessions of double filtration plasmapheresis. Immunosuppression consisted of MMF, Tacrolimus, Prednisolone and two doses of basiliximab. Rejection was treated with high dose methylprednisolone, or OKT3 or ATG. Some patients also received post-transplant plasmapheresis.

Pretreatment with plasmapheresis, pretransplantation, antibody(Ab) rise, Ab peak, onset of rejection, resolution of rejection and late samples were the time points chosen for analyses. Plasma samples were analysed using flowcytometry for estimating IgG, IgM and IgA ABO antibodies against reagent cells and the relative mean fluorescence was calculated. The main DSA, cumulative DSA and the 3rd party Abs were analysed using Luminex. In patients with 'O' and 'B' blood group tested against 'A1' reagent and 'A' plasma tested against 'B'cells, if pre treatment IgA levels were high (> or equal to 2 RMF) irrespective of IgG levels 7/10 (70%) of patients had rejection. But if they were low (< 2 RMF) 7/20 (35%) had rejection. Similarly, if pre treatment IgG levels were high irrespective of IgA levels 6/12 (50%) of patients had rejection as opposed to 7/17(41%) if they were low. Also, out of 17 patients with high pre-treatment peak DSA level (>5000), only 6 (35%) had high IgA ABO Abs. This was similar in relation to 3rd party as well. Thus, the correlation seemed to be independent to the level of DSA or 3rd party antibodies.

Thus, there seems to be a correlation between the pre-treatment levels of blood group IgA antibodies and occurrence of rejection, though the reason for this association is not clear.

P382

Do Viral and blood group antibodies follow DSA's in HLAi kidney transplantation?

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

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Non-HLA antibodies are thought to be responsible for both acute and chronic renal allograft outcomes. No study so far has looked at non HLA antibodies like viral and blood group antibodies to see whether an HLA specific immune response affects these antibodies. We therefore analysed 30 patients (17 F: 13 M) who underwent HLAi renal transplant at our centre from September 2005 to September 2007. Pre-transplant, patients were treated with double filtration plasmapheresis and immunosuppression according to standard protocol. Using the Liason machine CMV, VZV and Anti-HBs IgG antibody were quantified. The main DSA, cumulative DSA and the 3rd party HLA Abs were analysed using Luminex. Plasma samples were analysed using FC for estimating IgG, IgM and IgA ABO antibodies. The patients were divided into 2 groups; 1) higher post transplant peak DSA than pre-treatment levels (fig 1) and 2) had lower post transplant peak DSA than pre-treatment levels (fig 2). 10/14 patients in group 1 had rejection as opposed to 4/16 in group 2. There was no correlation between pretreatment DSA or 3rd party ab level with rejection. Inspite of the rises or falls in the cumulative DSA's and the peak DSA levels, there were no changes in the viral or the ABO abs in majority of these patients. Though the 3rd party HLA antibodies showed a rise post transplant above the prelevels, in group1, it was not associated with a fall in DSA's in group 2, possibly due to immune upregulation with crossreactivity. Thus, viral or blood group antibodies do not follow DSA in desensitized transplants and the rise in DSA and 3rd party Abs seem to be HLA specific, at least in the acute period post transplant.

Fig 1- Patients with higher post transplant peak DSA than pre-treatment levels

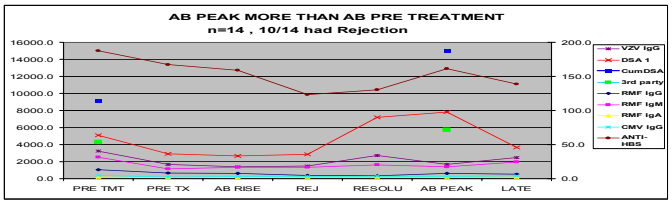
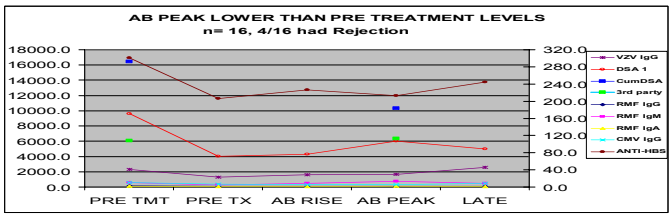


Fig 2- Patients with lower post transplant peak DSA than pre-treatment levels



P383

Risk of rejection after HLA antibody incompatible transplantation

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Transplantation of kidneys across a donor specific HLA antibody barrier may be successful, but there is a significant risk of acute antibody mediated rejection. It is important to try and identify the risk of rejection in advance of the transplant.

Sixty seven patients received HLA antibody incompatible transplants between 2003 and 2008. Donor-specific antibodies were assessed by microbead testing and conventional crossmatching.

Thirty six patients (54%) had rejection episodes in the first 12 months. In all but one case the histological and serological features were compatible with an antibody-mediated event. The risk of rejection was not related to age, gender or first graft/regraft status. The risk of rejection was associated with pre-treatment level and their HLA specificity/ies, as shown in the Table:-

HLA Class 1	x			x	x		x
HLA DR		x		x		x	x
HLA DP/DQ/DRB3-4			x		x	x	x
CDC +ve	1/1	0	1/3	1/2	1/2	0	6/8
FC +ve	5/12	0/1	1/4	2/2	1/3	3/4	5/5
FC –ve/bead +ve	5/12	1/1	0/3	1/1	0/2	0	0

(*table shows number with rejection/total number in category*)

The majority of patients fell into one of three groups. First, 24/25 patient with HLA Class 1 DSA only were cytotoxic (CDC) crossmatch (XM) –ve, and the rejection rate was 10/24 (42%), the same in both flow cytometric (FC) XM +ve and FC XM –ve groups. Second, 10 patients had DSA directed only against HLA DP or DQ or DRB3-4, and 2 (20%) had a rejection episode. Third, 13 cases had DSA against Class 1 +DR +DP or DQ or DRB3-4, 13/13 were CDC XM +ve or FC XM +ve, and 11/13 (85%) experienced rejection.

In summary, patients with HLA Class 1 DSA tended to have lower DSA levels, and a risk of rejection that did not depend on whether the FC XM was +ve or -ve. Those with DSA against only HLA DP, DQ or DRB3-4 had a low risk of rejection, but when there were also DSA against HLA Class 1 and DR, the crossmatch was positive and the rejection risk was high.

