Congress 2013

Joint Congress of the
British Transplantation Society & Renal Association

Bournemouth International Centre
13th – 15th March 2013

BTS British Transplantation Society

THE RENAL ASSOCIATION founded 1950

Welcome to Bournemouth

The British Transplantation Society and The Renal Association are delighted to welcome you to Bournemouth for our annual congress. This is the third joint meeting of the societies, and the first to be fully integrated over all three days.

The conference organising committee, led by Anthony Warrens and Alison Brown, have put together an excellent programme combining international and local experts and we are sure you will enjoy it.

We are grateful to our invited speakers for giving their time to share their knowledge with us, and to those of you who are presenting abstracts both orally and as posters for contributing to what promises to be a really interesting meeting. We would also like to thank all the session chairs and poster moderators for their help in making this a success.

We are indebted to the congress organising committees of both societies, and to Sam, Christine and Natalie and the staff at Kingston Smith Association Management for all their hard work in organising the conference.

Lastly we would like to thank our corporate partners and other industry stakeholders whose support has contributed to making this conference possible. Please take some time during the meeting to visit their stands, and come along to the lunchtime symposia.

This year the conference coincides with World Kidney Day, which is on Thursday. We are grateful to Kidney Research UK for helping to organise a fun run on Thursday morning to mark the event – come along and join us, either by running or cheering.

Yours sincerely

Chris Watson
President
British Transplantation Society

David Wheeler
President
The Renal Association

Acknowledgements

A formal thank you to the Programme Committee: Prof Chris Watson, Prof Anthony Warrens, Dr Richard Baker, Dr Iain MacPhee, Dr Alison Brown, Dr Jonathan Fox and Dr David Wheeler for putting together an educational and enjoyable programme.

The Programme Committee would also like to thank the abstract review panel which comprised of:

Mr Niaz Ahmad
Mr Jacob Akoh
Mr Murat Akyol
Mr Argiris Asderakis
Dr Damien Ashby
Dr Sunil Bhandari
Mr Simon Bramhall
Dr David Briggs
Prof Edwina Brown
Ms Lisa Burnapp
Dr Aine Burns
Mr Christopher Callaghan
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Dr Afzal Chaudhry
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Ms Jackie Spencer
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Dr Paul Stevens
Dr Maarten Taal
Dr Mark Thomas
Dr Charlie Tomson
Dr Nick Torpey
Dr David Turner
Dr Graham Warwick
Prof Chris Watson
Dr David Wheeler
Prof Steve Wigmore
Dr Martin Wilkie
Dr Graham Woodrow
Dr Daniel Zehnder

Abstracts

Parallel session

Wednesday 13th March

Renal dysfunction in the immunosuppressed

14:00 – 15:30

O1

B cell-dependent CD4 T cell alloimmunity is a predictor of graft outcome in renal transplant patients with antibody-mediated rejection

Kin Yee Shiu[1], Irene Rebollo-Mesa[1], H Terence Cook[2], Candice Roufosse[3], Paul Brookes[4], Jack Galliford[5], David Taube[5], Robert I Lechler[1], Maria Hernandez-Fuentes[1], Anthony Dorling[1]

[1]MRC Centre for Transplantation, King's College, London, UK, [2]Immunology & Inflammation, Imperial College, London, UK, [3]Department of Histopathology, Hammersmith Hospital, London, UK, [4]Histocompatibility and Immunogenetics Laboratory, Hammersmith Hospital, London, UK, [5]Imperial College Kidney and Transplant Centre, London, UK

Background: Alloantibodies, particularly against HLA (HLA Ab), are widely held to cause chronic graft loss. However, donor-specific B cells are required to produce HLA Ab, and may act as antigen-presenting cells to alloreactive T cells, so driving rejection. We studied renal transplant patients for evidence of these cells, and their role in determining graft outcome.

Methods: We recruited 61 patients: 15 post-protocol biopsy (PB) with Ab-mediated rejection (AMR), 46 post-biopsy for cause (BFC- included 33 AMR) at a median 0.7(0.6-0.9 IQR) and 4.9(1.0-11.7) yr post-transplant. Evidence of T cell donor-specific reactivity (DSR) and B dependence were tested for using IFNγ ELISPOT assay with allogeneic proteins, pre- and post-CD19 B cell depletion. HLA Ab were tested for by Luminex assay. Transwell, B cell specific antigen-presentation/processing inhibitor experiments, and multicolour flow cytometry T/B cell phenotyping were also performed (data to be presented). A subset of BFC patients were treated with protocolized FK/MMF± Rituximab for AMR, permitting evaluation of the effects on DSR, Ab and outcome.

Results: DSR was found in 13/32(41%) of PB and 32/83(39%) of BFC in a total of 115 viable samples. In 2/3 samples with DSR, there was a significant reduction in IFNγ producing cells post-B cell depletion and association between DSR and B cell dependence ($p \leq 0.01$). Median follow-up was 31.4mo (PB) and 35.6mo (BFC). Multivariate analysis found that ELISPOT at the time of PB predicted graft deterioration better than HLA Ab. In the BFC group, predictive factors included HLA Ab, C4d, proteinuria, MDRD eGFR and ELISPOT. Surprisingly, DSR at the time of BFC was not deleterious, whereas DSR on follow-up was associated with graft deterioration/loss ($p=0.02$), potentially due to treatment effects. FK/MMF± Rituximab stabilised 7/18(39%) patients at 3yr, without significant falls in HLA Ab levels. 4/5 with DSR stabilised post-treatment, all became non-DSR on follow-up.

Discussion: If these findings are replicated in larger studies, then in patients with evidence of alloreactive T and B cells e.g. on IFNγ ELISPOT assay, targeting these rather than Ab may be more effective in preventing premature graft loss.

O2

Using rituximab or cyclical plasma exchange and intravenous immunoglobulin does not improve allograft survival after a diagnosis of transplant glomerulopathy

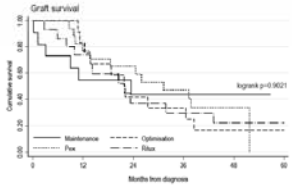
Candice Clarke[1], Kakit Chan[1], Kin Yee Shiu[2], Paul Brookes[1], Candice Roufosse[1], H Terence Cook[1], Anthony Dorling[2], David Taube[1], Jack Galliford[1]

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

Introduction: Transplant Glomerulopathy [TG] causes allograft failure and is commonly associated with donor specific anti-HLA antibody [DSAbs]. It has been reported that optimised immunosuppression may be of benefit, including Rituximab [Ritux] in the short term. The purpose of this study is to report medium term outcomes using Rituximab and cyclical plasma exchange [Pex] with ivIg to treat TG after immunosuppression optimisation with Tacrolimus [Tac] and MMF but not steroids.

Methods: 59 successive patients with TG [35M, 24F] were enrolled. 13/59 were on Cyclosporin based immunosuppression and were switched to Tac and MMF [Optimisation group]. 12/59 had already been on Tac and MMF, and did not undergo further treatment [Maintenance group]. 16/59 received 2x1g Ritux [Ritux group]. After a septic death in Ritux group this treatment was replaced by cyclical Pex with ivIg [Pex group] and given to 18 patients.

Results: 81% of patients had DSAbs at the time of diagnosis, 68% directed at the DQ. Allograft survival was 90.9%, 72.7%, 48.0%, 38.4%, 27.8% and 23.8% at 6,12, 24, 36, 48 and 60 months respectively. Cumulative allograft survival between groups is no different and is shown in the Figure below.



There were 6 serious infective adverse events requiring hospital admission; 1 in Maintenance group, 3 in the Ritux group and 2 in the Pex group.

Conclusion: This study shows that the use of Rituximab or cyclical Pex with ivIg does not prolong allograft survival therapy in TG and both carry risk. Further work is required to direct therapy, which may need administration on an individual basis and before the lesion develops.

O3

Non-invasive tests to help stratify risk of acute rejection in renal transplant recipients

M Runglall[1,2], I Rebollo-Mesa[1], Y Kamra[1,2], J Lo[1,2], M Jenkins[1,3], L Beswick[1], S Phin Kon[4], B Tucker[4], C Farmer[5], T Strom[6], G Lord[1,2], S Sacks[1,2], M Hernandez-Fuentes[1,2], P Chowdhury[1,3]

[1]King's College London, MRC Centre for Transplantation, London, UK, [2]NIHR Comprehensive Biomedical Research Centre at Guy's Hospital and St Thomas' Hospital NHS Foundation Trust in partnership with King's College London and King's College Hospital, London, UK, [3]Guy's and St Thomas' NHS Foundation Trust, London, UK, [4]King's College Hospital NHS Foundation Trust, London, UK, [5]East Kent Hospitals University NHS Foundation Trust, Kent, UK, [6]Beth Israel Deaconess Medical Center, Boston, USA

Background: Despite immunosuppression, acute rejection (AR) still affects a significant proportion of renal transplants. Presently, AR is suspected when there is already evidence of graft dysfunction indicated by a rise in blood creatinine levels and can only be confirmed by histological examination of a biopsy of the allograft. Molecular biomarkers could help risk stratify patients and reduce the need for invasive testing with biopsies. Furthermore, changes at a molecular level are likely to precede both histological findings and graft dysfunction, allowing earlier diagnosis and treatment to limit graft damage. Combinations of such markers might allow tailoring of anti-rejection medication for each individual recipient. The aim of our study is to identify and characterise biomarkers in blood and urine that can diagnose and predict AR in renal transplant recipients.

Methods: Blood and urine samples are collected from recipients before the transplant and over the first year post-transplant at 26 time-points and during episodes of graft dysfunction. RNA was extracted from blood samples collected into Tempus Blood RNA tubes and from urine sediment cells. cDNA was synthesised and pre-amplified for urine. Quantitative real time PCR was done for 20(blood) or 23(urine) target and 4 control genes.

Results: A pilot study consisting of 10 biopsy proven acute rejection (BPAR) and 18 stable patients revealed a significant over- expression of 5 genes in blood (SEMA7A, PF4, TGFB1, ITGAM, C6orf25) at week 2 after transplantation in the BPAR group, thereby predicting the subsequent development of rejection episodes occurring up to one year post-transplantation (Wilcoxon test, $p<0.05$, false discovery rate <5%). Using the expression of these 5 genes in a multivariate prediction model returned a probability score that predicted BPAR with a sensitivity of 0.7, specificity of 0.95, and an AUC of 0.80. For urine, the difference of gene expression 1-2 weeks and 3-4 weeks pre-biopsy was analysed in 7 BPAR and 7 stable samples at matched time points. Preliminary analysis suggests that differences in expression for perforin and FasL were detected between these groups. This suggests that it might be possible to use a urine test to predict a rejection episode with high specificity and sensitivity up to 4 weeks before it occurs.

Conclusions: Our pilot study suggests that measurement of mRNA levels in blood and urine could help risk-stratify patients for AR in kidney transplant recipients before the onset of rejection allowing potential individualisation of anti-rejection therapy. Validation of these findings in a larger cohort is clearly needed.

Parallel session

Wednesday 13th March

Latest trials update

14:00 – 15:30

O4

A randomised trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associated vasculitis: MYCYC

Rachel Jones[1], Lorraine Harper[2], Paul Brogan[3], Karen Dahlsveen[1], Peter Lanyon[4], David Jayne[1]

[1]Addenbrooke's Hospital, Cambridge, UK, [2]University of Birmingham, Birmingham, UK, [3]Great Ormond Street Hospital, London, UK, [4]Queens Medical Centre, Nottingham, UK

Background: Cyclophosphamide (CYC) induction regimens are standard therapy for ANCA-associated vasculitis (AAV) with major organ involvement. However CYC is associated with considerable toxicity. Mycophenolate mofetil (MMF) is a potential alternative to CYC. We performed an international, non-inferiority randomised trial comparing MMF to CYC for remission induction of AAV.

Methods: Eligible patients had newly diagnosed AAV and were randomised to receive up to 6 months of induction with either MMF 2-3mg/day (n=70) or 6-10 pulses of IV CYC 15mg/kg (n=70). Both groups received the same tapering oral prednisolone regimen and azathioprine maintenance therapy. The primary outcome was remission (absence of disease activity for ≥4 weeks while adhering to the glucocorticoid regimen). We hypothesized that MMF treatment would result in no more than 12% fewer remissions.

Results: The groups were similar at trial entry. The primary remission endpoint occurred in 46/70 (66%) MMF vs 48/70 (69%) CYC (risk difference -3%, 90% CI -16 to 10%; p=0.06 for non-inferiority). Remission induction irrespective of steroid compliance occurred in 61/70 (87%) MMF vs 54/70 (77%) CYC (risk difference 10%, 90% CI -1 to 21%; p=0.01 for non-inferiority). However, glucocorticoid dosing did not differ significantly between groups overall (p=0.96). Key safety outcomes did not differ significantly (Table 1).

Conclusions: In the primary analysis we were unable to demonstrate that MMF is non-inferior to IV CYC for remission induction at six months in severe newly diagnosed AAV. How glucocorticoid treatment affects remission induction with MMF requires further study. Longer term safety outcomes and relapse data are required to fully understand the role of MMF as induction therapy for severe AAV.

Table 1. Key safety outcomes

Safety Outcome	MMF	CYC	Risk Difference (95% CI)	p-value
Any SAE	32 (46%)	27 (39%)	7% (-9 to 23%)	0.39
Serious Infection	18 (26%)	11 (16%)	10% (-3 to 23%)	0.14
Dialysis	2 (3%)	3 (4%)	-1% (-8% to 5%)	0.99
Death	5 (7%)	4 (6%)	1% (-7 to 10%)	0.99

O5

Native vitamin D therapy in hemodialysis patient's results in reduced erythropoietin (EPO) requirements - a cluster randomised study

Tarun Kaushik, Mark Blunden, Martin Raftery, Ravindra Rajakariar, Magdi Yaqoob

The Royal London Hospital, London, UK

Background: Haemodialysis patients have low measured 25-OH Vitamin D levels. Native vitamin D supplementation in dialysis patients has been shown to reduce inflammation by lowering pro inflammatory cytokine. Sterile inflammation in dialysis patients is associated with EPO resistance resulting in higher dosage and increased morbidity and mortality .We therefore hypothesized that Vitamin D2 supplementation leads to reduced EPO requirements.

Methods: We conducted a cluster randomised study where half patients in a satellite unit were given oral ergocalciferol (n = 118) whilst remaining patients did not receive the treatment (n= 117) as per clinical preference of two physicians. In both groups combined, median 25 OH-Vitamin D level at baseline was 33 nmol/L (range 39.7– 48.4).The treated group (n= 118) received supervised 50,000 units weekly for 4 weeks followed by once monthly for 5 months. There was no difference in demographics, dialysis vintage, use of activated vitamin D and Cinacalcet in both groups.

Results: With treatment vitamin D levels rose from median of 42 to 78 nmol/L ($p<0.0001$) which remained unchanged in untreated group. In the treatment group, there was a significant reduction in EPO requirement as assessed by Hb index (weekly EPO dose in units/Hb g/dl) from a mean of 671 to 580 ($p<0.001$) but remained unchanged in the untreated group from mean of 795.0 to 743.1 ($p=0.12$) at 6 months. Furthermore, in the treated group the mean EPO dose per kg body weight per week reduced from 104 to 86 ($p=0.015$) but tended to increase non-significantly in untreated group (120 baseline to 160 at 6 months; $p=0.21$).Serum ferritin, calcium, phosphate, PTH and non hs-CRP were similar in both groups during the six month study period. Ergocalciferol was well tolerated with no adverse effects.

Conclusions: We conclude that native vitamin D2 in physiological doses leads to reduction in EPO requirement by an unknown mechanism. This simple and cheap strategy is both safe and well tolerated. The benefit of this therapeutic approach may potentially translate into significant cost saving and better patient outcomes.

O6

Eculizumab (ECU) in atypical hemolytic uremic syndrome (aHUS) patients (Pts) with a long disease duration and chronic kidney disease (CKD): 2-year data

Timothy Goodship[1], Christoph Licht[2], Petra Muus[3], Christophe Legendre[4], Kenneth Douglas[5], Maryvonne Hourmant[6], Yahsou Delmas[7], Maria Herthelius[8], Antonella Trivelli[9], Camille L Bedrosian[10], Chantal Loirat[11]

[1]Newcastle University, Newcastle upon Tyne, UK, [2]The Hospital for Sick Children, Toronto, ON, Canada, [3]Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, [4]Hopital Necker, Paris, France, [5]Beatson West Scotland Cancer Centre, Beatson, UK, [6]CHU Hotel Dieu-Nantes, Nantes, France, [7]CHU Pellegrin, Bordeaux, France, [8]Karolinska University Hospital, Hagalund, Sweden, [9]Instituto G Gaslini, Genova, Italy, [10]Alexion Pharmaceuticals, Cheshire, USA, [11]Hopital Debre, Paris, France

Introduction: ECU inhibits complement-mediated thrombotic microangiopathy (TMA) in patients with aHUS, a disease of chronic uncontrolled complement activation. We report follow-up data from a 26-wk, open-label phase II study that accrued patients (≥12 yrs) with long-duration aHUS and CKD who prior to initiation of study had received chronic plasma exchange/ infusion (PE/PI).

Methods: Following enrolment and 8 wks observation, pts stopped PE/PI and initiated ECU (900mg/week for 4 wks, 1200mg at wk 5, then 1200mg q2 wks thereafter). The 1' endpoint was TMA event-free status (≥12 consecutive wks without platelet count change of >25% + no PE/PI + no new dialysis).

Results: From the 20 pts enrolled in the initial trial, 19 continued ECU treatments in the extension period. The median time from diagnosis to screening was 48 months (0.66–286) and mean baseline eGFR was 30.8 (19.0). At data cut off (median ECU treatment duration of 114 wks [26–129]), 19 pts achieved TMA event-free status. No pt required PE/PI or progressed to ESRD/dialysis. Overall 8 pts achieved eGFR increase ≥15 mL/min/1.73m^2 (Table). ECU was generally well tolerated with only 3 SAEs related to ECU (severe, all resolved) and no meningococcal infections. One death occurred, which was unrelated to ECU (GI bleed).

Conclusions: Long-term ECU was well tolerated and was associated with sustained suppression of TMA, no new ESRD and significant improvements in renal function.

Key outcomes with ECU	**Wk 26**	**Median 114 wks**
TMA-event-free status, n (%)	16 (80)	19 (95)
eGFR increase ≥15 mL/min/1.73m^2, n (%)	1 (5)	8 (40)
CKD improvement of ≥1 stage, n (%)	7 (35)	12 (60)
Serum creatinine decrease of ≥25%, n (%)	3 (15)	11 (55)
Mean change in eGFR from baseline, mL/min/1.73m^2, mean (95%CI)	6.1 (3.3-8.8) P=0.0001	7.2 (0.76-13.6) P<0.05
Decrease in proteinuria ≥1 grade, n/N, (%)	8/20 (40)	10/16 (63)

Significance was tested with a repeated measures model.

O7

How does knowing bioimpedance measurements influence fluid management in PD? Results from the UK-Shanghai randomised control trial.

Simon Davies[1,5], Kay Tan[1,5], Zanzhe Yu[1,2], Wei Fang[2], Aiwu Lin[2], Zhaohui Ni[2], Jiaqi Qian[2], Graham Woodrow[3], Sarah Jenkins[4], Martin Wilkie[4]

[1]Keele University, Keele, UK, [2]Renji Hospital, Shanghai, China, [3]Leeds Teaching Hospitals, Leeds, UK, [4]Northern General Hospital, Sheffield, UK, [5]University Hospital of North Staffordshire, Stoke-on-Trent, UK

Purpose: to establish whether including bioimpedance BIA measurements as part of clinical assessment improves longitudinal fluid management in PD patients.

Study design: Multicentre, 3 UK sites, 1 Shanghai (Sh), randomised controlled trial with clinicians blinded to the BIA data in control subjects. Randomisation to 4 comparator groups was stratified by country and residual urine volume (>200 ml RRF+, <200 ml RRF-). BIA vector plots (Height^2/resistance, Height^2/reactance) using RJL single frequency (50MHz) devices was combined with clinical assessment (BP, oedema) to manage fluid status with capture of decision making. Primary endpoint: BIA derived fluid volumes (extracellular water, ECW) at 12 months; to detect a 1 kg difference in change from baseline required 25 patients per group, type I error of 5%, 80% power.

Results: 309 prevalent PD patients were randomised (1:1 active:control) to the four groups: UK/RRF+ n=131 , UK/RRF- n=18, S/RRF+ n=85, S/RR- n=75, that were well balanced, enabling pre-specified analysis in all but the UK/RRF- group. In the RRF+ control groups there was no change in fluid status from baseline (ΔECW: UK +0.2L, Sh +0.1L), total body water (TBW), target or clinical body weight. In the UK RRF+ active group there was no change in the ECW (ΔECW: +0.2l) despite the fact that clinicians set a significant reduction in target weight (-1.6 kg, P=0.01) causing a ΔTBW (-0.9 kg, P=0.05), whereas in the Sh RRF+ active group there was no change. In the Sh RRF- controls there was a relative increase in overhydration due to (ΔECW: +0.6L, ΔTBW: -1.7L, P=0.001 and ECW/TBW +0.03, P=0.013) not observed in the active group (ΔECW: -0.1L, ΔTBW: -1.0L, P=0. 18 and ECW/TBW +0.01, P=0.22). ECW was increased in controls compared to active group at study end (18.3 v. 17.4 L, P=0.03)

Conclusions: Non-anurics have very stable fluid status over 12 months, whereas anurics develop relative overhydration (loss in lean body tissues) mitigated by fluid assessment incorporating BIA. Reducing target weight in non-anurics to improve BP attributed to overhydration did not have the desired effect.

Parallel session

Wednesday 13th March

BSHI/BTS symposium: post transplant antibody monitoring

14:00 – 15:30

O8

Elevated intra-graft expression of endothelial activation and NK-cell activity transcripts can be detected by real-time qPCR and identify a subset of patients with *de novo* donor-specific antibodies who are at risk from subsequent immunological graft loss

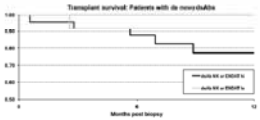
Adam McLean[1], Kathy Dominy[2], Hanneke De Kort[2], Michelle Willicombe[1], Paul Brookes[1], Jacques Behmoaras[2], Jack Galliford[1], Terry Cook[2], David Taube[1], Candice Roufosse[2]

[1]*Imperial Kidney & Transplant Centre, Hammersmith Hospital, UK,* [2]*Department of Medicine, Imperial College, UK*

Introduction: Transcriptome analysis by micro-array from kidney transplant biopsy cores has identified genes associated with endothelial activation (ENDAT) and NK cell activity (NK) which are present in grafts undergoing antibody-mediated rejection (AbMR). We have used a subset of the markers identified by Halloran *et al* to look for AbMR-associated transcripts by real-time quantitative PCR (qPCR) in renal transplant biopsy derived samples.

Methods: 54 Transplant biopsies (18 surveillance biopsies during stable graft function and 36 taken for cause after the development of *de novo* donor-specific antibodies) had one half core preserved for transcript analysis (but available for rescue to light microscopy). 5 ENDAT and 6 NK transcripts were examined by qPCR. Biopsies were scored as positive if any transcript had Z-score >1.

Results: The presence of elevated ENDAT or NK transcripts was strongly associated with the finding of dsAb (66% vs 33% χ^2 p=0.02), but their presence in surveillance biopsies was not associated with subsequent immunological graft loss (100% graft survival at 2 years post-biopsy). Within the dsAb+ve group, the detection of elevated ENDAT or NK transcripts was associated with immunological graft loss within 1 year of the biopsy (graft survival 77% vs 92%).



The presence of ENDAT or NK transcripts was correlated with the degree of microcirculatory injury (peri-tubular capillaritis or glomerulitis) on light microscopy.

Discussion: qPCR analysis of ENDAT and NK transcripts in biopsy samples provides a rapid method for identifying grafts at risk of immunological graft loss. These data provide a validation set for the results from micro-array analysis.

O9

Preventing the development of donor specific antibodies in kidney transplant recipients through optimal immunosuppression – a retrospective analysis of a single centre transplant unit

Stephen Hughes[1,2], Judith Worthington[1], Declan DeFreitas[1]

[1]*CMFT, Manchester, UK,* [2]*Leeds University, Leeds, UK*

Despite marked advances in immunosuppression over the last decade, there has been no real increase in long term kidney transplant survival, with approximately 25% of patients on the transplant list awaiting a re-transplantation. Life-long potent immunosuppression is prescribed following transplantation to prevent host detection of the allograft with ensuing rejection and subsequent failure of the organ. Detection of newly formed (de novo) donor specific antibodies (DSA) in the serum of transplant recipients indicates host immunity directed towards the allograft and has been shown to be responsible for late allograft failure. *De novo* DSA have been associated with under-immunosuppression, particularly in non-adherent patients. This study aimed to demonstrate that sub-optimal immunosuppression post-transplant was associated with the development of DSA.

Methods: This retrospective case-control study compared immunosuppression regimes in DSA positive patients, in a regional transplant centre (n=45), with DSA negative recipients with similar allograft dysfunction. The total immunosuppression prescribed in the 12 months prior to testing was measured as well as documented patient non-adherence. Baseline factors between the two groups, including time from transplant, age, induction therapy, acute rejection and HLA mismatch, where not significantly different. Sub-therapeutic dosing was defined as tacrolimus levels less than 4.5ng/ml, ciclosporin less than 50ng/ml or mycophenolate less than 50% of recommended dose.

Results: Patients with DSA were shown to be exposed to a significantly lower immunosuppression burden in the 12 months prior to testing (p=0.0022). This was most notable with CNI treatment, where sub-therapeutic serum CNI levels were associated with DSA detection (p=0.0011; RR 2.27 95% CI 1.3-3.97). A trend towards lower mycophenolate use was seen in DSA group but this was not significant. Steroids did not appear to affect DSA detection in this study. DSA detection severely affected allograft survival, with 14/49 and 1/48 graft failures in the DSA positive and negative group respectively. The median allograft survival post-DSA testing was of 36 months. Additionally, the addition or increasing of immunosuppression post-DSA detection by clinicians was shown to have no effect on allograft survival.

Conclusion: This single centre analysis demonstrates that sub-optimal immunosuppression is associated with the detection of DSA in a kidney transplant population. Drug minimisation and patient non-adherence of maintenance immunosuppression should be reviewed in each transplant recipient to prevent DSA production and subsequent allograft dysfunction.

O10

Post-transplant de novo donor-specific HLA antibodies predict pancreas graft outcome

Shruti Mittal, Suzanne Page, James Gilbert, Peter Friend, Edward Sharples, Susan Fuggle

Oxford Transplant Centre, Oxford, UK

Aim: Donor-specific HLA antibodies (DSA) are associated with poorer outcomes in kidney transplantation, however the role of DSA in pancreas transplantation is less well known. This study aims to assess the role of routine serial HLA antibody monitoring in identifying grafts at risk of failure after pancreas transplantation.

Method: The patient cohort included recipients of pancreas transplants performed at our centre between 2006 and 2011; 317 simultaneous pancreas kidney (SPK) and 126 isolated pancreas (IP) transplants. Prospective serial HLA antibody screening was performed by Luminex technology pre- transplant, at 0, 6, 12 and 24 months post-operatively, and at the time of clinical events. Samples were screened for the presence of antibodies using LABScreen® Mixed kits and antibody specification performed using LABScreenPRA® and Single Antigen beads. Demographic and graft outcome data was collected, including rejection episodes and graft failures (defined as return to insulin-dependence). The antibody monitoring results were analyzed for associations to pancreas graft outcomes.

Result: Pre-transplant HLA antibody screening was performed routinely on all 433 patients and 354 (81.8%) had post-transplant HLA antibody monitoring. Pre-transplant sensitisation status, number of HLA mismatches (0-6) and DR mismatch (0-2) were not associated with pancreas graft outcome. 141/354 (39.3%) recipients developed de novo HLA antibodies and 54/354 (15.3%) developed de novo DSA, of which 34 were SPK and 20 IP transplants. There was no association between the development of non-donor specific HLA antibodies and graft failure. However, the development of de novo DSA was significantly associated with poorer graft outcomes for both SPK and IP transplants. Inferior one and three year graft survival rates were achieved in SPK recipients who developed de novo DSA compared to those who did not (1 year graft survival, 78.3% vs. 94.7%; 3 year survival 63.6% vs. 92.5%; log rank p=0.001), but the differences were more pronounced in the IP group (1 year graft survival, 50.0% vs. 89.4%; 3 year survival 14.3% vs. 85.8%; log rank p=0.001).

Conclusion: This is the largest study to date to examine the association between de novo HLA antibodies following pancreas transplant and graft outcomes, and clearly demonstrates a strong association between development of DSA and graft failure particularly in the IP group. These high risk patients are a logical cohort to develop novel immune biomarkers and trials of novel immunosuppressive interventions.

O11

Impact of donor HLA mismatch grade on recipient HLA locus-specific sensitisation in patients returning to the kidney transplant waiting list following a failed primary kidney allograft

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Background: We have investigated the relationship between donor HLA mismatch and post-transplant alloantibody development in patients re-listed for transplantation following primary renal transplant failure.

Methods: A total of 131 patients returning to the waiting list following a failed primary kidney transplant between 1995 to 2010 were studied. Multiple sera obtained before transplantation; on re-listing and 3-monthly thereafter were screened using lymphocytotoxic panel screening (PRA), Luminex HLA class I and II antibody detection and Single Antigen Beads. The effect of donor mismatches at individual HLA loci (HLA-A, -B, -C, -DR and -DQ) on the calculated reaction frequency (cRF) against a panel of 10,000 HLA typed UK donors was determined.

Results: HLA mismatch grade correlated strongly with overall incidence and magnitude of post-transplant allosensitisation defined by PRA, Luminex and SAB-defined cRF ($p<0.001$). The risk and level of sensitisation against individual HLA-A, -B, -DR and -DQ loci increased with increasing number of donor HLA mismatches within each locus; this relationship was stronger for HLA-A and -DR loci [odds ratios of 3.0 (CI: 1.8-4.4) and 2.9 (CI: 2.1-4.2) respectively, $p<0.001$] which also best predicted overall post-transplant HLA class I and II sensitisation respectively. Incidence and mean cRF of post-transplant HLA-DR specific sensitisation increased by 12% and 5% respectively following failure of HLA-DR matched grafts, but 62% and 57% respectively for 2 HLA-DR mismatched grafts. Of patients with 2 HLA-DR mismatched grafts, 70% became highly sensitised (≥85% cRF) against class II alloantigens and 80% developed donor specific antibody. On multivariate analysis, HLA mismatch grade and immunosuppression weaning were independent predictors of HLA sensitisation whereas transplant nephrectomy was not.

Conclusion: This analysis is the most comprehensive to date, showing that donor mismatching, particularly for HLA-DR may lead to high levels of sensitisation following primary allograft failure, compromising options for future transplantation.

Parallel session

Wednesday 13th March

Fibrosis session

16:00 – 17:30

O12

Insulin-like growth factor-II is produced by, signals to, and is an important survival factor for the mature podocyte in man and mouse

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Podocytes are crucial for preventing the passage of albumin into the urine and when lost are associated with the development of albuminuria, renal failure and cardiovascular disease. Podocytes have limited capacity to regenerate; therefore pro-survival mechanisms are critically important.

Insulin like growth factor–II (IGF-II) is a potent survival and growth factor, however its major function is thought to be in prenatal development when circulating levels are high. IGF-II has only previously been reported to continue to be expressed in discrete regions of the brain into adulthood in rodents, with systemic levels being undetectable.

Using *in vitro* and *in vivo* techniques we now show in man and mouse that the podocyte is the major cellular source of, and target for IGF-II in the mature glomerulus. Functionally a loss of IGF-II signalling causes podocyte cell death *in vitro* and glomerular disease *in vivo* in an aged IGF-II suppressed transgenic mouse model.

Collectively this work reveals the fundamental importance of IGF-II in the mature podocyte for glomerular health across mammalian species.

O13

PLCε1 is involved in TGF-β1 signalling in podocytes, to regulate EMT.

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Mutations in the gene encoding the PLCε1 are associated with early onset nephrotic syndrome in children. Truncation mutations in *PLCE1* are associated with the development of Focal Segmental Glomerulosclerosis (FSGS). Injured podocytes in FSGS overexpress the pleiotropic cytokine TGF- β1, which is a regulator of epithelial-to-mesenchymal transition.

We generated a conditionally immortalised *PLCE1* mutant human podocyte cell line. The mutation is a homozygous stop variant that causes early truncation of the protein and therefore is predicted to be highly pathogenic. While canonical and non-canonical signalling responses to TGF- β1 were observed in wild type podocytes, the *PLCE1* mutant displayed diminished downstream TGF- β1 signalling responses.

This lack of signalling in response to TGF- β1 treatment also had functional consequences. Podocyte motility is increasingly being used as a surrogate marker of barrier function *in* vitro. TGF- β1 treatment rendered our wild type podocyte cell line significantly more motile. However, the same treatment had no effect on the motility of the *PLCE1* mutant cell line.

Phenotypically the mutant podocytes express typical markers such as nephrin, podocin, CD2AP and WT1 at similar levels to wild type cells, as measured by western blot. Interestingly, the mutant cell line significantly overexpresses the mesenchymal markers fibronectin and α-SMA. PAX2 expression has been detected in the mutant cell line using western blot and immunofluorescence techniques. This is despite the expression of WT1 which is a known suppressor of PAX2

Taken together these results suggest that a functional PLCε1 is involved in TGF- β1 signalling and regulates epithelial-to-mesenchymal transition.

O14

Hic-5 is the phenotype switch in mesangial cells causing transdifferentiation to an activated myofibroblast

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In the healthy glomerulus, the mesangial cell (MC) performs multiple important functions including maintenance of glomerular integrity and secretion of mesangial extracellular matrix (ECM). However, during glomerular disease, the MC changes its phenotype to that of an activated myofibroblast, secreting altered ECM which is resistant to proteolytic degradation, and showing an increased susceptibility to apoptosis. Previously, the switch in phenotype has been identified by the expression of alpha smooth muscle actin (aSMA), but the extra- and intra-cellular events leading to this phenotype change have been obscure.

We have been investigating the protein changes consequent upon MC attachment to abnormal ECM (over)expressed during glomerular scarring, compared to MCs attaching to normal ECM proteins. By proteomic methods, we identified several intra-cellular protein changes in MCs under these conditions including the novel expression of the LIM protein, Hic-5, the mammalian homolog of the lepiopteran death-associated LIM protein (DALP).

We have now studied the effects of over-expression and siRNA knockdown of Hic-5 in MCs cultured on different ECM proteins. We have found that attachment of MCs to collagen I is associated with increased expression of aSMA, but this is abrogated by Hic-5 knockdown. In MCs attached to collagen IV, forced overexpression of Hic-5 is associated with increased susceptibility to apoptosis in response to a variety of triggers. Furthermore, the matrix metalloproteinase inhibitor plasminogen activator inhibitor-1 is downregulated in MCs attached to collagen IV, upregulated in MCs attached to collagen I, and this effect is abolished by Hic-5 knockdown. We have previously shown that Hic-5 expression upregulates transcription of the abnormal ECM component procollagen I.

Taken together, these data indicate that Hic-5 acts as a molecular "switch", changing quiescent MCs into activated myofibroblasts in response to extracellular stimuli. Hic-5 is therefore an important potential target in therapies to reduce glomerular scarring.

Parallel session

Wednesday 13th March

BTS/BASL liver symposium

16:00 – 18:00

O15

Low viscosity aortic fluid perfusion correlates with a low incidence of biliary strictures following liver transplantation with grafts from donors after circulatory death

Hynek Mergental, Irene Scalera, Giorgia Catalano, Bridget Gunson, Simon Bramhall, John Isaac, Ravi Marudanayagam, Robert Sutcliffe, Thamara Perera, David Mayer, Darius Mirza, Paolo Muiesan

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Background: The progressive shortage of liver grafts drives the increasing usage of donors after circulatory death (DCD). Biliary strictures (BS), in particular ischaemic cholangiopathy represent the main long-term complication following DCD liver transplantation. We sought the risk factors for development BS in 163 patients who underwent transplantation at our center.

Methods: The inclusion criteria for the study were graft survival more than 3 months with presence of a patent hepatic artery, which were met in 122 patients. Detailed information about donor and recipient characteristics, retrieval and implantation timing and both procedures details were analyzed. Predictors of outcome were identified using univariate Chi-square test or Fisher's exact tests. Variables with a p-value ≤ 0.10 were included in a multivariate Cox regression analysis.

Results: The median follow up of the included patients was 31 months (range 3-96). Fifty eight (48%) graft were retrieved with aortic perfusion with Marshall's hypertonic saline, 64 by UW solution. In situ portal perfusion and back-table perfusion were done with UW solution. Ninety grafts (74%) were retrieved by our team. The majority of donors was male (55%), the median donors body mass index was 25 (18-37) kg/m^2, age 51 (12-75) years, donor warm ischaemic time counted from the systolic blood pressure below 50 mmHg to organ perfusion was 20 (5-35) and cold ischaemic time 433 (184-709) minutes. The overall incidence of biliary strictures was 15%. The only variable correlating significantly with development of BS was aortic perfusion with UW compared to Marshall's hypertonic citrate (odds ratio 3.515, 95% confidence interval 1.074-11.510, P=0.026).

Conclusion: The incidence of ischaemic cholangiopathy correlates with the retrieval technique and the organ perfusion fluid. Aortic flush with a low viscosity Marshall's hypertonic citrate significantly decreases the incidence of BS following DCD liver transplantation. Donor warm ischaemic times up to 30 minutes do not predispose to the development of BS.

O16

Prediction of short-term survival following liver transplantation based on comorbidity information derived from administrative data

Chutwichai Tovikkai[1,2], Susan Charman[2,3], Jan van der Meulen[2,3], Alexander Gimson[4], Raaj Praseedom[1,4]

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Introduction: Post-liver transplant survival models rarely include preoperative recipient comorbidities as risk factors. We assessed the value of adding comorbidity information derived from administrative data to improve the predictive ability of such models.

Methods: A linked UK Liver Transplant (UKT) registry - Hospital Episode Statistics (HES) database (1997-2010) was initially created. We modified the existing Royal College of Surgeons Charlson Score for use in liver transplantation. Relevant comorbidities were identified from the linked database during the year immediately prior to transplant. Multivariable logistic regression was used to estimate the impact of comorbidities on 90-day post-transplant survival in the presence of other risk factors included in the UK liver transplant audit 2011 *model*. Discriminatory abilities of the models with and without comorbidities were assessed with the c-statistic and the goodness-of-fit with the Hosmer-Lemeshow test.

Results: We included 3,837 elective liver transplants in adult from the linked UKT-HES database. Multivariable analysis revealed congestive cardiac failure and atherosclerosis to be statistically significant factors in predicting post-transplant survival [OR (95%CI) = 3.7(2.3-6.1) and 2.0(1.3-3.1), respectively]. A history of extrahepatic malignancy and renal disease approached significance [OR (95%CI) = 2.0(1.0-4.2) and 1.5(1.0-2.4), respectively]. When comorbidities were added to existing predictive models, the c-statistics increased significantly for all models. The UK liver transplant audit *model* with comorbidities had the highest c-statistic [0.69(95%CI: 0.65-0.72)]. This model also exhibited good calibration [p=0.84].

Discussion: Atherosclerosis, congestive cardiac failure, extrahepatic malignancy and renal disease are predictors for short-term survival after liver transplantation. Adding comorbidities derived from administrative data to existing prognostic models can improve the prediction of post-transplant survival.

O17

Isolation and expansion of regulatory T cells from liver transplant recipients at GMP standards; implications for cell therapy application

Henrieta Fazekasova[1], Niloufar Safinia[1], Cristiano Scotta[1], Sarah Thirkell[2], Andrew Bushell[2], Giovanna Lombardi[1], Robert Lechler[1]

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Long-term survival in liver transplantation (LT) recipients remains suboptimal because of the morbidity and mortality associated with long-term use of immunosuppression (IS). However IS weaning early post LT has been largely unsuccessful, supporting the need for active tolerance induction strategies. CD4+CD25+FOXP3+cells (Tregs) play an important role in immunoregulation and have been shown in animal models to promote transplantation tolerance, following adoptive transfer of ex vivo expanded murine and human Tregs. Phase I trials in bone marrow transplantation have shown that ex vivo expanded Tregs have an excellent safety profile, which is encouraging for the broader application of these cells in solid organ transplantation.

We have devised a GMP compatible protocol that produces functionally suppressive human Tregs (and in high numbers) that can be directly applied for adoptive Treg cellular therapy.

Tregs were successfully isolated from LT recipients at the time of transplantation, and a 580-fold expansion was observed, using anti-CD3/CD28 beads, IL-2 and rapamycin. The GMP standard ex vivo expanded Tregs were highly pure (97.4% CD4+CD25+ cells and 0.008% CD8+ cells) with high expressions of FoxP3 (99.6% of the CD4+CD25+ cells express FoxP3) and retained their suppressive function following expansion. Furthermore their suppressive capacity was higher following expansion compared to freshly isolated Tregs (1:1 ratio - expanded Tregs 91.1%, freshly isolated Tregs 28.6% suppression, 1:10 ratio - 80.7% compared to 20.8% respectively). Of particular importance in cell therapy, the ex vivo expanded Tregs were stable in the presence of inflammatory stimuli and addition of rapamycin shown to be essential to inhibit the conversion of Tregs to Th17 cells.In conclusion we have formulated a Treg expansion protocol that not only satisfies the rigours of GMP manufacturing standards but also produces Tregs from LT patients that are phenotypically stable and functionally superior compared to freshly isolated Tregs.

Parallel session

Wednesday 13th March

Free communications: progression of CKD

16:00 – 17:30

O18

Overweight across adulthood and kidney function at age 60-64 years

Dorothea Nitsch[1], Richard Silverwood[1], Mary Pierce[2], Claudia Thomas[3], Rebecca Hardy[2], Charles Ferro[4], Naveed Sattar[5], Peter Whincup[3], Caroline Savage[6], Diana Kuh[2],

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Introduction: There is little information on how life course exposure to obesity affects risk of chronic kidney disease (CKD). We hypothesised that prolonged exposure to overweight during adult life increases the risk of later CKD in a cumulative manner.

Methods: The Medical Research Council National Survey of Health and Development is a socially stratified sample of 5362 singleton children born in one week in March 1946 in England, Scotland and Wales, of which 1794 with complete data were initially analysed. A multiple imputation analysis expanded the analysis sample to 4584. Body mass index (BMI) was measured at ages 36, 43, 53 and 60-4 years, and self-reported at ages 20 and 26. The age at which a study participant first became overweight was related to markers of CKD at age 60-4 (creatinine- and cystatin C-based estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 and urine album-creatinine ratio (uACR) ≥ 3.5 mg/mmol) using logistic regression within a multiple imputation analysis.

Results: In analyses adjusted for confounding by childhood and adulthood social class, the presence of one or more CKD marker was associated with age at first overweight: odds ratio (OR) 1.94 (95% confidence interval (CI) 1.28, 2.93) at age 26 and OR 2.01 (95% CI 1.27, 3.17) at age 36 relative to being overweight only at age 60-64 or never, with less strong associations with increasing age (*P* for trend < 0.001). These associations were consistent for creatinine-based eGFR, cystatin C-based eGFR and uACR. Diabetes and hypertension were only moderate mediators of the age at overweight-kidney function association.

Discussion: These results suggest that preventing overweight in early adulthood may have a considerable effect on the prevalence of CKD in the population.

O19

Low birth weight and later renal function – the role of blood pressure, diabetes and adulthood obesity: results from the 1946 British birth cohort study

Dorothea Nitsch[1], Mary Pierce[2], Rebecca Hardy[2], Naveed Sattar[3], Peter Whincup[4], Charles Ferro[5], Caroline Savage[6], Diana Kuh[2], Richard Silverwood[1]

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Introduction: Low birth weight has been shown to be associated with later renal function, but it is unclear to what extent this is explained by other established kidney disease risk factors. We investigated the roles of diabetes, hypertension and obesity.

Methods: The Medical Research Council National Survey of Health and Development is a socially stratified sample of 5362 singleton children born in one week in March 1946 in England, Scotland and Wales, and followed up since. At age 60-64 years 2192 study members with complete data were analysed. A multiple imputation analysis expanded the analysis sample to 4584. Birth weight was related to three markers of renal function at age 60-64 (estimated glomerular filtration rate (eGFR) calculated using cystatin C, eGFR calculated using creatinine and cystatin C, and urine album-creatinine ratio (uACR)) using linear regression.

Results: Each 1 kg lower birth weight was associated with 2.11 (95% confidence interval (CI) 0.67, 3.55) ml/min/1.73m^2 lower cystatin C-based eGFR, 2.18 (95% CI 0.85, 3.51) ml/min/1.73m^2 lower creatinine and cystatin C-based eGFR, and 0.064 (95% CI -0.009, 0.137) log-mg/mmol higher log-uACR. These associations were not confounded by socioeconomic position and were not explained by diabetes or hypertension. There was some evidence that the birth weight-eGFR association was stronger in study members who were overweight in adulthood.

Discussion: Our findings highlight the role of lower birth weight in renal disease and suggest that in those born with lower birth weight particular emphasis should be placed on avoiding the deleterious effects of becoming overweight in adulthood.

O20

Cognitive and kidney function at age 60-64 years: results from the 1946 British birth cohort study

Dorothea Nitsch[0], Marcus Richards[2], Mary Pierce[2], Rebecca Hardy[2], Naveed Sattar[3], Charles Ferro[4], Caroline Savage[5], Diana Kuh[2], Richard Silverwood[1]

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Introduction: Previous studies have found associations between cognitive function and chronic kidney disease. We aimed to test this association and explore possible explanatory mechanisms.