P384

ABO-incompatible (ABOi) transplantation: Titre monitoring using synthetic A and B antigens as surrogates for red cells (RBCs) – a word of caution.

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Introduction: We have previously shown that there is heterogeneity within the antibodies (Abs) that bind to the xenoreactive carbohydrate αGal epitope, recognising many distinct carbohydrate structures, some with high affinity. It is our hypothesis that this same heterogeneity exists within antibodies to A & B carbohydrate antigens (Ags). Current titre methods use RBCs, but it has been suggested that synthetic antigen (SAg) incorporating bead technology (similar to Luminex™ in anti-HLA identification) should be employed as an alternative method. We have investigated the use of synthetic A & B antigens and have compared binding to these Ags and to RBCs (A, B & O).

Methods: *Sera:* from 10 normal volunteers. *Haemagglutination (HA):* using RBCs from the National Blood Service (NBS). HA titres (using the Colindale NBS method) were obtained against A, B & O RBCs. *ELISA*: Titres were obtained for IgG and IgM against A & B SAgs conjugated to BSA [Dextra UK].

Results: As expected for HA, there is binding in A sera to B RBCs (1/8-1/128) but not to A or O (as per Landsteiner), and in B sera to A RBCs (1/8-1/64) but not to B or O. However, in A sera there is binding not only to B~BSA (titres from 1/128-1/1024 [IgG], 1/256-1/1024[IgM]), but also to A~BSA (titres from 1/2-1/32 [IgG], 1/16-1/128[IgM]). Likewise in B sera there is binding to both A~BSA (titres from 1/32-1/1024 [IgG], 1/128-1/512 [IgM]) and B~BSA (titres from 0-1/256 [IgG], 1/64-1/1024[IgM]).

Discussion: This study reveals that there may be heterogeneity within anti-ABO Abs, and that synthetic Ag may pick up more Abs as revealed by the higher titre values, including other Abs (eg anti-αGal) which may not be relevant to ABOi transplantation. This is consistent with data from SAg immunoadsorption column work, with removal of relevant Abs being sub-optimal, but including irrelevant Abs. The only titre data fully validated for ABOi transplantation are by HA in the huge Japanese series. Any other method has to be validated against HA before it can be considered to be safe prior to a clinical decision to proceed with an ABOi transplant. This is manifestly not the case with SAgs as used in these assays, where, in most cases, the assay result would not even have been capable of identifying the individual's blood group.

P385

A novel algorithm for managing HLA antibodies (HLAab) in sensitised patients awaiting renal transplantation

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Introduction. We previously demonstrated that transplantation is possible in the presence of donor specific antibodies provided a negative NIH-CDC crossmatch. Consequently we changed our policy in Jan 2008, listing as unacceptable only a) Class I CDC defined HLAab detected in the previous 12 months, b) Class II HLAab detected in last 12 months, c) HLAab "untestable" by CDC screen. We studied the impact of this policy on our program.

Results. Unacceptable antigens were removed in 78% of sensitised patients awaiting transplantation. Between 1/1– 31/12/2008 there were 16 kidney offers for 15 patients in whom DSA had been removed, 4 did not go ahead due to recipient ill health but 12 transplants were carried out (DSA). Their outcomes were compared to contemporaneous matched controls (nonDSA). The median duration of RRT and transplant waiting times were greater in DSA (3087 and 2066 days) compared to nonDSA (1506 and 697 days) $p<0.05$. Patient survival at time of follow up (median 131 and 150 days for the DSA and nonDSA respectively) were 100% in both groups, with graft survival 92% DSA (1 graft lost to pyelonephritis) and 100% non DSA. BPAR occurred in 4 of the DSA group (3 C4d(+ve)). There were no rejection episodes in the non DSA group. Median creatinine, eGFR and urine PCR at last follow up were not significantly different being 126,43 and 27 for DSA compared to 155, 41 and 19 for nonDSA

Conclusion. This very early data suggests that adopting a policy such as that described is safe and provides good short-term outcomes for sensitized patients awaiting renal transplantation. Extended follow up and larger numbers are required to ensure acceptable long-term graft survival rates.

P386

Do we always need cross-match before proceeding to renal transplant?

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BACKGROUND.According to the guidelines of the British Transplantation Society, all potential kidney transplant recipients should have a pre transplant final crossmatch (FXM).Waiting for the result may delay the transplant and prolongs the total cold ischemia time (CIT).Longer CIT has been associated with increased risk of delayed graft function (DGF), rejection (AR), and worse outcome. We reviewed our experience to determine whether there are specific situations where FXM could be avoided

MATERIALS.Between August 2008 and November 2008 we performed 31 consecutive kidney transplant from deceased donor.12 of them (38.7%)had always negative HLA antibodies screening by CDC and Luminex, since listed for transplant. They were six male and six female, median age of 51. Five of black ethnicity (41.6%), 4 Caucasian (33.3%) and 3 Asian (25%) already on dialysis: 9 on haemodialysis (75%) and 3 on peritoneal dialysis (25%). Median of length of dialysis pre transplantation was 3 years. On admission, median serum creatinine (sCr) was 783. The donors were 6 heart beating (HBD) and 6 non heart beating (NHBD).

METHODS. Potential kidney recipient from deceased donor are regularly screened for anti-HLA antibodies by CDC and Luminex techniques every two to three months. Patients found always negative, with latest serum sample within three months from transplantation an no intercurrent sensitising events received a kidney transplant without the FXM result available. A retrospective XM was then performed the day after the transplantation by CDC and flow-cytometry XM.

RESULTS. The median of CIT was 11 hrs for recipients from HBD and 14,5 hrs for recipients from NHBD. Our data from 2007, when the FXM was always performed, showed length of CIT, for recipients from HBD and NHBD, being respectively 18.5 hours and 20 hours. Eight patients (66.6%) had DGF (defined as need for dialysis), 3 patients (3.3%) showed immediate function. The median length of DGF was 12.7 days. Median sCr at 7 days post-transplant was 651. 75% of the patients underwent renal biopsy at a median of 10 days. There was 1 case of border-line AR successfully treated with methylprednisolone.Median of length of hospital stay was 16 days. At one month post-transplant the median sCr was 160. All retrospective-XM were negative and there were no episodes of hyperacute rejections

DISCUSSION. Our experience suggests that, in well defined group of potential kidney recipients with careful antibody screening, it is safe to proceed to transplantation without a FXM result available. That allowed us to sensibly reduce the CIT and, subsequently, length and percentage of DGF and length of hospital stay. Retrospective XM has confirmed the safety of the procedure: we found no cases of positive XM and no episodes of hyperacute rejection.

P387

Significance of preformed anti-HLA antibodies in patients receiving steroid sparing immunosuppressive protocols

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There are few studies analysing the significance of preformed anti-HLA [HLAabs] and donor specific antibodies [DSabs] using solid phase techniques at the time of transplantation in renal transplant recipients receiving modern immunosuppressive regimes.

481 patients [295m, 186f, mean age 46.28 ±12.67 years, 267 live donor and 214 deceased donor grafts] transplanted at our centre between 2002-2008 had their pre-transplant sera retrospectively tested using solid phase techniques [luminex/ELISA]. 422 patients received their first renal transplant, 51 their second and 8 their third graft.

Single antigen luminex beads were used to determine antibody specificity and titre

All patients had a negative CDC and flow cytometric crossmatch at the time of transplantation. Patients received monoclonal antibody induction, Tacrolimus alone or with Mycophenolate Mofetil and a 7 day steroid sparing immunosuppressive regime. Mean follow up was 27.5 ±18.8 months.

81/481 [16.8%] patients were found to have anti-HLA antibodies at the time of transplantation. 39/186 [22.6%] female recipients were HLAabs +ve and the proportion was significantly higher compared to males [39/295 (13.2%), Fisher-exact p=0.009]. Patients who had previously been transplanted were more likely to have HLAabs [52.5% vs 11.8%, p<0.001]

Patient survival [HLA+ 96.2%, HLA– 96.8%, p=0.9] and censored allograft survival [HLA+ 89.6%, HLA- 94.7%, p=0.16] was the same in the HLAab –ve and HLAab +ve groups at 5yrs. The antibody mediated rejection free survival was significantly different in the HLA +ve [HLA+ 89.1%, HLA- 95.5%, p=0.007] and DSab +ve [DSA+ 78.3%, DSA- 97.2%, p=0.001] groups of patients. MDRD GFR was significantly decreased at 24 months in the DSab +ve patients [DSA+ 28.4mls/min, DSA- 53.8mls/min(p<0.05).].

This study shows that patients with preformed HLAabs and DSabs have a higher incidence of subsequent antibody mediated rejection and impaired allograft function and may benefit from pre-emptive enhanced immunosuppression.

P388

Acute rejection: Is it an independent risk factor for post transplant donor specific antibodies (DSA)?

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Background. The presence of post transplant DSA in recipients of kidney allografts is associated with poor graft outcomes. There is little data describing the risk factors responsible for their appearance, what there is suggests an important role for acute rejection. We studied all patients transplanted in our unit since the introduction of solid phase technology to clarify this question.

Methods. All 402 patients transplanted at our centre between 1.1.02 – 22.7.08 were included in this study. During this time maintenance immunosuppression consisted of Neoral/MMF/prednisolone. Induction therapy was used in 60% of patients. Only patients developing *de novo* DSA were included in the DSA group (21 patients), the controls (Con) included patients with any history of pretransplant DSA.

Results. The DSA group were younger (42.7 vs 48.6, $p>0.05$) but there was no difference in ethnicity, gender, degree of HLA mismatch or blood groups compared to Con. On univariate analysis, factors significantly associated with the development of *de novo* post transplant DSA were previous transplants, time since transplant, acute rejection, number of rejection episodes and induction therapy (all $p<0.05$). On multivariate analysis however time since transplant was the only independent risk factor for developing *de novo* post transplant DSA with an OR of 6.4 for 3.1-6yrs (CI 1.06-38.65, $p=0.043$) and 13.35 for >6yrs (CI1.67-106.6, $p=0.014$)(reference group 1-3yrs).

Conclusion. These data suggest that acute rejection is not a risk factor for developing DSA post transplant given the immunosuppression regimen used here, the only independent risk factor being time since transplantation. More research is needed to determine what can be done to prevent or treat this phenomenon.

Poster Session

Wednesday 22 April

13:00 – 14:00

Live Donation 1

Moderator Mr Nizam Mamode

P389

Right kidneys and multiple vessels are not contra-indications to laparoscopic live donor nephrectomy

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University of Leicester, Leicester, United Kingdom

Aims

Many laparoscopic surgeons remain reluctant to procure right kidneys and kidneys with multiple arteries. The aims of this study were to compare the outcomes of donor nephrectomy (LDN) and the subsequent renal transplants from right and left kidneys and kidneys with single and multiple renal arteries.

Methods

In a consecutive series of 235 transperitoneal LDN, 183 (78%) left and 52 right (22%) kidneys were procured. 194 (82.6%) kidneys had a single renal artery, 39 (16.6%) had two arteries and 2 (0.8%) had three arteries. Retro-caval dissection was performed in right kidneys where the renal artery bifurcated posterior to the IVC.

Results

Left kidneys had longer renal veins (38±11 vs 26±8 mm; P<0.0001), but there were no differences in arterial length (32±8 vs 30±6 mm; P=0.095). Three right kidneys required renal vein lengthening on the back table using recipient saphenous vein grafting. There were two conversions to open surgery during left LDN and none during right LDN. Operating time was shorter for right sided LDN (102±21 vs 145± 27 min; P<0.001) and for kidneys with single renal arteries (135±24 vs 151±30 min; P<0.001). The only graft thrombosis in this series (0.4%) occurred in a left sided kidney with a single artery and vein. Comparisons between right and left kidneys and between allografts with single or multiple arteries showed no differences in delayed graft function, urological complication rates, renal function or allograft survival.

Conclusions

Shorter operating times suggest that laparoscopic procurement of right kidneys and kidneys with a single artery is technically easier. The need to procure the right kidney or a kidney with multiple arteries should not be regarded as contra-indications to transperitoneal laparoscopic donor nephrectomy.

P390

Safety Profile of a consecutive series of 235 laparoscopic live donor nephrectomies

Yasha Johari, Adam Barlow, Phillip J Yates, Yutaro Higashi, Rosemary Elwell, Peter Veitch, Michael L Nicholson

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Introduction

Laparoscopic live donor nephrectomy (LDN) has the potential to overcome some of the disincentives to live kidney donation and is being increasingly widely adopted in the UK. This study presents the results of a consecutive series of 235 LDN from a single centre with an emphasis on postoperative complication rates.