Methods: The MRC National Survey of Health and Development is a socially stratified sample of 5362 children born in March 1946 in England, Scotland and Wales, and followed up since. At age 60-64 years 2036 study members with complete data were analysed. Cognitive function at age 60-64 years was quantified using five measures (verbal memory, letter search speed, letter search accuracy, simple reaction time and choice reaction time) and kidney function at the same age was measured using cystatin C. The cross-sectional association between cognitive and kidney function was sequentially adjusted for *a priori* confounding factors (socioeconomic position and educational attainment), prior cognition, then potential explanatory mechanisms (lifetime smoking trajectory, current body mass index, systolic blood pressure and C-reactive protein).

Results: Cognitive function was strongly and mainly linearly associated with cystatin C. For example, the highest quartile of verbal memory corresponded to a 0.047 (95% confidence interval 0.030, 0.064) mg/L improvement in cystatin C relative to the lowest quartile. Some of this association was explained by confounding due to socioeconomic factors, but it was not further explained by prior cognition. Potential mechanisms via smoking, obesity, high blood pressure and inflammation were found to explain little of the association.

Discussion: Cognitive and kidney function in late mid-life are associated even at only minor kidney function impairment. The implications for clinical care are profound and under-recognised. Further studies are required to elucidate fully the mechanisms by which this association operates.

O21

Effects of functional status on prognosis in patients with chronic kidney disease

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Background: Chronic kidney disease is associated with significantly increased morbidity and mortality. Though much work has been performed to describe the prognostic implications of co-morbid diseases, little data exist to describe how patient reported quality of life measures relate to outcome.

Method: 1220 patients were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). This is a prospective study of outcome in all-cause CKD. Annual records of functional status (Karnofsky score) were analysed in relation to all-cause mortality, rate of change in renal function and change in blood pressure. Survival analyses were adjusted for age and eGFR.

Results: 574 patients (47%) reported a maximum score of 100 at time of recruitment and 646 (53%) a reduction in functional state. For incremental reductions in functional status at baseline, increasing risk for death was observed:

Karnofsky score	100	90	80	70	60	50
Number	574	476	121	32	12	5
HR death	Referent	1.3*	2.4**	2.5**	2.9**	3.1

*HR – hazard ratio. Analyses adjusted for age and eGFR. * p<0.05. ** p<0.005*

Subsequently all patients with a reduced baseline score and a 12-month repeat measurement were considered (n=80). Patients reporting an unchanged state (n=24) formed the referent group. In patients with a one category (10-point) reduction in functional state at 12-months (n=8) there was an associated increase in risk for death (hazard ratio 5.6, p=0.01). Improved functional status did not associate with a reduced risk for death (HR 0.7, p=0.3). No significant difference in rate of change in blood pressure of eGFR was observed between patients with a stable / improving / worsening performance status.

Conclusion: Reduced performance status is associated with an increased risk for death independent of age and renal function. As performance score is influenced both by physical and psychological factors further work is required to consider where targeted interventions may benefit outcomes.

O22

Effects of aleglitazar on renal function in patients with stage 3 chronic kidney disease and type-2 diabetes

Matthias Herz[1], Luis Ruilope[2], Markolf Hanefeld[3], A. Michael Lincoff[4], Giancarlo Viberti[5], Sylvie Meyer Reigner[1], Dietmar Volz[1], Dominika Wieczorek Kirk[1], Klas Malmberg[1,6]

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Background: Aleglitazar (ALE) is a balanced PPAR-α/γ agonist in Phase 3 for CV risk reduction in patients following an acute coronary syndrome who have T2D. This phase 2b study (AleNephro) evaluated renal effects of ALE in stage 3 CKD patients with T2D.

Methods: Patients with stage 3 CKD and T2D were randomized to 52 weeks double-blind treatment with ALE 150µg/d or pioglitazone (PIO) 45mg/d, followed by an 8 week off-treatment period. The primary endpoint was non-inferiority for the difference between ALE and PIO in % change in eGFR from baseline (BL) to end of follow-up (EOF; 8 weeks after end of treatment [EOT]). A pre-specified exploratory analysis evaluated change in UACR in a subgroup with BL macroalbuminuria.

Results: The trial included 302 patients (ALE n=150; PIO n=152) with mean eGFR 47 mL/min/1.73m^2 and 81% on ACEi/ARB at BL. Mean eGFR change at EOT with ALE was –15% (95% CI: –19, –11) vs -5.4% (95% CI: –9.6, –1.2) with PIO and was non-progressive for both. Mean eGFR change from BL to EOF was –2.7% (95% CI: –7.7, 2.7) with ALE vs –3.4% (95% CI: –8.5, 1.8) with PIO, establishing non-inferiority (0.77%; 95% CI: –4.5, 6.0). In patients (N=48) with BL macroalbuminuria (>90% on ACEi/ARB), change in UACR at EOT was –59% (95% CI: –76, –29) with ALE and –51% with PIO (95% CI: –70, –20). The change in UACR at EOF was –54% (95% CI: –74, –20) with ALE and –33% (95%CI: –59, 9) with PIO. No major safety concerns or new toxicities were identified.

Conclusion: The primary endpoint in AleNephro was met, indicating that in stage 3 CKD patients with T2D, the eGFR decrease after 52 weeks treatment with ALE plus 8 weeks off-treatment was comparable (non-inferior) to PIO, implying reversibility. Mean on-treatment decrease in eGFR was mild, not progressive and accompanied by significant UACR reduction in patients with BL macroalbuminuria.

O23

Remote monitoring of chronic kidney disease: a novel model of renal service delivery

Ingi Elsayed[1], Arif Khwaja[1], Sue Siddall[1], Frances Mortimer[0,2]

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Introduction*:* Chronic kidney disease (CKD) is common affecting 5-10% of UK population and the burden of CKD on the NHS budget, is increasing. Therefore new sustainable service models are required to enable delivery whilst maintaining quality care.

Aim*:* To evaluate the impact of a remote, community-based disease management program (DMP) for patients with advanced CKD on disease progression, patient satisfaction and environmental outcomes.

Methods*:* A pilot program was initiated between the Sheffield Kidney Institute (SKI) and the Sheffield Central Consortium of GP practices. All patients with CKD managed in secondary care were selected for the remote management program except i) those on immunosuppressive drugs and ii) those who were likely to need renal replacement therapy within the next 12 months. Patients had an individualized care plan specifying frequency of laboratory and blood pressure (BP) monitoring, thresholds for escalation of care with appropriate management plan. Laboratory and BP monitoring were performed at the local GP practice. Laboratory data was automatically uploaded to renal IT system whilst BP and clinical data were sent manually to secondary care. The nephrology outpatient consultation was replaced with a telephone consultation with a nurse specialist based at SKI. Clinical, travel and patient satisfaction data were collated over 2 years before and 12 months after implementation of the DMP.

Results*:* There are 77 patients under remote management. There was no significant difference between the patients' eGFR over the 2 years before (28.7 mls/min/1.73m^2 (95%CI, 28.27-29.14)) and 12 months after (28.5 mls/min/1.73m^2 (95%CI, 28.14-28.86)) implementation of DMP. There was no significant change in mean haemoglobin after implementation of the DMP and the difference between mean BP before (142/69 mmHg) and after (136/69 mmHg) implementation of DMP was also not significant. 90% of our survey respondents said they preferred receiving their kidney care in the community and felt more empowered about managing their CKD. The median distance travelled by patients to hospital was 5.4 miles whilst only 0.6 miles to their GP surgery, generating an annual carbon saving of 507 kg CO_2 equivalent.

Conclusion*:* NHS Kidney Care estimates expenditure on CKD to be £1.45 billion per annum. Our pilot data suggests that remote monitoring of CKD is deliverable, clinically safe in selected patients, improves patient satisfaction and empowerment whilst delivering significant carbon savings. With the prevalence of CKD increasing with an ageing population, remote monitoring of CKD may be a more sustainable model of delivery of CKD care.

Parallel session

Thursday 14th March

Raine session

08:30 – 10:00

O24

Exhausted autoimmunity: refining therapy by measuring persisting responses to persistent antigen

Eoin McKinney[1,2], Paul Lyons[2], James Lee[1,2], David Jayne[3], Kenneth G C Smith[1,2]

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Following transient exposure to antigen, CD8 T cells undergo rapid proliferation, then contraction after which a persistent population of memory cells confer protective immunity. However where antigen persists, such as during chronic viral infection, CD8 T cells may develop progressive loss of function in a process termed "exhaustion". The exhausted cellular phenotype is also accompanied by profound changes in gene expression defining a 'signature' of CD8 exhaustion that is both characterised and driven by patterns of inhibitory receptor expression. Although individual T cell inhibitory receptors have been shown to play a role in the development of autoimmunity, the existence of an analogous exhausted state in patients responding to persistent *self*-antigen has not been demonstrated. We show that a common CD8 exhaustion signature indicating impaired viral clearance (in murine LCMV) or loss of viral control (in human HIV) also predicts outcome in four distinct autoimmune diseases (ANCA-associated vasculitis (AAV), systemic lupus erythematosus (SLE), Crohn's disease (CD) and ulcerative colitis (UC)) but with one exception – exhaustion of an anti-self response predicts a good prognosis in autoimmunity, but poor outcome in viral infection.

In chronic antigen exposure, robust CD8 responses critically depend on the provision of CD4 help. Consequently, the presence of CD4 help results in enhanced viral clearance and resolution of chronic infection. We performed *in-silico* modelling of the complete transcriptome of concurrently sampled CD4 and CD8 T cells from patients with active autoimmunity. This approach demonstrated strong inverse correlation between signatures of CD4 help and CD8 exhaustion, consistent with the capacity for CD4 help to avoid exhaustion. Measurement of overlapping exhaustion and help signatures in mixed cells has allowed independent validation of the proposed biomarker, confirming prediction of clinical outcome in a total of 1070 samples across 429 individuals with infectious disease (HIV, chronic hepatitis C, dengue), during vaccination (malaria, yellow fever, influenza) and with autoimmunity (pre-type 1 diabetes, CD, UC, SLE, AAV).

O25

ALchemy – a large prospective study of chemotherapy in systemic AL amyloidosis

Jennifer Pinney[1,2], Helen Lachmann[1,2], Thirusha Lane[1], Lisa Rannigan[1], Darren Foard[1], Simon Gibbs[1], Christopher Venner[1], Sanjay Banypersad[1], Ashutosh Wechalekar[1], Philip Hawkins[1], Julian Gillmore[1,2]

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Background: There are no large prospective clinical trials in AL amyloidosis.

Methods: ALchemy is a prospective observational study of chemotherapy in patients with AL amyloidosis. The study opened at the UK National Amyloidosis Centre on September 1st 2009. All newly diagnosed patients with AL amyloidosis requiring chemotherapy for their disease were eligible for study entry. Study participants underwent a detailed clinical and biochemical assessment of their disease at baseline, after completion of 3 cycles of chemotherapy and 6, 12, 18 and 24 months from baseline. Clonal disease assessment was performed after each cycle of chemotherapy and monthly thereafter. Details about tolerability, dose and toxicity of chemotherapy were collected via a case record form.

Results: More than 500 patients have been enrolled to date making this the largest prospective study in AL amyloidosis worldwide; recruitment is ongoing. Data from the initial 250 patients are presented below but will be updated to include all 500 patients before the Renal Association meeting. At baseline 20% of patients had Mayo stage 1 disease, and 40% each were stage 2 and 3. Presentation with renal dysfunction was most common (50%) followed by cardiac disease (31%). First line chemotherapy was with cyclophosphamide, thalidomide and dexamethasone in 77% of patients. Intention to treat analysis of clonal response after cycle 3 showed that 171 (78%) of 220 evaluable patients completed cycle 3 and 49 (22%) died beforehand. By intention to treat, 72 (33%) achieved a complete or very good partial response with 3 cycles, 53 (24%) achieved a partial response, and 46 (21%) had no clonal response. Hospitalisation from treatment toxicity was common, occurring in approximately 50% of patients, most commonly due to potentially avoidable fluid retention. After a median follow-up of 7 months, 29% of patients had died; risk factors for death were identified. Achieving a complete or very good partial clonal response by the end of cycle 1 of chemotherapy overcame the poor prognosis associated with Mayo stage 3 disease. There was an association between achieving an early clonal response and improvement in organ (renal and cardiac) function and quality of life within 12 months.

Conclusions: ALchemy is the largest prospective study in AL amyloidosis worldwide, and has provided a wealth of data to facilitate validation of clinical endpoints, to determine efficacy and toxicity of chemotherapy including causes of hospitalisation. Inclusion of all patients with all stages of disease indicates a persistently poor prognosis among a substantial proportion, notably those with Mayo stages 3 disease.

O26

Abnormal function of diabetic human glomeruli and improvement with $VEGF_{165}b$

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Diabetic nephropathy is a leading cause of renal failure. We have used an oncometric technique to measure the function (ultrafiltration coefficient: L_PA, $nl.min^{-1}.mmHg^{-1}$) of single glomeruli isolated from untransplantable kidneys from diabetic and non-diabetic donors, and tested whether diabetic glomerular function can be improved through direct modulation of the capillary wall.

[1] Human glomerular L_PA was 6.2±0.8 (25/3) {mean±sem (glomeruli/donors)}, significantly greater than L_PA of rat {1.0±0.1 (135/17} and mouse {1.2±0.1 (67/14} glomeruli ($p<0.001$). However, human glomerular volume (V_i: nl) (6.3±0.7) was also much larger than of rat (1.0±0.02) and mouse (0.7±0.1) glomeruli. When corrected for volume (L_PA/V_i, $min^{-1}.mmHg^{-1}$), human and rat glomerular function was indistinguishable (0.93±0.08 vs 0.99±0.05, $p>0.05$), but both were significantly different from mouse glomerular L_PA/V_i (2.03±0.15, $p<0.001$).

[2] L_PA/V_i of human glomeruli from diabetic donors {2.3±0.4 (16/3)} was higher than L_PA/V_i of glomeruli from non-diabetic donors {1.0±0.1 (25/3)} ($p<0.001$).

[4] Treatment with 1nM $VEGF_{165}b$ (1hr) restored L_PA/V_i to normal in diabetic human glomeruli {1.0±0.2 (13/3); $p<0.001$ vs vehicle-treated diabetic glomeruli}.

[5] $VEGF_{165}b$ appears to modify L_PA/V_i of diabetic glomeruli via activation of VEGFR2, since the actions of $VEGF_{165}b$ on STZ-diabetic rat glomeruli were prevented by the VEGFR2-blocker ZM323881 {diabetes: 1.4±0.1; diabetes+$VEGF_{165}b$: 0.8±0.1*; diabetes+$VEGF_{165}b$+ZM323881: 1.3±0.2; *$p<0.05$}.

[6] In the dbdb mouse model of diabetic nephropathy, bi-weekly intraperitoneal injections of $VEGF_{165}b$ for 8 weeks decreased albuminuria {$p<0.05$, 2-way ANOVA}, but did not alter GFR {$p>0.05$, 1-way ANOVA}.

In summary, these are the first measurements of the permeability of diabetic human glomeruli, and demonstrate altered single glomerular function (increased L_PA/V_i). This disrupted glomerular function in human diabetic nephropathy can be normalised by $VEGF_{165}b$. Long-term systemic treatment with $VEGF_{165}b$ also reduced albuminuria in an animal model of nephropathy in type 2 diabetes.

O27

Restoring the local angiopoietin balance ameliorates albuminuria and glomerular angiogenesis in diabetic nephropathy

David Long[1], Cecile Dessapt-Baradez[2], Kathryn White[3], Jiaqi Pan[2], Jennifer Huang[1], Karen Price[1], Maria Kolatsi-Joannou[1], Anthea Hayward[2], Maelle Locatelli[2], Marine Diennet[2], Adrian Woolf[4], Luigi Gnudi[2]

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Introduction: Diabetic nephropathy is characterised by structural changes in the glomerular filtration barrier leading to albuminuria. Critical to maintaining the integrity of the glomerular filtration barrier are vascular growth factors with healthy podocytes expressing both vascular endothelial growth factor (VEGF-A) and angiopoietin (Ang)-1. During the early phases of diabetes, the balance between VEGF-A and angiopoietins in the glomerulus is disrupted leading to low Ang-1 and high VEGF-A causing vessel destabilisation and proliferation of glomerular capillaries. Therefore, we hypothesised that increasing the expression of local Ang-1 within diabetic glomeruli would stabilise the vasculature and attenuate the progression of nephropathy.

Methods: We generated mice in which Ang-1 expression could be induced specifically in podocytes, and tested the effects of this strategy in mice with diabetic nephropathy induced by streptozotocin.

Results: Diabetes led to increased circulating glucose, albuminuria, creatinine clearance and blood pressure. Ultrastructually, the diabetic glomeruli had an expanded mesangium, increased glomerular basement membrane thickness. Diabetes also led to an elevation in the number of proliferating glomerular endothelial cells; this was accompanied by a deficiency in Ang-1 and Tie-2 levels and enhanced VEGF-A signalling. Podocyte overexpression of Ang-1 in diabetes altered the levels of vascular growth factors by preventing the Ang-1 deficiency and lowered VEGF-A signalling. This altered growth factor milieu stabilised the glomerular vasculature preventing glomerular endothelial cell proliferation which was accompanied by a 70% reduction in albuminuria. Ang-1 overexpression did not alter creatinine clearance, blood pressure or the ultrastructure of the glomerulus.

Discussion: This study provides the first evidence that targeting local expression of glomerular angiopoietins constitutes a novel treatment for the early phases of diabetic kidney disease.

Parallel session

Thursday 14th March

Acute kidney injury update

10:30 – 12:00

O28

The effect of pre-operative EPO or RIPC on cell cycle markers in the kidney after ischaemia-reperfusion injury in a porcine model

David Gardner[1], Simon Welham[1], Louise Lloyd[1], Tom McCulloch[2], Zsolt Hodi[2], Phillipa Sleeman[1], Mark Devonald[2]

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Introduction: Acute Kidney Injury (AKI) is common with no specific treatment. Ischaemia-Reperfusion Injury (IRI) is a common mechanism of AKI. IRI/AKI has been studied extensively in rodent models but few studies have used the pig, a better model for the disease in humans. Using a porcine model of IRI/AKI we have characterised serial renal histology, blood and urine biochemistry over a 48 period and have investigated the mode of action of two putative renoprotective interventions, intravenous erythropoietin (EPO) or remote ischaemic preconditioning (RIPC).

Methods: Thirty female pigs were subjected to sham operation or IRI (40mins bilateral renal artery cross-clamping] × 3 treatments (saline *vs.* EPO [1000 iu/kg] *vs.* RIPC [3×cycles of 5mins inflation/deflation]) via an abdominal incision under general anaesthesia. Blood, urine and renal biopsies were sampled at intervals to 48h reperfusion.

Results: 40mins IRI in the pig elicited marked histopathological injury at 24 and 48h, characterised by epithelial flattening in the proximal tubules and necrotic casts in the distal tubules. Renal oedema was noted in 30% of IRI samples and was validated by increased renal water retention. In all groups subjected to IR, significant increments in plasma, but decrements in urinary, creatinine and urea were noted. The change in the urinary albumin: creatinine ratio and in plasma NGAL offered the greatest potential as an early biomarker; both significantly increasing +2h IRI but returning to baseline by 24h. Renal cortical apoptosis was significantly increased after IRI, but in pre-treated groups (IR-EPO and IR-RIPC), the apoptotic cells were located almost entirely in distal necrotic casts and not the interstitium. The mean proportion of nuclei positive for phospho-histone 3 was increased by IRI but partially blunted by EPO and RIPC, suggesting less cells stalled in the G2-M phase of the cell cycle.

Conclusion: A large animal model of AKI has been established that exhibits many features of AKI in humans. Any postulated renoprotection by EPO or RIPC does not appear to prevent histological injury nor blunt plasma or urinary biomarkers in the short-term but may evoke cellular responses in the kidney that mitigate an acute-to-chronic transition in kidney disease. This latter aspect requires further investigation.

O29

Long term outcomes in biopsy proven acute interstitial nephritis treated with steroids

Maria Prendecki, Anisha Tanna, Alan Salama, Frederick Tam, Tom Cairns, David Taube, H.Terence Cook, Neill Duncan, Charles Pusey

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Background: There are no prospective randomised controlled trials describing the outcome of Acute Interstitial Nephritis (AIN) treated with steroids, and retrospective studies are limited. AIN is a common pathology found in 5% of native renal biopsies at our centre in 2000-2010.

Methods: All patients with an acute interstitial inflammatory infiltrate without glomerular pathology on native renal biopsy were identified. Patients on maintenance steroids were excluded. Treated patients received oral prednisolone or IV methylprednisolone followed by oral prednisolone. Data were collected retrospectively and outcomes analysed according to treatment prescribed.

Results: 158 patients were treated with steroids, 80 male, age 52.2 (range 16.4-85.3) years, follow up 39.9 (3-164) months. 29 were not treated, 18 male, age 53.8 (19.2-87.8) years, follow up 35.0 (4-121) months. There was no difference in median eGFR at time of biopsy, 20.5(5-110) ml/min in steroid group, 25.0(4-59) ml/min in untreated group (p=0.1351). 12.0% of steroid treated and 13.8% of untreated patients required renal replacement therapy (RRT) at the time of biopsy (p=0.32). Steroid treated patients showed greater improvement in eGFR (Fig 1.).

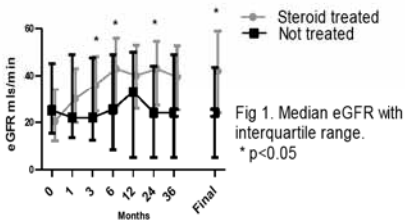

Fig 1. Median eGFR with interquartile range.
* p<0.05

Fewer patients in the steroid treated group were dialysis dependent at 6 months (3.2% vs. 20.6%, p=0.0022) and 12 months (4.4% vs. 24.1%, p=0.0016).

Discussion: This study suggests a benefit of steroids in treatment of AIN with improvement in eGFR and fewer patients progressing to end stage renal disease.

O30

Impact of a combined, hospital-wide improvement strategy on the outcomes of patients with acute kidney injury (AKI)

Nitin Kolhe, Rebecca Packington, John Monaghan, Richard Fluck, Nigel Lawson, Nicholas Selby

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Introduction: The 2009 NCEPOD report focussed attention on the high mortality rates and poor standards of care that many hospitalised patients with acute kidney injury (AKI) experience. In response, there have been widespread attempts to tackle problems around poor recognition of AKI and omissions in basic elements of care. However, the impact of such interventions on patient outcomes is not well studied. We report patient outcomes over a two year period since the introduction of a combined, hospital wide improvement strategy at our centre.

Methods: From 2010 onwards we instituted several interventions designed to improve recognition and management of AKI. These comprised of an electronic alert system for AKI, intranet guidelines on diagnosis and management of AKI, an AKI care bundle for use on admission units and an education programme developed in collaboration with a neighbouring hospital. To assess the impact of this combined strategy, data on the incidence and outcomes of all cases of AKI across our hospital were collected prospectively using the output from the electronic alert system. Four sequential six-month periods were compared since the introduction of the above interventions.

Results: Between Sept 2010 and Sept 2012 there were 8629 patients who sustained AKI at our centre. The mean age was 77 ± 14yrs. 65.2% had stage 1 AKI, 19.5% stage 2 and 15.3% stage 3. Although these proportions remained constant over time, there was a steady reduction in the absolute number of patients sustaining AKI (first six month period 2258, period two 2202, period three 2097, period four 2072).

As previously reported, mortality rates were high. In-hospital mortality for the entire period was 19.3% and 30-day mortality was 21.2%. However, comparing sequential six-month periods there was a progressive reduction in mortality rates over time (30-day mortality in periods one to four was 23.7%, 20.8%, 20.8% and 19.5% respectively, chi-square for trend p=0.006). This improvement in survival was maintained even after adjustment for the effects of age, co-morbid conditions, severity of AKI, elective/non-elective admission, baseline renal function (Cox regression).

Discussion: We have demonstrated that hospital wide outcomes in patients with AKI (the majority of who do not receive specialist management) can be improved with a combined approach to improve AKI recognition and management comprising of e-alerts, intranet guidelines, care bundles and a novel educational programme.

O31

The impact of acute kidney injury upon long-term outcomes following CABG: a matched propensity score analysis

Sean Gallagher, Matthew Lovell, Dan Jones, Sevda Hassan, Andrew Wragg, Rakesh Uppal, Magdi Yaqoob

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Background: The development of acute kidney injury (AKI) following coronary artery bypass graft (CABG) surgery is associated with increased short and long-term mortality. Whether AKI has a causal relationship with subsequent mortality or whether the development of AKI simply occurs in patients with more comorbidity undergoing more complex procedures remains unresolved.

Methods and results: This was an observational cohort study of prospectively collected data from 4694 patients who were discharged from hospital after first time CABG surgery at a tertiary cardiac centre between 2003 and 2008. AKI was defined using the RIFLE criteria, which requires at least a 50% increase in serum creatinine. The primary outcome measure was all-cause mortality determined via UK Office of National Statistics. 562 (12.0%) patients developed AKI following CABG surgery. Patients that developed AKI were older, more likely to be female and had more associated comorbidity than patients that did not develop AKI. In Cox multivariable analysis the development of AKI was an independent predictor of long-term mortality HR 1.72, 95% CI 1.43-2.07). Subsequently a comparison of 562 patients that sustained AKI with 562 propensity-score matched patients that did not sustain AKI was undertaken. After propensity matching, baseline clinical and operative characteristics were similar between both groups. After Cox multivariable analysis of the propensity-matched cohort AKI remained an independent predictor of long-term mortality (HR 1.52, 95% CI 1.20–1.94).

Conclusions: The development of AKI following CABG is a serious event associated with worse long-term survival. This excess mortality cannot be explained simply by coexisting comorbidity and surgical complexity.

Parallel session

Thursday 14th March

Medawar Medal abstracts

10:30 – 12:30

O32

Amelioration of ischaemia-reperfusion injury in a mouse model of cardiac transplantation using a novel mitochondria-targeted antioxidant

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Introduction: Accumulating evidence supports a key role for mitochondrial oxidative damage in ischemia reperfusion injury (IRI), which is a major cause of early graft dysfunction in transplantation. We therefore investigated the efficacy of a mitochondria-targeted small molecule antioxidant, MitoQ, in ameliorating IRI.

Methods: To induce a minimal and a severe ischaemic injury in a syngeneic C57Bl/6 mouse model of heterotopic cardiac transplantation, donor hearts were flushed with Soltran (± 50μM MitoQ), then stored at 4°C for 30min or 4h in UW solution (± 50μM MitoQ) prior to transplantation. Uptake of MitoQ was confirmed using mass spectrometry. The severity of IRI was assessed by cardiac troponin-I levels (ELISA) and histology. Mitochondrial reactive oxygen species (ROS) generation was measured using a ratiometric probe and mass spectrometry. Oxidative damage was assessed by measuring protein carbonyl formation (ELISA) and mitochondrial DNA (mtDNA) damage (qPCR). Serum cytokine responses were determined by immunoassay.

Results: Prolonged cold preservation (4h vs. 30min) resulted in greater IRI, with higher cardiac troponin (4.9ng/mL±1.2 vs. 0.6±0.2) and worse histological injury 24h post-transplantation. This was associated with a 2-fold increase in mitochondrial ROS generation, increased oxidative damage to myocardial proteins and mtDNA and a heightened pro-inflammatory cytokine response. MitoQ was successfully taken up into the donor myocardial tissue and mitochondria at 4°C and reduced the severity of IRI at 24h post-transplant: there was a reduction in cardiac troponin level (2.4ng/mL ±0.6 vs. 4.9±1.2; 4h group), reduced mitochondrial generation of ROS and a reduction in oxidative damage to proteins and mtDNA. This was accompanied by a diminished pro-inflammatory cytokine response.

Conclusions: Prolonged cold preservation of donor organs leads to increased mitochondrial oxidative damage at reperfusion and greater IRI severity, which can be successfully ameliorated with MitoQ. As MitoQ has already undergone Phase I-II clinical trials in a non-transplant setting it represents a promising candidate for transplant-related IRI.

O33

ABOUT-K study – a prospective study of ABO incompatible kidney transplants

Andrew Bentall[1,2], Manjit Braitch[2], Ian Skidmore[3], David Briggs[3], Simon Ball[1]

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Introduction: The UK antibody incompatible registry finds poorer outcomes in ABOi recipients than expected from international comparator groups. Nevertheless this remains a potentially important treatment strategy particularly for blood group O recipients who inevitably accumulate in paired exchange schemes. The ABOUT-K multicentre observational study of ABOi transplantation includes patients recruited from 10 centres in the UK. It aims to study clinical variables that might usefully inform risk stratification and optimise outcome.

Method: Clinical variables were collated using an electronic CRF maintained by Eclinso AG in accord with GCP and ethics committee approval. Samples for central antibody assessment were returned to NHSBT Birmingham for storage at -80^{0}C and subsequent analysis in parallel with clinical samples at 7 different time-points. Patients were treated according to local protocols. 100 patients recruited received an ABOi kidney transplant.

Results: The mean age of recipients was 48.1± 13.6years, 41% were female, 68% were blood group O. 59% of donors were blood group A1. 1 year follow-up has been reached in 80 patients. The median local titre against donor blood group at baseline was 32 (range 0-512) and at transplantation was 4 (0-64). 58% of patients received IA vs 28% PEx (either PEx or DFFP). The mean titre reduction per EART was 1.4±1.2 (IA) and 1.8±1.5(PEx). 1 year patient survival was 98.9% and 1 year DCGS 95.5%. Acute rejection occurred in 25.5% of recipients of which 22.9% this was reported as being antibody mediated (AMR). The three graft losses were reported to be secondary to AMR, in patients with baseline local titre against donor blood group > 1/64. 1 year creatinine in patients reaching follow-up is 132.7 ± 46.2 micromol/L. Significant inter-centre variability in blood group antigen specific antibody quantification is reported in another submission.

Conclusion: In the ABOUT-K study 1 year patient and graft survival approach UK antibody compatible live donor outcomes. The incidence of acute rejection and graft loss attributed to AMR is high, although the current study has not reported on control groups. It provides preliminary data on treatment, outcome and complications that will inform future multi-centre study and outcome optimisation in ABOi kidney transplantation.

O34

Generation of HLA-specific humanised mice using bone marrow-derived haematopietic stem cells from cadaveric organ donors

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University of Cambridge, Cambridge, UK

Introduction: 'Humanised' mice reconstituted with a functional immune compartment are an invaluable tool in the study of the immune response and can be generated using haematopoietic stem cells (HSCs) from a variety of sources. Bone marrow (BM) from cadaveric organ donors represents a potentially abundant source of HSCs of pre-specified HLA type. In addition, cells and tissues can be harvested from syngeneic and allogeneic cadaveric donors with which to challenge the immune system in the resulting humanised mice. We therefore examined the ability of BM-derived HSCs from cadaveric organ donors to generate a humanised mouse model to investigate human alloimmunity.

Methods: Bone marrow was aspirated from the lumbar vertebrae and iliac bones of human cadaveric donors after other organs were retrieved for transplantation and the mononuclear fraction was separated using Ficoll gradient and cryopreserved at -180°C in 10% DMSO+90% FCS. After thawing, live CD34+ HSCs were isolated using magnetic beads and adoptively transferred into sub-lethally irradiated immmunodeficient NOD/SCID/IL2rγ$^{-/-}$ mice (NSG; 1-5x10^{5} cells/animal). Engraftment with human CD45+ cells was assessed by flow cytometric analysis of weekly peripheral blood samples. Skin, splenocytes and mesenteric blood vessels from the same donors were also cryopreserved.

Results: BM was successfully aspirated (22-120 ml/donor) from DCD and DBD cadaveric donors (n=9; age 31–81 years). The CD34+ fraction of BM aspirates was 1% (range 0.8-1.4%) and post-thaw viability of the CD34+ fraction was >80%. NSG mice (n=9) were successfully reconstituted with CD45+ cells. Engraftment levels in the peripheral blood reached 94.5% at 30 weeks, consisting of 63.3% B cells (CD19+), 29.1% T cells (CD3+), 22.45 CD4 T cells and 7.8% CD8 T cells.

Conclusion: BM-derived HSCs survive circulatory arrest for several hours and maintain their engraftment potential in immunodeficient mice. This model enables the generation of HLA-specific humanised mice, using a readily available source of HSCs, to investigate human immune responses to alloantigens.

O35

Death occurring within the first year post kidney transplantation in England over the last decade – an epidemiological study of causes, classifications and predictors

Daniela Farrugia[1], James Cheshire[2], Irena Begaj[1], Daniel Ray[1], Adnan Sharif[1]

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Introduction: Death occurring within the first year post-transplant is an important audit measure for all kidney transplant centres. The aim of this study was to explore all deaths occurring within the first year post kidney transplantation in England over the last decade to determine causes, classifications and predictors of 1-year mortality.

Methods: Data was extracted from Hospital Episode Statistics (HES), an administrative data warehouse containing admissions to all National Health Service hospitals in England. Data extraction was facilitated utilising codes on procedural classification (Office of Population Censuses and Surveys Classification of Interventions and Procedures [OPCS-4]) and medical classification (ICD-10). We obtained data on all kidney transplant procedures (adult and paediatric) performed in England between April 2001 and March 2010. HES data was cross-linked with data from the Office for National Statistics to identify all mortality events occurring within one-year post kidney transplantation and obtain death certificate registrations. Logistic regression algorithms were performed (R stats package) to identify independent factors associated with mortality ($p < 0.05$ considered significant).

Results: 471 deaths occurred within the first year post-transplant (from 15,218 kidney transplant procedures performed). Cardiovascular disease, infection and malignancy were classified in 16.1%, 32.3% and 7.0% of all death certificates respectively. 40.0% of deaths from cardiovascular events were in recipients with a history of myocardial infarction n=15/36), compared to 14.0% of recipients with no history (n=61/435) (p<0.001). No difference was observed in 1-year mortality from cardiovascular death with prior history of cardiac failure, peripheral vascular disease, cerebrovascular disease or diabetes. There was borderline significance for 1-year deaths from infection occurring more commonly in recipients with versus without pre-transplant diabetes (41.8% versus 31.0% respectively, p=0.074). There was borderline significance for 1-year deaths from malignancy being less common in recipients with versus without pre-transplant diabetes (1.8% versus 7.7% respectively, p=0.081). 20.4% of deaths included kidney failure as a contributory factor on the death certificate. Independent variables associated with 1-year mortality by logistic regression analysis included: live-donor kidney (OR 0.49, 95% CI [0.38-0.65], p<0.001); South Asian ethnicity (OR 1.41, 95% CI [1.03-1.92], p=0.030); age (OR 1.05, 95% CI [1.04-1.06], p<0.001), residence in least socially deprived area (OR 0.57, 95% CI [0.40-0.79], p=0.001), history of pre-transplant diabetes (OR 1.58, 95% CI [1.25-2.01], p<0.001); history of pre-transplant MI (OR 2.06, 95% CI [1.39-3.04], p<0.001); history of pre-transplant heart failure (OR 4.11, 95% CI [1.90-8.88], p<0.001) and history of pre-transplant peripheral vascular disease (OR 2.05, 95% CI [1.20-3.50], p=0.008).

Conclusion: 1-year mortality post kidney transplantation is low at 3.1%, with infection the most common cause of death, and a fifth of all deaths occur with concomitant kidney failure. We also identify clinical predictors of mortality within 1-year of kidney transplantation that may identify high-risk recipients who merit more robust pre-transplant evaluation.

O36

T-cell help determines mode of alloantibody-mediated rejection

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University of Cambridge, Cambridge, UK

Introduction: What determines whether alloantibody mediates acute or chronic allograft rejection remains unclear; here we examine the role of CD4 T cell help.

Methods. BALB/c hearts were transplanted into T cell-deficient ($TCR^{-/-}$) BL/6 recipients or control BL/6 $Rag2^{-/-}$ recipients. T cell help was provided by transfer of either 10^5 or 10^3 TCR-transgenic TCR75 CD4 T cells that recognise MHC class I donor H2-K^d antigen as processed peptide via the indirect pathway.

Results: $TCR^{-/-}$ recipients reconstituted with 10^5 TCR75 T cells rejected BALB/c hearts acutely (MST 9 days, n=10), with high alloantibody titres. In contrast, heart grafts survived for > 50 days in similarly-reconstituted $Rag2^{-/-}$ recipients, with confirmation of an effector role for alloantibody provided by restoration of acute heart graft rejection in $Rag2^{-/-}$ mice following passive transfer of immune serum from the $TCR^{-/-}$ recipients. Although rejection in reconstituted $TCR^{-/-}$ recipients was associated with a splenic Germinal Centre (GC) reaction, GC responses were not detectable until after rejection, suggesting that strong extrafollicular responses driven by high T cell numbers are sufficient to mediate acute humoral rejection. Reconstitution of $TCR^{-/-}$ recipients with 10^3 CD4 T cells produced lower alloantibody titres, which increased gradually, with development of progressive allograft vasculopathy and eventual graft failure (MST 50 days, n=8). This rejection is likely due to chronic alloantibody-mediated damage, because endothelial complement deposition was evident and because heart grafts survived indefinitely, without complement deposition and with minimal vasculopathy, in T cell-reconstituted $Rag2^{-/-}$ recipients. Antibody levels increased concomitant with the development of splenic GCs suggesting that small helper T cell numbers generate weak extrafollicular responses, but can nevertheless support the development of late GC responses that can effect chronic humoral rejection.

Discussion: In this novel model of humoral rejection, the development of acute or chronic heart graft rejection is determined by the magnitude of the alloantibody response, which in turn is determined by the availability of T cell help.

O37

Long term graft and patient survival post renal transplantation in patients with a primary renal diagnosis of glomerulonephritis

Rishi Pruthi[1], Rommel Ravanan[2], Anna Casula[1], Mark Harber[3], Paul Roderick[4], Damian Fogarty[1]

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Introduction: Glomerulonephritis (GN) is the primary diagnosis in 20% of patients receiving a renal transplant. Despite this there are no UK data on long term graft or patient survival for specific glomerulonephritidies. This study aims to provide post-transplant long term data by analysing patient outcomes from across the UK.

Methods: Using data provided by the UK Renal Registry & NHSBT we analysed patient survival and graft outcomes in incident transplant patients between 1997-2009 who had a diagnosis of primary GN. Patients transplanted with adult poly-cystic kidney disease (PCKD) were used as a control group. A multi-variate cox regression model, adjusting for age, sex, type of transplant, ethnicity, donor age, time on dialysis, HLA mis-match, cold ischaemic time and graft failure (for survival analysis) provided adjusted hazard ratios for patient survival and graft failure. Survival probabilities at 1, 5, &10 years were derived from Kaplan Meier analysis.

Results: Of 5766 identified patients, 4932 patients (86% data completeness) were analysed in a fully adjusted multi-variate cox regression model. 3141 patients had glomerular disease, with 1791 patients having PCKD. The median follow up time was 4.3 years. Graft survival was significantly lower in those with MPGN type II (HR: 3.1, CI 1.6-6.1), FSGS (HR: 2.3, CI 1.7-3.2), MPGN type I (HR: 2.1, CI 1.4-3.0), Membranous (HR: 1.7, CI 1.2-2.5) and IgA (HR:1.3, CI 1.03-1.67). MPGN type II had the worst outcome with 55% 10 year graft survival compared to 82% in the PCKD control group. Graft outcomes in patients with Lupus or Wegener's did not show any significant difference. As for patient survival this was significantly reduced (even after adjusting for graft failure) in patients with MPGN type II (HR: 3.1, CI 1.1-11.3) and those with Lupus nephritis (HR:1.8, CI 1.1-3.1).

Conclusion: This study provides unique long term outcome data on transplant patients in the UK for a range of glomerular diseases. Further research is required to understand the reduced survival seen in Lupus nephritis and MPGN type II, and to improve overall graft outcomes. The results of this study should assist the pre-transplant counselling of patients and enable more accurate risk stratification.

O38

CMV drives expansion of cytotoxic $CD4^+CD27^{null}CD28^{null}$ T cells in renal transplant recipients resulting in NKG2D dependent endothelial stress, apoptosis and late graft dysfunction

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Introduction: Published work suggests CMV drives expansion of atypical cytotoxic $CD4^+CD27^{null}CD28^{null}$ T cells. To determine the role of these cells in renal transplantation, the phenotypic characteristics, antigen specificity, mechanism of damage and clinical sequelae were studied in 85 renal transplant recipients evaluated serially during the first post transplant year.

Methods: Phenotyping was performed by flow cytometry. Antigen specificity was evaluated in proliferation experiments following 5 day incubations with irradiated autologous PBMCs previously exposed to either CMV lysate or HLA peptides. After incubation of MACs sorted $CD28^{null}$ cells for 6h with immortalised glomerular endothelial cells (GECs), endothelial damage/apoptosis was assessed by vWF and fractalkine release, and by intracellular staining of GECs for active caspase 3.

Results: Expansion of $CD4^+CD27^{null}CD28^{null}$ T cells was solely observed in CMV seropositive recipients. Compared with $CD4^+CD27^{null}CD28^+$ cells, the $CD28^{null}$ cells expressed higher levels of the cytotoxicity markers perforin and NKG2D, and receptors involved in endothelial and matrix homing (CD11a and CD49d). Exposure to CMV lysate resulted in proliferation of $CD4^+CD27^{null}CD28^{null}$, whereas no such effect was seen following exposure to HLA peptides ($p<0.005$). Conversely, both CMV and HLA peptide increased proliferation of $CD4^+CD27^{null}CD28^+$ cells ($p<0.05$ for both). Following in vitro exposure to CMV lysate, incubation of $CD4^+CD27^{null}CD28^{null}$ cells with GECs resulted in increases in vWF and fractalkine release, and in capase 3 staining. This was abrogated by the addition of NKG2D-blocking antibody, and was not seen with $CD28^+$ cells. Finally, increased numbers of $CD4^+CD27^{null}CD28^{null}$ cells at 1 year was associated with subsequent decline in graft function over a maximum follow up of 44 months.

Conclusion: $CD4^+CD27^{null}CD28^{null}$ cells are associated with (and specific for) CMV, express tissue homing and cytotoxicity markers, result in endothelial damage, and graft dysfunction. Strategies to reduce these "indirect" effects of CMV may result in improved long term transplant outcomes.

O39

Surgical complication rates in patients receiving kidney transplants in England; analysis by transplant centre using linked registry and hospitalisation data

James Fotheringham[2,1], Badri Shrestha[2], Meguid El Nahas[2], Michael Campbell[1], William McKane[2]

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Introduction: Previous studies have found similar centre-specific graft and patient survival following first transplantation; however other measures of surgical performance have not previously been reported at a national level.

Methods: First transplants (Tx) in patients starting renal replacement therapy between 2002 and 2006 were identified in UK Renal Registry data linked with Hospital Episode Statistics (HES) data. Surgical complications out to 12 months and comorbidity at Tx were identified using HES diagnosis and procedure codes. Delayed graft failure (DGF) was defined as HES coded dialysis after Tx during Tx admission. Ureteric stent usage was determined by subsequent HES coded stent removal. Standardised complication rate ratios were determined using observed/expected counts predicted using logistic regression.

Results: 4,517 Tx were identified in both sources in 20 Tx centres. Surgical complication rates were: Any complication 22.3%, ureteric 7%, vascular 3.1%, wound 5.3%, venous thrombosis 1.3%, complication requiring exploration and nephrectomy 5.1% and 3.9% respectively, misc 4.8%. Deceased donor (DD) recipients and patients with diabetes had higher surgical complication rates (27.2% vs 21.1%, P<0.001, and 23.7% vs 19.5%, P=0.002). Wound complications were higher in Peritoneal dialysis than haemodialysis or pre-emptively transplanted patients (6.7% vs 4.9% and 3.1% respectively, P=0.002). Ureteric complications were similar in patients with and without ureteric stents (6.5% vs 7.5%, P=0.198). DGF was 17.6% in DD Tx and 3.6% in live donor Tx, with DGF associated with a higher incidence of surgical complication (20.2% vs 36.4%, P<0.001). Following adjustment for age, diabetes, donor type and centre coding depth the number of Tx centres with higher than expected surgical complications was increased from 4 to 5, with better than expected centres reduced from 4 to 1.

Conclusions: Routine linked data can enable the reporting of surgical complications and DGF a national level. Following adjustment, outlying centres persist. Agreed HES coding practice for Tx would strengthen future studies.

Parallel session

Thursday 14th March

Science: innate immunity in nephology and transplantation

14:00 – 15:30

O40

IgG immune complexes stimulate dendritic cell migration

Menna Clatworthy[1,2], Caren Petrie-Aronin[2], Rebeccah Mathews[1], Ken Smith[1], Ron Germain[2]

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Introduction: Antibodies are critical for defence against infection but may also play a pathogenic role in autoimmune conditions, such as systemic lupus erythematosus (SLE), when IgG immune complexes (IC) become deposited in tissues such as the kidney, causing inflammation. Many effector functions of antibody are mediated via Fc R, which are found on most immune cells, including dendritic cells (DCs). DCs acquire antigen in tissues and migrate to lymph nodes to present antigen to T cells, initiating an immune response. We sought to determine how Fc R cross-linking with IC might affect DC migration.

Methods: Bone marrow DCs (BMDCs) were stimulated with IC and injected subcutaneously (S/C) into the footpad or flank of C57BL/6 mice. Lymph nodes were harvested at 48 hours and DCs enumerated. An *in vitro, 3D* chemotaxis assay was performed by imaging murine BMDCs and human monocyte-derived DCs placed in a collagen matrix and subjected to a defined CCL19 gradient. *In vivo*, dermal DC were imaged by intravital two-photon microscopy in WT and Fc RIIB-/- CD11cEYFP mice following administration of IC or IC-containing serum.

Results: Fc R-crosslinking with IgG ICs increased BMDC migration from skin to draining lymph nodes. In a 3D collagen matrix, IC-stimulated murine and human DCs showed enhanced directional migration in a CCL19 gradient and increased CCR7 expression. Two-photon microscopy demonstrated that IC increased dermal DC mobilisation *in vivo* and that S/C application of autoantibody-containing serum from mice (NZB/WF1) and humans with SLE increased dermal DC mobilisation.

Conclusions: Our study demonstrates a novel effect of IC in increasing DC migration to lymph nodes. Furthermore, we show that dermal DC mobilisation *in vivo* is increased following S/C administration of IC or autoantibody-containing lupus serum. Together, these data suggest an additional mechanism by which ICs might drive autoimmunity in SLE via the inappropriate localisation of autoantigen-bearing DC.

O41

P2X7 deficiency attenuates renal inflammation and pancreatic beta cell injury in experimental diabetes

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[1]UCL Centre for Nephrology, London, UK, [2]Imperial College Kidney and Transplant Centre, London, UK

Introduction: Inflammation is a key pathogenic mechanism in both diabetes and diabetic nephropathy (DN). The P2X7 receptor is an ATP-gated cation channel with roles in inflammation and cell death; it is expressed in immune cells and also resident renal cells and pancreatic islets. We investigated the role of P2X7 in early DN and pancreatic injury using a mouse model of type 1 diabetes as well as human mesangial cells (HMC) cultured in a diabetic milieu.

Methods: Low dose (50mg/kg) streptozotocin injections (x5) were administered to wild-type (WT) and two strains of P2X7 knockout mice with differing profiles of residual receptor expression: Glaxo (GSK) and Pfizer (PF). Random blood glucose (BG), pancreatic insulin staining and islet Mac-2 staining were assessed at 3 weeks. Renal macrophages (CD68+) were assessed at 12 weeks in persistently diabetic mice. HMCs were grown for 2 days in 4mM or 30mM D-glucose media using the metabolically inactive L-glucose as an osmotic control. Secreted MCP-1 was measured by ELISA, and the effects of the selective P2X7 antagonist A438079 (10μM) and the P2X7 agonist BzATP (0.1M) were tested.

Results: 20/22 (91%) WT and 13/18 (72%) GSK mice achieved a BG >16mM at 3 weeks. In a separate experiment, 6/7 (86%) WT and 1/6 (17%) PF mice achieved this BG level. Islet insulin staining was relatively preserved in PF mice ($p=0.036$ vs WT) and was accompanied by reduced macrophage numbers (46%↓, $p<0.001$ vs WT). In persistently diabetic mice, renal macrophage accrual was reduced at 12 weeks in GSK mice in both glomerular (74%↓,$p<0.0001$ vs WT) and interstitial (64%↓, $p=0.01$ vs WT) compartments; urine albumin excretion was not increased at this time. *In vitro*, hyperglycemia enhanced MCP-1 secretion from HMCs by 31%, independent of osmotic stress, and this was reduced 51-100% by A438079. BzATP further augmented glucose-induced MCP-1 release by 23%.

Conclusions: P2X7 contributes both to early renal inflammation and beta cell injury in experimental diabetes. P2X7 appears to regulate glucose-induced MCP-1 release from HMCs which may, in part, explain the renal findings.

O42

DDAH2 (dimethylarginine dimethylaminohydrolase) is essential for a complete inflammatory response in a folate model of acute kidney injury

James Tomlinson[1], Blerina Ahmetaj[1,2], James Leiper[1]

[1]*Medical Research Council Clinical Sciences Centre, Imperial College, London, UK,* [2]*School of Pharmacy and Chemistry, Kingston University, London, UK*

Background: Nitric oxide (NO) released from activated macrophages contributes to tissue damage during inflammation. Pharmacological inhibition of iNOS has been of therapeutic interest for inflammatory conditions such as bacterial sepsis although to date no clinical benefit has been proven. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NO that is metabolised by dimethylarginine dimethlyaminohydrolase (DDAH) providing an alternative pathway for regulating NO bioavailability. Macrophages express the DDAH-2 isoform and genetic deletion reduces macrophage motility and phagocytic function. We hypothesised that genetic DDAH2 deletion is protective against renal inflammation in a folate model of acute kidney injury.

Methods: Wild-type (WT) and transgenic mice with global DDAH2 gene deletion (D2KO) received intra-peritoneal folate (180µg/g). Tissue was harvested at day 4 for analysis using; LC-MS/MS, qPCR and histological macrophage staining.

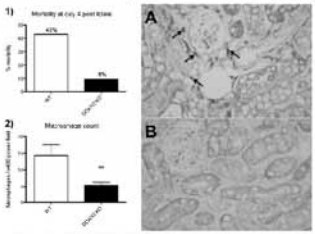

Figure 1. 1) WT mice had greater mortality (43% vs 9%; p<0.05). **2)** WT kidney (A) revealed significantly more macrophage infiltration (arrows) than D2KOs (B) (14 vs 5 per x400 hpf; p=0.0046).

Results: WT mice exhibited greater mortality and macrophage infiltration (Figure 1). Inflammatory cytokine gene expression was greater in WT kidney; iNOS (17-fold; $p<0.0001$), TNFα (30-fold; $p=0.001$) and IL1β (3-fold; $p<0.05$). NO activity (nitrate and nitrite) was elevated in WT urine compared to that of D2KOs (1.4 vs 0.59 mM/mg; $p=0.02$).

Conclusion: Global DDAH2 deletion reduces mortality and confers resistance to the renal inflammatory response to folate-induced injury. This is at least in part due to reduced nitric oxide activity suppressing macrophage recruitment and activation. These data identify DDAH2 as a potential therapeutic candidate for the treatment of acute kidney injury.

Parallel session

Thursday 14th March

B cell bench to bedside

14:00 – 15:30

O43

Human regulatory B cells (BRegs) are characterised by both IL-10 and TNF-α expression and are reduced in numbers with altered function in renal transplant recipients with immunological graft injury

Aravind Cherukuri[1], Alan Salama[2], Clive Carter[1], David Rothstein[3], Brendan Clark[1], Richard Baker[1]

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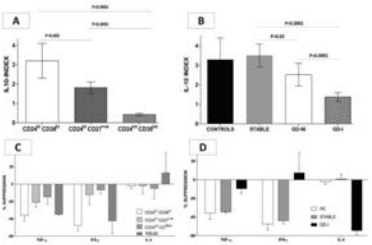
Human Bregs are defined by their ability to express IL-10 and suppress T cells in vitro. We noted that putative Breg subsets also produce pro-inflammatory cytokines, a finding that has not previously been addressed. Moreover, the clinical significance of Bregs in human organ transplantation remains unclear.

Herein, we define Bregs by the virtue of their polarization towards regulatory (IL-10) or pro-inflammatory (TNF-α) cytokines by **IL-10 Index** (Ratio of IL10+ to TNFα+ B cells within a specific B subset, relative to the remaining B cells) and study their relevance in renal transplantation. In 18 healthy volunteers IL-10 index distinguished 3 B cell subsets: $CD24^{hi}CD38^{hi}$(TRS), $CD24^{hi}CD27^{+}$(MZ), and $CD24^{+}CD38^{+}$(N). TRS have the highest IL10 index followed by MZ and then N (Fig-1A). In vitro, only TRS significantly suppressed Th1 but not Th2 cytokine expression by autologous CD4 T cells (Fig-1C). These B cell subsets were then analysed in renal transplant recipients-Stable: stable graft function (n=45); GD-NI: graft dysfunction-non immunological (n=22); GD-I: graft dysfunction-immunological (biopsy proven microcirculation injury, n=25). We observed a significant reduction in TRS in the PBMCs of GD-I vs. other groups. Moreover TRS cells when present in GD-I group exhibited a significantly lower IL-10 index suggesting a relative polarization towards an inflammatory cytokine phenotype (Fig-1B), and were unable to suppress Th1 cytokines (Fig-1D).

We have characterised the heterogeneity of Breg profiles by both pro-inflammatory and suppressive cytokines. Compared to other B cell subsets, TRS cells have the most suppressive phenotype and correlate with stable allograft function in renal transplant recipients. Immune mediated damage is associated with reduced number of Bregs and pro-inflammatory functional changes. To conclude, Bregs correlate with stable renal allograft function.



O44

Alloantigen-specific human regulatory T cells stimulated with cd40l-activated allogeneic B cells prevent allograft damage in humanized mouse model

Niloufar Safinia[1], Adam Laing[1], Amy Putnam[0,2], Eleonora Trotta[0,2], Greg Szot[0,2], Robert Lechler[1], Jeffrey Bluestone[0,2], Qizhi Tang[0,2], Giovanna Lombardi[1]

[1]King's College, London, UK, [2]University of California, San Francisco, USA

Transfer of human regulatory T cells (Tregs) has become an attractive therapeutic alternative to improve the long-term outcome in transplantation and thus reduce the side effects of conventional immunosuppressive drugs. Mouse models of transplantation have implicated murine and human Tregs with specificity for the graft to be more potent than polyclonal Tregs (PC-Tregs) in preventing rejection.

K562 cells, expressing CD40 ligand, were used to generate activated B cells that potently stimulate the expansion of alloantigen-specific, donor-reactive, human Tregs (drTregs). Our developed process can successfully generate over a billion of drTregs from one unit of blood using short-term ex vivo expansion. The expanded cells were highly donor-alloantigen reactive and maintained a phenotype of stable Tregs. The functional superiority of the drTregs over PC-Tregs in vivo was shown in a humanised mouse model of skin transplantation. Adoptive transfer of peripheral blood mononuclear cells led to rejection of established human skin allograft in otherwise immune-deficient mice. drTregs were more effective at reducing inflammation and allograft damage as compared to PC-Tregs (Ki67; dr-Treg v PC-Treg p=0.0015; CD31; dr-Treg v PC-Treg p=0.0009; Foxp3/CD3; dr-Treg v PC-Treg p=0.0131). This study supports the feasibility and efficacy of applying drTreg therapy to transplant patients and is timely in view of trials of Treg therapy being planned in solid organ transplantation.

O45

Transitional B cells contribute to tolerance status in kidney transplant recipients by IL10 production, low levels of BCR activation and absence of donor-specific responses.

Estefania Nova-Lamperti[1], Paula Mobillo[1], Yogesh Kamra[1], Graham Lord[2,3], Robert Lechler[3,4], Giovanna Lombardi[1], Maria Hernandez-Fuentes[1,2], Immune Tolerance Network GAMBIT Consortium[0], Consortium Indices of Tolerance[0]

[1]King's College London, MRC Centre for Transplantion, London, UK, [2]NIHR Comprehensive Biomedical Research Centre at Guy's and St Thomas' Hospital, London, UK, [3]NHS Foundation Trust in partnership with King's College London and King's College Hospital, London, UK, [4]King's Health Partners, London, UK

Background: Previous studies aimed to identify biomarkers of tolerance revealed that tolerant kidney transplant patients had an expansion of B cells and overexpression of B cell related genes in peripheral blood. Memory, Naive and Transitional B cells are the main B cell subsets in circulation. Transitional B cells, defined as cells with regulatory properties, were expanded in tolerant recipients compared to the rest of the patients, however how this population regulated transplantation tolerance was unclear. Here we report for the first time three different mechanisms to explain the contribution of Transitional B cell in transplantation tolerance.

Methods: Four groups of kidney transplant patients (tolerant, stables, in monotherapy and chronic rejectors) and healthy volunteers were included in this study. B cells from each group of patients were tested for antigen presentation, antibody production, cytokine production, and co-stimulatory function.

Results: Donor-specific antigen capture was assessed by fluorescent uptake using Image Stream and flow cytometry. B cells from chronic rejectors exhibited a significant increased in donor antigens capture compared to tolerant ($p=0.002$) and stable patients ($p<0.001$, K Wallis). Donor-specific antibodies were measured in serum samples by Luminex. Chronic rejector had the highest amount of donor-specific antibodies, both against class I and class II molecules. B cells stimulated with CD40 and CpG from tolerant patients produced higher levels of IL10 and lower amounts of TNF in comparison to chronic rejectors ($p<0.001$, RM ANOVA). Regarding BRC activation, B cells subsets from tolerant recipients failed to adequately phosphorilate ERK after BCR activation compared to healthy volunteers ($p=0.0055$, K. Wallis).

Conclusion: This is the first time that Transitional B cells from tolerant recipients have been shown to exhibit immune regulatory functions. These properties provide circumstantial evidence for an active role of Transitional B cells in the tolerant state.

Parallel session

Thursday 14th March

Marginal donors

14:00 – 15:30

O46

Immunosuppressive strategies for transplanting kidneys after excision of small renal tumours and role of acute rejection

Muhammad Arslan Khurram[1,2], Susan Stamp[3], David Rix[1], Neil Sheerin[1,3], Anne Cunningham[2], Noel Carter[2], David Talbot[1,2]

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Introduction: Kidneys from patients with small renal cell carcinoma have been used for transplantation after ex vivo resection of tumour with excellent results. Concerns regarding the behaviour of tumour under standard immunosuppression prevents this source from being popularised. We studied tumour behaviour with standard immunosuppression and immunosuppressives with anti-proliferative properties and the effect of MHC matching on tumour behaviour.

Methods: Luciferase labelled Wistar rat kidney tumour cells were injected subcutaneously into Wistar/Lewis rats to mimic well and poorly matched groups respectively. Both strains were divided into groups receiving Cyclosporine Cy, Sirolimus Sr (2mg/kg) and Sirolimus (0.5mg/kg) and Leflunomide Lf. Effects of matching on tumour rejection were studied by immunosuppression withdrawal in half of the animals within each group. Tumour progression was monitored with IVIS spectrum imaging system.

Results: With Cy immunosuppression, the tumour continued to grow in both strains. With high dose Sr, the tumour was eradicated within 2 weeks in Wistar and 3 weeks in Lewis rats ($p < 0.001$ between Cy v Sr). Both strains receiving low dose Sr also eradicated the tumour within four weeks of continuous treatment ($p < 0.01$ between Cy and Low dose Sr). In Lf group, 5/7 animals rejected the tumour within the 4 weeks of study period ($p < 0.001$ between Cy and Lf). After treatment withdrawal, the tumour rejection was noted among all groups. Again this rejection was significantly stronger in poorly matched animals than in well-matched combination ($p < 0.002$).

Conclusions: 1- Transplanted tumour continues to grow under Cyclosporine immunosuppression. 2- For tumour eradication Sirolimus was significantly better than Cyclosporine and Leflunomide; while Lf was significantly better than cyclosporine. 3- Acute rejection can lead to tumour eradication, more effectively in less well-matched animals. 4- Clinically, recipients of such restored kidneys should perhaps be less well-matched and immunosuppressed with agents with anti-proliferative properties eg Sirolimus to prevent/counter tumour recurrence.

O47

Risks and benefits of using organs from donors with known cancer

Rajeev Desai[1], Dave Collett[1], Chris Watson[2], Philip Johnson[3], Tim Evans[4], James Neuberger[1]

[1]NHS Blood and Transplant, Bristol, UK, [2]Addenbrooke's Hospital, Cambridge, UK, [3]University of Birmingham, Birmingham, UK, [4]West Midlands Cancer Intelligence Unit, Birmingham, UK

Cancer transmission from organ donors is a rare complication of transplantation. While some cancer histories in donors are classed as unacceptable or high risk of transmission, potential recipients endure significant risk of death whilst awaiting transplantation. We studied our donor cohort with regards to their cancer history, its impact on their recipients' outcome and evidence of cancer transmission.

Data for donors and recipients (1990-2008) were obtained from the National Transplant Registry and Cancer Registries. For donors with a history of cancer, guidelines from the Council of Europe and United Network for Organ Sharing were used for classification of cancer transmission risk.

Of the 17639 donors, 202 (1.15%) had a history of cancer. There was no significant difference in survival of single organ recipients (p=0.28) from donors with or without a history of cancer: 7.7 years (95%CI 5.4,-) and 8.6 years (95%CI 8.3, 8.8). Cancers classed as unacceptable or high risk of transmission were noted in 61 donors including cancer of breast (10), melanoma (3), lymphoma(5), colon(3), ovary(2), sarcoma(4) and central nervous system tumours(34). None of these cancers was transmitted to their 133 recipients. At 10 years from transplantation, recipients from unacceptable or high risk donors survived for 1148 life-years (95%CI1027,1269) with average survival of 8.6 years(95%CI7.7,9.5) per recipient.

Annual mortality rates among patients awaiting transplantation are high (5 to 15%) whereas the risk of cancer transmission, even from 'high-risk' donors appears to be very low. Among donors with non-CNS cancers, a selected sub-group of donors classed as unacceptable or high risk of cancer transmission can be a safe and valuable source of additional organs. Organs from donors with a history of superficial spreading type of melanoma, hormone receptor negative breast cancer, right sided colon cancer (cancer-free>5 years) or ovarian cancer (cancer-free>10 years) can be considered for transplantation as, in our study, these cancers did not transmit. Careful donor risk assessment and informed consent can result in significant survival benefit with low cancer transmission risk.

O48

Paediatric kidney donation: excellent outcome, yet an under-utilized resource. A review of 15 years of renal transplantation from paediatric donor kidneys in the United Kingdom

Syed Soulat Raza[1], Rajiv Dave[1], Abdul Hakeem[1], Michael Dawrant[1], Clare Ecuyer[1], Eric Finlay[2], Magdy Attia[1], Lutz Hostert[1], Richard Baker[3], Krish Menon[1], Niaz Ahmad[1]

[1]Division of Surgery, Department of Transplantation, St. James's University Hospital, Leeds, UK, [2]Department of Paediatric Nephrology, St. James's University Hospital, Leeds, UK, [3]Department of Nephrology. St. James's University Hospital, Leeds, UK

Introduction: Excellent graft and patient outcome can be obtained after renal transplant utilizing paediatric donors. Kidneys procured from paediatric donors less than 5 years of age are usually offered and transplanted en-bloc in to adult recipients. There appears to be a general reluctance in UK in offering, accepting and utilizing kidneys from younger paediatric donors (under 2 years of age). We report a 15-year review of paediatric kidney donation, utilization and outcome in the UK.

Methods: This is a retrospective review of paediatric kidney donation in the United Kingdom from January1997 to December 2011. Data held in NHSBT were stratified according to the donor age; **Group A:** donors <2years, **Group B:** donors 2-5 years & **Group C:** donors> 5-18 years. All continuous variables are expressed as mean & SEM. Significance was determined using ANOVA and Chi square tests whilst patient and graft survival were calculated using Kaplan- Meier analysis.

Results: Over 15 years 914 potential paediatric renal donors were identified. The donors are stratified in to three groups based on age as shown in table below. Subsequent progression of these potential donors, transplantation and outcome are discussed

Table: Paediatric kidney donation and utilization in the United Kingdom (1997-2011)

Donor Group* (n=714)	Donors identified	Donors offered	Donors proceeded	Conversion Rate (%)	Transplant (Adult/Paed)	Transplant (EKT/SKT)	Utilization Rate (%)€
Group A (0-2 years)	47	31	26	55	A 17 P 00	EKT 16 SKT 1	57%
Group B (2-5 years)	76	67	64	84	A 55 P 1	EKT 40 SKT 16	88%
Group C (>5-18 years)	790	769	764	97	A 902 P 441	EKT 9 SKT 1334	88%

* 1 donor excluded as age not known. € Assuming a single transplant resulting from each donor ≤ 5 years of age

Only 4 donors under the age of 1 year and no neonatal donor (< 1 month) were offered in this period. Majority were DBD donors (≥ 80%). Mean recipient ages were 36, 34 and 29 years with male preponderance in all three groups. Recipients from all 3 groups had similar characteristics in terms of BMI, ethnicity, donor type (DBD vs DCD), HLA mismatch cold ischaemic time. Majority of kidneys from Group A & B (94% & 74%) were transplanted en-bloc in single adult recipients. Graft survival was comparable in all groups with 82%, 85% & 77% (P=0.29) with a mean follow up periods of 9, 12.5 &11.8 years respectively. Patient survival were also similar at 100, 99& 90% respectively (P=0.087).

Conclusions: Paediatric donor kidneys produce excellent graft and recipient outcomes. Neonate (<1m) and infants (<2 year) are rarely offered or accepted for donation and kidneys procured from these donors are rarely utilized. Kidneys from donor under five years are usually transplanted en bloc and are not offered for paediatric recipient. Paediatric donors offer a scope for expanding the donor pool

Parallel session

Thursday 14th March

Specialist nurse symposium

14:00 – 15:30

O49

"Let's talk about organ donation": Can primary school children initiate the discussion with their families after attending a workshop?

Linda Selves, Bimbi Fernando

Royal Free Hospital, London, UK

Introduction: Schools education programmes on organ donation have focussed on children from secondary schools and there is little available for primary school children.This may reflect unsubstantiated concerns about exposing primary school children to this sensitive subject. We performed a pilot education project on organ donation for primary school children and report our early experiences of this programme in particular as to whether they could initiate a discussion with their parents/carers.

Methods: After gaining permission from local schools we ran educational workshops for 214 school children between the ages of 9 and 11 years. The faculty included a surgeon, a liver transplant coordinator and recipients of transplants.The interactive workshop covered involved basic anatomy, physiology, organ failure and transplantation. The supply of donor organs was then discussed and the pupils were challenged to discuss the subject with their parents, families and teachers. Questionnaires were sent to the pupils as well as their familiess.

Results: 214 children attended the workshops. 86% of pupils subsequently talked about organ donation with their peers, teachers and parents. The parents questionnaire had a 30% response rate. 60% felt that this was an important subject to discuss, 57% had not discussed organ donation before and 60% of parents were either on the Organ Donor Register or had already discussed their wishes with family members. 77% of parents felt it was an appropriate subject for their children to discuss and 77% people had a discussion with their child after they attended the workshop.

Conclusions: If handled sensitively educational workshops on organ donation are entirely appropriate for primary school children and they may have a significant role in initiating, highlighting and promoting this important discussion with their friends, families and teachers

O50

Identifying predictors of psychosocial outcomes after living donation

Hannah Maple[1], Joseph Chilcot[2], John Weinman[2], Nizam Mamode[1]

[1]Guy's and St Thomas' NHS Foundation Trust, London, UK, [2]Institute of Psychiatry (King's College London), London, UK

Introduction: Living kidney donation is the treatment of choice for patients with end stage renal failure. It is justified by the expectation that the psychosocial gain outweighs the risks of physical harm. The aims of this study were to identify factors of importance to living donors that may impact psychosocial outcomes and recovery after donation.

Methods: A cross-sectional qualitative study was performed in January 2012. A topic guide was devised following scoping interviews and discussions with the clinical transplant team and a sample of former living kidney donors. The sample was recruited to ensure a range of donor-recipient relationships were captured and represented. Both pre- and post-operative donors were interviewed. Each interview was recorded and transcribed verbatim. Transcripts were indexed, sorted by theme and summarised before being placed into frameworks for analysis.

Results: 23 in-depth interviews were conducted over a 6 week period. Several themes were identified from the study relating to decision making, familial concern, parental responsibility and the role of the donor as the recipient's carer. Being approached by the recipient and a lack of alternative possible donors was associated with increased stress and anxiety and feelings of entrapment. Those donors who were prime carers of their recipient and whose recipients had been on long-term dialysis sought to gain most from donation as they experienced similar physical constraints and an identical psychosocial impact on their own lives.

Discussion: This qualitative study has identified a number of factors important to living donors that may impact positively or negatively on their post-operative recovery and long-term psychosocial outcome. Factors such as the role of the donor as the primary carer, the donor's feelings towards donation (including feelings of entrapment) and other individual circumstances should be identified within donor-recipient pairs to ensure that donors are selected appropriately and adequately supported throughout their donation.

O51

Assessment of psychosocial characteristics and outcomes in 117 non-directed altruistic donors in the UK

Hannah Maple[1], Joseph Chilcot[2], Lisa Burnapp[3], Alastair Santhouse[4], Paul Gibbs[5], John Weinman[2], Nizam Mamode[1]

[1]Guy's and St Thomas' NHS Foundation Trust, London, UK, [2]Institute of Psychiatry (King's College London), London, UK, [3]NHS Blood and Transplant, Bristol, UK, [4]South London and Maudsley NHS Foundation Trust, London, UK, [5]Queen Alexandra Hospital, Portsmouth, UK

Introduction: Non-directed altruistic donation is becoming increasingly popular yet is still not performed in some UK centres or across many countries in Europe. Questions regarding motivation and characteristics of these donors persist, alongside concerns about regret and long-term psychosocial outcomes. The aims of this study were to compare physical and psychosocial outcomes in non-directed altruistic donors (AD) vs. directed (specified) donors (DD).

Methods: All 117 UK non-directed altruistic donors donating since the scheme commenced in 2007 until July 2012 were sent a postal questionnaire. A comparison group of 148 directed donors was similarly recruited from a single centre. Detailed assessment of psychosocial outcomes was made using 12 pre-validated outcome measures. Self-designed questions specific to donation were included as were questions regarding motivation, regret and anonymity for the AD group. Physical outcome data for the AD sample was obtained from NHSBT.

Results: 134 responses were received (85 AD vs.49 DD; 50.6%). AD were older (58yrs vs. 49yrs; $p<0.001$), predominantly white (97.6% vs. 79.6%; $p=0.001$) and had donated more recently (1.58yrs vs. 2.65yrs; $p<0.001$). There was no difference in psychiatric history or personality type ($p>0.05$). There was no difference in depression, anxiety, stress, self-esteem or wellbeing between the groups ($p>0.05$). AD were more engaged in other altruistic behaviours, such as blood donation and organ donor registration ($p<0.001$). There was no difference in physical outcomes, however AD recovered from surgery quicker ($p<0.05$). AD reported lower social rank and lower overall social support, both generally and for donating ($p<0.05$). 93% of AD did not regret their decision to donate.

Discussion: This study has demonstrated comparable psychosocial outcomes in non-directed altruistic donors when compared to a directed donor sample. Social support is lower in the AD group and this may indicate an increased level of social isolation worthy of further investigation. Unspecified donation should be supported, promoted and encouraged across transplant centres worldwide.

O52

Facilitation of eye retrieval within Scottish hospitals

Morag Vickers

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Introduction: SNODs (Specialist Nurse Organ Donation) in central Scotland have encountered changes when facilitating eye retrieval (enucleations). There has been an increase in donors but a reduction in the availability of trained retrievers. Centralisation of mortuary services and the redeployment of trained staff specifically within one health board have resulted in three hospital mortuaries not fully staffed. Opthalmology were retrieving out of hours, within unfamiliar environments and minimal assistance. It is thought that may have led to a loss of potential eye donors

Methods: Embedded SNODs of one health board attended an enucleation training course. This was undertaken as a pilot within the Scottish team. Loss of potential donors through absence of an eye retrieval, changes in post mortem times (death to consent and death to enucleation) were monitored. The purpose of the training is to determine whether training of SNODs to undertake eye retrieval leads to a reduction in loss of potential donors and facilitation of eye retrieval

Results: An additional six specialist nurses in the Scotland team have recently completed similar training. The specialist nurses achieved the level required to undertake retrieval and work alongside the Opthalmology /Retrieval services to carry out enucleations as required. There has been no loss of donors through absence of an eye retriever.

Discussion: The presence of SNODs trained in eye retrieval has led to an improvement in the number of donors and in measures of retrieval. Trained SNODs are able to act as mentors to their colleagues to become competent eye retrievers. This unusual step taken to train SNODs to enucleate will ensure that all referrals for eye donation will be facilitated in an efficient and timely manner.

O53

Patterns of usage of patient to patient peer support – an analysis of six years of peer support in one renal unit

Eleri Wood

King's College Hospital, London, UK

Introduction: Individuals with Chronic Kidney Disease (CKD) have been shown to value peer support, defined as informational, emotional and appraisal assistance provided by patients who possess personal experiential knowledge of living with CKD. Formal peer support schemes are being promoted through health policy and becoming a popular adjunct to standard renal care. However, little is known about their long-term utility. This was investigated through an analysis of six years of peer support in one large renal unit.

Methods: Data relating to all referrals, sessions of support delivered, and recipient and supporter characteristics were prospectively collected from service launch in late 2005.

Results: 166 patients received peer support, approximately 1.5% of the unit's population. The 31 peers supported an average of 1.39 patients per year. 75% of recipients sought informational support to facilitate renal replacement therapy decisions and 88% chose to meet their supporter face-to-face. Utilisation was equitable across demographic groups except for greater use amongst black patients than other ethnicities. Demand varied over time, dropping significantly after its peak in 2010. Approximately 8% of the unit's clinicians had made at least one referral into the service but 58% of all referrals came from two individual clinicians. Doctors and nurses made equal use of peer support but junior staff made very few referrals.

Discussion: Utilisation of peer support has varied over time and often been below expectation and capacity. The large variance in referral rates between clinicians suggests that its success is contingent not just on patient desire and characteristics but also clinician promotion and referral. The barriers impeding widespread interaction between professionals and peer support services are worthy of attention.

O54

The impact of age, socioeconomic status, ethnicity and transplant centre location on live donor kidney transplant access and outcomes

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Introduction: The prevalence of End-Stage Renal Disease is increasing and is ideally treated by live donor kidney transplant (LDKT). Non-medical factors such as socioeconomic status, ethnicity, age and transplant centre location have been associated with LDKT access and outcome variability. Our aim was to identify whether such associations exist in a previously unstudied U.K. region.

Methods: All renal transplants at our centre from Jan 2001-Dec 2010 were retrospectively analysed (n=762). LDKT recipients (n=201) were compared to cadaveric donor kidney transplant (CDKT) recipients (n=561) for age, socioeconomic status (from Scottish Index of Multiple Deprivation score), race and time/distance to transplant centre. Outcome measures were: Delayed Graft Function (DGF), Primary Non-Function (PNF), Biopsy-Proven Acute Rejection (BPAR) and serum creatinine, graft and patient survival at 1 year. Student's T-Test was used to analyse continuous variables, Pearson's Chi-Squared test for categorical variables and the Kaplan-Meier estimator for survival analysis.

Results: There was no significant difference between the percentage of donors from each socioeconomic quartile (p=0.45) but most offered kidneys to recipients from the same quartile (88%, 65.9%, 84.7%, 88.9%). 70% of LDKT and 50.1% of CDKT recipients were aged less than 45. Recipients aged 45-65 formed 26.5% of total LDKTs and 43.6% of total CDKTs and for over 65s these figures were 3.5% and 6.4%. LDKT access was not significantly affected by ethnicity (p=0.089), time (p=0.226) or distance (p=0.224) to transplant centre. Time and distance to transplant centre had no significant effect on graft loss (p=0.91, p=0.78 respectively) or recipient survival (p=0.97, p=0.08 respectively).

Discussion: Socioeconomic status, ethnicity and transplant centre location did not affect access to LDKT but older patients received proportionately fewer LDKTs and proportionately more CDKTs. Age, socioeconomic status, ethnicity and transplant centre location did not, however, significantly affect outcomes following LDKT in the population studied.

Parallel session

Thursday 14th March

Development, genetics and epigenetics

16:00 – 17:30

O55

A novel mutation specific cause of proximal tubulopathy and nephrocalcinosis in *HNF4A*

Alexander Hamilton[1,2], Tim McDonald[1], Paul Cook[3], Carol Inward[4], Sian Ellard[1], Andrew Hattersley[1], Coralie Bingham[2]

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Introduction: We have identified 5 individuals from 3 families with an *HNF4A* R76W mutation that co-segregates with Fanconi syndrome and nephrocalcinosis. *HNF4A* mutations cause maturity onset diabetes of the young (MODY), but are not among the 8 genes known to cause proximal tubulopathy. We aimed to describe this new phenotype and establish if this was a generalised or mutation specific effect by comparison with a cohort of patients with other *HNF4A* mutations.

Methods: We measured fasted urines in the R76W group and in 20 patients with other *HNF4A* mutations. Renal ultrasounds were performed in 15 patients. Results were compared using the independent samples median test or Z scores.

Results:	R76W (n=5)	Other *HNF4A* (n=20)	
Amino acids, mean Z score	20.42	-0.16	
α1-microglobulin mg/l, median	205	6.0	p=0.012
β2-microglobulin mg/l, median	71.1	0.3	p<0.001
Retinol binding protein mg/l, median	100.5	2.0	p<0.001
Glucose mmol/l, median	55.6	0.3	p=0.012
Nephrocalcinosis on ultrasound	5/5	0/10	

Discussion: Patients with the *HNF4A* R76W mutation have a novel and specific phenotype of proximal tubulopathy and nephrocalcinosis characterised by aminoaciduria, massive low molecular weight proteinuria and glycosuria. These features were not seen in 20 patients with other *HNF4A* mutations. *In silico* modelling suggests that the R76 residue is involved in DNA binding to promoters and we hypothesize that the mutation may affect target specificity. This is the first description of a mutation specific effect in the MODY genes, hitherto not known to be related to renal tubular dysfunction or renal tract calcification.

O56

Stability of microvesicle-free urinary microRNAs is conferred by complex formation with Argonaute 2 protein

Cristina Beltrami[1,2], Aled Clayton[3], Aled Phillips[1,2], Donald Fraser[1,2], Timothy Bowen[1,2]

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Background: microRNAs (miRs) are endogenous, short, non-coding single-stranded RNA transcripts that regulate gene expression at the post-transcriptional level. Recent work has shown that miRs found in serum and plasma are present in microvesicle-free and microvesicle-associated form, in each case showing a resistance to RNase activity that enhances their disease biomarker utility. Urinary miRs represent a potentially novel source of biomarkers for chronic kidney disease (CKD), but their localisation to microvesicles and sensitivity to degradation remain poorly characterized. The purpose of this study was to identify the location of miRs in urine, and to investigate their stability.

Methods: Microvesicle-free and microvesicular urinary fractions were prepared by sucrose gradient ultracentrifugation prior to analysis by flow cytometry, immunoblotting and RT-qPCR. Endogenous urinary miR stability was then compared with that of spiked-in, exogenous, *C. elegans*-specific cel-miR-39 using RNase or proteinase K digestion followed by RT-qPCR. Protein: miR associations were analysed by RNA-immunoprecipitation (RNA-IP).

Results: Over 95% of urinary miRs were present in microvesicle-free urine, with the majority of the remainder associated with exosomes. Endogenous miRs had significantly greater resistance to RNase degradation than cel-miR-39 in urine samples from both control subjects and proteinuric diabetic nephropaths. Proteinase K digestion significantly decreased endogenous miR stability, suggesting protection by protein binding partners. Investigation of putative partners using RNA-IP showed association between urinary miRs and Argonaute 2, a protein component of the RNA-induced silencing complex, but not albumin.

Discussion: Our data demonstrate that the majority of urinary miRs are not associated with microvesicles, provide a mechanism by which their stability is enhanced, and suggest that miRs do not freely cross the glomerular filtration barrier. These findings have important implications for the use of urinary miRs as a novel class of CKD biomarkers.

O57

Biallelic mutations in *LRIG2* cause urofacial syndrome

Helen Stuart[1], Neil Roberts[1], Berk Bergu[2], Sarah Daly[1], Jill Urquhart[1], Sanjeev Bhaskar[1], Murat Mermerkaya[2], Mesrur Silay[3], Malcolm Lewis[1], Beatriz Olondriz[4], Blanca Gener[5], Christian Beetz[6], Rita Varga[6], Fatoş Yalçınkaya[2], Adnan Gücük[7], Wyatt Yue[8], Edward McKenzie[10], Emma Hilton[1], Adrian Woolf[1], William Newman[1]

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Introduction: Congenital lower urinary tract (LUT) abnormalities are a common causes of renal failure in children. Whilst understanding of the genetic causes of kidney disease is expanding rapidly, to date, little is known about genetic causes of LUT disease. Urofacial syndrome (UFS) is an autosomal recessive condition characterised by non-neurogenic neurogenic bladder dysfunction, vesicoureteric reflux, urosepsis and risk of renal failure. Characteristically affected patients have an abnormal facial expression upon smiling and crying. We previously reported that some UFS cases are caused by biallelic, loss-of-function mutations in *HPSE2*, which encodes heparanase 2. However, there is evidence of genetic heterogeneity and this study aimed to discover further genes associated with UFS.

Methods: Autozygosity mapping and whole exome sequencing in UFS individuals with normal *HPSE2* sequencing. Screening of genes by Sanger sequencing in further individuals with UFS or non-syndromic bladder disease. Gene expression was sought in normal human embryonic urinary tracts.

Results: Biallelic loss-of-function mutations in *LRIG2* encoding the leucine-rich repeats and immunoglobulin-like domains 2 (LRIG2) were found in three unrelated UFS families. Importantly, we showed that variants in *LRIG2* may also be associated with non-syndromic voiding dysfunction. Autonomic nerve activity controls the bladder's abilities to act as a low-pressure reservoir which intermittently, completely expels its contents *per* urethra. LRIG2 and heparanase-2 were immunodetected in nerve fascicles growing between differentiating muscle bundles within the human fetal bladder, directly implicating both molecules in neural development in the LUT.

Conclusion: Biallelic mutations in *HPSE2* and *LRIG2* cause UFS with evidence of further genetic heterogeneity. This promises to lead to insight into the molecular pathogenesis of UFS with relevance to non-syndromic voiding dysfunction.

O58

Distinct methylation patterns in genes that affect mitochondrial function are associated with diabetic nephropathy

Elizabeth J Swan[1], Amy Jayne McKnight[1], Alexander P Maxwell[1,2]

[1]*Queens University Belfast, Belfast, UK,* [2]*Regional Nephrology Unit, Belfast, UK*

Introduction: Methylation is a key epigenetic feature that influences mitochondrial function. Genetic variants in mitochondrial DNA are associated with diabetic nephropathy and this study sought to evaluate if methylation differences were evident between individuals with and without diabetic nephropathy.

Method: A case-control study was conducted using two methylation platforms. Participants were white individuals from UK/Ireland diagnosed with Type 1 diabetes (≤35 years old). Controls were persons with ≥ 15 year duration of diabetes with no renal disease and not prescribed anti-hypertension medication. Cases were persons with ≥10 years duration of diabetes, diagnosed diabetic nephropathy, persistent proteinuria and hypertension. Methylation values (β) were obtained from the Illumina Infinium® Human Methylation27 BeadChip (93 cases, 94 controls) and Infinium methylation 450K BeadChip (150 cases, 100 controls) Stringent quality control was applied and methylation differences compared between cases and controls.

Results: Mitochondrial related genes (n=780) were identified from data within mitoproteome.org and methylation differences were thus compared in 437 individuals. The most significant difference ($P<10^{-8}$) in methylation status was observed for *MARC1* (1st exon in CpG island of mitochondrial amidoxime reducing component 1) and *ACSL3* (5' UTR in CpG island shore of acyl-CoA synthetase long-chain family member 3) genes.

Discussion: Differential methylation in genes that affect mitochondrial function is associated with diabetic nephropathy. The novel finding of significant epigenetic modifications to the *MARC1* and *ACSL3* genes adds to our understanding of the biological changes associated with diabetic kidney disease.

O59

The first steps in developing 3-dimensional human kidneys in vitro

Karen Price, Maria Kolatsi-Joannou, Chiara Mari, Patrik Bachtiger, David Long, Paul Winyard

Nephro-Urology Unit, UCL Institute of Child Health, London, UK

Introduction: The lack of transplantable kidneys provides an imperative to seek alternative sources of functioning renal tissue. We have previously generated human fetal mesenchymal cell lines from 70-84 day gestation that express classical renal markers such as PAX2, WT1 and SIX2. These cells proliferate and maintain a mesenchymal phenotype over many passages. Using known inducers of tubulogenesis, we demonstrated to a limited extent epithelial transformation: a key step in developing nephrons in vivo. Therefore, to further enhance differentiation, we utilised a new technique of disaggregation-reconstitution from whole kidneys and demonstrate de-novo development of human tubules and glomeruli in vitro for the first time.

Methods: Twelve ethically approved human kidneys were collected between the ages of 8-12 weeks gestation. They were dissociated using 0.25% trypsin to microscopically-proven single cells and then recombined together and cultured as a pellet on a filter. Samples were cultured for 5-7 days, in the presence of Rho kinase inhibitors for the first 24h, and then processed into wax for serial sections or labelled with fluorescent calbindin, laminin for whole-mount confocal microscopy. In some experiments, labelled mesenchymal cells from our earlier experiments were added in a 1:5 ratio to the reconstitution mix.

Results: Neo-organs survived and grew during the culture period. Initial appearance was amorphous, but those from 8-10 weeks gestation started to develop clear tubule-like structures and glomeruli by 5 days; confirmed by confocal and immunohistochemisty. Occasional labelled mesenchymal cells were observed but did not convincingly contribute to formed epithelia. Older organs failed to develop properly.

Conclusions: We report for the first time that 3-dimensional culture recapitulates normal human nephrogenic differentiation in vitro, albeit within a limited gestation. We need to develop better techniques to expand these cultures and potentially generate functioning human renal tissues in future.

O60

Investigation of epigenetic factors that influence chronic kidney disease

Laura Smyth[1], Alexander Maxwell[1,2], Amy Jayne McKnight[1]

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Introduction: DNA methylation is an important epigenetic modification that does not change the DNA sequence. DNA methylation profiles have been associated with complex disease and are altered in uraemic patients. This study investigated association between DNA methylation and chronic kidney disease (CKD) using a case-control approach.

Methods: The Infinium® methylation 450K BeadChip array (Illumina, Inc, USA) was used to analyse DNA methylation across the methylome in 255 CKD cases and 152 controls (MDRD eGFR>60 mL/min/1.73m^2). Following stringent quality control, methylation levels were analysed and results adjusted for multiple testing.

Results: Quantitative methylation values were obtained at single-CpG level for 485,577 features, encompassing all designable genes, including promoter, 5', and 3' regions, CpG islands outside coding regions, and miRNA promoter regions. Differential DNA methylation was observed in 23 genes where more than one CpG site per gene was identified with $P_{adjusted}<10^{-8}$. Top ranked genes are involved in cell migration, cell proliferation, vesicle trafficking and replication. Of particular interest are genes such as *ELMO1*, *CUX1*, *PTPRN2*, and *PRKAG2*, which have all been previously highlighted from experimental (functional and genetic) studies of renal disease.

Discussion: Epigenetic modifications have emerged as both a cause and consequence of disease. They may be altered by drugs, environmental factors and disruption of homeostasis. Patients with CKD have a uraemic cellular milieu which may modify DNA methylation. However, DNA methylation may also cause or accelerate renal injury. This pilot study has identified 23 strongly significant genes associated with CKD. Further work is required to elicit the effect of altered methylation status at these loci on the pathogenesis or progression of CKD.

Parallel session

Thursday 14th March

BTS free communications

16:00 – 17:30

O61

1-year outcomes of a prospective, open label, randomized, controlled trial of standard vs extended-release tacrolimus as maintenance monotherapy in kidney transplantation after alemtuzumab induction with rapid steroid withdrawal (TAESR trial)

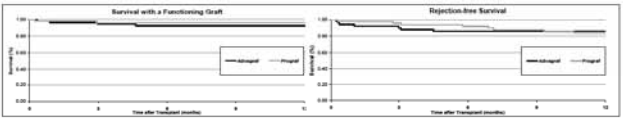
Adam McLean[1], Kakit Chan[1], Jack Galliford[1], Dawn Goodall[1], Rawya Charif[1], Michelle Willicombe[1], Candice Roufosse[2], Terry Cook[2], David Taube[0]

[1]Imperial Kidney & Transplant Centre, Hammersmith Hospital, UK, [2]Department of Medicine, Imperial College, UK

Introduction: Extended-release (ER, once daily) tacrolimus (Advagraf) has been shown to provide equivalent results to standard-release (SR, twice daily) tacrolimus in several regimens for immunosuppression after kidney transplantation, but not in the context of tacrolimus-based maintenance monotherapy.

Methods: We have undertaken a prospective, randomized controlled, investigator-led, single centre, open-label trial comparing ER with SR tacrolimus as maintenance monotherapy after alemtuzumab induction and rapid steroid elimination at 7 days. 50 patients recieved SR twice daily tacrolimus (Prograf) and 52 ER once daily tacrolimus (Advagraf). Randomization was stratified for live vs deceased donors, and the groups were balanced with respect to, age, sex, ethnicity, primary renal diagnosis,and prior sensitisation.

Results: The primary outcome measure was survival with a functioning graft at 1 year, and did not differ significantly between the two groups (SR 96% vs ER 92%). Rejection-free survival was SR 84%, ER 86%.



There were no significant differences between the two arms in mean tacrolimus level, dispersion of tacrolimus trough levels, or incidence of sub-clinical rejection or degree of interstitial fibrosis in surveillance biopsies taken at 3 months and 1 year post-transplant

Discussion: Under alemtuzumab induction with rapid steroid elimination, once daily extended-release tacrolimus maintenance monotherapy provides equivalent one-year survival with functioning graft to standard-release twice daily tacrolimus, with a very simple once-daily, single-agent regimen.

O62

Generic switch of tacrolimus in prevalent kidney transplant recipients

Paresh Jogia[1,2], David Oskiera[1], Stephen Booth[2], William McKane[0]

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Introduction: There are limited data on outcomes when switching between tacrolimus brands in prevalent transplant recipients. We have undertaken a monitored switch from Prograf to Adoport in prevalent patients.

Methods: All stable, prevalent patients were given written and verbal information in advance of the switch to Adoport. Patients were advised to use their Prograf stock before starting Adoport. Biochemistry and trough tacrolimus level were scheduled 7-14 days after switching, otherwise testing was as per routine practice. Data were analysed from the closest timepoint pre/post the switch (PRE/POST) as well as all data in the 6-month window pre/post the switch date (6Mpre/6Mpost).