Patients and methods

235 live donors (143 women and 92 men; mean age 44 yrs) underwent transperitoneal LDN. There was no selection on the basis of donor body mass index (range 18-45 kg/m^2) or because of difficult vascular anatomy, although in general the left kidney was preferred to the right in view of renal vein length. Subcutaneous heparin and TED stockings were used for thromboembolic prophylaxis in all cases. All donors were reviewed 6 weeks post-operatively and complications were recorded prospectively.

Results

There was no donor mortality and no episodes of thromboembolic disease. Two operations were converted to open procedures, both because of bleeding (one from the renal artery and one port site bleed). There were no bowel perforations or splenectomies but 3 bowel serosal tears and 2 splenic capsular tears were repaired intra-operatively. Two patients required laparoscopic division of adhesions. Other post-operative complications were:

Chest infection	15 (6.3%)
Wound infection	11 (4.7%)
Paraesthesiae of L1	9 (3.8%)
Ileus	2 (0.9%)
Testicular pain	6 (6.5%)
Persistent wound pain	1 (0.4%)
Wound hernia	3 (1.3%)

Conclusions

LDN is associated with a low rate of major or potentially life threatening complications but even in experienced hands there is an appreciable morbidity in fit healthy individuals undergoing LDN.

P391

Donor-gifted renal stone disease and the role of ureteroscopy at live donor nephrectomy

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Abstract

A report on the management of incidental asymptomatic urolithiasis found in potential kidney living donors, and the role of ex-vivo ureteroscopy to remove donor stones at the time of transplant.

Methods

We performed a retrospective analysis of all living donors identified with renal calculi on pre-operative computed tomography between 2004 and 2008.

Results

6 (3.9%) of the 158 living donors were found to have incidental renal calculi. In two cases the stone-bearing kidney was left in the donor. One of these donors subsequently experienced obstructive uropathy in their remaining native kidney two years post-operatively. In the remaining four cases the stone-bearing kidney was transplanted, with no subsequent history of urolithiasis in recipient or donor. Ureteroscopy was performed in three cases, with an embedded stone left in situ in one case, no stone found in the next case, and a small stone successfully removed in the most recent case.

Conclusion

The donor is the most important in the live donor/recipient combination and therefore the choice of kidney should reflect this, leaving the donor with the healthiest kidney. In order to do this strategies should be evolved to manage the stone in the transplanted kidney. One such strategy is to utilise ureteroscopy and possibly stone removal during the ex vivo stage.

P392

Pre-operative CT angiography in determination of clinically relevant arterial and venous anatomy in Laparoscopic live donor nephrectomy

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Introduction: Live donor kidney transplantation has been shown to be safe in terms of the donor well being whilst also conferring a higher level of graft survival and efficacy than that of cadaveric (heart-beating and non-heart beating) donors. Laparoscopic nephrectomy has rapidly become the preferred method in procuring donor kidneys due to the lower morbidity and hence higher acceptability for the donors. The pre-operative planning must take into account the renal vascular anatomy in the donor, where the number of major renal vessels is considered a major determining factor in the choice of side for donation. However, the renal vein tributaries and anatomical variants of these are frequently the cause of bleeding during the operative procedure and accurate identification of these vessels prior to surgery can reduce this risk and hence lower overall donor morbidity.

Methods: We have retrospectively analysed the pre-operative CT angiograms of 152 patients undergoing live donor nephrectomy at our centre over a 10 year period and correlated this with the operative findings both within the donor and on examination of the vessels on the back table during the graft preparation.

Results: CT angiography correctly identified the arterial and venous anatomy of the main renal vessels in 142 (93.4%) of patients. 289 of 354 (81.6 %) venous tributaries were also correctly identified. A 100 (65.8%) cases in total had all aspects of the vascular anatomy identified pre-operatively.

	Sensitivity	Specificity
Renal artery	89%	99%
Renal vein	77%	100%
Lumbar vein	80%	95%
Gonadal vein	84%	94%
Adrenal vein	95%	92%

Conclusion: CT angiography is not only capable of identifying with a high degree of accuracy the major renal vessels that are key in pre-operative decision making but also in providing the surgeon a detailed roadmap of the venous tributaries lowering the potential for uncontrollable haemorrhage and open conversion.

P393

Hem-o-lock clips are safe for vessel control in laparoscopic live donor nephrectomy

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Background: There has been some debate recently as to the safety of Hem-o-lock clips for vessel control in laparoscopic live donor nephrectomy. In light of this, the aim of this study was to audit this unit's experience of their use. Our rationale for use of the Hem-o-locks are firstly that there is less loss of length from the renal vessels as compared to stapling, and secondly warm ischaemic time is slightly reduced as there is no need to remove the staple line from the vessels prior to flushing.

Patients and Methods: The typed operation notes for all patients having undergone laparoscopic donor nephrectomy in this unit were reviewed to identify those where Hem-o-locks were used for vessel control. A retrospective case note review was performed to identify intra- and post-operative complications

Results: A total of 235 laparoscopic live donor nephrectomies have been performed in this unit. Hem-o-lock clips were introduced in 2005. Overall, we have used Hem-o-lock clips to control the renal vein in 141 cases and the renal artery in 137 cases. In the majority (n=138) the vein has been controlled with 2 Hem-o-locks, with 3 clips used in the remainder (n=3). The artery was controlled with 2 Hem-o-locks in 118 cases, 3 Hem-o-locks in 17 cases, 2 Hem-o-locks and a ligaclip in 4 cases and 1 Hem-o-lock and 2 ligaclips in 1 case. There have been no instances of post-operative bleeding from the renal vessels in any of these cases. Indeed, the only incident of significant intra-operative bleeding in this series occurred with use of the vascular stapler.

Conclusion: No method of controlling the renal vessels during laparoscopic donor nephrectomy is infallible. However, our results suggest that with close attention to technique, Hem-o-lock clips are safe for use in this situation. We feel a vital point to ensure is that no tissue is caught in the locking teeth of the clip. To this end, it is necessary to completely clear the renal artery and vein of surrounding tissue. On the left, the renal artery should be dissected down to the junction with the aorta. If there is any concern about the control of the vessels with two clips, either a further Hem-o-lock or a ligaclip should be applied.