Results: 768 tacrolimus levels from 106 patients were analysed: mean (SD) age 53yrs (14), weight 81kg (18), 69mth (45) post-transplant, 92% Caucasian, 63% Male, 14% DM. There were no episodes of rejection related to the switch.

Table 1: Mean (SD) tacrolimus level, eGFR and dose

	PRE	POST	p	6Mpre	6Mpost	p
Level	6.7 (2.3)	6.7 (2.0)	.80	6.6 (1.9)	6.8 (1.6)	.161
eGFR	49.9 (17.1)	50.0 (17.8)	.91	49.4 (17.3)	50.9 (18.2)	.002
Dose				4.3 (2.6)	4.1 (2.5)	.001

There was no significant change of tacrolimus levels in either the short or long-term analysis and the eGFR was stable. The tacrolimus dose changes [(6Mpre - increase 1, decrease 6), (6Mpost, increase 6, decrease 20)] are reflected in a small but significant fall in the mean dose. Only 4/106 required a reduction after the day 7-14 level. Intra-patient variation in levels was high but equivalent for Prograf and Adoport (mean Coefficient of Variation 19% v 21%, p=0.229).

Conclusions: In routine clinical practice, tacrolimus levels are intrinsically variable on both brands. The switch resulted in a small rise in dose change frequency and a marginal (<0.2mg/day) reduction in dose, with stable levels. Despite patient and clinician anxiety about generic switch, it can be safely achieved with good communication and minimal additional monitoring.

O63

Importance of 3 year surveillance biopsies in renal transplantation

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Most renal transplant [tx] surveillance biopsies [SBx] are taken within the first 12 months post-tx and there is growing evidence that the detection of subclinical rejection is a powerful tool in predicting subsequent clinical outcomes. The clinical use of late SBx, defined as biopsies taken in the absence of allograft dysfunction after the first year post tx is not well described. The aim of the study was to establish subclinical pathology on SBx carried out at 3yrs post-tx and to determine if they could be used to predict clinical outcomes.

We carried out 3 year SBx on 100 patients [64m, 36f, mean age 46.37 ± 12.4 yrs, 56 live donors, mean HLA mm 3.43 ± 1.53] transplanted between 2005-2009. The mean time to SBx was 3.21±0.37yrs post-tx; mean follow up post biopsy was 1.89±1.20yrs. All patients received monoclonal antibody induction, a week of steroids post-tx and a tacrolimus based immunosuppressive regime. All patients had stable allograft function [mean creatinine 125.53±35.54 µmol/l] and no proteinuria. The biopsy findings were not used to change immunosuppressive therapy.

The major histological findings are shown in Table 1. Of the patients with rejection, 9/16[56.3%] had ACR, 3/16[18.8%] AMR and 4/16[25.0%] had transplant glomerulopathy. 9/16[42.9%] patients had donor specific antibodies at the time of biopsy. Patients with DSA had significant evidence of microcirculatory inflammation; 5/9[55.6%] had glomerulitis, 4/9[44.4%] had peritubular capillaritis and 4/9[44.4%] had double contours.

Histological finding	Number
Normal	33/100
Arteriolar hyalinosis	23/100
Tubulo interstitial scarring	17/100
Rejection	16/100
De novo or recurrent GN	5/100
Other	6/100

This study shows that subclinical alloimmune injury is seen in a significant number of SBx at 3yrs post tx. These SBx may predict graft dysfunction and failure, signalling the need for augmented immunotherapy before it is too late

O64

The role of bladder drainage in pancreas transplantation alone: a single centre experience

Manuel Maglione[1], Gabriele Spoletini[1], Shruti Mittal[1], Edward Sharples[3], Srikanth Reddy[1], Rutger J Ploeg[1,2], Isabel Quiroga[1], Anil Vaidya[1], James Gilbert[1], Peter J Friend[1,2], Sanjay Sinha[1]

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Controversy remains whether there is still a role for bladder drainage (BD) in pancreas transplantation. Compared to excellent results in simultaneous pancreas kidney transplantation, pancreas transplantation alone (PTA) is still hampered by an up to 20% graft loss within the first year post transplantation. Herein we report our recent experience with bladder drained PTA. 34 consecutive PTA performed between February 2010 and September 2012 were retrospectively reviewed. Re-transplantations were not included. Induction immunosuppression consisted in two doses of Campath, maintenance immunosuppression in Tac and MMF. Exocrine enteric drainage (ED) was performed in half of the study cohort; the other half had exocrine BD. Median follow up of the ED and the BD group was 23 months (range 0 – 33) and 12 months (1 – 19), respectively. Donor BMI was significantly lower in the BD group (n = 0.02). All other donor and recipient demographics were not significantly different. 1 year graft survival in the ED group was 64.7% (n = 6), 4 patients experiencing acute rejection (1 case of non-compliance), and 2 losses due to intraabdominal sepsis. In the BD group 1 year graft survival is 100% (p = 0.01). In this group grafts were monitored by urinary amylase levels. In 7 patients 9 episodes with a drop in urinary amylase higher than 50% correlated with either acute rejection diagnosed by duodenal biopsy or with partial thrombosis of the main graft vessels. Following three day course of methylprednisolone or therapeutic dose heparin administration, respectively, urinary amylase levels recovered back to their baselines. Number of readmitted patients (8/17 ED vs 11/17 BD; p=ns) as well as incidence of patients readmitted more than once (2/17 ED vs 6/17 BD; p=ns) were higher in the BD group, however, without reaching statistical significance. So far, three bladder drained patients necessitated conversion to ED. Despite the higher incidence of readmissions, we observed significantly better short-term graft survival in bladder drained PTAs. One reason might be that close monitoring of the graft by urinary amylase prevents delays in treatment of early (non)immunological complications.

O65

The relationship between age and measured GFR (mGFR) in healthy living kidney donors is curvilinear, not linear – implications for living donation

David Goldsmith, Christopher Sibley-Allen, Rachel Hilton, Lisa Burnapp, Masood Moghul, Glen Blake

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

Background: Measurements of glomerular filtration rate (GFR) are frequently interpreted assuming a linear variation with age. Non-linear relationships may give a better representation of the changes associated with "normal aging" in a population (living donors) generally considered to be (even) healthier than age matched controls.

Materials and methods: This was a retrospective study of 904 subjects (468 women,436 men; age range 18-84 years) undergoing assessment as prospective living kidney donors . GFR was evaluated from ^{51}Cr-EDTA plasma clearance using blood samples taken at 2, 3 and 4 hours. The slope-intercept GFR was corrected for body surface area (BSA) using the Haycock formula and for the fast exponential using the Brochner-Mortensen equation. The relationship between age, gender and GFR was examined using best-fit curve analysis. Non-linear relationships with age were explored using fractional polynomials.

Results: There was no gender difference in BSA corrected GFR over five decades of age ($P = 0.40$). However, female donors with a body mass index > 30 $kg.m^{-2}$ had a statistically significantly lower GFR than non-obese women ($P < 0.01$). The best-fit relationship between age and GFR was non-linear and described using a fractional polynomial model of degree 1 ($GFR = 103.9 - 0.0061*Age^2$ $mL.min\text{-}1.(1.73\ m^2)^{-1}$) with an RMSE of 12.9 $mL.min\text{-}1.(1.73\ m^2)^{-1}$. The residual variance for this model was significantly smaller than for the best-fit linear model ($P = 0.006$).

Conclusions: GFR measurements in prospective healthy living kidney donors are best corrected for age using a *non-linear* relationship. Our results help to establish potential normative mGFR ranges for this important population.

O66

Unintentional consequences of the exclusion of unacceptable donor antigens against preformed low level HLA antibodies

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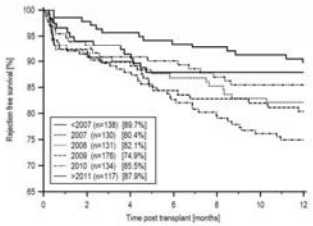
The presence of donor specific antibodies [DSA] at the time of transplantation increases the risk of antibody mediated rejection [AMR] and allograft failure. For sensitised patients with HLA antibodies [HLA Ab] 'unacceptable donor antigens [UDAs]' are defined as any HLA Ab which is likely to result a positive cross match [PCXM] against the corresponding donor HLA antigen. The relevance of low titre HLA Ab which do not result in a PCXM remains controversial in the modern era of immunosuppression. In 2005-6 our centre removed UDAs from those patients with low titre HLA Abs. Subsequent analysis of the impact of rejection rates and outcomes is described in this study.

826 patients received a renal transplant between 2005-11. 425[51.5%] deceased donors, 543[65.7%] males, 96[11.6%] regrafts, mean HLA mismatch 3.2±1.6.

Overall 1 year patient and allograft survival was 98.3% and 95.4%. 1 year rejection free survival decreased following the delisting of the UDAs being 89.7%, 80.4%, 82.1% and 74.9% in the patients transplanted in years 2006-2009 respectively, p<0.01. With a corresponding AMR free survival of 97.8%, 95.3%, 95.4% and 88.3% respectively, p<0.01. The presence of preformed DSA was found to be associated with rejection, with a rejection free survival of 83.5% and 65.3% in the DSA+ and DSA- groups respectively, p=0.0001.



Following this finding relisting of UDAs for low level HLA Ab was reintroduced. 1 yr rejection rates following this have significantly improved as shown in figure 1, p<0.01.

This study shows that low titre DSA in the setting of a negative XM are associated with rejection and should be listed as UDA.

O67

Clinical scale removal of HLA-DR11 specific antibodies from patient plasma

Dave Lowe[1,2], Curtis McMurtrey[4,5], Rob Higgins[3], Steve Cate[4], Rico Buchli[5], Rodney VanGundy[5], Dan Mitchell[2], Sunil Daga[2,3], David Briggs[1], William Hildebrand[4,5], Daniel Zehnder[2]

[1]NHSBT, Birmingham, UK, [2]University of Warwick, Coventry, UK, [3]University Hospital Coventry and Warwickshire, Coventry, UK, [4]University of Oklahoma, Oklahoma, USA, [5]Pure Protein LLC, Oklahoma, USA

Introduction: Strong humoral responses to allogeneic HLA preclude organ transplantation, promote hyperacute rejection, and contribute to chronic transplant rejection. Therapies exist to prevent B cells from secreting antibodies, and bulk antibody removal is also an option, but there is no means to specifically deplete antibodies that recognize allogeneic HLA molecules while leaving humoral immunity largely intact. We tested a sHLA Antibody Removal Column (SHARC) for removing class II anti-HLA antibodies from litre volumes of plasma.

Method: Approximately 70 milligrams of the soluble class II molecule HLA-DRB1*11:01/DRA1*01:01 (DR11) produced in mammalian cells was covalently coupled to a solid support matrix. The HLA-DR11 matrix was packed into a column for the purpose of removing anti-DR11antibodies from patient plasma. 2.5L of patient plasma containing anti-DR11 antibodies was run over the column at a clinically relevant flow rate of 40ml/min. Fractions of the flow through were taken and anti-HLA-DR11 antibodies were measured by single antigen bead assay.

Results: When patient plasma recognizing multiple HLA was passed over the DR11 matrix, antibodies specific for DR11 were removed while antibodies for other class II (DQ) passed through the SHARC intact. Additionally there was no change in bulk antibody concentration after the plasma was passed over the column. DR11 specific antibodies that bound to the column were recovered by elution and retained their reactivity for DR11 as well as other specificities with expected shared cross reactivity. Anti-HLA reactivity specific for DR11 could be reduced by over 80% in a single pass.

Discussion: Native class II molecules were coupled to an affinity matrix and antibodies specific for class II HLA were removed from patient plasma. The depleted antibodies were recovered intact from the column. These data represent a proof of concept for selective antibody desensitisation as a potential therapeutic.

O68

IgG subclass specific antibodies and antibody associated acute rejection in antibody incompatible transplantation

Dave Lowe[1,2], Natalia Khovanova[2], Rob Higgins[3], Daniel Zehnder[2,3], David Briggs[1]

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Introduction: Our studies of antibody incompatible transplant (AiT) cases have shown that not all HLA-specific DSA are detrimental. Others have shown that DSA IgG subclasses do not appear to predict development of acute rejection. We show that changes in subclass composition predict early rejection episodes.

Method: 51 AiT cases were selected comprising 26 rejectors and 25 non-rejectors, with rejection diagnosed on the basis of clinical symptoms and/or histology. Daily serum samples were taken post-transplant with total level of HLA-specific IgG determined by single antigen bead assay. IgG1,2,3 and 4 HLA specific antibody levels were determined for pretreatment, post-transplant peak IgG, and 30 days post-transplant samples for all cases

Results: Samples taken prior to starting antibody removal therapy showed no difference between rejector and non-rejector groups. Samples tested post-transplant at peak pan-IgG DSA (days 8-11 post-transplant) showed increase in the rejector group of donor-specific IgG1 ($p=0.01$), and also the proportion of the total IgG response attributable to the complement fixing isotypes IgG1/IgG3 ($p=0.007$). In addition the rejector group also showed a significant increase in donor specific IgG4 as the antibody response matured beyond 30 days post-transplant ($p=0.03$). This IgG4 response was limited to antibodies to class II HLA. An additional cohort of 35 patients confirmed the association HLA class II specific IgG4 DSA with development of AMR. In addition a significant association between HLA class II IgG4 DSA at pre-treatment and rejection was observed ($p=0.007$).

Discussion: These data show a clear link between acute antibody mediated rejection (AMR) and the increased presence of complement fixing IgG isotypes. Increased levels of IgG4 associated with AMR is a novel observation. Analysis of IgG subclass composition may be an important tool in the analysis of AMR in AiT. In addition elevated levels of HLA class II donor specific IgG4 may be a useful predictor of early rejection and is potentially a biomarker for patients at greater risk of acute rejection.

O69

ABO-incompatible renal transplantation recipients have decreased immunoregulatory capabilities and respond to rituximab with prolonged B cell depletion and decreased memory responses towards common antigens

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

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Introduction: Rituximab has been used to deplete B cells in various clinical trials focussing around ABO-incompatible (ABOi) transplantation. The repopulating B cell pool is hypothesised to be tolerised towards the transplanted graft. Previous research has demonstrated that this repopulating B cell pool is predominantly naïve with fewer memory B cells. This study aims to further characterise the effects of rituximab on lymphocyte phenotype and response to common antigens.

Methods: ABOi renal transplant recipients were administered 375 µg/mL rituximab 2-4 weeks prior to transplantation in addition to standard immunosuppresion. Blood was taken prior to rituximab administration, one week before, on the day of, one week after, three months after and one year after renal transplantation. PBMCs were analysed for T cell and B cell phenotypes (flow cytometry) and memory response to common antigens (whole/extract *Candida albicans* and CMV surface proteins) using ^{3}H-thymidine incorporation assays.

Results: Relative to healthy controls, patients had significantly fewer $CD4^{+}$ $CD25^{hi}CD127^{lo}$ regulatory T cells (T_{REG}) and FoxP3 expression in these T_{REGS} was significantly decreased (one-way ANOVA, $p<0.05$). No difference was seen in CD45RA, CD45RO, CD27 or CD39 expression across all time points analysed for T_{REGS} and conventional $CD4^{+}CD25^{-}$ T cells. As expected, rituximab administration significantly depleted $CD20^{+}$ B cells but after one year, there was evidence of $CD20^{+}$ B cell reconstitution. The memory response to *C.albicans* was significantly diminished following rituximab administration at all the time points analysed.

Discussion: The long term effects of a single dose of rituximab on B cell depletion remain noticeable over one year post administration. This depletion significantly influences responses to common antigens, particularly *C.albicans*, indicating a detrimental effect on memory cells. In addition, ABOi renal transplant patients may have deficient immune regulation as fewer T_{REGS} with lower FoxP3 expression are present. Future work will include cytokine analysis of memory responses and comparison of above results to lab based $CD20^{+}$ B cell depletion.

Parallel session

Friday 14th March

Haemodialysis: trials and tribulations

08:30 – 10:00

O70

Cardiac magnetic resonance tagging identifies abnormalities in the majority of incident haemodialysis patients

Aghogho Odudu[1,2], Mohamed Tarek Eldehni[1,2], Gerry P. McCann[3], Chris McIntyre[1,2]

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Introduction: HD patients with cardiac abnormalities are vulnerable to HD-induced ischaemia and early identification allows strategies to improve outcomes. 2D-echocardiography uses geometric assumptions which overestimate abnormalities. Cardiac magnetic resonance (CMR) is the gold-standard for analysis of cardiac morphology and strain analysis by tissue tagging detects early dysfunction in non-uraemic settings. Previous CMR studies of renal transplant candidates used prevalent, selected populations and did not investigate strain. **Objectives:** To study cardiac abnormalities in an unselected incident HD population and determine additional utility of strain.

Methods: 84 subjects were studied (54 HD, median vintage 170 days, 30 age and sex-matched controls). Left ventricular (LV) mass and volumes were determined by planimetry. Global and segmental peak systolic circumferential strains (Ecc) were determined from strain curves. Comparisons were made by the Mann-Whitney or T test depending on normality for continuous data and chi-squared test for categorical data.

Results: Median values±IQR are presented as HD vs Controls. Global LV function was reduced (Ejection Fraction (EF) 51.5%±11 vs 58.5%±5.4) with regionally reduced strains (Ecc 16.4%±3.7 vs 19.2%±3.5), all $p<0.001$. LV hypertrophy (LVH) was increased (LV mass 63.4g/m2±24 vs 45.9g/m2±9.3) as was LV dilatation (LV end-diastolic volume index 87.6±29.8ml/m2 vs 71.6±17.7ml/m2) all $p<0.001$. Subgroup analysis of HD patients and controls with EF >50% (n=59) showed reduced strain persisted despite normal EF (Ecc 17.5%±3.3 vs 19.9%±3.4 $p=0.02$). Using 2 Standard Deviations from the mean of the controls, sex-specific cut-offs were determined for abnormal morphology and function in HD patients. 34% (19/54) had abnormal morphology (increased LVH or dilatation) whilst 59% (32/54) had abnormal contractile function (reduced EF or strain) with overlap between categories. In total, 93% (50/54) of HD patients had abnormalities in morphology, contractile function or both. 35% of abnormalities (19/54) were identified by strain alone. Only 7% (4/54) had nc abnormalities (chi-squared, $p<0.001$).

Conclusion: CMR tagging identified a wide range of cardiac abnormalities in the majority of incident HD patients studied. Strain shows promise in early identification.

Discussion: This is the first study using strain by CMR tagging in a HD setting.

O71

How safe is renal replacement therapy? A national study of mortality and adverse events contributing to the death of renal replacement therapy recipients

Benjamin Bray[1], Jennifer Boyd[2], Conal Daly[7], Arthur Doyle[3], Ken Donaldson[4], Jonathan Fox[7], Andrew Innes[5], Izhar Khan[6], Bruce Mackinnon[7], Robert Peel[8], Ilona Shilliday[9], Keith Simpson[7], Graham Stewart[10], Jamie Traynor[9], Wendy Metcalfe[0]

[1]King's College London, London, UK, [2]ISD Scotland, Glasgow, UK, [3]Queen Margaret Hospital, Dunfermline, UK, [4]Dumfries and Galloway Royal Infirmary, Dumfries, UK, [5]Crosshouse Hospital, Kilmarnock, UK, [6]Aberdeen Royal Infirmary, Aberdeen, UK, [7]Glasgow Renal and Transplant Unit, Glasgow, UK, [8]Raigmore Hospital, Inverness, UK, [9]Monklands Hospital, Airdrie, UK, [10]Ninewells Hospital, Dundee, UK, [11]Royal Infirmary of Edinburgh, Edinburgh, UK

Introduction: Patients receiving treatment with renal replacement therapy (RRT) have high mortality and ensuring patient safety in this population is difficult. We aimed to estimate the incidence and nature of medical adverse events contributing to the death of patients being treated with RRT.

Methods: This population registry based retrospective case review study included all patients being treated with RRT for established renal failure in Scotland and who died between 01/01/2008 and 30/06/2011. Deaths were reviewed by consultant nephrologists using a structured questionnaire to identify factors contributing to death occurring in both the inpatient and outpatient setting. Reviewers were able to use any information source deemed relevant, including paper and electronic clinical records, mortality and morbidity meetings and procurator fiscal (Scottish coroner) investigations. Deaths occurring in 2008 and 2009 where avoidable factors were identified that may have or did lead to death of a patient were subject to further review and root cause analysis, in order to identify recurrent themes.

Results: Of 1551 deaths in the study period, 1357 were reviewed (87.5%). Cumulative RRT exposure in the cohort was 2.78 million person-days. RRT complications were the primary cause of death in 35 (2.6%). Healthcare associated infection had contributed to 9.6% of all deaths. In 3.6 % of deaths, factors were identified which may have or did contribute to death. These were both organisational and human-error related and were largely due to five main causes: management of hyperkalaemia, prescribing, out of hours care, infection and haemodialysis vascular access.

Conclusions: Adverse events contributing to death in RRT recipients mainly relate to the everyday management of common medical problems and not the technical aspects of RRT. Efforts to avoid harm in this population should address these ubiquitous causes of harm.

O72

Novel biomarkers associated with the progression of coronary calcification in chronic kidney disease

Ben Caplin[1], Joanne Marks[1], John Cunningham[1], Michael Rubens[2], David Wheeler[1]

[1]*Centre for Nephrology, UCL Medical School, London, UK,* [2]*Department of Radiology, Brompton and Harefield NHS Foundation Trust, London, UK*

Introduction: A number of recently described biomarkers have been identified as potential mediators of arterial calcification in patients with CKD. We investigated the relationship between a range of biomarkers and the progression of arterial calcification in subjects enrolled in the London Arterial Calcification, Kidney and Bone Outcomes study.

Methods: A cohort of 289 patients with CKD stages 2-5 (median MDRD eGFR 39.7 ml/min/1.73m^2) consented to undergo electron beam tomography (EBT) scans. Subjects underwent baseline then follow-up scans after a mean of 49 months. Serum fibroblast growth factor-23 (FGF-23), fetuin, pyrophosphate (PyrP); dephosphorylated, uncarboxylated matrix Gla protein and osteoprotegerin (OPG) along with routine biochemical measurements were quantified in baseline blood samples. Calcification scores for 4 coronary arteries were summed and progression of calcification (for both aortic and coronary territories) was defined as ≥ 2.5mm^3 increase in the square-root of the Agatson score between scans.

Results: At baseline, higher serum OPG and lower fetuin were associated with both higher coronary and higher aortic calcification scores in unadjusted analyses. However the relationship with OPG was no longer significant in an adjusted model. 157 subjects underwent follow-up EBT scans. Progression of coronary artery calcification was associated with higher serum FGF-23, OPG and PyrP on univariate testing. However after adjustment for age and diabetes only the relationship with PyrP (and a borderline association with FGF-23) remained significant in a logistic regression model. No associations between the biomarkers and progression of aortic calcification were observed.

Conclusions: Although these newly described biomarkers are associated with arterial calcification, measurement of serum levels may not provide useful information over and above routine clinical data. The association between PyrP and progression of coronary artery calcification may reflect a compensatory response and warrants further investigation.

O73

Membrane vs centrifuge based therapeutic plasma exchange – a randomized prospective cross-over study

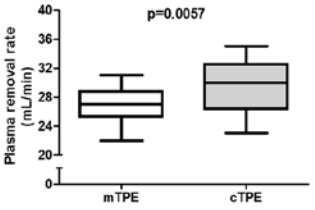
Carsten Hafer[1], Paulina Golla[1], Marion Gericke[2], Gernot Beutel[1], Bernhard Schmidt[1], Stef De Reys[2], Jan T Kielstein[1]

[1]Medical School Hannover, Hannover, Germany, [2]Terumo BCT, Lakewood, CO, USA

Background: Therapeutic plasma exchange (TPE) is increasingly used for the treatment of various diseases. It is either performed using a highly permeable filter with standard hemodialysis equipment (mTPE) or a centrifugation device (cTPE). Although both techniques are well established in clinical practice performance of these two means of TPE had never been compared systematically. Therefore we aimed to compare two commercially available therapeutic apheresis systems, one for mTPE (Octonova with Plasmaflo filter) and one for cTPE (Spectra Optia apheresis system) in a prospective randomized fashion.

Methods: Twenty-one patients age (51.6 ± 13.5 years; 10 F / 11 M; BMI 25.1 ± 5.0 kg/m²) were enrolled in this randomized, prospective, paired, cross-over, open label study with. First treatment (either mTPE or cTPE) was chosen by an online randomization list followed by the other mode of TPE for the 2nd treatment. The primary endpoints were plasma removal efficiency with 1.2 x of the total plasma volume exchanged. Secondary endpoints were total amount of plasma substances removed, such as IgG and fibrinogen. Further, the treatment effect on platelet count and treatment complications were evaluated.

Results: Despite a comparable volume of the removed plasma, mTPE treatment time was 10.5 % longer than in cTPE. ($p<0.05$), resulting in a 10 % lower plasma removal rate of the mTPE treatment (Figure). Both devices led to similar reduction of IgG, 63.3 % for mTPE and 67.8 % for cTPE. Correspondingly, the total amount of removed IgG was not different between treatments. The clearance of fibrinogen during TPE was higher with Spectra Optia (64 ± 9% vs 56 ± 16%, $p<0.05$). Platelet loss during mTPE was nearly double of that lost with cTPE (15 ± 9% vs 7 ± 9%, $p<0.05$).The processed blood volume required to remove 1.2 x TPV in mTPE was significant higher than with cTPE, (19.855 ± 3.423 L vs 6.456 ± 1.230 L, $p<0.05$). As a result, the plasma removal efficiency, was significantly higher in cTPE procedures (84 ± 11% vs 27 ± 5%,$p<0.05$).



Conclusion: Although the centrifugal procedures were conducted using flow rates easily obtained by accessing peripheral veins, plasma removal efficiency was significantly higher and treatment time significantly lower in cTPE as compared to mTPE. Despite this lower treatment time the decline in markers of procedure efficacy was comparable. Especially in centres performing many procedures per year cTPE in contrast to mTPE can reduce treatment time without compromising treatment efficacy.

Parallel session

Friday 15th March

Young laboratory science investigator award abstracts

10:30 – 11:30

O74

Inhibition of thrombin activated fibrinolysis inhibitor (TAFI) using UK-396082 increases survival and halts the progression of renal fibrosis in established kidney disease in the 5/6th subtotal nephrectomy (SNx) model of chronic kidney disease (CKD)

John Atkinson[1], Nick Pullen[2], Tim Johnson[1]

[1]*University of Sheffield, Sheffield, UK*, [2]*Pfizer Pharmaceuticals, Boston, USA*

Objectives: TAFI modifies fibrin so it acts as a poor co-factor for tissue-type plasminogen activator (tPA), lowering plasmin activation. Previously we've reported that application of 500nM TAFI inhibitor UK-396082 in an *in vitro* model of diabetic nephropathy increases plasmin activity by 40%, with a subsequent reduction in ECM levels of 58% due to reductions in total collagen (-69%), laminin (-71.5%) and fibronectin (-66.7%). We therefore hypothesised that UK-396082 could have value as an anti-fibrotic therapy in the kidney. To test this, experimental CKD was induced using the 5/6th SNx model with both preventative and remission treatment arms receiving UK-396082 over 60 days.

Methodology: Rats were subjected to SNx and fed either normal rat chow (n=24) or rat chow containing 60mg/kg/day UK-396082 from either day 14 post SNx (prevention, n=12) or day 35 (remission, n=12). 12 SNx rats were terminated at day 35 to establish the degree of fibrosis when treatment was commenced in the remission arm.

Kidney function (Serum creatinine, creatinine clearance), the plasmin system (serum plasmin, TAFI, uPA, tPA) and urine biomarkers of kidney damage (Albumin, NGAL, KIM-1, TG2, TIMP-1) were assessed periodically. Kidney fibrosis (Masson's Trichrome, immunofluorescence for collagens I, III, IV, laminin and fibronectin) and the renal plasmin system activity (TAFI, plasmin, uPA, tPA) were assessed in terminal kidney samples.

Results: 16% of untreated SNx rats survived to day 60 compared to 80% treated from day 14. Of those animals alive at day 35, 27% of those untreated survived to day 60 compared to 75% receiving UK-396082 from day 35. Serum TAFI activity increased (+20%) and plasmin activity decreased (-19%) in untreated SNx animals. UK-396082 reduced serum TAFI activity (-45% / -30%, prevention / remission) and increased plasmin activity (+52% / +52%,). Improved kidney function was seen with serum creatinine lowered (-35% / -29%, prevention / remission), creatinine clearance increased (+35%, prevention), proteinuria minimised (-45% / -26%, prevention / remission), and serum urea reduced (-65% / -32%,) . Urine markers of kidney injury NGAL (-31% / -24%, prevention / remission) and KIM-1 (-68.3% / -31.3%, prevention / remission) were reduced. Kidney scarring was ameliorated with total collagen (Masson's Trichrome) down in tubules (-77%) and glomeruli (-45%) due to reductions in collagen I (-60% /, -52%, tubules / glomeruli), collagen IV (-57% / -52%, and collagen III (-55% / ±0%). Basement membrane ECM proteins fibronectin (-72% / -46%,) and laminin (-11% / -33%) were also lowered. The reduction in collagen was confirmed by total kidney hydroxyproline (-65%). UK-396082 was shown to have no effect on blood pressure.

Conclusions: UK-396082 is a highly effective anti-fibrotic therapy when applied in the SNx model of CKD, both as a preventative agent and in treating established CKD. UK-396082 did not affect hypertension in this model and thus likely to be additive of ACE and ARB therapy. The large reduction in collagen suggests that much of the benefit of UK-396082 is by protecting plasmin activation of matrix metalloproteinases as collagens are poor plasmin substrates, unlike fibronectin and laminin. However, the mechanism of action could also be through reducing laminin and fibronectin which form the scaffold for collagen assembly. These data support the hypothesis that TAFI inhibition is a potential therapeutic target in kidney scarring and fibrosis.

O75

The delayed administration of IKK16, a specific IKKβ inhibitor, attenuates acute kidney injury in a rat recovery model of unilateral renal ischaemia

Florence Johnson[1,2], Massimo Collino[3], Elisa Benetti[3], Magdi Yaqoob[1], Christoph Thiemermann[1], Nimesh Patel[1]

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Acute kidney injury (AKI) caused by ischaemia-reperfusion injury (IRI) is being increasingly regarded as a risk factor for chronic kidney disease (CKD). Activation of nuclear factor-κB (NF-κB) is known to play a key role in the production of various cytokines and chemokines, and seen to be a significant contributor to injury following IRI. NF-κB is a diverse family of transcription factors that can be activated by IκB kinase (IKK). We hypothesised that the specific inhibition of IKK with IKK16 will aid in the attenuation of renal, glomerular and tubular dysfunction. Forty-three male Wistar rats were anaesthetised with ketamine (100 mg/ml) and xylazine (20mg/ml) (2:1; 1.5ml/kg i.p.) and underwent a right nephrectomy, and unilateral renal ischaemia by clamping the left renal artery with non-traumatic vascular clips for 30min. The rats were randomised into five groups; sham (no clamping of renal artery) (n=11), control (n=11), 0.1mg/kg IKK16 (n=5), 0.3mg/kg IKK16 (n=7), 1mg/kg IKK16 (n=9). IKK16 was administered i.v. 24h after the onset of reperfusion. Twenty-four hours prior to termination of the experiment, rats were placed into metabolic cages for the collection of urine at 48h. The experiment was terminated 48h after the commencement of reperfusion for the collection of serum and urine. When compared to rats subjected to sham-operation, rats subjected to unilateral renal IRI (control) demonstrated a significant increase in serum creatinine, creatinine clearance and fractional excretion of sodium indicating the development of renal, glomerular and tubular dysfunction, respectively. The administration of IKK16 demonstrated a dose dependant attenuation of dysfunction, which was seen to be significant in all three parameters when administered at a dose of 1mg/kg 24h into reperfusion ($P<0.05$). We have shown here, for the first time that the late administration of an IKK inhibitor accelerates the rate of recovery of renal, glomerular and tubular dysfunction. The late inhibition of IKK may, therefore, have therapeutic potential in the recovery of AKI and the prevention of CKD. Further investigations are required to determine the exact role of IKK in the development of CKD.

O76

HPSE2, mutated in human urofacial syndrome (UFS), directs neuromuscular differentiation

Neil Roberts[1], Raphael Thuret[2], Helen Stuart[1], Edward McKenzie[2], William Newman[1], Emma Hilton[1], Adrian Woolf[1]

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Objective: Homozygous mutations in *HPSE2*, encoding heparanase-2, cause UFS, characterised by congenital bladder dysfunction, constipation, and inability to smile. We investigated the developmental roles of this gene in animal models to further clarify UFS pathogenesis.

Methods: *Xenopus tropicalis* transcripts (*xhpse2*) were measured by qPCR during development and heparanase-2 localised by immunohistochemistry. Single cell frog embryos were injected with either splice-variant or ATG morpholinos to knock down *xhpse2*. Neuronal and muscle development were analysed with antibodies to acetylated-tubulin and 12/101 respectively. In addition, heparanase-2 was immunolocalised in normal human and mouse development and we phenotyped renal tracts of newborn mice carrying homozygous *Hpse2* mutations.

Results: Frog embryos showed increased *xhpse2* soon after gastrulation, with expression maintained through organogenesis. Using either x*hspe2* morpholino caused a phenotype comprising a bent tail and proctodeal/cloacal protrusion. The latter was associated with absent gut looping; instead, the gut remained as an ovoid endodermal mass. A similar malformation has been reported after knockdown of *Foxf1*, a BMP4-activated transcription factor expressed in lateral plate mesoderm fated to form gut muscle. In wildtypes heparanase-2 localised in nascent skeletal and smooth muscle, and morphants had impaired muscularisation. Heparanase-2 was also expressed in the neural tube and hindbrain, and morphants showed compromised neural outgrowths from these structures. In normal fetal human and mice, heparanase-2 was immunolocalised in the neuromusculature of developing urinary bladders. Homozygous mutants uniformly showed grossly distended bladders at birth, similar to the megabladders which occur in human USF fetuses.

Conclusion: Heparanase-2 plays a key role in vertebrate neuromuscular development. Phenotypic defects in these models will provide targets for future experimental therapies for UFS.

O77

Targeting the vasculature to treat polycystic kidney disease

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Introduction: Polycystic kidney disease (PKD) is characterised by the growth of multiple fluid-filled cysts leading to a loss of normal kidney structure and function that may result in end-stage renal disease. Therapeutic strategies have focussed on inhibiting epithelial proliferation; but an alternative approach may be to target the underlying vasculature providing nutrients and energy to support cyst growth.

Methods: We investigated the renal blood and lymphatic vasculature in congenital polycystic kidney (*cpk*) mice; a model of autosomal recessive PKD (ARPKD) by real-time PCR and immunohistochemistry through different stages of disease progression. Furthermore, to determine the functional role of the renal vasculature in PKD, we treated animal models of ARPKD and autosomal dominant PKD (ADPKD, *Pkd1*-mutant) with a targeted vascular growth factor (patent application in progress) and assessed the effect on disease progression.

Results: Surrounding the smaller cortical cysts of *cpk* mice, the blood vasculature was more prominent than in wild-type littermates with intense CD31 staining; structurally, these vessels were dilated and disorganised. In larger medullary cysts, there was regression of the blood vasculature. This was accompanied by reduced kidney mRNA levels of endothelial markers *Vegfr1*, *Vegfr2*, *Tie1*, *Tie2* and *Pv1*. Using VEGFR-3 immunostaining, the lymphatic vasculature was more pronounced in *cpk* mice compared to wild-type littermates and mRNA levels of *LYVE-1* and *podoplanin* were upregulated. Treatment of *cpk* and *Pkd1*-mutant mice with a vascular growth factor during the exponential phase of cyst growth led to reduced kidney/body weight ratio of cystic mice compared to vehicle (30-40% reduction in both *cpk* and *Pkd1*-mutant mice, $n = 8$, $p < 0.05$). Renal function was improved and histology showed that treated mice had a better preservation of renal structure in the cortex compared to vehicle with less pronounced cysts.

Conclusion: The vasculature in PKD is disorganised with changes in the balance between blood and lymphatic vessels. Treatment targeting the renal vasculature may be a novel therapy for both ARPKD and ADPKD.

Parallel session

Friday 15th March

BTS science: immunology and tolerance

10:30 – 12:30

O78

Validation of a 10-gene signature of tolerance for clinical application in kidney transplant recipients

Irene Rebollo-Mesa[1], Paula Mobillo[1], Sonia Norris[1], Yogesh Kamra[2,1], Manohursingh Runglall[2], Rachel Hilton[3], ' GAMBIT consortium[5], ' Immune Tolerance Network[6], ' Indices of Tolerance Consortium[7], Graham Lord[2,1], Robert Lechler[4,1], Maria Hernandez-Fuentes[1,2]

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Introduction: Long-life immunosuppression is an important factor that contributes to shorten the long-term survival of kidney transplant recipients. Identifying patients in whom donor-specific tolerance has developed would constitute a major advance in their care. Since this ability would allow the minimization or even withdrawal of immunosuppressive therapy in selected patients. We and others have previously identified a unique set of genetic markers of transplantation tolerance using microarray in peripheral blood. The present study aims to translate these defined biomarkers of tolerance into clinically useful identities.

Methods: Platform transition from microarray expression to RT-PCR has been performed. Housekeeping gene was HPRT. Elastic net models were used for multivariate prediction of tolerance. At time point one there were 29 CAN, 177 Stable, and 12 Tolerant samples. At time point two 14 CAN, 150 Stable and 10 Tolerants. There were 134 patients with two samples. The average time between samples was 6.89 months (sd= 3.46).

Results: In the original cohort, 10 genes provided a sensitivity of .92 and specificity of .85 in the training set, and .81, and .80 in the test set. In the pesent cohort the 10 gene signature provided an AUC of 0.88, with a sensitivity of 0.75 and a specificity of 0.81. Using the algorithm estimated on time-point 1 to classify the time-point 2 samples, provided an AUC of .74, a sensitivity of .73, and specificity of 0.78. 78.35% of the samples were equally classified at both time-points. There were no statistically significant changes in the classification according to the algorithm between repeated samples (McNemar Chi-squared =0.034, p=0.852). 6 out of 9 tolerant patients were correctly classified twice, 1 was misclassified twice, and 2 appeared to loose the signature on the second sample. 9% of Stable patients were classified as tolerants, and 70% as non-tolerant in the two samples.

Discussion: Tolerant recipients can be identified using blood gene expression of 10 genes measured by RT-PCR with stable predictive accuracy. Validation for routine clinical use of these biomarkers would bring to the fore the possibility of personalized medicine.

O79

Expression of CD161 characterizes a subpopulation of human regulatory T cells that converts to Th17 in a STAT-3 dependent manner: implications for cell therapy

Behdad Afzali[1], Peter Mitchell[1], Francis Edozie[1], Sophie Dowson[1], James Canavan[1], Cristiano Scotta[1], Gina Walter[2,3], Bina Menon[2,3], Wafa Khamri[1], Shahram Kordasti[4], Prabhojat Chana[6], Susanne Heck[6], Bodo Grimbacher[7], Timothy Tree[3], Andrew Cope[5], Leonie Taams[2,3], Robert Lechler[1], Susan John[3], Giovanna Lombardi[1]

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Introduction: Cell-based therapy to induce transplant tolerance is now realistic. Suppressive $CD4^+CD25^{hi}CD127^{lo}$ "natural" regulatory T cells (Tregs) are prime candidates as cell products for clinical trials since they can be expanded from healthy blood *ex vivo* under good-manufacturing practice conditions without losing function. However, Treg lineage commitment is more plastic than originally thought, with Tregs retaining the capacity to express the phenotypic profile of pro-inflammatory Th17 cells. As Th17 cells are implicated in transplant rejection, such Treg plasticity represents a significant safety concern for programs of Treg-based cell therapy. Here, we set out to identify the human Treg sub-population that can undergo lineage reprogramming and to characterise its phenotypic features.

Methods: Healthy donor Tregs were isolated in the laboratory and studied *in vitro* using standard cell culture and molecular biology techniques and assays of function.

Results: "Whole" human Tregs converted to Th17 when activated in the presence of IL-1□, in a STAT3-dependent manner. Th17 plasticity occurred only in population III ($CD4^+CD25^{hi}CD127^{lo}CD45RA^-$) Tregs that expressed the NK marker CD161. At baseline, these cells were functionally as suppressive and had similar phenotypic/molecular characteristics to other sub-populations of Tregs, but had the potential to convert to Th17 when in the presence of an inflammatory signal. These plastic Tregs expressed less *Helios* than other Tregs and were absent in cord blood, suggesting their development in the periphery. They were found to accumulate at sites of inflammation, namely synovial fluid of patients with inflammatory arthritis.

Conclusion: Identifying plastic Tregs populations enables their exclusion from Treg-based cell products, e.g. by CD161 depletion. Identifying the mechanism(s) of Th17 conversion facilitates the design and/or use of drugs/small molecule inhibitors of Treg to Th17 conversion *in vivo*, particularly important if plastic Tregs are induced to develop from other Treg populations *in vivo*.

O80

Tolerance related gene expression in urine from kidney transplant patients

Mark Jenkins[1], Mano Runglall[1], Irene Rebollo-Mesa[1], Paula Mobillo[1], Yogesh Kamra[1,2], Estefania Nova-Lamperti[1,2], Sonia Norris[1], GAMBIT Consortium[3], Graham Lord[1,2], Robert Lechler[4], Maria Hernandez-Fuentes[1]

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Background: Long-term graft survival in renal transplantation relies on continuous immunosuppression with drugs that can cause high morbidity. Tolerance is an emerging clinically recognised event. A set of biomarkers has been previously defined in peripheral blood and is currently being validated within the GAMBIT study.

Aims: To test whether the proposed biomarkers of tolerance in kidney transplant recipients' blood are expressed in urine samples to allow a completely non-invasive diagnostic test.

Methods: Recruited groups include (HC) healthy controls (n=9); (TOL) recipients with stable kidney function that have stopped taking all immunosuppression (n=12); (STA) recipients with stable kidney function on standard immunosuppression (n=22) and (CR) recipients with immunologically driven chronic allograft nephropathy despite standard immunosuppression (n=5). RNA was extracted from urinary sediment and pre-amplified. Quantitative RT-PCR was performed with the housekeeping gene of reference HPRT and results were analysed using the Mann-Whitney U-test.

Results: Most of the previously reported tolerance-related overexpressed genes in blood were not observed in urine samples. Interestingly FOXP3 is overexpressed in TOL vs. HC ($p<0.001$) and TOL vs. transplanted patients ($p=0.057$), in parallel to what is observed in blood. Whereas H3ST1 was underexpressed in TOL vs. transplanted patients ($p<0.005$) and TOL vs. HC ($p<0.004$), the latter also in parallel to blood. An expression algorithm is being developed for a diagnostic test in urine. This test will complement the already available algorithm for blood.

Conclusions: Validation of the urine algorithms in addition to blood will provide an additional tool for the detection of biomarkers of tolerance. This will form the basis for a test for safe immunosuppression minimization or withdrawal.

O81

Germinal centre responses drive epitope diversification in an autoantibody-mediated model of heart allograft vasculopathy

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Introduction: Autoantibody following organ transplantation is increasingly correlated with poor graft outcome. We have reported that in a MHC class II mismatched mouse heart transplant model, GVH recognition by donor CD4 T cells is critical for development of humoral autoimmunity, but that the response is thereafter maintained by recipient CD4 T cells. Here we address the contribution of the recipient population on autoantibody production.

Methods: The role of donor and recipient CD4 T cells was investigated by transplanting bm12 heart grafts with/without CD4 T cells into either wild type (WT) or T cell deficient ($TCR^{-/-}$) B6 mice. Germinal centres (GCs) were identified on immunofluorescence staining of splenic sections as PNA and GL7 positive B cell follicles. Autoimmune responses were examined by Hep-2 analysis and anti-vimentin antibody ELISA. Chronic allograft vasculopathy (CAV) was assessed on EVG staining by quantifying degree of luminal stenosis.

Results: Transplantation of bm12 heart allografts into B6 provoked production of long-lasting autoantibody and 68±3% of the splenic B cell follicles differentiated into GCs at week 7. Autoantibody also developed following transplantation into $TCR^{-/-}$, but without GC differentiation (8±2%), unless the host CD4 T cells population was restored by adoptive transfer of B6 CD4 T cells (55±2%). Interestingly, late (after 10 weeks) anti-vimentin autoantibody developed in WT mice, but was only detectable in $TCR^{-/-}$ upon reconstitution with B6 CD4 T cells, suggesting that diversification of the humoral autoimmune response is dependent upon GC activity. Histological examination of grafts revealed significant CAV only in recipients that also developed GCs (bm12 to B6 76±3%, bm12 to $TCR^{-/-}$ with B6 CD4 T cells 72±9%;cf1±1% in bm12 to $TCR^{-/-}$). Finally, transplantation of CD4 T cell depleted bm12 hearts into B6 resulted in minimal CAV (12±8%) without autoantibody and GCs.

Conclusion: Donor and recipient CD4 T cells are essential for progression of allograft vasculopathy, most likely because of their cooperation to promote GC autoantibody responses. These diversify to target additional, and potentially damaging, graft-related autoantigens.

O82

Sildenafil enhances renal blood flow but does not protect against ischaemia reperfusion injury in a model of donation after circulatory death kidney transplantation

Lucy V Randle[1], Sarah A Hosgood[2], Meeta Patel[2], Christopher J Watson[1], J Andrew Bradley[1], Michael L Nicholson[2]

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Introduction: Sildenafil has been used as a pre-conditioning agent to protect against ischaemic injury, although there is little evidence for its benefit in reducing ischaemia reperfusion (I/R) injury in renal transplantation. The aim of this study was to assess the effects of sildenafil on I/R injury in a porcine model of donation after circulatory death (DCD) kidneys.

Methods: Kidneys were subjected to 20 minutes warm ischaemia followed by 18 hours cold storage. After preservation kidneys were reperfused on an *ex vivo* perfusion system for 3 hours with an oxygenated blood based solution. Kidneys were treated with 0.2mg (n=4), 0.7mg (n=4) or 1.4mg (n=6) or no (control, n=6) sildenafil during reperfusion. Renal function and renal injury markers were measured throughout reperfusion.

Results: Renal blood flow was increased in a dose dependent manner with a significantly higher flow in the 1.4mg treated kidneys compared to the controls [mean area under curve (AUC), (1.4mg) 482±99, (0.7mg) 469±123, (0.2mg) 387±115, (Control) 360 ± 47ml/min/100g; P=0.021]. There was no significant improvement in renal function [AUC creatinine clearance; (1.4mg) 2.9±0.8, (0.7mg) 2.5±0.6, (0.2mg) 3.0±2, (control) 4.5±2.0ml/min/100g; P =0.099], tubular injury [neutrophil gelatinase-associated lipocalin (NGAL); P = 0.060], levels of inflammatory cytokines (IL-6; P=0.357, TNFα; P=0.340) or neutrophil infiltration (P=0.106) between the groups.

Conclusion: Sildenafil had a vasodilatory action but did not affect recovery of renal function or protect against I/R injury. This suggests that sildenafil is not renal protective during the early reperfusion phase in an *ex vivo* DCD model.

O83

Identification of molecular biomarkers of chronic lung allograft rejection

Isaiah Tega James Atugba, Chris Ward, John A Kirby, Simi Ali

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Background: Transplantation is the only potentially curative treatment for end-stage respiratory disease. Chronic allograft rejection however, results in the progressive and irreversible reduction of airway function termed Bronchiolitis Obliterans Syndrome. The aim of this work was to analyse the expression of a panel of genes implicated in chronic allograft rejection by PCR array.

Methods: Lung epithelial cell line (A549), patient derived primary bronchial epithelial cells (PBECs) and frozen post transplantation Broncho Alveolar Lavage (BAL) samples were used. Immunofluorescence on H_2O_2 treated A549 cells was performed to identify mesenchymal markers. A549 and PBECs were also treated with IFN-γ, RNA extracted and cDNA synthesis performed. We have used a custom array synthesised with 48 candidate genes likely to be associated with interstitial fibrosis, cytokines/chemokine expression and chronic inflammation. Changes in gene expression were calculated using the integrated web based software.

Results: Oxidative stress of A549 cells induced Epithelial to Mesenchymal Transition (EMT) and this was evidenced by a significant reduction of epithelial cell proteins, Cytokeratin 7 and E-cadherin ($p<0.05$), and an increase in mesenchymal proteins, S100A4 and Vimentin, with treatment time ($p<0.05$). IFN-γ stimulated, A549 and PBECs had significant increase in expression of chemokines (CXCL6 and CCL2), cytokines (IL-6, IL-8), Indoleamine 2,3-dioxygenase (immunoregulatory enzyme), and BMP7 an EMT mediator. Furthermore, patient BAL samples had significant upregulation ($p<0.01$) of Heparanase, Versican and IL-8 which are documented to be associated with chronic allograft rejection.

Conclusion: These results suggest that A549 cells are a satisfactory model for chronic lung allograft research and the feasibility of using BAL samples for microarray analysis. Thus further research using Biobank patient BAL samples could be used to validate these biomarkers of chronic lung rejection.

Parallel session

Friday 15th March

Controversies in transplantation

10:30 – 12:30

O84

New onset diabetes after transplantation: clinical and genetic risk factors

Jennifer McCaughan[1,2], Amy Jayne McKnight[1], A. Peter Maxwell[1,2]

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As short term graft survival has improved, novel challenges have emerged in kidney transplantation. New onset diabetes after transplantation (NODAT) is a common complication and is associated with reduced recipient survival. The pathophysiology of NODAT is incompletely understood but immunosuppression appears to contribute to this process. The aim of this study was to identify clinical and genetic factors to predict recipients at risk of developing NODAT.

Methods:

- All adult recipients who received a first deceased donor kidney transplant in Belfast between 1986 and 2005 were included.
- NODAT was defined as a new requirement for hypoglycaemic agents post transplantation.
- Clinical data has been collected prospectively on all recipients.
- Top ranked SNPs associated with NODAT were identified by GWAS.

Results:

- The incidence of NODAT was 12.3%.
- In proportional hazards regression, NODAT was associated with age (HR 1.40, p=0.003), weight at transplant (HR 1.03, p=0.008), percentage weight gain in first year (HR 1.03, p=0.006) and female gender (HR 2.2, P=0.02).
- 27 SNPs were associated with NODAT ($p<10^{-5}$). Genotype success >99%.
- Top hits were in candidate genes implicated in mitochondrial function, beta cell apoptosis, insulin sensitivity and cell signalling.

Discussion: NODAT is associated with cardiovascular disease and mortality in kidney transplant recipients. Clinical factors allow identification of individuals at risk of NODAT. The top ranked SNPs in this population were in biologically plausible genes, particularly implicated in mitochondrial pathways. This correlates with animal models where immunosuppression-induced diabetes is associated with reduced mitochondrial numbers and impaired mitochondrial function.

O85

Length of stay and hospital admission rates in patients receiving kidney transplants in English centres using linked registry and hospitalisation data

James Fotheringham[2,1], Meguid El Nahas[2], Michael Campbell[1], William McKane[2]

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Introduction: Previous UK transplant outcome studies have been limited to graft and patient survival. Admission rates are reported in other countries but adjusted, centre-specific rates and location of hospitalisation have not been explored.

Methods: Initial length of stay (LoS) and admission rate in the first year (censored for death) were determined in recipients of first transplants (T1) who started renal replacement therapy between 2002 and 2006, using UK Renal Registry data linked with Hospital Episode Statistics (HES). Comorbidity was determined from HES diagnosis coding prior to transplant. Delayed graft function (DGF) was defined as HES coded dialysis after T1. Standardised admission rate and LoS ratios were determined using observed/expected counts predicted using linear and negative binomial regression respectively.

Results: 4,517 T1 were identified in both sources in 20 transplant centres (TxC). Median LoS was 10 days and median admission rate was 1/year with 32% having none. 74% of admissions were to the TxC (centre-specific range 31 – 92%). Age > 50 years, dialysis vintage > 1 year, diabetes, non-transplanting parent centre were each associated with an additional one admission and one extra day in hospital at T1 ($P<0.001$). Deceased donor status and each additional comorbid condition increased LoS by 1 day ($P<0.001$) but had no effect of admission rate. Longer LoS was associated with greater 30-day admission rate (LoS < 8: 25% admitted, LoS 8 – 14: 30% admitted, LoS > 14: 38% admitted, $P<0.001$). DGF was associated with higher admission rates and longer LoS (median admissions 2 vs 1, median LoS 15 vs 10 days, $P<0.001$). Following adjustment for the above factors the number of TxC with higher than expected admission rates decreased from 5 to 2, but one centre with higher than expected LoS persisted. Location of admissions (TxC vs non-TxC) did not influence admission rate or days in hospital.

Conclusions: Patient demography and comorbidity heavily influence admission rates and LoS at T1, but despite adjustment variation in TxC specific rates exist. Understanding matching, sensitisation and rejection may further reduce variation.

O86

Risk of post transplant cancer: does cytomegalovirus play a role?

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NHS Blood and Transplant, Bristol, UK

The role of Cytomegalovirus (CMV) in development of post-transplant de novo cancer is not established. Some previous studies have suggested that CMV exposure is associated with an increased overall risk of cancer and in contrast, one study showed higher incidence of cancer among CMV-naïve recipients. Here we report the data from a large national registry assessing the impact of CMV exposure on incidence of post transplant cancer.

The data from the National Transplant Registry were linked with the data from the Office for National Statistics to identify all cases of post-transplant cancer (except non-melanoma skin cancer) in recipients of first organ transplant (1980-2007, restricting to those with known CMV sero-status). The recipients were divided into three groups based on CMV IgG sero-status: CMV exposure before transplant, exposure at transplant from CMV positive donor and CMV-naïve. Kaplan-Meier estimate, log rank test and Cox regression were used for analysis.

A total of 22464 recipients were studied including 13218(59%) kidney, 4814(21%) liver, 2686(12%) heart and 1746(8%) lung recipients. Of these, 12423(55%) were CMV-exposed prior to transplant(group 1), 4520(20%) received a CMV positive graft(group 2) and 5521(25%) were not exposed to CMV(group 3). The unadjusted incidence rates of cancer at 10 years after transplant in groups 1, 2 and 3 were 8.9% (95%CI 8.3, 9.5), 7.0% (6.0, 7.9) and 6.4% (5.5, 7.2) respectively ($p<0.001$), however the age-gender adjusted hazard of cancer was not significantly different in the three groups (hazard ratio compared to group 1): group 2, 1.0(0.8, 1.1) and group 3, 0.96(0.8, 1.1), $p=0.84$. Cox regression analysis showed no significant difference, for the risk-adjusted hazard of developing any of the 21 types of cancers including cancer of anus, bladder, breast, cervix, colon, Kaposi's sarcoma, kidney, lip, liver, leukaemia, lung, lymphoma, myeloma, oesophagus, oral cavity, ovary, pancreas, melanoma, stomach, thyroid or uterus.

From this large national data, we conclude that exposure to CMV before or at the time of transplant does not affect the incidence of post-transplant cancer.

O87

Transplant tourism – a single-centre experience

Philip J Whatling, Si Huei Tan, Sophie Collier, Gareth Jones

Royal Free Hospital, London, UK

Background: A low availability of donor kidneys in the UK may prompt patients to seek renal transplantation abroad. Frequently these patients return to the UK for ongoing care, and unfortunately the details of transplantation remain obscure for the receiving clinician. We report the rate of complications and the adequacy of documentation for this cohort of patients.

Methods: A retrospective case series study at a single centre between 1 Jan 2006 and 31st November 2012 on patients who had received renal transplant abroad.

Results: 22 patients who sought renal transplantation abroad were identified. 2 patients were lost to follow-up, and there was 1 death that was unrelated to transplantation. There was no allograft loss as of November 2012. 8 patients returned with multi-drug resistant bacterial infections and 4 contracted Hepatitis C around the time of transplant. Surgical complications included ureteric complications (2), renal artery stenosis (1), lymphocoele (2), and wound infection (2). Only 23% patients returned to UK with adequate documentation regarding their transplant. 50% returned to UK with no documentation regarding the utilization of a transplant ureteric stent.

Conclusions: The number of patients seeking transplantation abroad remains relatively small. We report a high proportion of infectious complications arising from transplantation abroad. Furthermore this cohort of patients often returns back to the UK for post-transplant follow-up with little information pertaining to their transplant. Patients considering transplantation abroad should be counselled on the heightened risks of infectious complications. They should also be advised to obtain the details of their transplant to facilitate their long-term care in the UK.

O88

Live donor kidney transplantation from overseas donors: a single centre experience

Alison Richardson, Bethan Hood, Catherine O'Malley, David Curran, Bimbi Fernando, Gareth Jones

UCL Centre for Nephrology, London, UK

Background: Live donor kidney transplantation provides the optimal treatment of choice for patients with kidney failure but can be problematic when potential living donors reside overseas. In our unit, the increasing ethnicity of potential transplant recipients has lead to a greater reliance on overseas donors. We describe our experience of evaluating overseas donors over a 5 year period.

Methods: A retrospective analysis of overseas donors referred to our centre between 2007 and 2012. Referred donors underwent a medical examination and minimal donor investigations in their own country. Suitable donors were virtually cross matched with their potential recipient before visa applications were made.

Results: A total of 87 overseas donors were referred by 69 potential recipients. 74% of potential donors lived outside of Europe with a third originating from Africa. 38 donors were ruled out prior to assessment in the UK (8 on medical grounds, 13 incompatible donor, 4 recipient received other transplant, 13 donor unable to obtain visa). Of the 49 donors assessed in the UK, 13 were ruled out on medical grounds, 2 absconded into the UK, 3 are awaiting donation and 31 have donated. During evaluation, 12% were found to have exposure to Hepatitis B, 10% had active or prior syphilis and 4% had asymptomatic malaria infection. The median time for donor evaluation was 27.5 days (range 1 – 371); some donors returned home during evaluation, 4 donors required renal biopsies, one donor required open heart surgery prior to donation to repair an atrial septal defect discovered during work up and one donor required evaluation of intracranial bullets prior to donation. 31 donors gave their kidneys after a median time of 69 days (range 7 – 547) from initiation of work up. All 31 transplanted kidneys had primary function. Only 26% of donors received over 4 weeks of post donation follow up.

Conclusions: Overseas donors provide an excellent source of kidneys for transplantation to recipients in the UK but require careful donor evaluation and meticulous investigation for transmissible infections and undiagnosed medical conditions. Long term donor follow up and visa availability remain a concern.

O89

Effectiveness of peer education outreach for increasing the numbers of black and minority ethnic people (BAME) who register as organ donors

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Introduction: Black & minority ethnic (BME) communities are disproportionately affected by inequalities in transplant services in the UK. They are at greater risk of developing organ failure, less likely to be organ donors & wait longer for transplants (Randhawa, 2011). The aim is to describe the model that was adopted by our team to increase awareness & improve the numbers of BME people registering onto the NHS Organ Donor Register (ODR).

Methods: Peer Educators (PE): lay people from these targeted communities who are enthusiastic to promote the issue & the ODR, have a natural empathy in terms of culture & religion – were supported & trained with an accredited course in organ donation. PE's were drawn from a range of BME communities in London. The PE project took 2 forms: in the larger settings at social, cultural, & religious events, with a stand; usually in smaller settings, presentations were given. At both, the PEs provided relevant information & attempted to address misconceptions about donation whilst at the same time encouraging members of BME communities to register on the ODR. The team have developed a quiz which they use as an 'ice-breaker' and as a way of opening up a discussion about organ donation.

Results: Highly motivated PE's held >100 events, engaging with gatekeepers. The PEs grew in confidence in addressing sensitive issues. From our project's unique identifier code, NHS BT report 1304 responses & 867 new registrations: a higher than usual proportion of new registrants. An independent evaluation showed 9% of people who had not already signed up did so on the day increasing the overall proportions of those signed up from 13.7% to 20.9%.

Discussion: This programme has resulted in significant numbers of individuals from BME groups signing the ODR. It has stimulated thought & reflection & thus raised awareness in these groups as a whole. The relevance is that the findings strongly indicate that this approach is highly 'fit for purpose' as it increases numbers from BME communities registering as organ donors. The evaluation argued it is critical that PEs continue to attend these types of local and national events, & to do so in greater numbers.

Parallel session

Friday 15th March

Donor and organ management

10:30 – 12:30

O90

Time zero biopsy analysis of pre-existing donor kidney disease in predicting outcomes following deceased donor kidney transplantation

Vasilis Kosmoliaptsis[1], Mark J Salji[1], Vicky Bardsley[2], M Finlay[2], Hannah C Copley[1], M Griffiths[2], J Andrew Bradley[1], Gavin J Pettigrew[1]

[1]Dept of Surgery, University of Cambridge, Cambridge, UK, [2]Dept of Pathology, University of Cambridge, Cambridge, UK

Background: Increasing numbers of Donation after Circulatory Death (DCD) kidneys are retrieved from Expanded Criteria (EC) donors, but uncertainties persist regarding how best to assess suitability for transplantation. We examined the impact of pre-existing donor kidney disease on outcomes following DCD and Donation after Brain Death (DBD) kidney transplantation.

Methods: All consecutive, deceased donor, single kidney transplants performed in our centre between 06/2006 and 08/2010 (n=313) were studied. Implantation biopsies were scored for glomerular, tubular, parenchymal and vascular disease (global histology score; 0-12 as per Remuzzi et al; NEJM 2006). Predictors of patient and graft survival [mean (SD) follow up: 3.5 (1.2) yrs] and renal function (estimated Glomerular Filtration Rate, eGFR) were examined.

Results: There was no difference in graft survival and 1-year eGFR between DCD [n=213, median (range) donor age: 54 (14-78) yrs] and DBD [n=100, median (range) donor age: 50 (5-82) yrs] kidneys, although the incidence of delayed graft function was higher in the former (61% vs 44% respectively, p=0.04). Although procurement from EC donors (n=111) had no impact on outcomes, survival of kidneys with global histology scores of ≥5 was significantly poorer than those that scored less (HR: 3.8. CI: 1.1-13.3, p=0.0009), with multivariate analysis confirming only cold ischaemic time over 12 hours and global histology score as independent predictors of graft survival. High histology scores conferred the same survival disadvantage for DCD and DBD kidneys, even those procured from EC donors. Recipient age ≥65 years was the sole predictor of patient survival (HR: 4.5, CI: 1.4-17.1, p=0.0001) and multivariate analysis revealed donor age as the only predictor of eGFR at 1 year (-0.27ml/min/1.73 m^2 per year age increase, p=0.015).

Conclusion: Donor baseline kidney disease and donor age influence outcomes following deceased donor kidney transplantation but their effect is not greater for DCD kidneys. Pre-implantation biopsy analysis may aid evaluation and use of DCD and DBD kidneys from EC donors.

O91

Changing profile of organ donor and its impact on the risk of cancer transmission

Rajeev Desai[1], Dave Collett[1], Christopher Watson[2], Philip Johnson[3], Tim Evans[3], James Neuberger[1]

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Donor origin cancer (DOC) in transplant recipients may be transmitted with the graft (donor-transmitted cancer [DTC]) or develop subsequently from the graft (donor-derived cancer [DDC]). Recipients with DOC between January 1, 2001, and December 31, 2010, were identified from the National Transplant Registry and database search at transplantation centres.

Of 30,765 transplants from 14,986 donors, 18 recipients developed DOC from 16 donors (0.06%): 3 were DDC (0.01%) and 15 were DTC (0.05%). Of the 15 DTCs, 6 were renal cell cancer; 5, lung cancer; 2, lymphoma; 1, neuroendocrine cancer; and 1, colon cancer. Recipients with DTC underwent explant/excision (11), chemotherapy (4), and radiotherapy (1). Of 15 recipients, 3 (20%) recipients with DTC died as a direct consequence of cancer. Early DTC (diagnosed ≤6 weeks of transplantation) showed a better outcome (no DTC-related deaths in 11 cases) as opposed to late DTC (DTC-related deaths in 3 of 4 cases). Five-year survival was 83% for kidney recipients with DTC compared with 93% for recipients without DTC (p=0.08). None of the donors resulting in cancer transmission was known to have cancer at donation. The risk of cancer transmission was significantly associated with donor age ≥45 years (OR 9, 95%CI 1·2, 69·6). Donors after circulatory death had a higher risk of cancer transmission than Donors after brain death but this difference was not statistically significant (OR 1·9 for DCD, 95%CI 0·6, 6·5).

DTC is rare but frequently results in graft loss and death. The risk of cancer transmission cannot be eliminated because, in every case, the presence of cancer was not known at donation. As the donor age is increasing, the risk of cancer transmission is likely to increase. This information will allow informed consent for prospective recipients. Explantation/excision is likely to benefit recipients with localized cancer, but in non-renal transplants, the benefits should be balanced against the risks of re-transplantation.

O92

Older DCD kidneys for older recipients: is this the way forward to manage the growing number of older people on the waiting list?

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Introduction: Controlled DCD kidneys represent a valuable source of kidney transplants and in UK represent up to 30% cadaveric kidney transplants. The proportion of DCD donors among deceased transplants has increased from 8% to 40 % with a striking increase in the mean age of DCD by 10 years to 53 years. Older recipients over the age of 65 years represent more than 25% of the total transplant waiting list in our centre. On the basis of that we expanded significantly the acceptance criteria for DCD kidney donors so they now represent 60% of our cadaveric program and 40% of our overall program.

Aim and methods: The aim of this study is to present the updated results of the program of transplanting older donor (>60 years old) DCD kidneys to older (>60 years old) recipients to see if it is an appropriate use of these extra resource of organs.

Results: Over a period of 30 months 145 renal transplants from DCD donors were performed, 94 of them from donors over 60 (67%) and 62 of those kidneys (43% of the total) were transplanted to recipients over 60 years. Median age of those donors was 69 (range 61-80) years (with 30 of those donors over 65), whereas the median recipient age was 68 (range 60-80) years. Median follow up was 14 months. Delayed graft function (DGF; defined as need for dialysis in the first week) was seen in 44 patients (71% and it lasted a mean of 7.5 and a median of 3 days. Median length of stay was 13 days. There was 1 case of PNF (1.5%), 4 cases of graft failure, (at 1mo, 3 mo, 6 mo, 1 year) and 3 deaths (2 in the 1st year) giving a 1-year mortality of 3.2% and an uncensored 1-year graft survival of 89%. The median GFR at 1,6 and 12 months was 34,37 and 37 respectively.

Conclusion: Older DCD donors represent an excellent source of transplanted kidneys. They have a low PNF and an adequate eGFR when transplanted to older recipients. It also gives them a survival far outweighing that on dialysis. Our preliminary results support the use of those 'marginal' kidneys to this recipient group.

O93

National prospective multi-centre study of decline of kidney offers for paediatric renal transplant recipients

Jodie H Frost[1], E. Jane Tizard[2], Lisa Mumford[3], Stephen D Marks[1]

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Introduction: Paediatric renal transplant recipients (PRTR) often have complex anatomy and/or history and require optimal donor organs as may require retransplantation. This prospective study looks at the reason for all declined offers across the United Kingdom.

Method: Prospective study of UK Transplant declined offers for DBD (donation after brain death) kidney donors to all ten paediatric renal transplant centres from 1 January 2011 to 31 December 2011. All centres submitted a supplementary form for all declined offers. Primary and secondary reasons for declined offers were recorded as well as additional reasoning. Eventual outcome of the declined graft was recorded as well as donor and recipient age, weight and height for those grafts transplanted. Cost analysis was undertaken with regard to the difference of current renal replacement therapy for those patients with declined offers.

Results: In total, there was 100% return rate of data on 62 offers for individual paediatric patients from 51 donors (102 potential kidneys) which were declined. Nationally, 46% of all offers were declined although across individual centres this ranged from 22% to 75%. The commonest primary reason was donor size in 11% (7) cases with donor medical history 6% (4); the supplementary data correlated with the data on the UK Transplant Registry in 84% of cases. 77% (79) kidneys went on to be successfully transplanted with 20% (16 of 79) allocated to other paediatric patients. Cost analysis showed a potential annual difference of £309,256 spent on haemodialysis for potential recipients whose organ offers were declined and £78,224 for peritoneal dialysis annually.

Conclusions: Our study suggests that organ allocation in the paediatric population continues to have a degree of variability across centres in the UK. Acceptance of renal allografts and the reason for declined offers should have a more robust and evidence based practice. This is especially important where donor size is used as the reason with the potential of living donors being excluded for those patients (especially the youngest donors who may be on dialysis).

Parallel session

Friday 15th March

Free communications: peritoneal dialysis

10:30 – 12:30

O94

Encapsulating peritoneal sclerosis in children on chronic PD – a survey from the European paediatric dialysis working group

Rukshana Shroff[1], Constantinos J. Stefanidis[2], Alberto Edefonti[3], Mesiha Ekim[4], Gema Ariceta[5], Sevcan Bakkaloglu[6], Michel Fischbach[7], Günter Klaus[8], Aleksandra Zurowska[9], Claus Peter Schmitt[10], Alan Watson[11]

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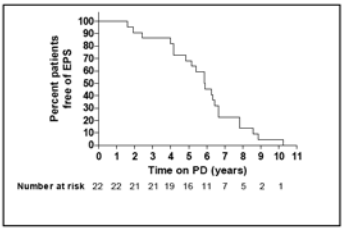
Background: Encapsulating Peritoneal Sclerosis (EPS) is a rare complication of peritoneal dialysis (PD) that is associated with significant morbidity and mortality in adults. There are scarce data for children. We performed a 10-year survey to determine the prevalence, risk factors and outcome for EPS in children.

Methods: Chronic PD patients in 14 dialysis units participating in the European Pediatric Dialysis Working Group between January 2001 and December 2010.

Results: Twenty-two cases of EPS were reported (prevalence 1.5%; 8.7 per 1000 patient-years on PD). Median PD vintage was 5.9 (1.6–10.2) in EPS and 1.7 (0.7–7.7] years in the remainder of the PD population (p<0.0001). EPS patients had 4.8 (0–10) peritonitis episodes. EPS was diagnosed while the child was on PD in 17 (77%), after conversion to hemodialysis in 3, and after transplantation in 2. 15/17 (88%) developed ultrafiltration failure. The median interval between UF failure and presentation with bowel obstruction was 2.8 (0.02–5.8) months. Twenty (91%) had clinical and radiological signs of bowel obstruction. Enterolysis was performed in 14 and 19 received immunosuppression or tamoxifen. Nine required parenteral nutrition. At final follow-up 4.8 (1.3–8.7) years after EPS diagnosis, 3 patients have died, 11 have a functioning transplant and 8 are on hemodialysis.



Conclusions: The prevalence of EPS in European children on PD is comparable to that of adult PD patients, but mortality from paediatric EPS is significantly lower. A high index of suspicion is required for the diagnosis of EPS in children with a longer dialysis duration, high peritonitis rate and ultrafiltration failure.

O95

A random glucose in non-diabetic prevalent peritoneal dialysis patients is strongly predictive of death: results from the GLOBAL fluid study

Mark Lambie[1], James Chess[2], Paul Williams[3], Andrew Williams[2], Yong-Lim Kim[4], Sara Davison[5], Nick Topley[6], Simon J. Davies[1]

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Background: Glucose control is a significant predictor of death in diabetic patients. In peritoneal dialysis (PD), the local toxic effects of peritoneal glucose are well recognized, but despite large amounts being absorbed, the systemic effects are not clear.

Methods: The Global Fluid Study is a multi-national multicentre prospective incident and prevalent PD patient cohort study with up to 9.5 years follow-up. Data included demography, comorbidity, modality, prescription, membrane function; Dialysate and Plasma IL-1β, TNF-α, IFN-γ and IL-6 measured by electrochemiluminescence and locally measured random plasma glucose levels. A Kaplan-Meier plot with log rank test was used for univariable survival analysis of glucose levels, and a Cox model stratified by centre with robust standard errors for clustering was used for an adjusted analysis. Multivariable multilevel analysis was used to determine predictors of random glucose levels.

Results: On univariable analysis, higher glucose levels significantly predicted worse survival in non-diabetic prevalent PD patients (log rank test $p<0.0005$). Survival analysis adjusted for age, plasma IL-6, comorbidity, peritoneal solute transport rate, albumin, duration of PD and residual renal function, demonstrated random glucose levels to be highly significant predictors of death in non-diabetic prevalent PD patients, (HR 1.50 (1.11-2.03) for levels 6-10, HR 1.57 (0.74-3.36) for levels >10 compared with levels <6, $p=0.03$ overall), but not in incident patients. On multivariate analysis random glucose levels were significantly associated with only daily dialysate glucose (0.018mmol/l increase per 1 litre 1.5% equivalent, $p=0.001$) and serum albumin levels (0.014mmol/l decrease for 1g/l increase, $p<0.0001$). Peritoneal Solute transport was positively associated until albumin was included.

Conclusions: Random glucose levels are strongly predictive of survival in non-diabetic prevalent PD patients, and these levels are partly determined by dialysate glucose.

O96

Intra-peritoneal versus systemic inflammation and survival during peritoneal dialysis: results from the GLOBAL fluid study

Mark Lambie[1], James Chess[2], John Bankart[1], Hi-Bahl Lee[3], Hunjin Noh[3], Jun-Young Do[4], Marc Dorval[5], Nick Topley[6], Simon J. Davies[1]

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Introduction: Systemic inflammation, as evidenced by circulating inflammatory cytokines such as IL-6 predicts worse survival in Dialysis patients. Intraperitoneal IL-6 is an established determinant of peritoneal solute transport rate in Peritoneal Dialysis (PD) patients, which has also been linked to patient survival. We sought to determine the link between systemic and local intraperitoneal inflammation and establish their independent effects on patient survival.

Methods: The Global Fluid Study is a multi-national multicentre prospective incident and prevalent cohort study with up to 9.5 years follow-up. Data included demography, comorbidity, modality, prescription, membrane function, and Dialysate and Plasma IL-1β, TNF-α, IFN-γ and IL-6 measured by electrochemiluminescence. Unadjusted and adjusted Cox models stratified by centre with robust standard errors for clustering were used for survival analysis of Dialysate and Plasma cytokines. Proportional hazards were checked.

Results: 426 survival endpoints occurred in 559 incident and 358 prevalent patients from 10 centres in Korea, Canada and the UK. On univariable analysis, increased Plasma IL-6 and TNF-α and Dialysate IL-6 were significantly associated with worse survival in incident and prevalent groups (with a trend to significance for Dialysate IFN-γ). After adjustment for age, gender, residual renal function, peritoneal solute transport rate, comorbidity, BMI, duration of PD and albumin, both plasma IL-6 and TNF-α in incident and plasma IL-6 in prevalent groups, but not dialysate IL-6, remained independent predictors of patient survival.

Discussion: This is the first study to demonstrate that local intra-peritoneal inflammation does not affect patient survival unless it contributes to systemic inflammation. Plasma TNF-α provides additional predictive information over Plasma IL-6 in incident PD patients.

O97

A national multi-site audit of peritoneal dialysis access in the United Kingdom - initial results and observations

Victoria Briggs[1], David Pitcher[2], Fiona Braddon[2], Damian Fogarty[2], Martin Wilkie[1]

[1]*Sheffield Kidney Institute, Sheffield, UK,* [2]*UK Renal Registry (UKRR), Bristol, UK*

Introduction: Peritoneal dialysis (PD) is the renal replacement therapy of choice for 1 in 5 dialysis patients in the United Kingdom (UK). Clinically successful PD requires sustained catheter functionality without complication. Despite such requirements, until recently, no formal data collection process relating to PD catheter survival or complications has existed in the UK. To address this, a multi-site audit in collaboration with the UK Renal Registry (UKRR) has recently been initiated to gather such information. Selected data is presented here.

Methodology: Funding was acquired from the Healthcare Quality Improvement Partnership (HQIP). All adult UK renal units were approached for vascular and peritoneal access data relating to all new dialysis patients initiated on therapy during 2011. Existing UKRR tables were refined by initial audit information sourced from the Yorkshire and the Humber (Y&H) region during a 2010 pilot phase. Refined data fields were collected by spread sheet circulated by the UKRR.

Results: 43 of 65 centres (66%) submitted data relating to first PD catheter insertions during 2011. Of 917 catheters, 39% were females, 61% male; 1 patient (younger than 16 years upon PD initiation) was excluded. Insertion technique was reported in 793 patients (86%) with open surgical technique used in the majority (52%). PD catheter functionality was retained at 3 months for 75% of patients. Early peritonitis, catheter flow complications and failures were more common in percutaneously placed catheters. Diabetics did not have higher rates of catheter failure or early peritonitis. Importantly, PD utilisation was less common in higher deprivation areas when compared to haemodialysis.

Conclusions: These data highlight patterns that may aid quality improvement in UK PD service delivery. Such information demonstrates the value of prospective data collection.

Parallel session

Friday 15th March

Hot topic science session

13:30 – 15:00

O98

Identifying mechanisms that promote injury and repair in diabetic kidney disease using a novel rodent model

Boris Betz, Tara Sheldrake, Jonathan Manning, Donald Dunbar, Jeremy Hughes, John Mullins, Bryan Conway

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Introduction: In patients with moderately advanced diabetic nephropathy (DN) regression of fibrosis has been observed with prolonged normoglycaemia after pancreas transplantation, however the underlying mechanisms remain obscure.

Methods: In the Cyp1a1mRen2 rat model of DN, we induced diabetes with streptozotocin and hypertension by inducing the murine renin transgene with dietary indole-3-carbinol (I-3-C). After 28wks of diabetes and hypertension, an 'injury cohort' (n=10) was culled and in the remaining rats the blood glucose was tightly controlled with insulin implants and the BP was normalised by removing I-3-C from the diet for a further 8wks (reversal cohort, n=9). The gene pathways activated in the kidney during and following reversal of injury were compared alongside a group of non-diabetic, normotensive control rats by microarray.

Results: 28wks of diabetes and hypertension resulted in marked albuminuria, which declined rapidly following reversal. Compared with controls, in the injury cohort there was significant glomerulosclerosis and tubulointerstitial fibrosis, which persisted in the reversal cohort. 84 'injury' genes were up-regulated in the renal cortex of the injury cohort, but reverted to control levels following reversal, including multiple myofibroblast and extracellular matrix (ECM) genes. 317 'repair' genes remained persistently elevated during reversal, including multiple macrophage and T-cell markers, Wnt pathway and metalloproteinase (MMP) genes. Conversely, MMP activity was *reduced* in kidney lysates from both the injury and reversal cohorts in association with a persistent increase in expression of tissue inhibitor of metalloproteinase-1 (TIMP-1) protein. Physical separation of MMPs and TIMP-1 by gel zymography restored MMP activity.

Conclusion: In a rodent model of DN, tight blood glucose and BP control is sufficient to switch off excess ECM production. Several ECM-degrading pathways are persistently activated in the diabetic kidney, however regression of fibrosis is slow due to the presence of TIMPs, therefore neutralising the effect of TIMPS represents an attractive therapeutic strategy to accelerate resolution of fibrosis.

O99

11β-hydroxysteroid dehydrogenase type 1 null mice are protected from insulin resistance in chronic kidney disease

Ananda Chapagain[1], Paul Caton[1], Julius Kieswich[1], Petros Andrikopoulos[1], Steven Harwood[1], Martin Raftery[1], Jonathon Seckl[0,2], Roger Corder[1], Magdi Yaqoob[1]

[1]*Queen Mary, University of London, London, UK,* [2]*Queen's Medical Research Institute, Edinburgh, UK*

Background: Insulin resistance and its metabolic sequelae are common in chronic kidney disease (CKD) but the pathogenesis is unclear. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) catalyses intra-cellular regeneration of active glucocorticoids, promoting insulin resistance in liver and other metabolic tissues. Previously, using two experimental rat models of CKD (subtotal nephrectomy, adenine-diet) that show early insulin resistance, we found upregulation of 11β-HSD1 activity and mRNA in liver, associated with intrahepatic but not circulating glucocorticoid excess, and increased hepatic gluconeogenesis and lipogenesis. The non-specific 11β-HSD1 inhibitor carbenoxolone given orally to uraemic rats was found to improve glucose tolerance and insulin sensitivity and reduce hepatic expression of gluconeogenic and lipogenic genes.

Aim: In order to show 11β-HSD1 specific changes we investigated the effects of CKD on 11β-HSD1$^{-/-}$ mice.

Method: Mice were split into 4 groups with wild type (WT) and 11β-HSD1$^{-/-}$ type 1 null mice both given an high adenine or normal control diet for 2 weeks (n=8).

Results: Following consumption adenine 11β-HSD1$^{-/-}$ and wild type mice developed similar levels of renal dysfunction. Uraemic WT mice were dyslipidaemic and had significantly impaired glucose tolerance and reduced insulin sensitivity as demonstrated in intra-peritoneal glucose and pyruvate tolerance tests compared to 11β-HSD1$^{-/-}$ animals (n=8, P<0.01). 11β-HSD1$^{-/-}$ mice had a lipid profile similar to control (non-uraemic) animals with a significant reduction in plasma cholesterol and plasma triglycerides compared to uraemic WT animals (both P<0.01).

Conclusion: This study clearly demonstrates the specificity of elevated hepatic 11β-HSD1 as an important contributor to early insulin resistance and dyslipidemia in uraemia. 11β-HSD1 inhibitors, therefore, potentially represent a novel therapeutic avenue for the management of insulin resistance in patients with CKD.

O100

Novel *in vivo* techniques confirm a role for the ADMA-DDAH pathway in the regulation of proximal tubular sodium transport

James Tomlinson[1,2], Tracy Bell[3], Olga Boruc[1], Ben Caplin[2], Zhen Wang[1], William Welch[3], David Wheeler[2], Chris Wilcox[3], James Leiper[1]

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Background: Numerous reports have demonstrated that nitric oxide (NO) influences sodium reabsorption in the proximal tubular cell (PTC) and regulates blood pressure (BP). Data from animal studies are contradictory reporting NO either increasing or decreasing natriuresis. This may be explained by systemic versus local effects, non-specific NOS inhibition and time-/dose-dependent responses. Asymmetric dimethylarginine (ADMA) is a naturally occurring inhibitor of NO synthesis and is metabolised by dimethylarginine dimethylaminohydrolase (DDAH) providing an alternative mechanism for regulating NO bioavailability. Renal DDAH1 is mainly restricted to the PTC. We hypothesised DDAH1 activity in the PTC increases local NO, enhances sodium reabsorption and elevates BP.

Methods: We used novel genetic and pharmacological approaches to disrupt DDAH1 activity in a PTC-specific manner. Female mice were bred to express kidney androgen-sensitive protein-Cre and DDAH1 floxed alleles allowing for time-dependent PTC-specific gene deletion with testosterone treatment (PTC-D1KO). DDAH1 expression, ADMA, NO activity along with responses to high/low salt diet and BP were examined. In a second study, proximal tubule microperfusion in anaesthetised rats was used to assess the impact of pharmacological NOS and DDAH1 blockade on sodium transport.

Results: Tubular isolates from PTC-D1KO mice revealed substantially diminished DDAH1 expression with a rise in ADMA and reduction in NO but there were no detectable differences in plasma or other tissues confirming PTC-specific DDAH1 deletion. High salt feeding induced a 2-fold increase in renal DDAH1 gene expression that was abrogated in PTC-D1KO mice. Initial studies reveal lower BP in PTC-D1KOs on both low and high salt diets. In rat microperfusion studies, the DDAH1 inhibitor L-257 reduced sodium reabsorption (*Jv;* 3.1±0.3 to 1.8±0.2nl/min/mm; $p<0.05$)) and increased urinary flow rate (2.1±0.3 to 9.0±1.8µl/min; $p<0.05$) consistent with effects observed with NOS inhibitors.

Conclusion: These data suggest the DDAH-ADMA pathway regulates proximal tubular NO and sodium reabsorption. These novel approaches allow the time- and site-specific effects of endogenous NO signalling on solute transport and BP to be explored *in vivo*.

Parallel session

Friday 15th March

Free communications: clinical nephrology/paediatrics

13:30 – 15:00

O101

Nephrotoxicity from the use of 5-aminosalicylate (5-ASA) therapy in inflammatory bowel disease

Kenji So[1,3], Naomi Edney[2], Claire Bewshea[3], Andrew Muller[4], Michael Delaney[5], Richard D'Souza[2], Chris Mulgrew[2], Jonathan Kwan[2], Mark Silverberg[9], Graham Radford-Smith[8], Gillian Watermeyer[14], Renata D'Inca[12], Vito Annese[13], Epameinondas Tsianos[11], Richard Russell[6], Richard Oram[2], Rinse Weersma[10], Ian Lawrance[7], Tariq Ahmad[1,3]

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Introduction: Nephrotoxicity is a rare reaction to 5-ASA therapy, most commonly characterised by a progressive interstitial nephritis. This study aims to a) describe the clinical features of this rare complication b) explore the underlying mechanisms and c) identify clinically useful predictive genetic markers so that these drugs can be avoided, or monitoring intensified, in high-risk patients. Here we report the clinical features.

Methods: Patients were recruited from 185 (130 UK) international sites and DNA extracted. Inclusion criteria comprise normal renal function prior to commencing 5-ASA + ≥50% rise in creatinine and medical opinion implicating 5-ASA justifies drug withdrawal. An adjudication panel of expert nephrologists and gastroenterologists assessed causality from case report forms. Patients were assigned as "definite" (requires positive rechallenge), "probable", "possible" or "unlikely" cases of 5-ASA nephrotoxicity using the validated Liverpool Adverse Drug Reaction Causality Assessment Tool.

Results: 156 (71.9% male) patients have been recruited to date. These include 4 definite, 105 probable, 20 possible, 3 unlikely cases and 14 to be adjudicated. The side effect was seen with all 5-ASA therapy. 5-ASA nephrotoxicity occurred at a median age of 38.2 years (range 7.7-87.7). Two patients had a confirmed family history of 5-ASA-induced renal impairment. 75% of cases were detected by routine blood monitoring. The interval between 5-ASA introduction and first abnormal blood test was 0.2-521.3 months with 22.4% occurring in the first 12 months. The mean peak creatinine recorded was 296.8 µmol/litre (range 112 -1726). A renal biopsy was performed in 46.9% cases. 81.1% had a ≥ 20% recovery in peak creatinine on drug withdrawal; of these the mean time to best recovered renal function was 29.7 months (range 0.1-252.8 months). Seventeen patients required renal replacement therapy (RRT), 15 transplantation.

Conclusions: This is the largest study of 5-ASA induced nephrotoxicity. Whilst the incidence is low, morbidity is high with 12% of patients requiring RRT. Early recognition and drug withdrawal leads to renal recovery in only 81.1%. Genome-wide association sequencing will be done in February 2013.

O102

Automated estimated albumin excretion rate reporting improves the interpretation of urine albumin: creatinine ratios

Timothy Ellam[1,2], James Fotheringham[1,2], Michael Campbell[1], Meguid El Nahas[2,3]

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Background: Glomerular filtration rate estimation equations use demographic variables to account for predicted differences in creatinine generation rate. In contrast, urine albumin: creatinine ratio (ACR) correction is at best confined to gender-specific albuminuria cutpoints, potentially distorting albuminuria prevalence estimates across age/race groups.

Objective: To derive and validate an equation for the prediction of urine creatinine excretion rate (uCER) based on age, gender and race, allowing automated ACR correction and estimated albumin excretion rate (eAER) reporting.

Methods and results: Polynomial regression was applied to the Modification of Diet in Renal Disease (MDRD) study cohort (N=1695) to derive an equation for uCER prediction based on age, gender and race. Application of this equation improved the accuracy of albuminuria quantification in the Chronic Renal Insufficiency Cohort (CRIC, N=3645) and Diabetes Control and Complications Trial (DCCT, N=1179): The percentages of CRIC subjects with eAER within 15% and 30% of measured albumin excretion rate were 33% and 60% respectively, vs. 24% and 39% for uncorrected ACR. Equivalent proportions in the DCCT cohort were 52% and 86% for eAER vs. 15% and 38% for uncorrected ACR. Performance of eAER was also more consistent across age categories, correcting an underestimation bias in younger subjects and males. Conversion of ACR to eAER in the combined US NHANES 1999-2008 cohort increased the total estimated albuminuria (>30mg/24h) prevalence from 9.4% (95% CI 8.9 - 10.0%) to 11.6% (11.1-12.2%), corresponding to an additional 4.5million US adults classified as albuminuric. Prevalence estimates were particularly increased in younger age groups, with attenuation of the age-associated prevalence increase. Gender-associated prevalence differences were reversed by uCER correction from 8.7% (8.1 - 9.3%) vs. 10.2% (9.5 - 10.9%) for men and women respectively to 12.9% (12.2-13.6%) vs. 10.4% (9.7-11.1%).

Conclusion: Automated eAER reporting is potentially a useful approach to improve the accuracy and consistency of albuminuria assessment.

O103

Eculizumab (ECU) in atypical hemolytic uremic syndrome (aHUS) patients (Pts) with progressing thrombotic microangiopathy (TMA): continued improvements at 2-year follow-up

Neil Sheerin[1], Christophe Legendre[2], Larry Greenbaum[3], Sunil Babu[4], Richard Furman[5], David Cohen[6], Osama Gaber[7], Yahsou Delmas[8], Camille L Bedrosian[9], Chantal Loirat[10]

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Introduction: ECU, a terminal complement inhibitor, is indicated for the treatment of pts with aHUS, a genetic disease of chronic uncontrolled complement activation and systemic TMA with poor outcomes. Here we report 2-year findings from an extension of an open-label 26 wk Phase II trial in pts with progressing TMA despite plasma exchange/plasma infusion (PE/PI).

Methods: aHUS Pts ≥12 yrs, platelets <150x10^9/L at screening, received ECU: 900mg/wk for 4 wks, 1200mg at wk 5, 1200mg q2 wks thereafter. Platelet count change (primary endpoint) and other data were measured over a median period of 100 wks (range, 2–145).

Results: Of 17 pts enrolled in the initial study, 13 continued in the extension study. In the 17 pts, the median time from onset of current aHUS manifestation to screening was 0.75 months (0.23–3.7). ECU treatment continued to increase platelet count from wk 26, and additional pts achieved key renal endpoints (Table). ECU was generally well tolerated (1 serious AE [severe hypertension] possibly drug-related).

Conclusions: Long-term ECU therapy resulted in significant and continuous improvements in renal function in aHUS pts with progressing TMA.

Key outcomes with ECU	**Wk 26**	**Median 100 wks**
Mean change in platelet count, x10^9/L (95% CI)	73 (40, 105) P=0.0001	88 (63, 112) P<0.0001
TMA-event-free status*, n (%)	15 (88)	15 (88)
eGFR increase≥15 mL/min/1.73m^2, n(%)	8 (47)	10 (59)
CKD improvement of ≥1 stage, n (%)	10 (59)	12 (71)
Creatinine decrease of ≥25%, n(%)	11 (65)	13 (76)
Mean change in eGFR from baseline, mL/min/1.73m^2 mean (95%CI)	32.1(14.5-49.4)P=0.001	35.2 (17.3-53.1) P=0.0005
Decrease in proteinuria ≥1 grade, n/N	12/15	7/9

Significance was tested with a repeated measures model. *≥ 12 consecutive wks without plt count >25% from baseline + no PE/PI + no new dialysis. Baseline mean eGFR 22.9ml/min/1.73m^2 (14.5).