P394

The Process Of Establishing Hand-Assisted Extra-Peritoneal Laparoscopic Donor Nephrectomy: Liverpool Experience

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A reduction in the morbidity associated with live donor nephrectomy procedure would confer social and economic benefits. Stakes are high. Due to the high stakes as the procedure involves healthy individuals, it is imperative that all necessary steps are taken to ensure the highest standards of safety when a new approach is introduced in a unit. We report the process of introduction of hand-assisted laparoscopic extra-Peritoneal donor nephrectomy (HALN) programme in Liverpool.

Two consultant surgeons initiated the programme over a period of 3 years. In the first phase, they spent a combined total of 16 weeks in six centres outside the United Kingdom, observing nephrectomy by total laparoscopy or hand-assisted procedures trans-peritoneal or extra-peritoneal and working on anaesthetised pig models (n=6). An initial series of 20 cases was carried out by 2 consultant surgeons assisting each other first 12 cases were mentored by the visiting expert. In addition 4 other patients requiring nephrectomy for non-functioning kidney were operated, including 3 for polycystic kidneys.

Following the introduction of the programme, audit data shows the median duration of inpatient stay to be 5 days (range 3 – 6 days) for HALN and 5 days (range 4-10 days) for open procedure. Mean blood loss for open procedure was 283mls versus 44mls for the HALN group. In the HALN group, one patient developed delayed graft function, and another developed adhesive bowel obstruction needing laparotomy.

Following the careful and planned introduction of a laparoscopic approach, we can demonstrate no disadvantage when this technique is used. Initial data also reveals a reduction in intra-operative blood loss in the HALN group. The option of hand-assisted laparoscopic retroperitoneal nephrectomy allows direct handling of tissues and hence better haemostatic control compared to standard laparoscopic procedure. The bowels is not exposed, reducing the risk of injury and paralytic ileus, thus potentially enabling a more prompt return to normal function.

P395

Predicting glomerular filtration rate before and after live donor nephrectomy

Adam Barlow[1,2], Alice Taylor[1], Rosemary Elwell[2], Adele Buttress[2], Jennifer Moorhouse[2], Michael Nicholson[1,2]

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Background:

Serum creatinine-based estimates of glomerular filtration rate (GFR) are inaccurate in healthy individuals. Therefore, their use in assessment prior to live donor nephrectomy has been restricted. There is less data on their use post-donor nephrectomy. This study assessed three GFR estimates against Cr^{51} EDTA radioisotope GFR (iGFR) in the same cohort of patients before and after donor nephrectomy.

Method:

206 patients underwent iGFR measurement prior to donor nephrectomy and this was repeated in 187 patients 6-8 weeks post-surgery. The iGFR was compared with the Modification of Diet in Renal Disease (MDRD), Cockcroft-Gault (CG) and Mayo Clinic equation (MCe) estimates of GFR.

Results:

Preoperatively all GFR estimates performed poorly against iGFR; however MCe GFR provided the most reliable estimate. MDRD underestimated iGFR by 23.6 ml/min, CG by 8.08 ml/min and MCe overestimated by 0.72 ml/min. Post-donation all estimates again performed poorly, but MDRD and MCe outperformed CG GFR. MDRD underestimated iGFR by 9.13 ml/min, MCe by 9.44 ml/min and CG overestimated by 12.50 ml/min. There was no correlation between post-operative GFR estimates as a percentage of pre-operative GFR estimates for MDRD GFR (R^2=0.01, P=0.1019), CG GFR (R^2=0.02, P=0.0502) or MCe GFR (R^2=0.001, P=0.5496) against iGFR.

Conclusion:

No GFR estimate performed sufficiently well to supersede iGFR measurement prior to donor nephrectomy. Performance post-donation was little better, bringing to question whether iGFR should be measured routinely post donor nephrectomy. The debate is whether the benefits of increased accuracy of post-operative iGFR outweigh the inconvenience, cost and risks to the patient.

P396

Is determination of isotope differential function essential in assessing potential kidney donors?

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Introduction: When assessing potential donors the function of individual kidneys is assessed to avoid donating the kidney with better function. The aim of this study was to determine correlation between differential function (on nuclear scan) and difference in kidney size as assessed by ultrasound scan.

Patients & Methods: Between March 2003 and November 2008 a total of 85 potential kidney donors went through the full assessment process. Of these eight did not proceed to donation and seven donated at other centres. Of the 75 donations locally complete data was available for 56. Data was collected retrospectively. This included kidney length on ultrasound scans, differential function by nuclear scan, pre-donation donor GFR, and GFR in recipients 1, 3 and 6 months post transplant. The patients were divided into four groups on the basis of the differential function on nuclear scan (A: 0%, B: 1 to 10, C: >10 and <20, D: >20%). The difference in length between the two kidneys was calculated as a percentage of the combined length of both kidneys, and compared to the split function on nuclear scan through Pearson's correlation analysis. The donated GFR was calculated as a percentage of the total donor GFR according to the split function of the donated kidney. The donor-recipient pairs were also divided according to gender of the donor and recipients into four groups. The average donated GFRs and the GFRs in the recipients at 1, 3 and 6 months were then analysed.

Results: Of the 56 donations 29 were in group A, 16 in B, 10 in C and one in D. The donated GFR was highest in group A and progressively decreased to 32 in D. The median GFR in recipients from group A, B and C at six months (54, 58 and 56 respectively) were similar, but was lower (31) for group D. Male donors had a higher average total GFR, but their donated GFR was lower due to a higher split function (mean 10 as compared to 7.5 for females). In 10 (12%) cases the nuclear and ultrasound scans didn't agree as to which kidney had greater function. However, there was good correlation between differential function and ultrasound scan on Pearson's analysis ($r = 0.28$).

Conclusions: Ten patients would have had their better kidneys removed if US findings alone were used. We advocate that differential function is used to assess all potential donors prior to kidney donation. Donated GFR is a good index to predict renal function in the recipients.

P397

Correlation of steady state free precession magnetic resonance angiography (MRA) and contrast enhanced MRA with operative findings in renal donors.

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Purpose: Contrast enhanced MRA (CE) is widely used to detect complicated renal vascular anatomy and exclude renal artery stenosis (RAS) in potential renal donors. Free breathing steady state free procession MRA (SSFP) avoids contrast administration and has an excellent negative predictive value for RAS. We compared CE and SSFP with the operative findings in live kidney donors.

Materials and Methods: 7 healthy potential donors (3 female, median age 40 years, range 24-60 years) were studied using 1.5T Achieva MRI system. Post-processing and image analysis was performed using Viewforum Cardiac Package V3.4. Data were analysed using Wilcoxon's matched pair test.

Results: In each case, the left kidney was procured. For these kidneys SSFP and CE correctly identified the number of main renal arteries (including the 2 accessory arteries) and veins demonstrated at surgery. No subject had any degree of RAS. Compared to CE-MRA, SSFP-MRA allowed a significantly longer length of artery to be resolved (75mm vs 58mm ($p=0.03$)). Early branching of the main renal artery determined at surgery was identified in 4/4 cases with SSFP and in 3/4 cases with CE.

Conclusion: Our data suggests that SSFP provides better visualisation of the renal arteries than conventional CE, with a greater length of artery demonstrated and accurate identification of early arterial branching. SSFP may provide an alternative to CE for vascular assessment and surgical planning in potential renal donors, avoiding the need for intravenous contrast.

Poster Session

Thursday 23 April

13:30 – 14:30

Liver

Moderator Prof Derek Manas

P398

Transcatheter arterial chemoembolisation as a bridge to orthotopic liver transplantation

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Introduction: Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. Orthotopic liver transplantation (OLT) guided by the Milan criteria is considered the optimal treatment. The demand for donor organs remains greater than the available supply, leading to increased waiting times for OLT and subsequent increased risk of tumour progression and patient dropout. In order to maintain patients within the Milan criteria the use of regional ablative therapies has become widespread. Transcatheter arterial chemoembolisation (TACE) is the most commonly used bridging procedure.

Objectives: 1) To investigate the efficacy of neoadjuvant TACE in patients awaiting OLT.

2) To assess the impact of receiving neoadjuvant TACE on disease recurrence post transplant.

Methods: A retrospective comparative study of 36 patients listed for OLT between October 2001 and January 2007 was conducted. TACE was deemed successful in those patients where disease remained within, or was reduced to within, transplant criteria.

Results: 8 patients who were within transplant criteria at diagnosis received neoadjuvant TACE with the aim of maintaining disease within the transplant criteria. This was successful in 87.5% and unsuccessful in 12.5%. 5 patients had disease out-with the transplant criteria at diagnosis and received neoadjuvant TACE with the aim of downstaging their disease. This was successful in 40% and unsuccessful in 60%.

In the group that received TACE prior to OLT there was recurrence in 16%. Recurrence following OLT alone was 10%.

Conclusions: Our experience demonstrates that TACE is a successful means of maintaining patients awaiting OLT within transplant criteria. However, incidence of recurrence is seen to be greater in those receiving TACE prior to OLT.

P399

Prevalence of risk factors contributing to renal dysfunction and cardiovascular morbidity in liver transplant recipients

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Improvements in survival after liver transplantation over the last 3 decades are reflective of improved survival in the first year. The difference in longer term survival after this period is insignificant[1]. Non hepatic causes account for more than half the deaths in those that survive for more than 3 yrs post transplantation[2].

Aims: To quantify the prevalence of renal failure, hypertension, hyperlipidemia, diabetes and calculate the 10 yr cardiovascular mortality risk in liver transplant recipients.

Methods: Data was collected prospectively from 105 liver transplant recipients. Hypertension was defined as a systolic BP≥140 or a diastolic BP≥90. 10 yr cardiovascular risk in non diabetics was calculated using the Framingham Score[3].

Results: Mean age was 53±14 yrs; 50% were male and 25% smokers. Median time from transplant was 6 years. 53% were hypertensive and 43% of these were not on antihypertensives. 18% were diabetic at the time of review with a mean HBA1C of 6.5±1.4. 12% had eGFR measuring less than 30 ml/min/1.73m^2 and these patients had a significantly higher systolic ($p<0.01$) and diastolic ($p<0.05$) blood pressure than those with normal renal functions. No significant difference in the prevalence of diabetes was noted in those with and without renal impairment. 86% of all recipients were on a calcineurin inhibitor. 58% had a BMI≥25. Mean total and LDL cholesterol were 5.1±1.4 and 2.8±1.16 respectively. 55% had LDL cholesterol≥2.6 and of these, 83% were not on any treatment for their hyperlipidemia. The mean 10 yr cardiovascular risk in those without diabetes was 9.2%. Conclusions: The long term care of liver transplant recipients remains suboptimal. National guidelines promoting proactive monitoring, prompt detection and early addressal of risk factors contributing to renal and cardiovascular morbidity may improve long term survival.

1. KM Barber et.al. Long-term transplant survival for liver recipients in the UK

2. Pruthi J et al. Analysis of causes of death in liver transplant recipients who survived more than 3 years Liver Transplantation 2001; 7: 811-815

3. Wilson PW, et.al. Prediction of coronary heart disease using risk factor categories Circulation. 1998; 97(18):1837-1847

P400

Outcome of Liver Transplantation for the Treatment of Haemophilia

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Backgroud: Prior to routine screening of blood products many haemophiliacs were infected with hepatitis C virus (HCV), and have subsequently developed end-stage liver disease. We report our experience of liver transplantation (LT) in these patients.

Patients and Methods: Patients transplanted from 1994 to date were identified retrospectively. Patient demographics, pre-, intra- and post-operative details, and outcome were documented.

Results: Of 3800 LT performed, 13 were performed for haemophilia A, 4 for haemophilia B and 1 for factor X deficiency. All were male, with a median age of 52 years (range 26-59), all were HCV-RNA positive and 5 (28%) were HIV-RNA positive. Four patients had hepatocellular carcinoma (HCC). 16 patients received a whole liver, of which two were non-heart-beating, and 2 received a right lobe split graft. Median intra-operative blood loss was 4.2L (0.8 to 12L), and all received coagulation factor support. Postoperatively coagulation was unsupported by 72 hours in all recipients. Two patients (11%) had postoperative bleeding, one of which, a subdural bleed, was fatal. At a median follow-up of 90 months, 8 patients, 4 of who were HIV positive, have died from sepsis (1), bleeding (1) and HCV recurrence (6). The median survival of patients with and without HIV co-infection was 26 and 64 months (p=0.011).

Conclusions: LT in patients with haemophilia cures the coagulation disorder, and in the absence of HIV-HCV co-infection is association with excellent patient survival.