O104

Renal impairment associates with less functional improvement after acute stroke

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Introduction: Despite a higher incidence of stroke in patients with chronic kidney disease [CKD] there is very little data on the presentation and access to acute stroke services & clinical outcomes in these populations. We therefore examined the association between renal function and clinical outcome measures within the Stroke Improvement National Audit Programme [SINAP].

Methods: This retrospective cohort study examined patients presenting to acute stroke services at our centre [1st Jan 2011 – 1st March 2012]. Patient demographics, laboratory and clinical variables that were recorded as part of SINAP were examined. eGFR was calculated using the CKD-EPI equation with CKD defined by an eGFR<60ml/min. The primary outcome measure was an improvement in the modified Rankin Score [mRS] at discharge and secondary outcome measures included inpatient mortality.

Results: Overall 1805 cases were studied [mean age 69.4±16.6yrs]. 1122 [62%] were acute strokes [87% ischaemic, 13% haemorrhagic], 9% transient ischaemic attacks and the remainder stroke mimics. Overall 27% stroke patients had CKD [28% ischaemic vs. 21% haemorrhagic strokes, p=0.09]. 11% patients with ischaemic stroke received thrombolysis however CKD was associated with less thrombolytic use [19% vs. 29%, p=0.03] despite similar times to presentation compared to non-CKD cohorts [p=0.2] and more disability at presentation [median mRS 4 vs. 3, p=0.0001]. Higher eGFR independently associated with a greater chance of improvement in mRS by discharge on multivariate analysis [11% per 10ml/min eGFR, p<0.001]. Older age [p<0.001], lower haemoglobin [p=0.01] and higher white cell count [p=0.003] associated with a higher risk of death but CKD was not [p=0.2].

Conclusion: Renal impairment independently associates with greater stroke disability at presentation and worse functional outcomes despite modern stroke care. Nonetheless these patients are also less likely to be thrombolysed for acute ischaemic stroke, which suggests a possible inequity in access to healthcare that requires urgent study.

O105

The diagnosis of urinary tract infection in young children (DUTY) study: a clinical algorithm to improve the recognition of urinary tract infection (UTI) in pre-school children

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Introduction: Diagnosing urinary tract infection (UTI) in pre-school children is difficult and around 50% are currently missed in the UK.

Objective: To develop a clinical algorithm based on symptoms, signs and urine dipstick results to assist the identification of children who require urine sampling, antibiotic treatment and /or laboratory analysis.

Methods: We conducted a diagnostic cohort study of children <5 years presenting acutely (≤28 days) unwell to primary care in the UK. We collected detailed information on the presence/absence and severity of presenting symptoms and signs, as well as socio-demographic and past medical history data. Urine was sampled by clean catch (preferred) or nappy pad, 'dipsticked' and sent to (i) the local NHS laboratory (the priority sample) and (ii) a reference laboratory. Blind to children's clinical symptoms and signs, the NHS and research laboratories processed urine samples according to their standard operating procedures.

Results (preliminary): 7,163 children were recruited with NHS and research urine sample results available for 6,328 (88%) and 5,257 (73%) respectively. Of the 5,017 children without missing data and with urine results from both laboratories: mean age was 2.2 years (s.d.=1.4); 49% were male; 54% urines via clean catch, 45% via nappy pads and 1% via bag. UTI rates were 2.8% and 3% from clean catch and pad samples respectively. Among clean catch samples, the following were independently associated with UTI: history of UTI; parental report of smelly urine; pain/crying while passing urine; clinician's global impression of illness severity; and on dipstick: nitrites, leukocytes and blood (area under the ROC = 0.87 (95% CI 0.82 to 0.92). Among the nappy pad samples, the factors were: female gender; age; smelly urine; darker urine; and on dipstick: nitrites, leukocytes and blood (ROC = 0.78 (0.72 to 0.83)).

Conclusions: These results will be developed into an algorithm to help clinicians select which children should have: a urine sample obtained and /or sent for laboratory culture and who should receive immediate antibiotic treatment.

O106

Novel urine biomarkers for monitoring disease activity in juvenile lupus nephritis: A prospective longitudinal validation study

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Background: Systemic Lupus Erythematosus (JSLE) is a severe autoimmune condition with lupus nephritis (LN) seen more frequently in juvenile disease wher up to 80% have renal involvement [1]. The renal biopsy is crucial for diagnosis and classification but has a limited role in monitoring. Current methods of monitoring renal disease activity over time rely on a variety of standard laboratory markers and the use of disease activity tools such as the British Isles Lupus Assessment Group index score (BILAG). Improving methods of monitoring and predicting disease activity changes may allow earlier intervention and improve the long-term renal outcome.

Aims and methods: This prospective longitudinal study aimed to identify whether standard and/or novel biomarkers are useful for monitoring and predicting LN disease activity. Using patients recruited to the UK JSLE study, urine and blood samples were collected during routine clinical reviews. The study had full ethical approval.

Results: The JSLE cohort (n=64), seen at 3 (interquartile range IQR: 2-5) clinical reviews over 364 (182-532) days were aged 14.1 (11.8-15.8) years and 80% female. Active renal episodes (23% total; renal BILAG A/B) had significantly increased concentration of; monocyte chemoattractant protein 1 (MCP1), neutrophil gelatinase associated lipocalin (NGAL), erythrocyte sedimentation rate, anti-double stranded DNA, urine albumin:creatinine ratio (UACR), creatinine, and reduced complement 3 (C3), C4 and lymphocytes. Multivariate analysis demonstrated MCP1 and C3 as independent variables ($p<0.001$) for active renal disease. MCP1 was an excellent predictor of improved renal disease (area under the curve AUC: 0.81; $p=0.013$; concentration 343pg/ml, specificity 71%, sensitivity 70%); NGAL was a good predictor of worsened renal disease activity (AUC 0.76; $p=0.04$; concentration 30ng/ml, specificity 60%, sensitivity 61%). Urine MCP1 and uNGAL changed as subsequent renal disease changed (MCP1 $p=0.015$; NGAL $p=0.038$). Standard markers could not predict disease activity changes.

Conclusion: We have demonstrated that biomarkers (MCP1, C3) perform well for monitoring renal disease in JSLE, and novel biomarkers (MCP1, NGAL) out perform standard markers for predicting change. Biomarker-led monitoring may facilitate the titration of medication and allow earlier diagnosis and intervention opportunities. Collaboration with industry to develop point of care urine biomarker testing is now in progress.

References

1. Watson L, Leone V, Pilkington C, Tullus K, Rangaraj S, McDonagh JE, Gardner-Medwin J, Wilkinson N, Riley P, Tizard J *et al. Arthritis Rheum* 2012.

Poster session

Wednesday 13th March

18:15 - 19:25

Access to transplantation

P1

Should a history of cancer preclude transplantation?

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A past history of cancer is a relative contraindication to undergoing organ transplantation because of the risk of cancer recurrence. However, the extent of this risk is not fully established. To determine the risk of recurrence of cancers after organ transplantation, we used data from the UK Transplant Registry to link all solid organ transplant recipients (1985-2010) in the West Midlands region with the regional Cancer Registry to identify recipients with a history of cancer diagnosed before organ transplantation (excluding liver recipients transplanted with liver cancer) and those who developed a cancer recurrence following transplantation. The study cohort of 4835 recipients included 3321 (69%) kidney, 821 (17%) liver, 495 (10%) heart and 198 (4%) lung recipients. A history of cancer was noted in 64 (1.3%) recipients, including cancers of breast(8), kidney(8), colon (7), leukaemia(6), lymphoma(6), prostate(4), melanoma(4), bladder(4) and others (18). In total, 5 recipients developed cancer recurrence with rate of recurrence within 10 years of transplant of 11.9% (95%CI 0.4,23.5). All 5 recipients with recurrence had been cancer-free for less than 5 years pre-transplant. There were no cases of recurrence of cancer in 59 recipients of whom 39 underwent transplantation more than 5 years after the cancer diagnosis. Melanoma recurred in 3 of the 4 patients with a previous diagnosis; the other two cancers which recurred were leiomyosarcoma and testicular cancer. In all 5 cases, the recipients died as a direct consequence of recurrent cancer. Because of the increasing recipient age and higher cancer incidence in patients with renal failure/cirrhosis, more patients with previously treated cancer are considered for transplantation. Our data suggest that a cancer-free period of 5 or more years is associated with a very low risk of cancer recurrence in this selected cohort. Careful risk-benefit assessment should be adopted prior to offering transplantation to patients with a cancer treated within the previous 5 years, particularly in cases with melanoma. As the recurrence of cancer was fatal in every case, informed consent will play an important role in clinical management and also has medico-legal implications.

P2

Timely listing for kidney transplantation: improving access in a non -transplant centre

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Introduction: Kidney transplantation is the best form of replacement therapy for patients with end stage renal disease (ESRD). In the absence of a living donor, patients with ESRD are expected to be registered on the deceased donor transplant list within six months of their anticipated start of dialysis. Despite the benefits of kidney transplantation, pre-emptive transplantation is unusual in the UK with only 2.5% of chronic kidney disease (CKD) patients undergoing transplantation as their first renal replacement therapy. Numerous challenges and barriers impede the provision of timely patient education and kidney transplant listing especially in non-transplanting centres.

Aims and objectives: The Timely Listing for Kidney Transplantation Project was undertaken in a tertiary hospital over a six month period. The aims were a) to identify barriers to listing in CKD 5 patients; b) to identify how these obstacles can be overcome, c) increase patient referrals for transplantation d) to adopt a cultural change in clinical practice favouring pre-emptive kidney transplantation.

Methods: A series of clinical audits and a patient survey were undertaken to identify problems and barriers to the transplant work-up process and timely listing of patients onto the transplant register. These identified a) the percentage of CKD 4 and CKD 5 patients with a documented transplant waiting list status reported by consultant assignment b) delayed referral for recipient evaluation +/- listing and c) waiting times for investigations required for recipient evaluation in preparation for transplant listing. Discussions were held with other multidisciplinary teams who provide services for patients as part of the transplant work-up process, with a view to improving access for potential recipients and donors.

Results: The patient survey and audits revealed late referral of CKD 4 and CKD 5 patients for education and pre-transplant assessment. This was due to variations in estimated glomerular filtration rate (eGFR) at which patients were referred; variations in senior medical input to support the work-up process; an imbalance between nursing staffing and work load; deficits in documenting the transplant work-up process; and long waiting times for performance of and reporting of transplant work-up investigations. Delays in pre-transplant cardiac investigations were commonly identified. Strategies were put in place to resolve these problems. This led to an increase in numbers of patients referred for patient education and transplant assessment - a 25% increase in number of patients with documented transplant waiting-listed status. Completion of transplant work–up documentation improved. Negotiations with the cardiac business group led to an allocation of two dedicated appointment slots per week for a recipient and donor, thus improving the waiting time, transplant work-up process, timely listing of patients onto the transplant list and patient experience of the listing process.

Conclusion: The project has had a number of benefits including the adoption of a "transplant-first" culture and the promotion of pre-emptive transplantation amongst patients and staff. We hope that these improvements will enable us to continue to provide timely access to transplantation for our patients with advanced kidney disease.

P3

Timely listing for transplantation: quicker isn't always better

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Introduction and aims: It would seem logical to fast track the transplant work up for unplanned starters but many patients do not engage with this process and listing is often delayed. We decided to evaluate patients' perceptions and experience of the transplant workup process after they had started dialysis in an unplanned fashion. We then planned to use the outcome to change the pathway for these patients in the future.

Methods: Five patients were approached and 4 agreed to be interviewed. A semi-structured interview question guide which was used to conduct the interviews. Results of the interviews were reviewed and changes to the patient pathway were made as a result.

Results: Although there were a small number of patients several themes emerged which were remarkably consistent; patients who remembered having information but felt unable to take it in and patients who could not remember being given the information at all. Patients were asked to suggest the timing of workup, most did not give a specific time but one patient suggested 3-5 months post starting dialysis. The other 3 patients all felt the process should be somewhat delayed.

Conclusion: The universal theme was the inability to take in information during the initial shock of starting dialysis. Patients do not universally feel that pushing transplant listing earlier is beneficial to them and felt the process should happen after they have come to terms with dialysis and were mentally ready. Patients need a tailored pathway and this may in fact be a delayed pathway. We have taken the decision to delay invitation to transplant assessment in these patients which we believe is a bold decision to take at a time when external pressures are to assess more early.

P4

Patients' views on the kidney allocation system in UK

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Introduction: The aim of this study was to assess patients' views and understanding on how kidneys are allocated on the deceased donor list in UK. A further aim was to assess what patients think the priorities should be.

Methods: A two-part questionnaire was sent to all patients awaiting kidney transplantation at 6 Renal/Transplant units in UK after ethics approval (Ref 10/H083/61). Part-1 assessed patients' knowledge and priorities. Part-2 assessed patients' understanding and agreement after reading the UK kidney allocation guidelines taken from the NHSBT website and included in the correspondence.

Results: Response rate was 410/1221 (34%). 18 responded that they did not want to participate. The main issues patients think should be taken into consideration are the degree of tissue matching between recipient and kidney (84%), the time spent on the waiting list (76%), the likelihood the patient will die soon (74%), whether the patient will take their medication after transplantation (75%) and if they have a rare tissue type (69%). The ability to pay (76%), contribution to society (54%), patient's ethnic origin (56%) and whether the recipient smokes (35%) were issues that most did not think should be part of the guidelines. 9% thought the ability to pay for a kidney is part of the allocation system. Moreover, 32% thought that patient contribution to kidney failure is part of the allocation system and 51% thought that it should be part of it. After reading the enclosed guidelines, there was an increase in understanding of the system from 39% to 84% saying that they mostly or completely understand the guidelines now. Finally, 81% said they mostly or completely agree with the current guidelines.

Conclusions: Patients were aware of some aspects of the current UK allocation system but seemed incompletely informed with respect to other aspects. When provided with the appropriate information the majority agree with the prioritization criteria. We deduce that provision of more information as well as greater patient involvement should increase understanding of the system and help with management of expectations for patients on the transplant waiting list.

P5

Obesity and lung transplants – it's an age thing

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Background: The primary aim of lung transplantation for end-stage lung disease is to prolong life. The International Society for Heart & Lung Transplantation's recipient selection criteria include obesity (body mass index [BMI] above 30kg/m²) as a relative contraindication. Although studied in the US, there is little evidence from Europe suggesting whether high BMI alone affects survival.

Methods: All complete data from the Cardiopulmonary Transplant Database for patients over the age of 16 at primary lung graft between 01/01/1998 and 31/12/2011 were retrospectively analysed with a minimum follow-up period of 10 months. 550 patients were stratified into four BMI groups <18.5 (underweight), 18.5-24.9 (normal), 25-29.9 (overweight) and ≥30 (obese). Kaplan-Meier survival analysis was performed on BMI groups and p-value calculated using the Mantel-Cox test. Multivariate survival analysis was performed using Cox regression incorporating 3 variables (BMI, age and pre-transplant diagnosis).

Results: Obese patients had a significantly lower 10-year survival - 28.5% compared to 51.4%, 46.6% and 32.1% in the normal, underweight and overweight groups respectively (p=0.004). However on multivariate survival analysis using Cox regression, age was found to be the only significant variable (p=0.0003).

Conclusions: In contrast to some other reports, obese patients did not have a worse early outcome. When accounting for confounding variables, only age was a significant predictor of survival - BMI was not. This may reflect a difference in BMI distribution with age in the UK compared to US.

P6

Timely listing for kidney transplantation: optimising the use of existing resources to achieve sustainable improvements in performance

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Background: Early renal transplantation contributes to improved outcomes for patients with chronic kidney disease. "Bottlenecks" in assessing patient suitability for transplantation may result from delayed referral or pathway inefficiencies. The NHS Kidney Care Timely Listing Project provided an opportunity to examine the collective impact of various initiatives on timely referral and listing in our centre.

Methods: Structures and processes for transplant assessment were reviewed as part of a mapping exercise. Prompts to initiate transplant assessment were introduced and key elements of the assessment pathway were streamlined. Relationships with key partners in primary and secondary care were strengthened to achieve prioritisation of investigations and disintermediation of processes. Education and engagement of staff helped to embed changes in practice, for example the setting of a higher eGFR threshold for initiating transplant assessment, arranging tests at the time of referral rather than in the assessment clinic, and communicating more effectively with primary care teams through the sharing of electronic patient health records. A Cultural and Health Improvement Officer ensured that patients of South Asian origin received appropriate support.

Results: We observed a "shift to the left" in terms of earlier referral for suitability assessment and shortened pathway duration (median of 105 vs 183 days), the latter resulting from more efficient processes such as a reduced waiting time for cardiac ultrasound (median of 15 vs 43 days). The percentage of patients listed for transplant in the pre-dialysis phase increased from 35% in 2011 to 62.5% in 2012.

Discussion: The NHS Kidney Care Timely Listing project has facilitated a comprehensive review of the transplant assessment pathway, allowing us to establish new ways of working that complement existing service developments. We have successfully engaged a number of stakeholders in delivering a streamlined care pathway at no extra cost. Future plans include a review of feedback from patient satisfaction surveys and the introduction of a handheld patient record to promote the involvement of patients in the assessment process.

P7

Timely listing for kidney transplants– improving time from referral to activation

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[1]Southwest Transplant Centre, Plymouth, Devon, UK, [2]Peninsula Renal Network, Southwest Peninsula, UK

Introduction: Renal Transplant is acknowledged as a 'Gold Standard' modality treatment for suitable patients approaching end stage renal failure. The Renal association recommends that CKD patients be assessed and placed on the waiting list if judged to be within 6 months of their anticipated dialysis start date. It is also recommends that assessment should start earlier (eGFR 20 mls/ min) where live donor is being considered and that patients should be offered pre-emptive transplantation if commencing the live donor pathway. However barriers exist impeding the timely listing of patients and these comprise of delays in prompt work up and further delays following referral to activation potentially reducing listing of patients pre-emptively.

Method: A 6 month project funded by NHS Kidney Care enabled the kidney patient pathway from referral to activation to be processed mapped. The transplant centre receives referrals for transplant assessment from two other renal centres and it was discovered that the average time frame from referral to transplant centre to activation onto the waiting list was 150 days. It was also noted that the average eGFR of CKD patients on referral to transplant assessment clinic was 15. The main reasons for the delays to the listing of patients were a lack of referral criteria resulting in inconsistent workups prior to referral and no time frames along the pathway to enable monitoring. Concern was raised that patients were not being adequately prepared for pre-emptive transplant if they were referred with an eGFR of 15 and then wait for a further 5 months to be listed. A referral criteria was developed and a pilot commenced in the three centres. The criteria included recommended eGFR and workup investigations on referral.This was supported by the implementation of a teaching programme involving all staff to highlight the benefits of pre-emptive transplantation. Changes were also made to the patient education programme to ensure adequate information was given at appropriate times by appropriate health care professionals to promote timely referral and timely listing.

Results: The referral proforma was sent to the three centres and commenced in August 2012. This included time frames to enable monitoring and the highlighting of delays once the referral had been received at the transplant centre.

Table 1: Time frames and numbers pre and post implementation of referral criteria

	Median eGFR on referral to transplant centre	**Median time from referral to activation on waiting list**	**Number of pending patients**	**Number of patients on waiting list**
March 2012	15	150 days	53	83
September 2012	14	83 days	28	96

Conclusion: The pilot study has shown an improvement in the time taken from referral for transplant assessment to listing from 150 days to 83 days. This is the beginning of the pilot and we would expect to see a further improvement when the audit is repeated in March 2013. Ongoing monitoring and education programmes with both staff and patient groups will determine whether pre-emptive transplant rates improve.

P8

Cardiac evaluation using myocardial perfusion scanning prior to kidney transplantation

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Introduction: The use of non-invasive cardiac stress testing is recommended in patients with end stage renal disease (ESRD) and cardiovascular risk factors prior to transplant listing. Myocardial perfusion scanning (MPS) is a non-invasive test used to screen for coronary artery disease (CAD) in this cohort of patients. However the predictive and prognostic value of MPS in patients with ESRD remains controversial. In this retrospective analysis, we studied the association of an abnormal MPS in predicting cardiac events and mortality, and the correlation of abnormal MPS with the presence of CAD in patients undergoing pre-transplant evaluation.

Methods: This is a single centre retrospective analysis performed in a UK District General Hospital. Adult potential kidney transplant recipients who had an MPS were included in the review. The patients were classified into four groups based on the following risk factors: age > 50 years, diabetes and previous ischaemic heart disease. The four groups were labelled: group 1 (3 risk factors), group 2 (2 risk factors), group 3 (1 risk factor) and group 4 (no risk factor). The analysis of outcome is from the time of the MPS to September 2011, or death. The outcomes analysed in each group were the % of patients with abnormal MPS, incidence of cardiac events (STEMI, non-STEMI), overall mortality, cardiac mortality and presence of coronary artery disease confirmed by coronary angiography. An abnormal MPS was defined as the presence of fixed defect and/or reversible defect.

Results: 144 patients had an MPS study from 2002 -'09. 56% (N=80) of these patients had an abnormal MPS. In group 1 (very high risk: n=4), all 4 patients had an abnormal MPS. 50% patients in group 1 suffered a cardiac event and 50% died from any cause. In group 2 (high risk: n=42), an abnormal MPS was also present in all patients. The incidence of cardiac events was 19%. 12% of patients died from a cardiac cause and 31% of patients died from any cause. In group 3 (intermediate risk: n=88), 69% of patients had an abnormal MPS. 5.6% had a cardiac death and had a prior abnormal MPS. 23% in group 3 died from any cause. The incidence of cardiac events was 5.6%. In group 4 (low risk: n=10), 30% of patients had an abnormal MPS and none of them had a cardiac event or cardiac death. A total of 32 patients with a reversible defect and a left ventricle ejection fraction of >40% from all groups proceeded to have a coronary angiogram. Only 56% of these patients had overt CAD. None of these patients belonged to group 4.

Conclusion: In low risk patients, MPS is of limited value and may not be used in these patients. In higher risk groups, an abnormal MPS predicts cardiac events and mortality. A reversible defect on MPS does not accurately predict CAD. MPS provides useful information on the type of cardiac defect and this may help determine suitability for further cardiac evaluation prior to transplant listing.

P9

Access to transplant and transplant outcome measures (ATTOM): exploring healthcare professionals perspectives on access to renal transplantation in the UK

Rishi Pruthi[1], Melania Calestani[2], Rommel Ravanan[3], Geraldine Leydon[2], Paul Roderick[2]

[1]UK Renal Registry, Bristol, England, UK, [2]University of Southampton, Southampton, England, UK, [3]Southmead Hospital, Bristol, England, UK

Introduction: Achieving equitable access to kidney transplantation is a challenge facing many countries, with a variety of studies demonstrating variation to access. As part of the qualitative work-stream of ATTOM this study aims to highlight the practice patterns for transplant wait-listing that exist across the UK, and understand the perceived barriers of key stake holders.

Methods: Semi-structured interviews were conducted with 45 'key stakeholders' involved in transplant listing (including clinical directors, physicians, surgeons, and nursing staff) in a purposive sample of nine renal units across the UK. Units were stratified by data on degree of listing for transplantation, whether a transplant or dialysis centre and geography to include spread of deprivation and ethnicity. Interviews were recorded and transcribed verbatim. Double coding was performed to improve validity of coding and thematic analysis undertaken using Nvivo 10.

Results: Thematic analysis identified a series of themes which included the role of cardiac services, with recipient cardiac work-up being a major source of ambiguity and delay. Variation in cardiac service delivery and granularity seen in both interpretation of test results and management strategies, were also seen as a source of strain on interpersonal relationships and subject to variable resource issues. Pathways of care involving living donation and pre-emptive transplantation was another major theme which was seen to pose ethical and financial dilemmas, and was a source of both dispute and innovation. Staff fatigue was another major theme seen across many professional ranks, often linked to resource shortages, feeling unappreciated and helpless whilst receiving little professional support.

Conclusion: Reaching a consensus on cardiac work up and resolving areas of contention surrounding living donation are important in improving access to transplantation and equity. There is also a need to address the causes of staff fatigue in renal services and improving support provisions whilst promoting innovation. It is hoped that the results of this study will inform a national survey aimed at identifying centre practice patterns influencing access to Transplantation

P10

Access to transplant and transplant outcome measures (ATTOM): exploring patient perspectives on access to transplantation

Rishi Pruthi[1], Melania Calestani[2], Geraldine Leydon[2], Rommel Ravanan[3], Paul Roderick[2]

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Introduction: Research into understanding inequity in accessing renal transplantation has to date largely focused on understanding societal demographics and health care systems. As part of the qualitative work-stream of ATTOM this study aims to highlight patient perspectives on this complex process to aid development of more patient centric equitable access to transplantation.

Methods: Semi-structured interviews were conducted with 53 patients in a purposive sample of nine renal units across the UK. Units were stratified by data on degree of listing for transplantation, whether a transplant or dialysis centre and geography to include spread of deprivation and ethnicity of the catchment areas. A purposive maximum variety sample was identified to include patients who were active on the transplant waiting list, who had not yet been listed, who were deemed unsuitable post assessment, and patients who had received a transplant. Interviews were recorded and transcribed verbatim. Double coding was performed to improve validity of coding and thematic analysis performed using Nvivo 10.

Results: Thematic analysis identified a series of major themes. This included information acquisition; with timely information delivery and adjusting delivery to individual patient characteristics being seen as important in overall perceived success. Pathways of care was another important theme, with logistic complexities, lengthy processes, and inadequate information/awareness about the listing process being associated with negative experiences. Lack of psychological support within the pathway was also highlighted as an area for improvement. Decision making was another major theme associated with sourcing information, varying levels of involvement, isolation and self-reflection.

Conclusion: This study provides a unique perspective of patient views on access to renal transplantation. Effective fit for purpose education, empathetic patient tailored pathways of care, patient specific communication and empowering decision making initiatives appear important in improving equitable access to renal transplantation.

Poster session

Wednesday 13th March

18:15 - 19:25

Antibody incompatible transplantation 1

P11

Increasing the efficacy of the national live donor kidney sharing scheme: the value of a combined approach to antibody incompatible transplantation

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Introduction: For patients with a living donor to whom they have antibody (ABO or HLA), options include entry into the 'paired scheme'; direct transplantation with antibody removal, finding an alternative donor or continuing to wait for a deceased donor kidney offer. In 2011, 22% of those registered in the paired scheme were transplanted. At our centre, entry into paired scheme is offered to all antibody incompatible pairs. If unsuccessful in the paired scheme, direct antibody incompatible transplantation is considered.

Methods: We reviewed all patients in our centre entering the paired scheme between June 2006 & June 2012 comparing CRF; listed antibody incompatibility (ABO or HLA) and blood group in 3 groups: those transplanted through the paired scheme; those successfully transplanted out with the paired scheme (ABOi, HLAi, Alternative Live Donor or Deceased Donor) and those untransplanted.

Results: Of the 63 patients (77 registered pairs) 68% were transplanted. 15 patients (24%) were matched through the paired scheme. A further 28 (43%) of patients were transplanted at our centre. 20 patients remain untransplanted. There was no difference in CRF between transplants occurring through or out with the scheme ($p = 0.88$). Of the total number of Blood Group O patients entering the paired scheme, only 9% receive a transplant through the scheme, the remaineder being transplanted through the routes above ($p = 0.004$). There is no difference between listed ABO or HLA compatibility status between those transplanted in the paired scheme, or out with it ($p = 0.26$). Comparison of listed ABO incompatibility, HLA compatibility & Blood Group between the untransplanted group and patients transplanted at our centre out with the paired scheme showed no significance.

Conclusion: An aggressive combined approach leads to successful transplantation of patients with a live donor to whom they have antibody compatibility. Combination of the paired scheme with direct incompatible transplantation after unsuccessful runs yields a high rate of transplantation.

P12

Beyond C4d: The ultrastructural appearance of endothelium in ABO incompatible renal allografts

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Background: ABO incompatible (*i*ABO) kidney transplantation is a well established intervention with encouraging long term results. The frequent finding of C4d positivity in renal transplant biopsies from these patients is assumed to represent graft accommodation. However, ultrastructural examination of glomerular and peritubular capillary endothelium might reveal antibody mediated complement-dependent and independent damage invisible by conventional light microscopy.

Methods: We studied the ultrastructural appearance of the endothelium in 67 biopsies from 21 patients with *i*ABO allografts and compared it to 17 patients (26 biopsies) with ABO compatible (*c*ABO) grafts with c4d positivity and 14 control patients without evidence of microcirculation injury. Graft function was compared at the time of biopsies and follow up (*i*ABO 34.7 months ± 18.8, *c*ABO 50.6 months ± 36.4, controls 72.3 months ± 27.3).

Results: 10 different parameters to indicate chronic and acute endothelial damage in transmission electron microscopy in glomerula and peritubular capillaries were semiquantitatively graded and expressed in a sum score. This was slightly worse in *i*ABO compared to controls though not statistically significant. In contrast, *c*ABO had the highest sum score that differed significantly from *i*ABO ($p=0.004$) and controls ($p=0.012$). The score was not different between C4d positive and C4d negative *i*ABO allografts. Graft function (eGFR) was significantly worse at the time of biopsies and at follow up in *c*ABO compared to *i*ABO. The latter were not different from controls.

Conclusion: Although ultrastructural signs of endothelial damage are detectable in iABO allografts this does not seem to impact on the graft function. In contrast to *c*ABO grafts, C4d positivity in the ABO incompatible situation does not necessarily indicate injurious activation of the complement cascade.

P13

In ABO incompatible renal transplant patients microcirculation injury associates with donor-specific anti-HLA antibodies

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Detecting antibody-mediated damage in ABO incompatible (ABOi) renal transplants has been hampered by the lack of usefulness of C4d staining. We assessed the relevance of the microcirculation inflammation (MI) score, defined by combining glomerulitis (g) and peritubular capillaritis (ptc), in this population.

The first biopsy taken ≥1 year after ABOi transplantation was classified according to Banff '09 (n=39). Data were analyzed using clinical information on donor, recipient and post-transplantation variables. Median follow-up was 4.2 (IQR 3.0-5.4) years. Median time to biopsy was 16.7 (IQR 14.4-34.1) months. Clinical characteristics comparing MI0 (n=26) and MI≥1 (n=13) were analyzed with binary logistic regression, either univariate or forced-entry multivariate (including all parameters with p≤0.150). The Kaplan-Meier product limit method was used to estimate time to transplant glomerulopathy (TG) and renal graft failure, with log-rank test to detect differences between the two groups.

On univariate analysis the MI+ and MI- groups differed significantly for donor-specific antibodies (DSA) and incidence of TG development, both were associated with a MI+ score. In multivariable analysis, donor age, DSA, TG development and death-censored graft survival were entered and only DSA was associated with MI+ (OR 5.7 [95% CI 1.03-31]). Survival estimates show a trend to more development of TG (p=0.091) in patients with an MI+ score, with TG free survival at 3-years post-biopsy in 91% (MI-) vs 66% (MI+). No significant difference could be found in graft survival estimates between the MI groups, with 3-year graft survival rates from biopsy of 94% (MI-) and 71% (MI+) (p=0.162).

MI only correlated with the presence of DSA (both pre and post-formed antibodies). From ABO compatible studies we know that in sensitized and *de novo* DSA renal transplant patients the MI score associates with graft failure. Unfortunately, due to the small sample size, medium term follow-up and low incidence of MI no correlation for MI with outcome could be found.

P14

Precise and simultaneous measurement of different blood group-specific antibody classes by multi-colour flow cytometry assay

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Introduction: The haemagglutination assay (HA) has been the main stay for measurement of blood group-specific antibodies. Despite effort at standardisation, the HA is associated with poor reproducibility and inability to measure antibody levels in continuity. We describe a multi-colour flow cytometry (MC-FC) based assay that measures IgG, IgA & IgM blood group-specific antibodies simultaneously.

Method: Reagent, pooled red cells (RBC) were fixed and diluted prior to incubation with plasma. Fluorophore labelled IgG, IgA and IgM specific antibodies with non-overlapping emission spectra were added as a multiplex assay. The blood group specific antibodies were then quantified using BD FACS Canto II.

Results: The assay had good precision at clinical decision time point (HA titre of 1:8) and at various other titres. The coefficient of variance (CV) for measurement of anti-A IgG by MC-FC at HA titres of 1:2 was 3%, 1:8 was 3.5% and 1:2048 was 3.6%. Similarly the CV for measurement of anti-A IgM at HA titres of 1:2 was 5%, 1:8 was 11% and 1:512 was 6.3 % respectively. The results of precision experiment were similar for anti-B antibodies. The association of relative median frequency (RMF) on MC-FC and concentration of antibodies had linear relationship up to a dilution range of 1:64 compared to 1:16 for HA (Figure 1).

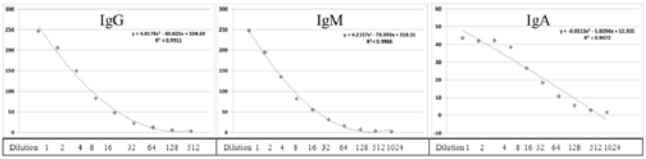

Figure 1: Linearity of RMF (y-axis) and dilution of samples on flow-cytometry assay

Conclusion: Multi-colour flow cytometry based assay is precise and more sensitive in measurement of blood group-specific antibodies.

P15

Outcomes after combined HLA/ABO-incompatible renal transplantation

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Introduction: We have an active antibody incompatible program for ABO-incompatible or HLA-incompatible patients requiring renal transplantation. Desensitisation and immunosuppression is tailored to each patient, according to results of a test plasma exchange or antibody titres. We have also undertaken combined transplantation in the context of both ABO & HLA antibodies in 11 patients, 7 of whom had a positive flow cross match. Few data are available regarding the outcomes in these patients: the aim of this study was to compare graft survival and rejection in this group.

Methods: We reviewed 7 patients with both HLA & ABO incompatibility '(HLA-ABOc) patients requiring antibody removal for a positive flow cross match, and compared them to our pure HLA-incompatible (HLA-i) patients (positive flow cross match, n = 27), and our ABO-incompatible patients (n = 62).

Results: There was no difference observed between groups for distribution of age at transplant, sex or dialysis modality. There was no difference between HLA-i and HLA-ABOc in repeat mismatch or pre-treatment MFI (Mann Whitney p=0.9). There was no difference in ABO antibody titres between ABO-i and HLA-ABOc. HLA-ABOc antibody incompatible transplantation is associated with a greater risk of graft loss at 3months (GS 71% vs 89% vs 89% p = 0.009) and 1 year (p = 0.017). 6 (86%) of the HLA-ABOc group have experienced 1 or more episodes of biopsy proven rejection, however this was not found to be significantly higher than the other groups, which may relate to group sizes and follow up period.

Discussion: Although initial MFI and ABO antibody titre levels may be similar, the risk of early graft loss in combined HLA & ABO transplantation is higher than for pure ABO-incompatible or pure HLA-incompatible transplantation. We propose that a synergistic mechanism of action leads to early aggressive rejection. Outcomes after combined ABO & HLA antibody incompatible transplantation should be monitored carefully, and such transplants may require additional therapy to prevent rejection.

P16

Binding kinetics of polyclonal blood group-specific antibodies can be calculated by using mathematical protocols with surface plasmon resonance assay

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Background: Previously we have shown measurement of affinities on monoclonal murine anti-A and anti-B antibodies using surface plasmon resonance (SPR) based assay. Binding kinetics and affinity of an antibody varies in the course of an immune response. Estimating the binding affinities of a polyclonal antibody from patient blood samples underlying blood-group incompatible kidney transplantation could characterise and distinguish harmful antibodies.

Method: SPR experiments were conducted on polyclonal blood-group specific antibodies eluted from a glycorex column. Blood group A-trisaccharides in three different concentrations were immobilised onto an SPR chip and purified antibodies flowed over the chip. Mathematical protocols were applied to the outputs from these experiments to calculate two ranges of affinities.

Results: The expanded model demonstrated vastly improved fit (see figure 1), reducing the residual sum of squares by a factor of more than 200. The estimated affinities were: 6.7E-2mm^3/ng and 7.6E-4 $7.6 \times 10^{-4} \frac{mm^3}{ng}$ for IgG; $2.6 \times 10^{-4} \frac{mm^3}{ng}$ 2.6E-4mm^3/ng, 4.9E-4mm^3/ng $4.9 \times 10^{-4} \frac{mm^3}{ng}$ for IgA; 4.4E1 $2.6 \times 10^{-4} \frac{mm^3}{ng}$ mm^3/ng, 6.7E-6mm^3/ng for non IgG/A. The non IgG/IgA protein sample had the highest binding affinity, by a factor of 1000 10^3.

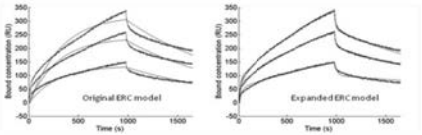

Figure 1 the effective rate constant (ERC) model (grey) fitted to data from parallel experiments (black)

Conclusion: Calculation of binding kinetics and affinity from a polyclonal antibody sample is possible using mathematical protocols and will allow distinguishing the antibody affinity characteristics. Further clinical study is planned to describe evolution of affinities following kidney transplantation and relate with clinical outcomes.

P17

Double column immunoadsorption in ABO-incompatible transplantation – twice as good?

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Introduction: Prior to transplantation, ABO-blood group incompatible patients undergo a tailored program of desensitisation to reduce antibody titres. For patients with high starting tires (>1:128) this may require several sessions of immunoadsorption (IA) prior to transplantation. At our centre we have started using double IA columns (Glycorex) the day before surgery in order to increase the plasma volume processed, and reduce ABO titres sufficiently to allow safe transplantation.

Methods: We compared 5 ABO-incompatible patients in whom double column (DC) IA was used the day before surgery (Day -1), with a group of patients with a baseline antibody titre not less than 1:64 in whom single column (SC) IA was used at the same time point.(n = 9) ABO antibody titres were expressed as dilutions

Results: 80% (n = 5) of the DC group had the highest baseline was 8 (titre of 1:256), compared to 11% (1) of the SC group. The mean reduction in antibody dilution was 3 dilutions for the DC (95% CI 1.5-4.5) and 1.4 antibody dilutions for the SC group (95% CI 0.6-2.2), this was significant (p=0.01) The mean volume of plasma processed was greater in the DC group (14.4L) compared to the SC group (7.5L), which was significant (p = 0.0019). The mean number of IA sessions required pre-transplant was less for the DC group (2.6) compared to the SC (4.1) however this was not statistically significant (p = 0.12)

Discussion: Double column IA allows for a more effective reduction of ABO antibody levels by processing a greater volume of plasma. DC IA probably reduces the number of IA sessions required for high titre ABO-incompatible desensitisation, although our sample size is too small to show this effect. We now have greater confidence in high baseline titre ABO-i patients that desensitisation will be complete for the scheduled day of surgery. This increased efficiency represents a saving in time and cost. Outcomes are unaffected by this procedure. The rapid reduction in ABO tire by a single treatment of double column IA raises the possibility of deceased donor ABO-i transplantation.

P18

ABO incompatible renal transplantation without augmented immunosuppression or antibody removal - report of 10 cases

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Introduction: Many centres now perform renal transplants from live donors into ABO blood group incompatible (ABOi) recipients. Treatment protocols are varied but include some or all of pre-transplant rituximab, splenectomy, IVIG, T-cell depleting antibody induction, and antibody removal. The aim of such treatment is to reduce recipient ABO antibody titres to 'safe' levels (typically a titre of 1:8 or less) on the day of transplant. Here we report 10 successful ABOi transplants in patients with a baseline titre of 1:8 or less, none of whom received antibody removal or augmented immunosuppression.

Methods: Between 2006 and 2011 20 patients have received an ABOi live donor transplant in Newcastle. In 10 of these the baseline IgG and IgM ABO antibody titres (measured using DiaMed gel-cards) were consistently 1:8 or less (1:8 for 3 patients, 1:4 for 3 and 1:2 for 4). Five of these patients were blood group O, with two A1, two A2 and one group B donor. The other 5 recipients were group A, with two AB and three B donors. Outcomes were compared to a cohort of 32 patients receiving an ABOi transplant in either Newcastle or Cambridge over the same time period. ABO titres in this cohort were between 1:8 – 1:2048, and immunosuppression included both Rituximab and plasma exchange.

Results: All patients received basiliximab induction followed by tacrolimus, MMF and prednisolone maintenance immunosuppression. All patients had primary graft function. There have been no episodes of either biopsy-proven or clinically determined rejection. 8 patients have stable graft function with a mean serum creatinine (SCr) of 111µmol/L (range 86-140) after 21 months follow up (2-74). One patient required ureteric reimplantation after a period of obstruction, and now has a stable SCr of 198µmol/L at 2 years follow up. The tenth patient has impaired graft function with SCr of 185µmol/L in the setting of very substantial weight gain. These results compare favourably to outcomes in the comparison cohort in which 1 year patient survival was 94%, and death-censored 1 year graft survival 93%. AMR was diagnosed in 2 of these 32 patients (6.25%), leading to graft loss in 1 case (albeit with a very high pre-treatment titre of 1:2048).

Conclusions: ABOi live donor renal transplantation can safely be performed without antibody removal or enhanced immunosuppression in patients with a baseline antibody titre of 1:8 or less. We suggest that ABO antibody titres should be measured in all patients with an ABOi live donor. We also believe that ABO antibody titres may usefully be measured in ABO group O patients on deceased donor waiting lists. ABOi kidneys could be offered to those with low titres, something that may be of particular benefit to HLA sensitized group O patients.

P19

Steroid sparing abo incompatible renal transplantation with alemtuzumab

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ABO incompatible [ABO] live-donor renal transplantation is a successful and accepted form of treatment for patients with renal failure. Most antibody removal protocols are complex and expensive, usually with rituximab [RTX] induction. In this study we compare the use of RTX with Alemtuzumab [ALZ] as induction agents with a steroid sparing regime. 63 [39m, 24f; mean age 47 ±11.9 years] ABOi patients received a steroid sparing regime. 24 patients received induction with RTX [1gm x 2] and Daclizumab with tacrolimus [tac] and MMF. 39 patients received ALZ induction [50 mgs] and tac monotherapy. Blood group antibody was removed by plasma exchange. Rejection was biopsy proven. Antibody mediated rejection was treated with plasma exchange, ivIg, MMF and steroids and T cell rejection with steroids and MMF.

There was no difference in patient survival at 1 and 3 year [yr] post transplantation between the 2 groups. [RTX 100% and 95.8% vs. 97.4% and 97.4 % ALZ group; p=0.74]. Similarly, 1 and 3 yr censored allograft survival did not differ between the 2 groups [RTX 90.9% and 86.4% vs 94.4% and 90.5% ALZ group; p=0.32]. 25/63 [40%] patients experienced rejection. Rejection free survival was similar in both groups; [RTX 70.8% and 58.3% vs 71.8% and 59.9% ALZ group at 1 and 3 yrs respectively [p=0.78]. The incidence of AMR and TCR was similar in both groups. Infection free survival was similar the 2 groups; RTX 61.1% and 50.0% vs ALZ 56.4% and 51.0% at 1 and 3yrs respectively [p=0.71]. Allograft function [MDRD eGFR] was similar in both groups; [RTX 50.7 and 53.6 mls/min and ALZ 51.8, 47.3mls/min at 1 and 3 yrs respectively]. This study shows that induction with either RTX or ALZ produces similar results in ABOi transplantation using a steroid sparing regime.

Poster session

Wednesday 13th March

18:15 - 19:25

Antibody incompatible transplantation 2

P20

ABOUT-K study – a prospective study of ABO incompatible kidney transplants

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Introduction: The UK antibody incompatible registry finds poorer outcomes in ABOi recipients than expected from international comparator groups. Nevertheless this remains a potentially important treatment strategy particularly for blood group O recipients who inevitably accumulate in paired exchange schemes. The ABOUT-K multicentre observational study of ABOi transplantation includes patients recruited from 10 centres in the UK. It aims to study clinical variables that might usefully inform risk stratification and optimise outcome.

Method: Clinical variables were collated using an electronic CRF maintained by Eclinso AG in accord with GCP and ethics committee approval. Samples for central antibody assessment were returned to NHSBT Birmingham for storage at -80^{0}C and subsequent analysis in parallel with clinical samples at 7 different time-points. Patients were treated according to local protocols. 100 patients recruited received an ABOi kidney transplant.

Results: The mean age of recipients was 48.1± 13.6years, 41% were female, 68% were blood group O. 59% of donors were blood group A1. 1 year follow-up has been reached in 80 patients. The median local titre against donor blood group at baseline was 32 (range 0-512) and at transplantation was 4 (0-64). 58% of patients received IA vs 28% PEx (either PEx or DFFP). The mean titre reduction per EART was 1.4±1.2 (IA) and 1.8±1.5 (PEx). 1 year patient survival was 98.9% and 1 year DCGS 95.5%. Acute rejection occurred in 25.5% of recipients of which 22.9% this was reported as being antibody mediated (AMR). The three graft losses were reported to be secondary to AMR, in patients with baseline local titre against donor blood group > 1/64. 1 year creatinine in patients reaching follow-up is 132.7 ± 46.2 micromol/L. Significant inter-centre variability in blood group antigen specific antibody quantification is reported in another submission.