P401

Impact Of Use Of T-Tube For Biliary Reconstruction In Orthotopic Liver Transplantation In Patients With Fulminant Liver Failure.

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Use of T-Tube for biliary reconstruction in Orthotropic Liver Transplantation (OLT) has diminished. However in OLT for fulminant liver failure (FLF) T-tube may facilitate postoperative imaging and decrease the need for postoperative ERCP. Our aim is to evaluate the incidence of biliary and infectious complications in OLT with and without use of T-tube.

Methods: Retrospective analysis was performed on prospectively collected data for all sequential liver transplants for FLF f from the years 1990 to 2007.This included demographic details, details of biliary reconstruction, early/late biliary and infectious complication, in addition to other confounding factors.

Results: Out of 1000 OLT154 patients were transplanted for FLF (15.4%).36 had biliary reconstruction with T-Tube (A) where as 118 had no T-tube (B). Bile leak in group A was 8.3 % and 9.7 % in group B (P=0.3539).Biliary stricture was recorded only in group B (3.2%). The rate of wound infection was 16.6% and 28% in group A and B respectively (P=0.0921). Intra-abdominal sepsis was 11.1% and 28.8% in group A and B respectively(p value=0.0145).Arterial complications included haemorrhage (16.6% = A and 15.2%=B) and hepatic artery thrombosis [2.7%=A and 10.1%=B(P=0.1270)]. Median hospital stay was 45 and 42.5 days in group A and B respectively

Conclusion: Use of T-tube in OLT for FLF is not associated with increase in infectious or biliary complication, and may permit avoidance of difficult invasive tests such as ERCP to identify biliary complications. However a larger study is needed to assess the impact of T-tubes in this setting.

P402

The use of plasmapheresis for the treatment of severe rejection in liver transplant recipients

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Steroid-resistant rejection is an uncommon problem in liver transplantation. The use of plasmapheresis for the treatment of refractory rejection in the presence of donor specific antibody has not been widely reported after liver transplantation. The aim of this study was to evaluate the use of plasmapheresis as means of graft salvage in patients having liver transplantation.

5 patients (4F:1M, median age 37 yrs) with refractory allograft rejection associated with donor specific antibody received plasmapheresis as part of their treatment regime. Indications for liver transplantation were PSC (n=2), polycystic liver disease (n=1), acute liver failure (n=1) and secondary biliary cirrhosis (n=1). 3 were in the immediate post-transplant period, and 2 were cases of late rejection. Maintenance immunosuppression comprised tacrolimus, azathioprine and steroid with later conversion of azathioprine to mycophenolate mofetil in all cases. The median number of plasma exchanges was 5 (range 5-8). Liver grafts were salvaged in 4 cases and all have good function at most recent follow-up (8, 58, 84, and 119 months post-transplant). One of the 5 patients required re-transplantation 5 years after her original transplant for ductopenic rejection.

In conclusion from this preliminary experience plasmapheresis is a useful adjunct for the treatment of refractory rejection in liver transplant recipients.

P403

Donor age, senescence and graft outcome in liver transplantation

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Introduction: The imbalance between the supply of livers and demand for transplantation has led to the use of older donors, although these livers have been associated with a decreased regenerative capacity, and graft/patient survival. This study examined patient survival and acute rejection following usage of livers from donors in their sixties and seventies.

Methods: All transplants carried out in Scotland since 1992 were analysed using the Scottish liver transplant database.

Results: Patients transplanted with a liver from a donor in their sixties had similar survival to those with donor livers between thirty and sixty. Using donors in their seventies led to a lower median patient survival than younger donors (seventies: 21.73 months; sixties: 49.80 months). This was not significant. Donors in their twenties produced the highest median patient survival (88.67 months). Acute rejection did not increase with donor age, however, HCV, cross-gender transplants, male recipients and older male donors were associated with lower survival.

Conclusions: There is some potential for using donors in their sixties to meet demands for transplantation. Usage of livers from donors in their seventies warrants further investigation and should be assessed on an individual basis in terms of the benefits and risks of transplantation, or remaining on the waiting list.

P404

Acute Dual Vessel Thrombosis Post Liver Transplantation. Our Experience.

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Aim: Thrombosis of both arterial and venous inflow vessel into the liver after liver transplantation can raise concern about the outcome from a re-transplant as the failure could be due to patient factors just as much as it could be due to technical errors. Due to its rarity, such occurrences have never been studied except as single case reports.

Methods: We retrospectively reviewed our records over the past 20 years to identify all such cases. Cases found were studied in detail (including donor data) to find possible unifying patient or organ risk factors during the pre or intra-operative period. Clinical patterns that might aid in diagnosis were looked for.

Results: From 1989 to date there were 3296 liver transplants performed in our unit of which 769 were in children. We identified 4 cases in whom there had been thrombosis of both hepatic artery and portal vein either simultaneously or one following the other acutely. All were children 8, 7, 7 months and 8 years old, three of whom had EHBA and one had familial sclerosing cholangitis. All Biliary Atresia patients had had previous Kasai procedures. All recipients received left lateral segment split grafts. Diagnosis was made or suspected on transabdominal ultrasound in each and all needed a re-transplant (day 1, 3, 7, and 3) with or without an arterial conduit. No significant donor features were found and cold ischemia time was 12 hours in the longest. None of the children were positive for identifiable pro-thrombotic screens and all are alive on recent follow-up.

Conclusion: Dual thrombosis is a rare but potentially life threatening complication of liver transplantation and in our series always required a re-transplant. Adults appear to be spared this particular complication presumably due to large volume, high capacity livers relatively resistant to pressure changes. Day 1 ultrasounds are a valuable part of post-transplant management and should be routine.

P405

Liver Transplantation for HIV infected patients. Are prophylactic measures for late arterial thrombosis required?

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Aim: It is recognised that HIV positive patients are prothrombotic as a result of their disease. We analyzed our cohort of liver transplantation recipients to review the incidence of post operative arterial complications, estimate the risk of such complications and develop recommendations for post operative prophylaxis.

Method: We reviewed our patient cohort of 3296 patients transplanted between 1989 to the present date and identified 21 liver transplant recipients infected with HIV. These were analysed further in terms of their primary operation, post-operative course with specific regard to their arterial complications, and long-term outcome. Other factors that could influence risks of arterial complications were looked for.

Results: Of the 3296 liver transplants, 21 recipients were infected with HIV. [Median age 40 years, all except one with whole liver grafts]. Of the 5 arterial complications, 3 were Hepatic artery thrombosis (One in a NHB donor), and one with generalised arteriopathy on angiography and another with endoarteritis on liver biopsy although flow was present in the HA. Of note 7 out of 21 had more than one arterial anastomosis and all of the HATs occurred within this cohort. One of the HATs needed a re-transplant, the second ERCP and stent for ischemic cholangiopathy and the third had a re-laparotomy and creation of an arterial conduit.

Conclusion: The prothrombotic state associated with combined HIV and liver disease is a cause of significant morbidity post liver transplant. The risk of HAT appears higher (14%), particularly in the presence of complex arterial reconstruction. Prophylactic anti-coagulation should include heparin in the early post –operative stage and either Aspirin or Warfarin later. Thromboelastography may help guide management in these patients.

P406

Non-anastomotic biliary strictures after liver transplantation. A single centre experience

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Introduction
Non-anastomotic biliary strictures (NABS) are important complications after liver transplantation (LT). We present our centre's experience of NABS after LT.

Methods
Over a period of 10 years, 22 patients were diagnosed to have NABS based on clinical presentation and imaging. Data regarding the management was collated by review of the case notes, clinic letters and imaging studies.

Results
Seven (32%) patients had received non-heart-beating grafts. Ten (45%) patients presented within 3 months of transplant, three (14%) 3-6 months, four (18%) 6-12 months, three (14%) between 1-2 years, and two (9%) at >2 years. Four of the 22 patients had early hepatic artery thrombosis (HAT) and underwent emergency revascularization. NABS was classified based on the site and extent of the biliary lesions. Four patients had involvement of the donor CHD alone. 6 had involvement of intra-hepatic bile ducts alone. 12 had involvement of both intra and extra hepatic ducts. The extent of intra-hepatic duct involvement varied from single sectoral duct involvement in 2 patients, multiple hepatic and sectoral duct strictures in 11 patients and diffuse involvement of all peripheral ducts in 5.

All patients with NABS underwent CT angiography to assess the hepatic artery. This identified 3 patients with late HAT and 7 with hepatic artery stenosis. Angioplasty was possible in five patients with stenoses. All patients were started on medical therapy with oral ursodeoxycholic acid and antibiotics for episodes of cholangitis. This was the definitive treatment in four patients. ERCP and spincterotomy was carried out in 11 patients in whom imaging had suggested a dominant extra-hepatic stricture. Of these, 5 patients had trial stent placement and 2 had stricture dilation. This was definitive treatment in one patient. Percutaneous dilation of a dominant stricture was attempted in two patients (1 success). Biliary reconstruction was carried out in 4 patients, it was therapeutic in two patients. 2 further patients await biliary reconstruction surgery. Re-transplant was not possible in 3 patients despite failure of above therapies (2 were unfit for surgery, one patient refused). 10 patients (45%) were re-transplanted due to presence of HAT or failure of other therapies. At median follow up of 56 months, graft survival was 9/22 (41%) while 16 patients (73%) were alive

Conclusion
NABS have an ischaemic aetiology and commonly associated with non-heart-beating-grafts and hepatic artery problems. Management should be multi-disciplinary and tailored to each patient based on the clinical symptoms, associated hepatic artery problems, extent of stricturing and fitness of patients. Optimum use of all therapeutic modalities including re-grafting improves patient survival.

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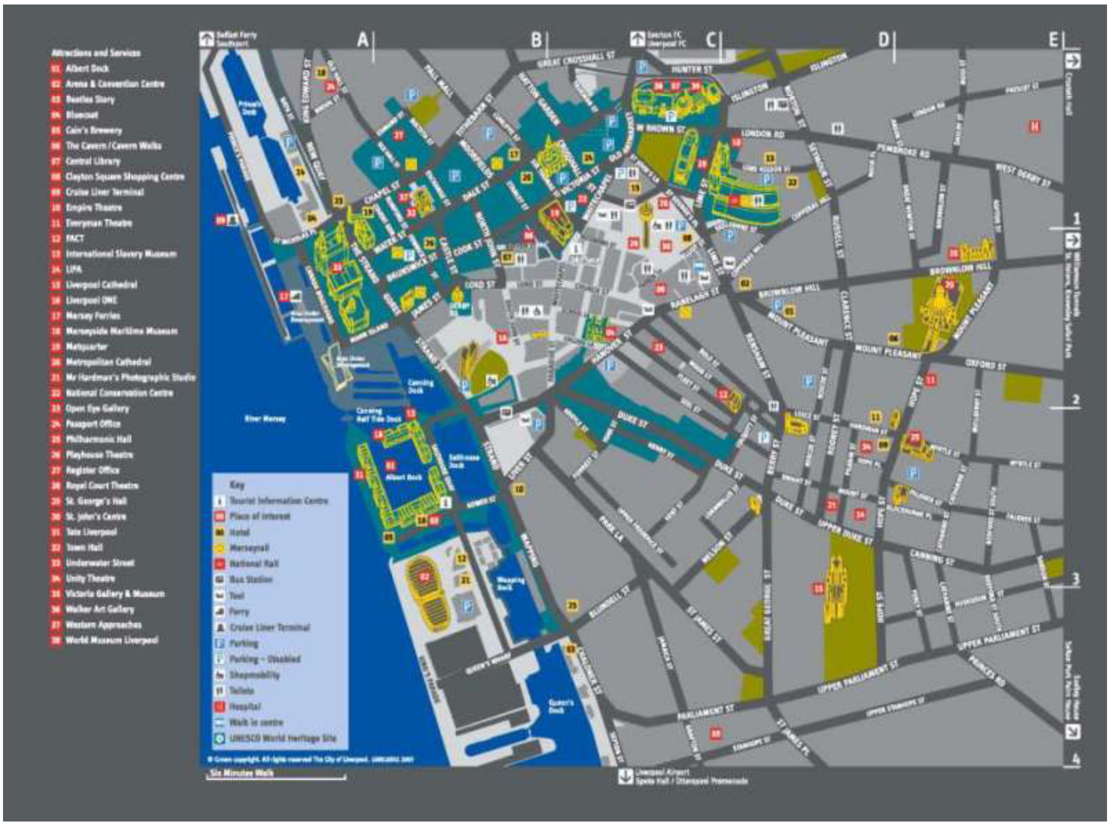
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