Conclusion: In the ABOUT-K study 1 year patient and graft survival approach UK antibody compatible live donor outcomes. The incidence of acute rejection and graft loss attributed to AMR is high, although the current study has not reported on control groups. It provides preliminary data on treatment, outcome and complications that will inform future multi-centre study and outcome optimisation in ABOi kidney transplantation.

P21

Biomarker predictors of rejection in hla incompatible transplants

Melanie Field[1,4], David Lowe[2], Rob Higgins[3], Andrew Ready[1], David Briggs[2], Mark Cobbold[4], Nick Inston[1]

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Background: Whilst results from HLAi transplants continue to improve, as protocols for immunological modulation evolve, graft survival is lower than in the standard live donor transplants and rates of rejection are significantly higher. We wanted to determine whether a panel of serum biomarkers would be able to inform on those recipients who would subsequently develop rejection.

Method: Serum samples from 59 patients undergoing HLA incompatible transplantation were analysed at the timepoints of pre-transplantation, day 1 post-transplant and 30 day post-transplant. These were analysed for a panel of five biomarkers. Levels were determined by a multiplex microsphere platform and then correlated to the outcome as either rejection in the first 30 days following transplantation or no rejection.

Results: Biomarker levels were not shown to differ between the two groups pre-transplant but on day 1 following transplantation statistically significant differences were seen between NGAL (p=0.002), IP-10 (0.048) and Cystatin C levels (p=0.017) with higher levels correlating to those patients who subsequently developed rejection in the first 30 days following transplant. NGAL was the most significantly different with an AUC of 0.74. NGAL levels at 30days were not statistically different suggesting that treatment for the rejection episode had ameliorated the difference.

Conclusions: This data suggests that NGAL levels at very early time points post transplantation may have a predictive role in determining rejection within the first 30days in the HLAi patients. The return to comparable levels between the two groups following rejection treatment suggests it may also have a role for ensuring sufficient immunosuppression is being used. This suggests the possibility of either identifying those at higher risk and increasing treatment regimes or identifying those at lower risk and modifying immunosuppression accordingly.

P22

Clinical significance of the flow cytometric cross match in the luminex era of kidney transplantation

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Introduction: Flow cytometric crossmatch (FXCM) and solid phase assays are used to identify kidney transplant recipients at risk of rejection. The clinical significance of the FXCM in the presence or absence of Luminex donor specific antibodies (DSA) remains a contentious area. We compared patients transplanted across a positive FXCM to patients transplanted across a negative FXCM in the presence and absence of DSA.

Method: All incident kidney transplant patients at our centre between 2007-2011 were retrospectively analysed and divided into four groups. Patients transplanted across a positive FXCM were compared with patients transplanted across a negative FXCM with and without detectable DSA.

Results: The incidence of rejection was highest in patients with detectable DSA transplanted across a positive FXCM (p=0.003). Patient and graft survival were also lowest in this group. Patients without detectable DSA transplanted across a positive FXCM had similar rejection rates and graft survival to patients without detectable DSA transplanted across a negative FXCM (p=0.26, p=0.13).

	DSA –ve FXCM -ve	DSA +ve FXCM –ve	DSA -ve FXCM +ve	DSA +ve FXCM +ve
N	230	37	84	52
DGF	25.65%	21.62%	21.43%	42.31%
Rejection at 1 year	18.26%	18.92%	13.1%	34.62%
Graft survival at 1yr	90%	78.38%	94.05%	80.77%
Patient survival at 1yr	94.35%	94.59%	96.43%	88.46%
Proteinuria (mg/mmol)	44.78	44.08	38.67	157.19
Mean eGFR at 1yr	47.46	49.2	51.12	47.2

Discussion: Patients transplanted with DSA- FXCM+ have similar outcomes to patients who were DSA-FXCM-. Low risk immunosuppressive regimes maybe used in this subset of patients. Patients with DSA and positive FXCM have poor outcomes and need to be treated with caution.

P23

A systematic review of the use of rituximab as desensitisation therapy in renal transplantation

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Introduction: Rituximab is a B-lymphocyte depleting agent used to treat lymphoma and autoimmune diseases. Recently, it has gained interest as an immunomodulator in renal transplantation. This systematic review evaluates the evidence for its use as desensitisation therapy in ABO-incompatible and highly-sensitised recipients.

Methods: A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. 4 databases and 3 trial registries were searched for studies comparing rituximab with non-rituximab desensitisation protocols. Poor study quality precluded meta-analysis and thus a narrative review was conducted.

Results: 20 manuscripts met the inclusion criteria, relating to 10 individual retrospective cohort studies. 5 studies compared rituximab to splenectomy in ABO-incompatible patients; most found no significant differences between protocols. The remaining 5 studies focused on highly-sensitised recipients and provide stronger evidence. All 3 studies reporting changes in sensitisation levels found a significant improvement with rituximab. This resulted in 3 studies reporting a significantly lower incidence of rejection with rituximab; the remaining 2 found a strong trend in this direction. Further benefits with rituximab included better patient (1 study) and graft survival (3 studies) and graft function (1 study). No study reported significantly poorer outcomes with rituximab; indeed 2 found that it significantly reduced incidence of viral infection.

Discussion: A number of retrospective studies suggest that rituximab-based desensitisation protocols might be efficacious in renal transplantation. Randomised controlled trials are required to better define its effects, long-term safety and optimal dosing regimen.

P24

Differences in anticoagulation strategies between membrane and centrifugal therapeutic plasma exchange

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Introduction: Therapeutic Plasma Exchange (TPE) can be delivered using membrane filtration (mTPE) or centrifugal (cTPE) techniques. Comparison of the techniques in the literature is limited. We had the opportunity to retrospectively compare the use of both techniques in a group of 3 patients in whom systemic anticoagulation would be hazardous. Centrifugal TPE was available to us intermittently during their treatment.

Methods: Three patients with immunologically mediated kidney diseases (2 anti-GBM and 1 SVV-ANCA) underwent TPE using both mTPE and cTPE. We compared practical elements of these 2 methods in 9 mTPE (Prisma device; TPE2000 set; Gambro) and 27 cTPE (Spectra Optia apheresis system; TPE protocol; Terumo BCT) procedures. Heparin was used in mTPE procedures according to standard guidelines using heparin bolus (30-40 IU/kg) and infusion rate (1000-2000 IU/h). ACT monitoring was not available in our unit. Citrate anticoagulation of the extra-corporeal circuit was employed in cTPE. The incidence of clotting, successful completion of procedures, heparin dose required to prevent filter clotting, systemic anticoagulation, treatment times and citrate adverse effects were reviewed.

Results: In mTPE procedures, large doses of heparin were required to prevent filter clotting. mTPE sessions took longer to complete and repeated set-up of the circuit for mTPE contributed. No clotting was observed during cTPE procedures using citrate as an anticoagulant. Out of the 9 mTPE procedures, 2 could not be completed. In contrast, all 27 cTPE were successfully completed. Minor citrate adverse effects were observed in one patient during 1/27 cTPE session.

Discussion: mTPE procedures using our protocols were associated with a need for substantial heparin doses, frequent filter clotting and were time-consuming and labour intensive. Our limited experience of cTPE suggests practical advantages. These need to set against capital investment and consumable costs.

P25

Development of surface plasmon resonance based assay to measure binding kinetics and affinity of HLA-specific antibodies

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Introduction: HLA-specific antibodies have varied clinical responses and several characteristics have only partly explained the varied response. We aimed to develop a surface plasmon resonance assay to characterise binding kinetics and affinity. The potential impact of these on graft outcome has not been studied yet.

Method: HLA-A2 proteins were immobilised on an SPR chip and probed with antibodies in a flow system. Human HLA-specific monoclonal antibodies produced by hybridomas and polyclonal HLA A2-specific antibodies from plasma effluent were purified using affinity chromatography. Mathematical protocols were used to calculate binding kinetics and affinities.

Results: The binding kinetics at various concentrations of the monoclonal (A) and polyclonal (B) HLA A2-specific antibodies is shown in figure 1. The binding kinetics calculated using Langmuir with mass transport model are as follows:

	Monoclonal	Polyclonal
K_a (association rate constant)	1.06E +05 1/Ms	9.67E+05 1/Ms
k_d (dissociation rate constant)	1.14E-04 1/s	3.65E-09 1/s
KD (equilibrium dissociation constant)	1.08E-09 M	3.77E-15 M

The affinity of polyclonal HLA-specific antibody is higher compared to the monoclonal HLA-specific antibody.

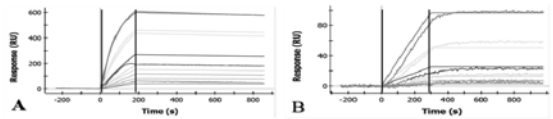

Figure 1: Binding kinetics curves and fitting of mathematical protocols for monoclonal (A) and polyclonal (B) HLA-specific antibody

Conclusion: Binding kinetics and affinity can be measured using mathematical protocols over surface plasmon resonance assay. A longitudinal clinical study is planned to describe evolution of affinity following kidney transplantation.

P26

Clinical scale removal of hla-a2 specific antibodies from human plasma

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Introduction: Although the study of HLA antibodies has advanced rapidly in the last few years because of sensitive microbead assays for their measurement, it has not been possible remove HLA antibodies specifically from patients' plasma. This ability to remove HLA antibodies would allow better investigation of the properties of these antibodies, and potentially open windows for new therapies.

Method: HLA–A2 was produced in milligramme quantities in soluble form from mammalian cells. After purification, it was linked onto sepharose and the specificity and binding capacity checked using the pan-HLA class I monoclonal antibody W6/32. A column containing 65ml HLA-sepharose was used to remove antibodies from human plasma. Plasma from three patients treated with double filtration plasmapheresis prior to transplantation was stored frozen, thawed, filtered, and then diluted with PBS so a level of A2 antibody with microbead reactivity of 2000-7500 units was used in experiments. 2.5 litres of plasma, a plasma volume representative of a 50kg patient, was run through the column in each pass at a rate of 50ml/min, washed with PBS, and then antibody was eluted from the column.

Results: Monoclonal antibody studies showed a column capacity in the region of 25mg. In the three patient samples HLA-A2 specific antibodies were reduced by over 80% in all cases following a single pass through the column. In all cases large amounts of HLA-specific antibody (15-20mg) was isolated from the column and specificity was confirmed using single antigen bead assays and the HLA MatchMaker analysis package.

Discussion: These experiments show that it is feasible to produce large quantities of HLA protein and link them to sepharose at a scale sufficient to significanty reduce specific antibodies from sensitised patients. Eluates from these columns comprise purified HLA-specific antibodies. This approach has notable potential applications, including direct measurement of antibody characteristics, use in cell culture systems, and potential for therapeutic intervention.

P27

Antibody incompatible transplantation: comparable outcomes to standard live donor transplantation

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Background: Antibody incompatible living donor transplantation is an increasingly viable option for patients who do not have a compatible donor. Despite the potential survival benefits to the recipient, UK data suggests a loss of the live donor graft survival advantage. We describe our experience over a 5 year period.

Methods: A retrospective analysis of 20 recipients who underwent ABO incompatible (ABOi) or flow crossmatch positive HLA incompatible (HLAi) transplant between 2007 and 2012. All patients received anti CD20 monoclonal antibody and plasma exchange prior to transplantation. ABOi patients received basiliximab induction while HLAi patients received a single dose of IVIg and ATG induction. Maintenance therapy was with Tacrolimus, Mycophenolate Mofetil and tapered steroid withdrawal.

Results: 15 patients underwent ABOi transplantation with Anti A/B titres ranging from 1:256 to 1:4. Four patients underwent HLAi transplant with pre donor specific antibody of 5000 to 14000 MFI. A further patient underwent a combined ABOi and HLAi transplant. Median follow up was 29.1 months (range 7.1 – 67.5) one year graft and patient survival was 100%. One patient died of pneumocystis pneumonia at 19 months. a further patient developed recurrent C3 nephropathy at 8 months post transplant. Six patients (30%) experienced 7 episodes of rejection (4 T cell and 3 antibody mediated). Median serum creatinine at 12, 24 and 36 months was 110, 100 and 98umo/l respectively.

Conclusions: Our results show that selected patients undergoing antibody incompatible transplantation using a standard plasma exchange technique can achieve similar outcomes to compatible living donor transplantation, without the loss of live donor advantage.

P28

Complement fixing HLA antibodies predict outcome in HLA incompatible renal transplantation

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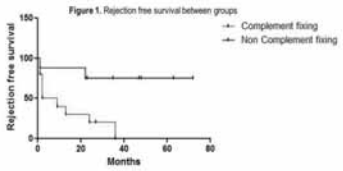
HLA incompatible [HLAi] transplantation after desensitisation is associated with a higher incidence of antibody mediated rejection [AMR] and transplant glomerulopathy [TG]. In this study we show that HLAi transplant patients with complement fixing donor specific antibodies [C1q+DSAbs] have a higher incidence of AMR and TG than patients with non-complement fixing DSAbs [C1q-DSAbs]. 18 HLAi patients [m3, f15, mean age 47.9±13.83 years] underwent desensitisation [DS] with plasma exchange, IVIg and monoclonal antibody induction pre transplant and Tacrolimus, MMF and a week of steroids post-transplant. Rejection was diagnosed by biopsy. Stored serum samples from patients pre and post DS and at the time of rejection were retrospectively analysed with a C1q assay [One Lambda] to determine C 'fixing IgG and IgM DSAbs. Death censored graft survival was 100% at 1 year and 77.8% at 5 years. 4 patients lost their grafts [3 from rejection; all had C1q+DSAbs].10/18 (55.6%) patients had C1q+DSAbs and patients with C1q+DSAbs were significantly more likely to develop rejection compared with C1q-DSAbs patients [(fig 1) 90% vs. 25%, p=0.01]. 8/11 patients who developed rejection had complement fixing antibodies at the time of their first rejection episode;.C1q+DSAbs patients had poorer allograft function and more proteinuria than C1q-DSAbs patients [p<0.001]. Peritubular capillaritis [p=0.01] and glomerulitis [p=0.01] were more common in biopsies from C1q+DSAbs patients. 4 patients with C1q+DSAbs progressed to TG.

This study shows that HLAi transplant patients with C1q+DSAbs have a significantly higher incidence of rejection and graft loss; pre-screening for C1q+DSAbs identifies high risk patients.



P29

Deceased donor HLA antibody incompatible renal transplantation without antibody removal – high incidence of acute rejection reduced by T-cell depleting induction therapy

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Introduction: Screening for HLA-specific antibodies (Ab) is routine for patients on kidney transplant waiting lists, and HLA antigens to which a patient has detectable Ab are listed as 'unacceptable mismatches'. Many units use a stringent definition of unacceptable, for example any HLA antigen to which Ab can be detected with an MFI >1000 (using the Luminex® platform). Whilst this approach is effective in preventing a positive crossmatch (XM) following allocation, it also precludes the offer of organs to sensitized patients. Here we describe our experience of deceased donor (DD) renal transplantation knowingly performed in the presence of donor-specific anti-HLA Ab (DSA).

Methods: 26 patients received HLA Ab-incompatible (HLAi) DD transplants in one of two circumstances: (1) Patients in whom the threshold for 'unacceptable' for any HLA specificity was increased to a Luminex MFI > 3000 (n=8), and (2) Patients with a positive flow cytometry B-cell crossmatch (FC-BXM) in whom pre-formed DSA were confirmed post-transplant (n=18, 12 with isolated DP DSA). Complement-dependent cytotoxicity crossmatch (CDC-XM) using a recent pre-transplant serum sample was negative in all patients. FC-BXM was positive in 17 (65%). The mean DSA MFI was 5268 (range 1086-16356) and mean follow-up length was 24.2 months (range 1-76). All episodes of antibody-mediated rejection (AMR) and T cell-mediated rejection (TCMR) were analyzed.

Results: All patients received tacrolimus, MMF and prednisolone. Induction agents used were Basiliximab (n=8), Alemtuzumab (n=14) and Thymoglobulin (n=4). No planned Ab removal was used, but DSA monitored. Patients with rising DSA titre or graft dysfunction underwent allograft biopsy. Death-censored 1 year graft survival was 94.4% (17/18 patients with >12 months follow up). Acute rejection (AR) was significantly more common in those receiving basiliximab at induction compared to a T-cell depleting agent (75% (6/8: 3 with TCMR and 3 with AMR) versus 22% (4/18: all AMR) respectively, ***p=0.018***). Patients developing AMR were more likely to have a positive CDC-XM using historic serum (5/7 with AMR versus 2/19 without AMR, ***p=0.028***). Of the 12 patients with isolated DP DSA, 2 experienced AMR and 2 TCMR. All episodes of AMR were reversed with plasma exchange. Mean creatinine for those patients with graft function at baseline (23/26) was 137µmol/L and at 1 year was 133µmol/L (n=17). There were 4 deaths (post-operative haemorrhage at 2 weeks, disseminated aspergillosis at 3 weeks, sepsis at 2 months and a cerebral lymphoma at 4 years) and 1 graft loss (graft rupture with Banff 2B AR at 1 week).

Conclusions: HLAi DD renal transplantation is associated with a high incidence of AR, with AMR in 27% of patients despite negative CDC-XM. Our limited experience suggests that: (1) T-cell depleting induction is beneficial, (2) A current negative but historic positive CDC-XM could prompt prospective antibody removal (3) In this small cohort, AMR was successfully reversed in all patients using a plasma exchange-based protocol and (4) donor HLA-DP genotyping should be routine practice. Despite high rates of AR, transplantation in these high-risk recipients is still achievable with satisfactory allograft function at up to 5 years post-transplant.

P30

HLA antibody-incompatible (HLAi) live kidney transplant between Jehovah's Witnesses (JW)

Aryeh Greenberg[1], Iain MacPhee[1,2], Joyce Popoola[1,2], Deborah Sage[3], Rehana Iqbal[1,4], Nicoletta Fossati[1,4], Sarah Heap[2], Mohamed Morsy[2], Nicos Kessaris[5]

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Introduction: Haematological complications of HLAi transplantation coupled with the medical requirements of JW make this procedure challenging. We report a successful case of HLAi transplantation between JW.

Methods: Both donor (daughter, age 27) and recipient (mother, age 50) were JW. CDC crossmatch was negative but flow cytometric HLA crossmatch was positive due to Class I DSA defined using Luminex™ assay to HLA-A36, B53 and Cw4 (MFI 1880, 4149 & 4427 respectively) and to Class II (DP1, MFI 5399). Donor and recipient were keen to proceed, accepting the high risk in case of bleeding due to their religious beliefs. They agreed to have cell salvage intraoperatively as well as IVIg as part of the desensitization regimen, albumin, cryoprecipitate, iron and erythropoietin as necessary but under no circumstances were they willing to have blood, fresh frozen plasma or platelets. A single IV dose of rituximab (375mg/m^2) was given 1 month prior to transplantation. Prednisolone (30mg), tacrolimus aiming for trough whole blood concentration of 10-15µg/L and mycophenolate mofetil (1g twice daily) were commenced 10 days before transplantation. The patient underwent four sessions of Double Filtration Plasma Exchange (DFPE) each followed by low dose IVIg (0.1g/kg). **Results:** The donor underwent laparoscopic hand-assisted retroperitoneoscopic nephrectomy. The organ was transplanted into the recipient successfully. Cell salvage was not needed intraoperatively. There were no complications and blood loss was 110ml for the donor and the same amount for the recipient. Prior to transplantation, the recipient received methylprednisolone (1g) and basiliximab (20mg) with a second dose on day 4. On the second post-operative day, the patient had a planned session of DFPE. DSA titres were checked daily initially and no further DFPE was required. After 16 months the serum creatinine is 70µmol/L with no rejection episodes.

Discussion: A multidisciplinary approach made this procedure possible. This is the first case of HLAi kidney transplantation in JW described in the literature and thus may allow further such transplants to be carried out in the future.

Poster session

Wednesday 13th March

18:15 - 19:25

Complications of transplantation 1

P31

Lung cancer in organ transplant recipients

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The burden and impact of lung cancer among transplant recipients and a comparison between recipients of lung and other organs has been studied in small cohorts with limited follow-up. Here we report the incidence and outcome of lung cancer in lung recipients as compared to recipients of other solid organs from a large national registry data.

The data from the National Transplant Registry was used to link the details of solid organ recipients (1990-2007, excluding those who died within a month of transplantation), with the Cancer Registries to identify all recipients diagnosed with lung cancer after transplantation. Of a total of 33658 recipients, 300 (0.89%) developed lung cancer. The standardised incidence ratio (incidence compared with age-gender-year-matched general population) for lung cancer was significantly higher ($p<0.0001$) in lung recipients (9.3) compared to other organ recipients (2.2). Among those diagnosed with lung cancer within 10 years after transplantation, lung recipients developed lung cancer significantly sooner following transplantation ($p=0.001$) than other organ recipients (median time to diagnosis 3.4 years [95%CI 1.6, 5.2] and 5.5 years [95%CI 4.9, 6.1] respectively). The higher incidence and earlier development of lung cancer among lung recipients was not associated with poorer outcome: median survival from diagnosis of lung cancer among lung recipients was 131 days (95%CI 65, 220) and other organ recipients 137 days (95%CI 99, 190). Small cell subtype of lung cancer (which has poorer prognosis) was more common among other organ recipients (10%) than lung recipients (3%).

Lung cancer is a significantly greater challenge among lung recipients compared to other solid organ recipients, affecting more patients earlier in their post-transplant period. Possible reasons for absence of poorer survival among lung recipients may include lower proportion of small cell type of cancer and diagnosis at earlier stage of cancer due to routine post transplant imaging of lungs.

P32

Screening and management of the new onset of diabetes after transplantation – a single centre experience

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Introduction: New onset diabetes mellitus after transplantation (NODAT) is a serious complication in renal transplant recipients associated with increased risk of cardiovascular morbidity and mortality, accelerated graft loss and reduced patient survival. Identification of high-risk patients, early detection of NODAT cases and aggressive management of the condition may improve long-term outcomes. The aim of our study was to determine the incidence and management of NODAT in our tertiary nephrology centre.

Methods: This was a retrospective study on patients transplanted in the North East of England between January and December 2009. Patients with known pre-existing diabetes and previous organ transplantation were excluded. The demographic characteristics and risk factors for developing NODAT were documented. Over a follow up period of 30-42 months, all screening tests for the detection of NODAT were reviewed and diagnosis of new cases recorded.

Results: Of 36 renal transplant recipients, 27 fulfilled the inclusion criteria for this study. 18.5% developed NODAT and 11.1% developed new impaired glucose tolerance. Further 11.1% cases were found to have undiagnosed abnormal glucose homeostasis pre-transplantation. The median time to first abnormal screening test (blood glucose/ HbA1c) was 12 weeks (range 1-152). The median time from the abnormal screening test to diagnosis was 16 weeks (range 0-36). All but one case developed NODAT within 12 months of transplantation with the incidence being the highest in the first 6 months (14.8%).

Conclusion: The incidence of NODAT in our study is comparable to that reported in the literature. Our patients were screened in keeping with recommendations. There was an observed delay in the diagnosis and, therefore, management of NODAT and transplant associated hyperglycaemia overall. This highlights the need for ongoing collaboration between nephrologists and diabetologists in the development of departmental guidelines.

P33

Colorectal cancer in the liver transplant population: a multicentre epidemiological analysis over 20 years

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Introduction: Liver transplant (LTx) recipients are at an increased risk of developing de novo malignancies; although this risk is less clear for colorectal cancer (CRC). We aimed to determine if the risk of CRC is increased after LTx in all patients and specifically in LTx patients with inflammatory bowel disease (IBD), and to compare survival with the general population.

Methods: This is a UK multicentre study across 5 Liver Transplant Units of all patients undergoing LTx between 1990 and 2010 in the United Kingdom. NHSBT provided LTx data. The National Cancer Intelligence Network (NCIN) and individual units provided the CRC and IBD data.

Results: 7726 patients had a liver transplant and 41 (0.5%) were subsequently diagnosed with CRC giving a standardised incidence ratio of 1.56 compared with the UK population. The median (IQR) time from LTx to CRC diagnosis was 5.6 (3.9, 8.8) years. Of the 41 CRC diagnoses, 18 (43.9%) occurred on a background of colitis, most commonly ulcerative colitis. The SIR of CRC in patients with colitis was 15.57 (95% CI (9.4, 24.5). 19 (51.4%) patients died during follow up. Median survival from CRC diagnosis was 4.7 years in patients with CRC and 10.4 years in patients with cancer and colitis. Median survival time from liver transplant for all patients was 17.2 years (95% CI (16.2, 18.1)).

Conclusion: The risk of de novo CRC among LTx patients is comparable to the general population and an intensified screening programme cannot be recommended based on these findings. Patients with colitis would benefit from a regular screening programme.

P34

Hyperuricaemia increases the risk of new onset diabetes after renal transplantation

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Background: New onset diabetes after transplant (NODAT) is a common complication of solid organ transplantation and has a significant effect on graft and patient survival. A number of shared risk factors with type II diabetes have been described. Here we present data on the association between pre-operative urate concentration and NODAT.

Methods: We performed a retrospective analysis of kidney transplants performed in a single centre. Diabetes was diagnosed using WHO criteria based on random glucose levels. Baseline clinical and demographic data were recorded including pre-operative uric acid level. Patients received standard follow-up and were monitored for primary outcome measure of development of diabetes.

Results: A total of 306 transplants were performed. Thirty nine recipients (12.7%) were diabetic before transplantation. Mean follow-up period was 1963 days (sd 513days), during which 55 cases (18%) of NODAT were identified. Diabetes was diagnosed after mean 113 days. Age (OR 1.05 [95%CI 1.02-10.7]) and serum urate (OR 1.005 [1.001-1.008]) were found to be associated with an increased risk of developing NODAT using logistic regression. Median age and urate in the upper quartile were used to generate a dichotomus model. Age>50 years at transplant (HR 2.51; p=0.004), and urate>370μmol/L (HR 2.69; p=0.002) were associated with an increased risk of NODAT in univariate and multivariate models

Discussion: Increasing age is an established risk factor for NODAT. To date, urate has not been linked with the condition despite evidence of an association in type II diabetes mellitus. This study suggests urate should be considered as a candidate risk marker for NODAT.

P35

Early identification of skin cancer in renal transplant recipients through a nurse-led skin surveillance service

D Choi, RM Montero, C Harland, M Wahba

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Introduction: Non-melanoma skin cancer (NMSC), has become one of the major causes of morbidity and mortality in renal transplant recipients (RTRs), with a 20 fold increase of NMSC rates in RTRs. Previous studies predominantly address the incidence of these cancers in white populations while little is available to compare ethnically diverse populations such as that found in London. This study was to determine the incidence of skin lesions occurring in RTRs and the impacts of skin surveillance screening clinics.

Methods: 152 RTRs were seen in our renal and transplant unit nurse-led skin screening clinic between September 2010 and November 2011, 27 were excluded (16 DNA, 5 declined, 3 reviewed elsewhere, 1 death, 1 notes were unavailable). A total of 125 RTRs were reviewed for diagnosis of de novo skin lesions in consultant/nurse led clinics. Diagnoses of de novo skin lesions, demographics and clinical data were collected retrospectively from patients' notes.

Results: Male to female ratio 2:1, mean age 53.4yrs. 65% White, 17.6% Asian, 15.2% Black and 1.6% not stated. NMSC were found in 13 patients (12 BCC, 1 SCC), no melanoma was found. There were 17 pre-malignant lesions (PMLs) in 15 RTRs (11actinic keratosis, 5 Bowen's disease, 1 lentigo maligna). Total NMSC in this cohort was 10.4% with total PML of 12%. The incidence of NMSC in this cohort was 6.8%, and PMLs of 9%. Both NMSC and PML occurred in less than 5years and more than 10 years post 1st renal transplant.

Discussion: The incidence of NMSC and PMLs in this cohort supports the need for skin surveillance screening in RTRs. It also indicates both NMSC and PML are present in RTRs within 5 years of transplant and would support early screening post transplant. Long term follow up should also be considered in view of NMSC and PML detected at more than 10 year post transplantation. This nurse-led service with early detection and relatively simple and inexpensive treatments represents a cost effective way of post-operative skin management for RTRs and warrants further economic investigation.

P36

The natural history and risk factors identified for development of skin cancer in renal transplant recipients

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Introduction: There is no consensus regarding the guidance and recommendations of skin cancer surveillance in Renal Transplant Recipients (RTRs). In this cross-section observational study all RTRs attending skin surveillance clinic were reviewed to determine the natural history of skin lesions occurring in RTRs and identify risk factors associated with development of these lesions.

Methods: A total of 125 RTRs were reviewed for diagnosis of de novo skin lesions in nurse led clinics between Sep 2010 and Nov 2011. Immunosuppressive regimen, Age, gender, and skin type were looked as potential risk factors. Spearman's correlation was used for data analysis.

Results: 13 Non Melanoma Skin Cancer (NMSC) and 17 Premalignant lesions (PMLs) were found in this cohort. Increasing age significantly correlated with the development of Bowens disease (BD) ($p=0.03, r=0.20$). BCC had a predilection for male RTRs ($p=0.01$). A bimodal distribution appeared in both NMSC and PML at <5yrs (mode for BCC: 3 yrs) and >10yrs post 1st renal transplant (RT). RTRs on Prednisolone (P)+ Cyclosporin (CYA) correlated with development of PML; BD ($p=0.01, r=0.246$). The combination of P + Tacrolimus (FK) + Mycophenolate Mofetil (MMF) correlated with the development of BCC ($p=0.03, r=0.197$). FK+ Aza developed cases of BCC ($p=0.03, r=0.194$) and Actinic Keratosis (AK) ($p=0.03, r=0.19$). All of the skin lesions found occurred in those with skin types I-IV with BCC, AK and BD predominantly in the lower skin type (Spearman's correlation $p<0.001, p=0.001, p=<0.01$, respectively). NMSC and PML develop before 5 years and rise steadily with a similar rate of growth by 20 yrs post 1st RT

Discussion: Early screening is recommended in view of high detection rates <5yrs of NMSC and PML in RTRs post 1st RT. The high incidence of BCC in <5yrs post 1st RT suggests a role for rigorous pre-transplant screening as BCC are slow growing lesions. Risk factors for NMSC include skin types I-IV, length and combination of immunosuppression. We recommend skin surveillance from 3yrs to 20yrs should occur as a minimum in RTRs post 1st RT.

P37

Radiological diagnosis and management of transplant renal artery stenosis

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Introduction: Transplant Renal artery stenosis (TRAS) is an uncommon vascular complication following renal transplantation, usually presenting with high blood pressure and deteriorating renal function. The diagnosis is confirmed radiologically by either Doppler ultrasound scan (USS) or angiogram and treatment is usually by means of angioplasty+/-stenting.

Aim and methods: The aim of this study was to evaluate the role of radiological imaging in the diagnosis and management of TRAS.

Results: We analysed 72 patients in whom the diagnosis of TRAS was suspected on Doppler USS between 2000 and 2012. All patients then underwent transplant renal artery angiogram with a view to proceed to angioplasty after measuring the pressure gradient across the suspected stenotic area. The median time from transplant to angiogram was 4 months (range 1-30 months). In 52 (72%) patients angiography confirmed a stenosis, which were located in the proximal renal artery (52%), origin (22%), mid artery (13%), distal artery (3.7%) branches (5.5%) or diffuse/not specified (3.8%). Angioplasty was attempted in all cases and 9 patients also needed a stent to achieve a satisfactory result. Radiological success was achieved in 96.2% patients with failure in two cases, of which one was associated with a complication. There were a total of five complications; a branch occlusion (fully resolved with balloon), rupture (managed non-operatively with covered stent), two minor dissections (managed conservatively) and one main renal artery thrombosis requiring a nephrectomy. There were two cases of residual stenosis after initial angioplasties which were stented successfully in a second attempt. There were four cases of recurrent stenosis in three patients, all of which were satisfactorily treated with repeat angioplasty.

Conclusion: US Doppler is an excellent first line investigation in the diagnosis of TRAS. Percutaneous transplant renal artery angioplasty+/- stenting is highly successful in treating the condition with a low rate of complications, the majority of which are manageable without surgical intervention.

P38

Transplant renal artery pseudoaneurysms – an endovascular solution for adults and children

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Introduction: Pseudo-aneurysmal formation of the transplant renal artery is a rare phenomenon with an estimated incidence of 0.3%. However complications associated with pseudoaneurysms include life threatening haemorrhage from rupture and allograft loss. Management primarily aims to prevent catastrophic rupture and if possible preservation of graft function, via either surgical or endovascular radiological intervention.

Methods: We report 3 patients (2 adults and 1 paediatric) who developed large (size range 5-6cm) transplant renal artery pseudoaneurysms arising from the anastomosis. These pseudoaneuryms presented late after the transplanted organ had ceased functioning. In all 3 cases the pseudoaneurysms were managed by endovascular repair (placement of covered stent in the 2 adult cases and an uncovered stent and coil embolisation of pseudoaneurysm sac in the paediatric case). Clinical and radiological follow up was between 7-12 months.

Results: The procedure was technically successful in all cases with satisfactory exclusion of the pseudoaneurysm sac and no significant clinical or radiological sequelae.

Discussion: Percutaneous endovascular radiological treatment using covered stents is a safe, effective and feasible treatment modality for late presenting transplant renal artery pseudoaneuryms in both adults and children who have undergone previous transplantation.

Poster session

Wednesday 13th March

18:15 - 19:25

Complications of transplantation 2

P39

The impact of statins on graft vessel disease in heart transplantation – a systematic review

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Background: Graft vessel disease (GVD) is a significant cause of morbidity and mortality amongst patients following cardiac transplantation. Hyperlipidaemia is a risk factor for GVD, and the majority of patients will display abnormal lipid profiles in the years following transplant. This systematic review aims to establish the impact of statins on GVD by critically appraising the literature on this subject.

Methods: A literature search for randomised studies assessing the use of statins in prevention of GVD was undertaken. The Cochrane Central Registry of Controlled Trials, Medline, Embase, clinicaltrials.gov, and the Transplant Library from the Centre for Evidence in Transplantation were searched. The primary outcome was presence of GVD. Secondary outcomes included graft and patient survival, acute rejection rates and adverse events. The quality of trials was assessed with the Jadad score, and by recording evidence of intention to treat (ITT) analysis, and adequate allocation concealment. Meta-analysis was precluded by poor trial quality, so narrative synthesis was undertaken.

Results: Eight randomised controlled trials (RCTs) were identified. The RCTs were of a poor quality; with only two trials attaining a Jadad score greater than 3, though 5 studies reported evidence of ITT analysis and adequate allocation concealment. The studies reporting measures of GVD indicate that statins do confer some benefit, demonstrating significant reductions in both incidence and severity. However, outcome reporting amongst these studies was varied. There is possibly a modest survival benefit from statin use. The included studies report a low incidence of adverse events attributable to statins. There was no difference in the overall number of episodes of rejection, but statins may reduce the risk of clinically severe rejection.

Conclusion: The published evidence supporting the use of statins to prevent GVD is of poor quality. Despite this, the evidence indicates benefit from their use, and the rate of adverse events in the trials identified is low.

P40

Case series for implantation of kidneys following tumour excision for malignancy; complications and experience to date

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Introduction: With a huge deficit between donors and recipients for renal transplantation innovative sources of organs are being sought. Many kidneys are discarded annually following radical nephrectomy for small malignant tumours. Utilising these organs safely could be cost efficient particularly for elderly recipients. This small case series describes our initial experience of transplanting kidneys following radical nephrectomy for small renal cell carcinomas.

Methods: Three potential donors were identified following their independent decision to undergo a radical nephrectomy for small renal cell carcinomas. The donors were tissue typed and their GFR's checked prior to surgery. Elderly recipients were selected and the procedures performed in a domino format.

Results: One recipient lost their renal transplant early secondary to renal vein thrombosis. Two patients achieved immediate graft function and remain dialysis independent. One of these patients had a protracted urine leak from the tumour resection which was managed conservatively. The other had an arterio-venous fistula within the kidney which was managed radiologically. To date there have been no complications related to tumour recurrence or micro-metastatic seeding although the follow-up period is currently limited.

Conclusion: Domino transplantation of kidneys following excision of small tumours offers an unique opportunity for patients unlikely to achieve a deceased donor transplant to live an improved quality of life and health without dialysis. Further development is required in surgical technique to minimise complications from the tumour excision site and longer follow-up to accurately assess the long-term risk of recurrence of tumour. This series shows promise in offering greater access to transplantation to marginal recipients.

P41

Transplant renal artery angioplasty - institutional review and short term follow up

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Background; Transplant renal artery stenosis (TRAS) is a vascular complication in renal transplantation with an incidence varying from 1% to 23%. TRAS presents clinically with hypertension and/or decreased renal function. Percutaneous trans-luminal angioplasty (PTA) is the initial treatment of choice for TRAS. However, evidence is limited to retrospective case series of 9 – 77 patients with conflicting data regarding the efficacy of PTA. We reviewed our case series of TRAS angioplasty and its outcome.

Material and methods: A retrospective review of patients referred for PTA of TRAS between 2006 and 2012. We reviewed patient demographics, clinical manifestation of TRAS, imaging findings, technical success, clinical success and complications with 3 months follow up. Clinical success was defined as more than 10% reduction in mean arterial pressure and/or reduction in antihypertensive medications. In renal failure group clinical success was defined as improved eGFR by 15 ml/min.

Results: 15 patients with TRAS had 17 PTA procedures. Male/Female ratio was 11:4, average age 52 years (range 30 - 66 years). Seven had uncontrolled hypertension, four had worsening renal function and four patients had both. 14 patients had peri-anastomotic stenosis and one patient had anastomotic and iliac vessel stenosis. PTA was technically successful in all but one patient. The procedure was clinically successful in five of the 11 patients in hypertensive group and two of the seven patients in renal failure group. Two patients with worsening hypertension required repeat PTA. One patient had procedure related acute kidney injury.

Conclusion: This case series adds to the available limited evidence that some patients with TRAS benefit from PTA, which has a high technical success and low complication rate.

P42

The incidence of hypercalcaemia following renal transplantation

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Introduction: There is an association between hyperparathyroidism pre transplant and development of tertiary hyperparathyroidism post transplantation. This study investigated the occurrence of hypercalcaemia post transplant, its relationship with parathyroid status, and effect on renal graft function.

Methods: 137 patients receiving a renal transplant between August 2006-2008 at our regional transplant unit were studied. Demographic details, type of transplant and nature of RRT/pre-emptive status recorded. Patients were followed for a mean of 60 months. Using our renal data base/ patient notes, PTH control pre transplant and subsequent episodes of hypercalcaemia post-transplant were recorded, noting magnitude of calcium rise, timing, duration and likely aetiology. Creatinine was recorded at 6m, 3y & study end.

Results: Of the 137 patients transplanted, 77 were male. Mean age at transplantation was 47.4 y (range 17-84); 105 were established on dialysis (35PD, 70HD), 32 pre-dialysis (including 4 failing transplants). PTH (pretransplant) was measured within the recommended 6 months in 70% and maintained between target 16.5-33pmol/l in only 27%. 10% of patients exhibited severe hyperparathryoidism with PTH values being over 4 fold the upper range. 23% had suppressed PTH levels < 16.5pmol/l. Mean PTH pre transplantation was 57.7pmol/l (0.3-593). Of the 137 patients, 53 (39%) were hypercalcaemic at some point (range 2.6-3.73), mean duration 321 days (range1-1470 days). 6 had severe hypercalcaemia (>3 mmol/l). Mean PTH pre transplant for those hypercalcaemic was 69.6pmol/l (76.6pmol/l in those severely hypercalcaemic). Mean rise in serum creatinine (umol/l/month) for all transplants was 4.77, and for those with post transplant hypercalcaemia the mean rise was 4.99.

Discussion: In this retrospective single-centre study hypercalcaemia was surprisingly frequent (39%). PTH control pre transplantation was found to have no clear correlation with development of hypercalcaemia. Hypercalcaemia however, had no effect on graft function or survival within a 5yr follow up.

P43

The influence of lower limb amputation on outcomes following renal transplantation

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Introduction: Peripheral vascular disease (PVD) is common in patients with established renal failure and is associated with considerable morbidity. However, the impact of severe peripheral vascular disease on graft survival in patients undergoing renal transplantation is poorly defined. The aim of our study is to assess outcomes in renal transplant recipients who have severe peripheral vascular disease necessitating major lower limb amputation.

Methods: Data for 762 patients undergoing renal transplantation in a single centre from January 2001- December 2010 was extracted from a regional transplant database. Patients undergoing lower limb amputation pre- and post-transplantation were identified and outcome measures were compared with the patients who did not undergo amputation. Outcome measures included: delayed graft function (DGF), biopsy-proven acute rejection (BPAR), serum creatinine at one year and graft loss and recipient survival at one year and long-term. Student's *t*-test and Pearson's Chi-Squared test were used to compare patients with and without amputation and Kaplan-Meier curves were used for survival analysis. A p-value <0.05 is considered statistically significant.

Results: Only 4 (0.5%) renal transplant recipients had major lower limb amputation prior to transplantation. A further 16 (2.1%) patients underwent amputation after their renal transplant. There was no difference in patient or graft survival at 1 year, serum creatinine at 1 year, DGF, or BPAR in patients who had amputation pre-transplantation when compared to those who did not. Serum creatinine at one year was significantly higher in patients who had amputation following transplantation (308.5 +/- 60.8µmol/l vs. 177.6 +/- 6.4µmol/l; $p = 0.03$). Graft loss at 1 year was also higher in patients who had amputation post-transplant than those who did not. However, this difference was not significant (18.8% vs. 7.9%; $p = 0.12$). There was a non-significant trend towards increased BPAR and DGF in patients who underwent amputation following transplant compared to those with no amputation (31.2% vs. 20.6%; $p = 0.3$ and, 31.2% vs. 18.1%; $p = 0.18$, respectively). There was no difference in 1 year survival in those patients who were amputated post-transplant compared to those who were not (100% vs. 97.4%; $p = 0.52$). However, Kaplan-Meier survival analysis demonstrated that over longer follow-up (mean: 2053.1 +/- 58.3 days), patients who underwent amputation after transplantation had a higher rate of graft loss ($p < 0.01$) and higher death rate ($p < 0.01$) than those who did not.

Conclusion: The concern regarding the risk of transplanting patients with severe PVD is evidenced by the small number of patients transplanted after major lower limb amputation. The requirement for amputation after renal transplantation is associated with a poor long-term graft and patient survival and higher serum creatinine at 1 year. Wherever possible, patients at increased risk of severe PVD should be identified prior to transplantation and measures should be taken to reduce the long-term risk.

P44

The role of urinary dipstick testing in the detection of urinary tract infection in renal transplant recipients

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Background: Urinary tract infection (UTI) is the most common bacterial infection to affect renal transplant recipients. Currently all patients attending the renal transplant clinic at the University Hospital of Wales have a urine sample sent for microscopy and culture to detect the presence of UTI. This has significant cost and workforce implications, due to the large number of samples sent daily from our clinics (70 samples/day at £2.28/sample). The aim of this prospective study was to evaluate the use of urinary dipstick testing in the diagnosis of UTI's in this population.

Methods: All patients attending twice weekly transplant clinics between 20th January and 7th February were eligible for enrolment into the study. Pts were provided with a questionnaire to asses for any symptoms, number of UTI's since transplantation, technique for providing the urine specimen and co-morbidities. Urine samples underwent dipstick urinalysis (Combur7 test, Roche) and were then sent as per usual practice for microscopy and culture. A result of $>10^4$ cfu/ml was used as the gold standard for diagnosis of bacteruria.

Results: 270 patients were included in the study. Of these 215 answered the questionnaire and had dipstick urinalysis performed. The sensitivity and specificity of using the questionnaire alone to detect UTI was 25% and 78%, with 27 UTIs being missed by this approach. The sensitivity and specificity of the dipstick alone in detecting UTI was 81% and 72% with 8 UTIs being missed. Using both tests in parallel gave an overall sensitivity and specificity of 86% and 58%. Using such an approach the total number of samples sent for culture could be reduced by nearly half, however 7 cases of bacteruria would have been missed.

Discussion: The use of a simple questionnaire in parallel with urinary dipstick testing is an effective screening tool for the detection of UTI in the transplant population and can provide significant savings in terms of cost and workforce utilisation. However these benefits must be weighed against the risk of missed diagnoses.

P45

Early renal artery stenosis on duplex scan of renal allograft is not a marker of poor graft outcome.

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Background: Last year the radiological reporting of early renal artery stenosis (RAS) at Liverpool transplant centre was perceived to be high as compared to previous years. We intend to assess if reported radiological findings had any correlation to graft function, graft survival and recipient related co-factors.

Methods: Eighty eight renal transplants carried out between March 2011 and February 2012 underwent routine post-transplant duplex scanning. The duplex scan velocities of renal artery were graded into Grade 0 (velocities-1cm - 200 cms/sec), Grade 1(201 – 400cm/sec), Grade 2(401 -600 cm/sec) and Grade 3 (> 600 cm/sec) with grade 0 as normal. All the other grades were marked as renal artery stenosis (RAS). The serial duplex scans were followed till graft dysfunction or intervention. Medcalc 18.1 was used for statistical analysis. Non Parametric Correlation was derived with Spearmann Rho test. Parametric data was analysed using Mann-Whitney test .Univariate and multivariate analysis were done with significance levels set at <0.05.

Results: Retrospective analysis showed that sixty (68%) were males, 28 (32%) were females. N=220 duplex scans were done, Grade 0-175, Grade 1 -37, Grade 2- 06, Grade 3 -02. RAS reported were not associated with graft dysfunction during the first 6 months but RAS persistent for 24 weeks and beyond correlated to worsening graft function (p=02).None of the grafts were lost due to reported RAS. Recipient diabetes (p=0.4), hypertension (spearman rank correlation) and absence of aortic patch on the renal artery (p=0.3) were not associated with development of RAS. Per-operative atherosclerosis was significantly related to RAS at 4 weeks (p=.002). The overall allograft success rate at Liverpool was comparable to previous years.

Conclusion: Probably because of the sensitive ultrasound technology and increasing experience of radiologist, there was reported increased incidence of RAS which was not significant in the first six months. Bigger sample size is required to prove the statistical significance and the study carries on prospectively.

Poster session

Wednesday 13th March

18:15 - 19:25

Donation

P46

South Asian attitudes to organ donation in the United Kingdom

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Introduction: South Asians in the United Kingdom are over-represented on the organ transplant waiting list but under-represented as organ donors. Despite concerted efforts in recent years to raise awareness of organ donation, organ registration and procurement has been lagging amongst this population. In this study we surveyed South Asian opinion with regards to organ donation, aiming to guide national strategic planning.

Methods: We conducted a survey inviting voluntary completion of an anonymous, 41-part survey by South Asians in the United Kingdom. No limitations on participation were made, although the survey was conducted in the English language only. Survey promotion was electronically conducted through internet groups/associations/internet forums and by hand distribution in local religious centres. For a population target of approximately 2.4 million, we targeted a completed sample size of 385 to achieve a 5% error margin and 95% confidence interval (assuming 50% response distribution). Logistic regression analysis was performed to assess multivariate associations with organ donation approval.

Results: 556 survey responses were analysed (481 full completions, study completion rate 86.5%). 42.8% of respondents were Indian (or British Indian), whilst 57.2% were Pakistani (or British Pakistani) and Bangladeshi (or British Bangladeshi) respectively. Religious breakdown of respondents was Muslim (70.8%), Hindu (15.9%) and Sikh (13.3%). 68.4% of respondents agreed with organ donation but only 13.3% were registered organ donors. Muslims were less likely than Hindus or Sikhs to agree with organ donation (59.3% versus 92.2% versus 88.7%, $p<0.001$) or be registered donors (5.0% versus 40.3% versus 25.8%, $p<0.001$) respectively. Pakistani/Bangladeshi respondents were less likely to agree with organ donation compared to Indian respondents (60.1% versus 80.8% respectively, $p<0.001$). Respondents living with parents were less likely to be registered organ donors (living with versus living without parents, 3.1% versus 21.3% respectively, $p<0.001$). Religious guidance was more likely to influence Muslim attitudes, while parental pressure was more influential for Hindu respondents. Distrust of the health service, poor publicity and apathy was ranked as very important factors by 24.5%, 48.0% and 43.8% of the total cohort respectively, with no discernable difference between different faith groups. On logistic regression independent variables associated with organ donation approval were; young age, independent living from parents, non-Muslims, awareness of organ donation shortages, family member on dialysis/registered donor and secular religious belief (all $p<0.05$).

Conclusion: South Asians in the United Kingdom are a heterogeneous group of different faiths, cultures and values. We believe a targeted strategy is required to raise awareness of organ donation based upon a clear understanding of religious, sociocultural and environmental influences.

P47

Time critical, fact or fiction?

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Introduction: Historically the UK has one of the worst records for organ donation in Western Europe.[1] The Organ Donation Taskforce (2008) set out to increase organ donation by 50% in the UK within five years, and made 14 recommendations in order to achieve this target. Despite embracing the increase in organ donation from critical care, there are concerns that the time it takes to facilitate the donation process is protracted and increasing over time.

Objectives: We sought to review all the donation activity in our trust since 2007 and investigate the 'fact or fiction' to the claim that time to donation is increasing over time.

Methods: We reviewed all patients that have been consented for organ donation in our Critical Care Units since the earliest accurate records began in 2007.

Results: The average time from consent to surgical start time in Donation after Brain Death (DBD) was 12.37 hr:min, and for DCD time from consent to withdrawal of life sustaining treatment 9:33 hr:min.

Discussion: From 2007-2010 the time for DBD has increased in our trust but remains in line with national data. Historically DCD donations were quicker to facilitate, however this time is increasing; for a multiple of reasons.

Conclusion: We should not accept that these times are the standard; is this fair on our patients, their families, unit activity, theatre resources, SN-OD workload and organ quality? More should be done to streamline this process and maximise every gift of donation - time is critical.

[1] Department of Health 2008. Organs for Transplants. A Report from the Organ Donation Taskforce

P48

Respiratory management of brain stem dead potential organ donors – a clinical audit of current United Kingdom (UK) practice

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Introduction: Numerous physiological changes occur after brain stem death (BSD), and studies suggest that early utilisation of strategies aimed at preventing organ damage may increase yield and quality of transplantable organs (1, 2). Strategies which may protect the lungs include regular physiotherapy/suction, recruitment manouvres, maintenance of continuous positive airway pressure (CPAP) during apnoea testing, lung protective ventilation, and administration of high dose steroids (1, 2). We describe current UK practice with regard to respiratory management of brain stem dead potential donors within the age limit for lung donation (<=65 years old).

Methods: We reviewed a database of 287 brain stem dead potential organ donors collected by Specialist Nurses in Organ Donation (SN-OD) over a 6-month period (30/04/11-31/10/11) across multiple UK centres. We analysed data on respiratory management post BSD. Patients over the age of 65 were excluded as they were outwith the upper age limit for consideration of lung donation.

Results: 236 patients met inclusion criteria and the following results are expressed as a % of this group. Where data was missing this was interpreted as not performed/given. After BSD 189 (80.08%) patients received endotracheal suction, and 64 (27.12%) received chest physiotherapy. Apnoea testing was performed with CPAP in 57 patients (24.15%). Lung recruitment manouvres were performed in 76 (32.3%) of the cohort. Methylprednisolone was recorded as given in 151 (63.98%) of our cohort. For those patients not already on a lung protective ventilatory strategy at initial SN-OD review, initiation on protective measures was variable (see Figure 1).

Conclusions: From our cohort it would appear that there is large variation in current UK management of potential organ donors following BSD with only the minority of patients appearing to receive recruitment manouvres, chest physiotherapy, or the application of CPAP during apnoea testing. We welcome the current interest in donor management care bundles and the drive towards standardization of care.

References (1) Van Raemdonck, D et al; "Lung Donor Selection and Management"; Proc Am Thorac Soc, 2009, 6, p28-38, **(2)** Venkateswaran, RV et al; "Early Donor Management Increases the Retrieval of Lungs for Transplantation"; Ann Thoracic Surgery, 2008, 85, 278-86

Figure 1

P49

Management of diabetes insipidus (DI) in brain stem dead potential organ donors – an audit of current United Kingdom (UK) clinical practice

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Introduction: DI occurs in approximately 60% of potential organ donors after brain stem death (BSD) as a result of pituitary ischaemia (1). It can lead to gross physiological changes including cardiovascular instability and severe hypernatraemia which can have deleterious effects on the suitability of organs for donation (1). We describe current UK practice with regard to the management of DI.

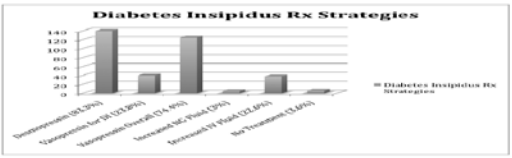
Methods: We reviewed a database of 287 brainstem dead potential organ donors collected by Specialist Nurses in Organ Donation (SN-OD) over a 6 month period (30/04/11-31/10/11) across multiple UK centres. We searched for patients with evidence of DI (ie clinical suspicion of DI and/or an initiated treatment plan for DI). We then anaylsed the use of laboratory testing for DI and use of specific treatments within the DI cohort.

Results: 168 (ie 58.5% of the overall cohort) patients had evidence of DI, the results below are described as a % of those with DI, where data was missing we interpreted this as not done/given. Seventeen (10.7%) DI patients were documented as having laboratory confirmation of DI. Desmporessin was the most commonly documented DI treatment – used in 140 patients (83.3%). Vasopressin was documented as being used specifically for DI in 38 (22.6%) patients, although when analysed across the whole period post BSD it was used in 125 (74.4%) DI patients for a variety of indications. Specific treatments used for DI are summarized in figure 1.

Conclusions: The incidence of DI in our cohort is similar to that previously described. There appears to be variation in practice and a preference for Desmopressin. There was limited use of laboratory testing to confirm DI. We welcome the development of donor management care bundles and the drive to standardize care of the potential organ donor.

References: 1) Gordon, JK et al; "Physiological changes after brain stem death and management of the heart-beating donor"; Continuing Education in Anaestheisa, Critical Care & Pain; 2012, doi: 10.1093/bjaceaccp/mks026 First published online: May 24, 2012

Figure 1:



P50

Performing clinical trials in organ donors: what are the limits?

Stephen McNally[1,2], Ewen Harrison[1,2], John Forsythe[0,1], Stephen Wigmore[1,2]

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Introduction: Solid organ transplantation is dependent on the procurement of suitable organs. Donor optimisation improves the quality of retrieved organs. There is an ethical duty to test new measures to improve organ function. The aim of this was to determine study design and consent procedures in trials involving organ donors.

Methods: Pubmed was search for the terms "Brain death donor" AND "clinical trial" or for "Organ donor management" AND "clinical trial". Details of study design, allocation, randomisation and consent were extracted from the manuscripts

Results: 377 records matched the search criteria. 16 relevant clinical trials were identified involving either thoracic or abdominal DBD donation. Interventions were were: pharmacological (11); different ITU management (3); and alterations to the retrieval procedure (2). 14 were RCTs, and 8 were blinded. Only 5 studies obtained consent from the donor family, of which two obtained consent after treatment commenced. No studies obtained consent from the organ recipients.

Discussion: There is a paucity of clinical trials in organ donors in the literature. Clinical trials in organ donation vary widely in their approach to consent. Donor consent could be readily obtained for all studies performed in DBD donors. Nevertheless this is not acquired in the majority of published and ongoing studies. As organs are often implanted in regions different to their retrieval site, obtaining recipient consent may not be practical, particularly in multi-organ donors.

Conclusion: Donor variability and practical constraints necessitate the use of new trial designs and approaches to consent. A national framework for undertaking trials in organ donors is urgently needed to establish the ethical and practical boundaries. This will enable more high quality studies to be performed in donation.

P51

Governance of deceased donor clinical trials - are ethics committees fit for purpose?

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Performing clinical trials in organ donors is both ethically and practically challenging. Culturally the randomised controlled trial is the gold standard design, and informed consent is its cornerstone. Deceased donor research is a unique setting where the donor is unable to exert their autonomy, and the recipient's autonomy is threatened by their dependent position when offered an organ from a trial donor, particularly if non-participation may prevent them receiving a graft.

Changes in legislation as part of the Human Tissue Act emphasise the importance of the wishes of the deceased to donate their organs. Their decision to donate could be viewed as justification for taking part in clinical trials which aim to directly improve the quality of retrieved organs, as this would lead to improved outcomes and overall success of the donation-transplantation paradigm.

Current guidelines for regional ethical committees focus on patient choice and the level of information provided to the participants. Trials in deceased donors would find difficulty in meeting standard requirements. Practical considerations in adapting treatments for the donor which may enhance post-transplant organ function may limit the ability to obtain consent. Difficulties in performing such studies may explain the paucity of high quality studies in deceased donors.

It is now essential to develop a system of ethical approval for donor trials that puts the responsibility with the ethical committee or another body to provide reassurance that the aims of the trial are reasonable, that the trial is safe, acceptable in terms of intervention and timings and has a chance of equivalency or better than standard donor management, and that there is a robust system for monitoring outcomes and reporting serious adverse events. This should address studies in both DBD and DCD donation. Ethically, such a system would meet the dual demands of non-maleficence and beneficence, and in practical terms it would facilitate the approval and successful completion of clinical trials in this key area.

P52

Attitude and knowledge of organ donation among Muslims across the global: is the fault at our end? An outcome of a survey report

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Background: Islam is the second largest religion of the world consisting of over 1.8 billion Muslims who account for 23% of world population. Since the global success of organ transplantation and its establishment as a lifesaving procedure there has been a drive to increase the donor numbers. From internationally published literature so far it seems that the organ donation rate among Muslims is not high enough. To understand various factors associated with this reluctance in donation we conducted a global online survey using social media networking.

Materials and methods: A 32 point online survey was send using social media networking. The survey remained open for four weeks. We received 1057 responses that are all included in this study.

Results: There were almost an equal number of male and female responders with median age of 39 years. More than 75% had postgraduate education with 29% with medical background. 87% and 60% were aware of living and deceased donation respectively. However <30% were aware of difference between DBD and DCD donation. 84% and 62% were supportive of living and deceased donation. Less than 1% believed that living donation is prohibited in Islam but about 40% were not sure. Likewise < 2% believed that deceased donation is not allowed in Islam but about 49% were not sure. 14% wanted to donate their organs to Muslims only however for more than 66% religion of the recipient was irrelevant. More than 92% expressed their wishes to acquire more knowledge about organ donation and transplantation and thought that it will help them improving their decision in particular and organ donation among Muslims in general.

Conclusion: We have noticed a significantly positive attitude towards organ donation among Muslims across the globe. However the amount of knowledge they currently have is not sufficient. This is our responsibility as medical personals to explore the way to get people educated about organ donation and transplantation. This is the only way we can sustain a successful transplant programme.

Poster session

Wednesday 13th March

18:15 - 19:25

Donor-specific antibodies 1

P53

An analysis on changes in HLA antibodies profile following renal transplantation

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Introduction: Antibodies (Abs) against Human Leucocyte Antigen (HLA) that appears following transplantation (de-novo HLA Abs) play an important role in transplantation. The aim of this study is to analyse the changes in patients Abs profile after renal transplant.

Methods: A prospective study of renal transplants performed in a single Transplant Centre from January 2009-December 2010. All patients had their HLA-Abs profile established prior to transplantation. This is then compared to post-transplantation sera collected at Day 10, 1 month, 3 months and thereafter at 3 months interval. All sera were initially screened using Luminex based technology.

Results: 177 patients with sera samples tested from January 2009-June 2012. There were 63 females (36%) versus 114 males (64%). 133 (75%) patients did not have pre-existing HLA-Abs. 110 (83%) patients remain free of HLA Abs whereas 23 (17%) patients has developed de-novo HLA-Abs. Following transplantation, 13 (57%) patients developed HLA I, 6 (26%) patients developed HLA II and 4 (17%) patients developed HLA I+II. There were 44 (25%) patients who had pre-existing HLA-Abs prior to transplantation. Of these, 19 (43%) patients had pre-existing HLA I, 9 (21%) patients had HLA II and 16 (36%) patients had HLA I+II. 42% of patients with HLA I continue to have the same HLA Class Abs compared to 56% in Class II and compared to 69% in Class I+II.

Conclusions: This suggests that majority of patients without pre-existing HLA- Abs does not develop de-novo HLA-Abs. Of those with pre-existing HLA-Abs, HLA I are the most common, followed by HLA I+II and HLA II. However, following transplantation, those with pre-existing HLA I+II are the least likely to have changes to their profile followed by HLA II then HLA I.

P54

A prospective analysis on appearance and changes in hla antibodies profile and their outcome in renal transplant patients

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Introduction: Antibodies (Abs) against Human Leucocyte Antigen (HLA) that appears following transplantation (de-novo HLA Abs) play an important role in transplantation. The aim of this study is to analyse the development of de-novo Abs in patients without pre-existing HLA Abs and also changes in patients with pre-existing HLA-Abs after renal transplant. We also look at the development of Donor Specific Antibodies (DSA); and to establish whether they are transient or persistent. Outcome in terms of rejection rates are then compared.

Methods: Prospective study of renal transplants performed in a single Centre from January 2009-December 2010. All patients were transplanted with negative cross match (Complement dependent cytotoxicity assay and Flow Cytometric Analysis) and did not have DSA pre-transplant. Sera samples were collected at Day 10, 1 month, 3 months and thereafter at 3 months interval. They were screened using Luminex based technology and positive findings (MFI>500) were subsequently tested with Single Antigen Beads to look for presence of DSA (positive if MFI>1000).

Results: 177 patients with sera samples from January 2009-June 2012. 133 (75%) patients did not have pre-existing HLA-Abs and 23 (17%) of them developed de-novo HLA-Abs but none are DSA positive. 44 (25%) patients had pre-existing HLA-Abs prior to transplant. 17 (39%) out of 44 patients developed DSA Abs. However, only 7 (41%) out of 17 DSA Abs were persistent. Majority of the DSA Abs were of HLA Class I. Patients with pre-existing HLA Abs have higher rejection rates. (25% vs 18%). Patients with DSA have higher rejection rates (29% vs 22%) and those with transient DSA have higher rejection rates (40% vs 14%).

Conclusions: Our study shows that only a minority of patients without pre-existing HLA-Abs develops denovo HLA-Abs and none are DSA positive. Development of DSA Abs are only found in patients with pre-existing HLA-Abs but only minority of them are persistent during serial testing. Majority of the DSA are HLA Class I. Patients with pre-existing HLA Abs or DSA or transient DSA have higher rejection rates.

P55

MICA antibodies in renal transplantation

Olivia Lucas[2], Afzal Chaudhry[1], Sarah Peacock[4], Gemma Brewin[4], Helen Morgan[4], Craig Taylor[4], Andrew Bradley[3], Nick Torpey[1], Menna Clatworthy[1]

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Introduction: Pre-transplant, donor-specific HLA antibodies are associated with antibody-mediated rejection and reduced graft survival. The effect of non-HLA antibodies, including MHC class I–related chain A (MICA) antibodies is less clear. MICA are polymorphic antigens present on many cells, including endothelial cells. We wished to determine: i. The prevalence of MICA antibodies in renal transplant recipients. ii. Their association with HLA antibodies. iii. Sensitisation factors associated with the development of MICA antibodies. iv. The effect of MICA antibodies on transplant outcome.

Methods: We performed a single centre, retrospective study to assess MICA antibody status in 713 consecutive patients undergoing renal transplantation from 2008-2011. Testing for MICA antibodies is performed as part of routine antibody screening. Additional data collected included graft function (serum creatinine), HLA mismatch, HLA antibody status, donor type, cold ischaemic time, rejection episodes, and CMV status. Univariate and multivariate analyses were performed.

Results: Pre-transplant MICA antibody status was available in 686 patients. Of these, 23% had a positive test. In 16%, the antibody was only detectable intermittently (defined as one or more positive result followed by one or more negative result). There was no significant association between the presence of pre-transplant MICA antibodies and allograft rejection, function or survival. There was a significant association between HLA class II antibodies and MICA antibodies ($p=0.029$). The relative risk of being MICA antibody positive if sensitised to HLA class II was 1.44 (95% CI 1.061-1.945).

Discussion: In this large dataset, with longitudinal information on MICA antibody status, MICA antibodies did not appear to impact on clinical outcomes in renal transplantation. The principle limitation of the study is the lack of information on donor and recipient MICA genotype, thus detectable antibodies may be of variable significance.

P56

Complement-activating low-level preformed donor- specific antibodies detected by c1qscreen™ predict early antibody- mediated rejection in renal allografts

Christopher Lawrence, Michelle Willicombe, Paul Brookes, Candice Clarke, Eva Santos-Nunez, Pippa Dodd, Candice Roufosse, Anthony Warrens, David Taube

Imperial College Kidney & Transplant Centre, London, UK

Renal transplant recipients with negative CDC [CDC-XM] and Flow crossmatch [Flow-XM] and low level DSA [by Luminex] have worse outcomes compared to non-sensitized patients. The aim of this study was to confirm, using C1qScreen™, the results of our previous study, using C4d beads, showing that the ability of preformed DSA to activate the classical pathway of the complement cascade dictates pathogenicity and predicts acute antibody-mediated rejection.

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

Pre-transplant sera were retested with the commercially available C1qScreen™ SAFB assay using Phycoerythrin-labelled anti-C1q antibody to detect C1q bound to the Fc portion of anti-HLA IgG on microbeads.

Complement fixing anti-HLA antibodies were detected in 22/52 [42%] patients, 6 class I, 9 class II and 7 with both class I+II. 12/52 patients had C1q positive DSA [$C1q^{+}DSA$], 10/52 patients had C1q positive third party, non DSA, anti-HLA antibodies [$C1q^{+}TPA$] and 30/52 patients had no C1q positivity [$C1q^{-}DSA$].Overall graft survival was 94.2% and 87.5% at 1 and 3 years. 14/52 [27%] patients had antibody-mediated rejection [AMR] diagnosed at indication biopsy. Preformed anti-A, B or DR $C1q^{+}DSA$ strongly predict the occurrence of AMR despite negative crossmatch [all patients with preformed anti-A, B, DR $C1q^{+}DSA$ experienced AMR, $p<0.001$]. AMR did not occur in all patients with Cw, DQ or DP C1q+DSA. This study confirms our previous findings, using C4d beads that patients with low level preformed complement fixing DSA are at high immunological risk. The C1qScreen™ assay can identify these patients prospectively and allow intervention to reduce this risk.

P57

Complement-activating DSA: which assay in which setting?

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

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The presence of pre-formed and de novo donor specific antibodies [DSA] are associated with antibody mediated rejection [AMR] and graft loss [GL]. We and others have shown poor outcomes in patients with complement-activating [C' activating] DSA.C'-activating DSA are detected by Luminex, either by detecting C4d covalently bound to the bead, or C1q bound to the Fc portion of DSA.

Both methods involve a second-layer modification to the standard Luminex technique. To our knowledge there are no studies directly comparing the two techniques. We compared the two methods in 122 renal transplant recipients with DSA [52 pre-formed, 70 de novo]. All patients were transplanted with Alemtuzumab induction, steroid sparing and tacrolimus. Rejection was diagnosed at indication biopsy. Graft survival, AMR and Receiver Operator Characteristic curve [ROC AUC] analysis was used to compare the two methods.

In patients with low level preformed DSA the C4d assay was superior to the C1q assay for the prediction of GL [AUC 0.63 v 0.56] and AMR [AUC0.68 v 0.57]. In patients who developed de novo DSA the C1q assay outperformed the C4d assay for the prediction of GL and AMR [See table].

In our hands the C4d assay is best for detecting C'-activating DSA patients with pre-formed DSA and predicts AMR with a sensitivity of 0.5 and specificity of 0.85. In contrast the C1q assay is the test of choice for detecting C'-activating DSA in patients with de novo DSA and predicts AMR with a sensitivity of 0.69 and specificity of 0.75. It is possible that the difference between the two assays is due to technical aspects which may be overcome by adaptations to the protocol.

	Graft Survival						**AMR-Free Survival**				
	n	**1 Yr**	**3 Yr**	**p**	**AUC**	**P**	**1 Yr**	**3 Yr**	**p**	**AUC**	**p**
C1q +	23	83%	64%				65%	40%			
C1q -	47	94%	90%	*<0.005*	0.72	*0.01*	85%	72%	*<0.05*	0.66	*<0.05*
C4d +	29	83%	65%				68%	44%			
C4d -	41	95%	92%	*<0.05*	0.67	0.06	85%	71%	0.14	0.59	0.2

P58

Responses of donor specific HLA antibodies post transplant - importance of pregnancy induced sensitisation

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Introduction: Acute antibody mediated rejection and graft loss after HLA antibody incompatible renal transplantation are related to antibody levels. The aim of this study was to look in detail at changes in antibody levels in the first 30 days after transplantation, according to sensitising event, and pre-treatment antibody levels and specificity.

Methods: Responses to 260 HLA specificities in the first 30 days after transplantation were evaluated in 78 patients. Peak DSA levels greater than MFI 10,000u post-transplantation were confined to patients with a pre-treatment DSA level of MFI >500u. Peak MFI >2,000u occurred in 1/43(2.3%) specificities with low starting levels and no identifiable pre-sensitising event, representing a low rate of de novo DSA production.

Results: Comparing specificities with prior sensitisiation by pregnancy, transfusion, or transplantation, the greatest increase was seen in those stimulated by pregnancy, with a median (IQR) increase in MFI of 1981u (94u – 5870u); the next highest group was for those sensitised by transplant with repeat epitope mismatch on the current graft, change of 546u (-308u – 2698u) ($p<0.01$).For specificities with pre-treatment MFI <1000u, peak level of >10,000u occurred in 10/36 (28%) stimulated by pregnancy, 2/16 (13%) stimulated by transfusion group, and 0/12 stimulated by prior transplantation ($p<0.01$).

Discussion: We observed a high rate of antibody production to specificities stimulated by pregnancy. By contrast, re-transplantation was associated with a lower rate of antibody resynthesis, even when HLA mismatches from previous transplants were repeated.

P59

In renal transplant patients with de novo donor-specific antibodies microcirculation inflammation is superior to peritubular capillary basement membrane multilayering for outcome prediction

Hanneke de Kort[1,3], Michelle Willicombe[1], Paul Brookes[1], Linda Moran[2], Eva Santos-Nunez[1], Jack Galliford[1], Adam McLean[1], David Taube[1], Jill Moss[2], H. Terence Cook[1,3], Candice Roufosse[1,3]

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In renal transplant patients with *de novo* donor-specific antibodies (DSA) we compared peritubular capillary basement membrane multilayering (PTCBML) counts with microcirculation inflammation (MI) score to predict development of transplant glomerulopathy (TG) and renal graft failure.

The first biopsy after transplantation with material available for electron microscopy was classified according to Banff '09 (n=52). *De novo* DSA were defined by negative donor-specific Luminex single antigen beads (MFI<300) before transplantation, and after transplantation DSA with a MFI>500. BML was scored in 25 PTC. PTCBML+ was defined as an average of ≥2 layers (n=22). MI, defined by the combination of glomerulitis (g) and peritubular capillaritis (ptc), was positive when MI score was ≥2 (n=17). Median follow-up from biopsy: 3.4 (IQR 2.0 to 4.7) years. Median time to biopsy: 0.7 (IQR 0.4 to 1.7) years. Median time between DSA development and biopsy: 0.3 (IQR -0.1 to 0.9) years. The Kaplan-Meier product limit method was used to estimate time to TG development and renal graft failure.

MI and PTCBML score did not correlate with each other (p=0.136). MI and PTCBML score were not significantly associated with time to biopsy from transplantation or with time from DSA development to biopsy. An MI+ score on index biopsy was associated with worse graft survival (p=0.015), while PTCBML count (p=0.637) did not correlate. TG development could only be assessed in 42 patients as 10 patients had no follow-up biopsy (n=9) or had TG on index biopsy (n=1). MI+ and PTCBML+ score both associated with TG development (p=0.007 and p=0.020, respectively).

In renal transplant patients with *de novo* DSA, PTCBML count is inferior to MI score for prediction of graft survival. MI score and PTCBML count are both associated with TG development. In this population, PTCBML count does not add information to the MI score in the early post-transplant period to assess antibody-mediated injury to the graft.

Poster session

Wednesday 13th March

18:15 - 19:25

Donor-specific antibodies 2

P60

Resolution of low levels of donor specific antibodies in paediatric renal transplant recipients

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Introduction and aim: The development of *de novo* donor specific antibodies (DSA) is associated with long term renal allograft dysfunction in adult renal transplant recipients. We aim to describe the DSA characteristics in paediatric renal transplant recipients (RTR).

Methods: DSA was measured prospectively at 6-12 monthly intervals and during acute graft dysfunction using Luminex bead assays beginning from January 2006. Multiple mean fluorescence intensity (MFI) values of DSA within the same class were added together. Results are presented as median (interquartile range).

Results: 216 RTR had DSA measurements for 3.0 (1.1-6.0) years post-transplant. DSA developed in 68 (31%) children, of whom 21 (31%) were Class I, 35 (51%) Class II and 12 (18%) both Class I and II positive. DSA levels fluctuated and 47% became negative at last measurement. Younger age and lower MFI predicted patients with transient DSA (table 1). Patients above a MFI threshold of 4000 at first detection have an odds ratio of 6.0 (95% CI 2.1-17.3) for persistent DSA.

Table 1: Comparison of children who had persistent or resolved DSA

	DSA resolved	DSA persisted	P value
Time post-transplant at first DSA detection (yr)	0.27 (0.10 – 2.93)	2.04 (0.30 – 4.10)	0.08
Age at first DSA detection (yr)	13.28 (8.26 – 15.60)	16.03 (11.65 – 17.88)	0.005
MFI at first DSA detection (units)	3030 (1515 – 4111)	5921 (3092 – 9022)	0.0002
Maximum DSA (units)	3135 (1550 – 4327)	8192 (5150 – 11520)	0.0001
DSA Class (Class I/Class II/both)	11/19/2	10/16/10	0.06

Conclusion: Low levels of DSA in paediatric RTR may resolve. Further studies are required to correlate DSA with renal allograft function and survival.

P61

The impact of *de novo* donor specific antibody development on 12 month graft outcome after islet transplantation

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Introduction: Islet Transplantation (IT) is associated with *de novo* donor-specific HLA antibody (DSA) development, particularly following withdrawal of immunosuppression after graft failure. We undertook a prospective study to elucidate the temporal relationship between DSA development and graft dysfunction in IT recipients.

Methods: Islet allograft recipients at a single National Commissioning Group-funded centre were assessed prospectively at 1, 3, 6 and 12 months post-first IT, including DSA (Luminex assay) and 90-minute meal tolerance test C-peptide (MTT90) assessment. All had a negative pre-transplant crossmatch.

Results: Ten recipients (Female n=9; islet transplant alone [ITA] n=8; islet after kidney [IAK] n=2) received 16 transplants (solitary transplant n=4; two transplants n=6). Induction was with alemtuzumab (90% first graft; 17% second graft) or basilixumab (10% first graft; 83% second graft). All received tacrolimus and mycophenolate mofetil maintenance immunosuppression. Four recipients (ITA n=2, IAK n=2) developed *de novo* DSA within one month of a sensitising graft (first graft n=2; second graft n=2). Those developing DSA were younger (DSA: 47±4.7 years vs no DSA: 55.5±6.2 years; p=0.03) and had a significantly reduced MTT90 at 12 months post-first transplant (DSA: 35.8±33.3 pmol/l vs no DSA: 998.7±703.3 pmol/l; p=0.02). IT mass (DSA: 9764±5389 islet equivalents/kg/recipient vs no DSA: 9975±2044 islet equivalents/kg/recipient; p=0.99) and number of transplants received (DSA: 1.7±0.5 transplants vs no DSA: 1.5±0.6 transplants; p=0.65) were not significantly different between groups.

Discussion: Early *de novo* DSA sensitisation occurred in 40% of IT recipients in a single centre prospective study and predicted significantly impaired graft function at 12 months.

P62

The clinical impact of pre-formed hla donor specific antibodies in liver transplantation

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Introduction: Antibody mediated rejection mechanisms are well established for renal and cardiac allografts and increasingly recognised for lung and pancreatic allografts. Alloantibody rejection in ABO compatible liver allografts has been viewed as less significant in clinical transplantation. However recent evidence suggests that HLA donor specific antibodies (DSA) may have an impact on liver allograft survival.

Methods: 265 consecutive liver transplants from 2007-2010 were retrospectively reviewed. Those with day of transplant sera that screened positive for Class I or Class II HLA antibodies (n=128) went on to have their stored serum retested using Luminex® single antigen beads to determine the presence of DSA. The cumulative mean fluorescence intensity (MFI) value of DSAs was used to group patients into MFI <1000 (negative), 1000-3000, 3000-5000, 5000-10000 and >10000. Clinical outcome data of biopsy proven acute rejection (BPAR), graft loss, death and liver function test deterioration were evaluated for each MFI group. Complement dependent cytotoxicity (CDC) T&B cell cross match and HLA mismatches were also correlated with the same clinical end points.

Results: 69.5% of patients were negative for DSA, 10.7% had an MFI of 1000-3000, 6.0% had an MFI of 3000-5000, 5.2% had an MFI of 5000-10000 and 8.6% an MFI of >10000. Neither presence nor absence of HLA antibodies at the time of transplant, nor any of the MFI groups, showed any significant difference in BPAR, graft loss, death or deterioration in liver function. Similarly there was no difference between CDC T&B cell cross match positive or negative patients with any of the clinical end points. Patients with 0-3 HLA mismatches compared to patients with 4-6 HLA mismatches also showed no difference in any of the clinical end points.

Discussion: This study did not demonstrate any clinical impact of pre-formed HLA DSA in liver transplantation. Persisting DSA rather than pre-formed DSA *per se* may have more clinical significance. This unit now monitors patients prospectively for persistent HLA DSA to enable future evaluation of clinical impact.

P63

Interpreting luminex defined donor specific antibodies: the clinical application of serial serum dilution

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Introduction: The presence of HLA donor specific antibodies (DSA) can be detected using Luminex technology, but this is not a quantitative assay. Although a higher Mean Fluorescent Intensity (MFI) may represent a higher antibody concentration, this cannot be used reliably to guide clinical management due to variability in bead antigen expression, saturation of antigen binding and the prozone effect. The use of serial serum dilution can improve interpretation of Luminex results, and provide a guide to desensitization.

Methods: Serum dilution has been used to assess the significance of HLA DSA in three clinical settings: i. Prior to a living donor (LD) transplant, when a positive cross match is present, to predict the likelihood of success of a desensitisation strategy using plasma exchange, ii. To define truly low level antibodies to facilitate a LD transplant via a combination of desensitisation and the kidney sharing scheme, or iii. When considering de-listing apparently low level antibodies for potential recipients awaiting deceased donor (DD) transplantation.

Results: Seventeen patients have undergone successful desensitisation prior to an HLA antibody incompatible LD transplant, guided in seven by the results of dilution testing. One patient has received a DD kidney following failed desensitisation, with de-listing of low level antibodies. One patient has received a LD transplant through the kidney sharing scheme following a combination of selective de-listing and plasma exchange. Dilution testing of six highly sensitized patients awaiting DD transplantation demonstrated a marked prozone effect, and prevented inappropriate de-listing of significant antibodies.

Conclusions: Luminex testing of serial serum dilutions in selected patients is a useful adjunct both when planning desensitisation and considering de-listing apparently relatively low level HLA antibodies to achieve an acceptable match through the kidney sharing scheme, or for patients awaiting DD transplantation.

P64

HLA-specific IgG antibody monitoring post kidney transplantation – result of a three-year prospective clinical study

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Introduction: Studies on de novo HLA-specific antibodies showed that they had a poor predictive value for rejection but the infrequency of sampling made definite conclusions difficult to reach. The purpose of this study was to study the evolution of IgG HLA response following kidney transplantation and relate to outcomes.

Method: 85 cases with negative cross match were prospectively followed. Samples were collected at day 0, 7, 14, 21 and monthly for the 1st year, tri-monthly for the first 3 years and yearly afterwards. Serological tests were carried out by one-lambda mixed screen beads for screening and life Code single antigen beads (SAB) to define specificities.

Results: The median time for clinical follow-up was 1027 days and for serological test was 679 days. 11 cases developed de novo donor specific HLA (DSA) and 23 cases developed de novo non-donor specific HLA (NDSA). 17 cases had pre-formed NDSA and 4 had low level of pre-formed DSA. 33% of de novo DSA were detected in first 6 months following kidney transplantation and median time for detection was 285 (55-743) days. From 11 cases with de novo DSA, 2 had antibody mediated rejection (AMR) resulting in allograft failure whilst the remaining 9 had stable graft function. In both cases DSA preceded AMR. None of the cases with de novo DSA developed persistent significant proteinuria and long term graft function was comparable to cases without de novo DSA. From 23 cases with de novo NDSA, 6 had episode of acute rejection with one failing from AMR. In 1 case with de novo NDSA persistent proteinuria was noted associated with transplant glomerulopathy. The mean eGFR of cases with de novo NDSA were comparable with cases without any HLA antibodies during the study duration.

Conclusion: Development of de novo HLA specific antibodies did not always predict rejection and poor outcome in majority of the cases in midterm follow-up. Longer-term follow-up in these cases will delineate the effect on graft survival.

P65

De novo HLA-specific IgM antibody response following kidney transplantation is not associated with poor outcome in a three year prospective clinical study

Sunil Daga[1,2], Shazia Shabir[4], Dave Lowe[1,3], Daniel Zehnder[1,2], Simon Ball[4], Robert Higgins[1,2], Richard Burrows[4], David Briggs[3]

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Introduction: Preformed IgM HLA-specific antibodies are not considered contraindication for kidney transplantation. Role of de novo IgM HLA-specific antibodies developing after transplantation is not clear and controversial. The purpose of this study was to study evolution of IgM HLA response following kidney transplantation and relate to outcomes

Method: 85 cases with negative cross match were prospectively followed. Samples were collected at day 0, 7, 14, 21 and monthly for the first year, three monthly for the first three year and yearly afterwards. Serological tests were carried out by one-lambda mixed screen beads for screening and life Code single antigen beads (SAB) to define specificities.

Results: The median time for clinical follow-up was 1027 days and for serological test was 679 days. 3 cases developed de novo donor specific HLA (DSA) and 17 cases developed de novo non-donor specific HLA (NDSA). None of the cases developed class-2 IgM HLA antibody. Mean time for development of IgM DSA-HLA specific antibody was 290 (6-726) days and mean time for development of IgM NDSA was 250 (2-850) days. 2 out of the 3 cases with de novo IgM DSA, DSA developed following an episode of rejection (day 57 & 712 respectively) and remaining one case had stable graft function. Of the 17 cases with de novo IgM NDSA, 4 cases had rejection. In 3 cases the NDSA developed after rejection and in one case accompanying rejection episode. 25 cases had episode of rejections but in none cases IgM HLA (DSA or NDSA) preceded rejection. There was no new case of persistent significant proteinuria and the renal function (mean eGFR) was not statistically different in cases with or without IgM HLA-specific antibodies. Out of 7 cases with allograft failure, 1 had IgM HLA-specific antibody but this was associated with IgG HLA response too.

Conclusion: De novo IgM HLA-specific antibodies alone did not result in poor outcomes in mid-term follow-up.

P66

Compromised perfusion following development of donor-specific HLA antibodies against pancreas transplant Y-graft in a case of arterial reconstruction: a case report

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Donor pancreas grafts are implanted into diabetic recipients using Y-grafts derived from donor iliac vessels. In cases when pancreas grafts are received at the retrieving centre without donor iliac vessels, alternative methods for arterial anastomosis must be employed.

We describe a case of an untransfused 31 year old male who underwent simultaneous pancreas kidney (SPK) transplantation using vessels from a second donor for arterial anastomosis of the pancreas graft. Pre transplant HLA antibody screening was negative and the crossmatches against both donors were negative, by both complement dependent cytotoxicity and flow cytometry. The patient had initial good pancreas and kidney function, and apart from a blood transfusion on the fourth day post-operatively made an uneventful recovery. However at 30 months post- transplant, pancreas dysfunction was detected and vascular occlusion of the Y-graft was demonstrated radiologically. Pancreas graft failure resulted and the patient was recommenced on an exogenous insulin regime.

Routine post-operative HLA antibody monitoring was performed 6 weeks post transplant and was negative. 30 months post transplant significant levels of HLA class I antibodies were detected by Luminex Single Antigen beads, reactive with HLA-A29, A30, A26, A34, A43, A80, B44, B45, B76, B82, B27, B37, B47, B50 and low level of class II antibodies against HLA-DR7. Epitope analysis shows that most of these antibodies are directed against mismatches on the donor vessels and not on the SPK donor. Although the patient had received a post transplant blood transfusion, HLA antibody monitoring was negative 6 weeks later and there were no other known sensitising events.

HLA type	HLA-A*	HLA-B*	HLA-C*	HLA-DRB1*	HLA-DRB3/4/5	HLA-DQB1*
Patient	02:01, 03:01	07:02, 51:01	07:02, 15:02	01:01, 04:02	DRB4*01 :01	05:01, 03:02
SPK Donor	***01:01***, 03:01	07:02, ***08:01***	07:02, ***07:01***	***15:01, 03:01***	***DRB3*01 :01,*** ***DRB5*01 :01***	***02:01, 06:02***
Vessel donor	02:01, **29:02***	**44:02*,** **44:03***	***05:01, 16:01***	***07:01, 15:01***	DRB4*01 :01, ***DRB5*01 :01***	***02:02, 06:02***

This case shows that allogeneic vessels can cause HLA sensitisation and highlights the dangers of using material from a second donor during transplantation, even when presented with a negative pre-transplant crossmatch. Although rejection had not been directed against the transplanted organ, pancreas graft failure resulted due to hypoperfusion. We argue that consideration must be given to the additional risks involved in the use of allogeneic material for arterial reconstruction.

Poster session

Wednesday 13th March

18:15 - 19:25

Immunosuppression - CNI

P67

Calcineurin inhibitors in kidney transplantation: long term pain for short term gain?

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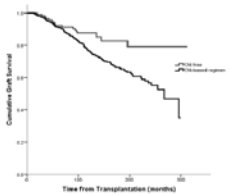
In an era of excellent first year graft survival, the focus in kidney transplantation is moving towards long term complications. Transplant failure has major implications both for recipients and healthcare providers. Calcineurin inhibitors (CNIs) have contributed to the reduction in acute rejection and the improvement in early allograft outcomes. The aim of this study was to investigate the long term effects of these potentially nephrotoxic drugs.

Methods: All recipients who had 1st deceased donor kidney transplants in Belfast between 1986 and 2005 were included. Clinical data, including immunosuppressive regimens and outcomes, have been recorded prospectively for this cohort.

Results:

- There were 707 first, deceased donor, kidney transplants during this period.
- 78.8% of recipients had a CNI-based immunosuppressive regimen.
- Recipients receiving CNI-based immunosuppression had improved one year graft survival compared to those not prescribed CNIs ($p<0.001$).
- For recipients with a functioning graft at 12 months, a CNI-based regimen was associated with death-censored graft failure ($p = 0.003$) (Figure 1). This persisted after Cox regression analysis.



Discussion: CNIs have contributed to the early improvements in kidney transplant outcomes. However, their nephrotoxic effects may also propagate graft loss in the longer term. Transplant recipients should be stratified by their immunological risk and have their immunosuppression tailored accordingly. CNI withdrawal may be appropriate in low risk groups.

Fig. 1: CNIs and Graft Survival in Recipients with a Functioning Graft at 12 Months

P68

Assessment of post transplantation results of adoport compared to prograf. A short sample study

Hemant Sharma, Adham El-Bakry, Chang Wong, Rahul Sinha, Khalid Abunabi, Karen Ward, Helen Machin, Daniel Ridgway, Sanjay Mehra, Ajay Sharma, Abdul Hammad

Royal Liverpool University Hospital, Liverpool, UK

Background: Generic FK 506 (Adoport) was introduced in the UK in 2010 and experience with generic FK 506 to date is still limited even though different centers from across UK have reported no adverse events. Our study aims to assess the outcomes of Adoport in a selected cohort of renal Transplant patients at Liverpool.

Aims: To assess the short term outcomes of Adoport in Renal Transplant patients at RLUH. To compare the results with age, gender and time matched cohort prescribed with Prograf and to identify any need for change in practice.

Methods: We reviewed the case notes of all patients prescribed Adoport in our renal Transplant Unit.Age, Gender, Time match cohort of Prograf prescribed patients selected by 3 independent assessors (AEB*,HS*, HM*). Adoport was prescribed in same dose as Prograf. Independent Sample T test was used to compare the two groups and variance ratio (F Test) was used to calculate variation in mean FK 506 levels. Spearmann Rho test was used to calculate any correlation amongst the co- variables.

Results:

	Adoport Cohort (N=11)	Prograf Cohort (N=12)
Median Recipient age	50 (20-69)	50 (21-68) (p=0.32)
Median Donor age	42 (29-69)	48 (21-78) (p=0.32)
Peak PRA > 20%	N=1	N=2
Induction	Campath N=6 Simulect N=5	Campath N=7 Simulect N=5
Rejection	N=2	N=1 (p=0.63)
Median FK 506 Level 1 month/no of dose changes	9.1 ±1.19/ median 3 (1-4)	7.5 ±1.77/median 2 (0-3) Variance ratio 4.9.p=0.02 (F Test)
Median FK 506 Level 2 month/no of dose changes	7.9 ± 2.95/ median 2 (0-2)	7.4 ± 1.47/median1(0-2) *Variance ratio 4.02 p=0.04 (F Test)*
Median FK 506 Level 3 month/no of dose changes	8.3 ± 1.51 / median 1 (0-2).	7.2 ± 2.03/median1 (0-2) Variance ratio 1.8 p= 0.3 (F Test)
Median FK 506 Level 3 month/no of dose changes	7.5 ± 1.51 / median 1 (0-2)	7.0 ± 1.72/median1 (0-2) Variance ratio 1.2 p= 0.6 (F Test)

Conclusions: Adoport was not associated with any different short term adverse reactions. The Adoport Levels were erratic over first 8 weeks prompting numerous dose changes. A longer term study needed to confirm the facts. In short term, Adoport can be an alternative to prograf with some reservations.

P69

An investigation into the differences between adoport® and prograf® in kidney transplant recipients

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Until January 2011 standard maintenance immunosuppression following kidney transplantation consisted of Prograf® and mycophenolate mofetil. Following the patent expiry and subsequent availability of a branded generic version of tacrolimus, it was agreed that patients transplanted after January 2011 would receive Adoport® instead of Prograf®. This change only applied to newly transplanted patients; patients stabilised on Prograf® continued on this brand of tacrolimus. At the same time initial induction therapy was also changed. This enabled the use of single agent tacrolimus instead of the combination with mycophenolate mofetil. Following the change in formulation it appeared clinically that some patients on Adoport® had unpredictable tacrolimus levels in relation to the dose prescribed. It was therefore agreed to examine this phenomenon in more detail to ensure patient safety. Specific parameters of interest were:

- Differences between trough levels for each brand.
- Mean tacrolimus dose 1 month post transplantation.
- Relationship between tacrolimus level and serum creatinine 3 months post-transplant, as a predictor of long term graft survival.

Results: Median trough tacrolimus levels for Prograf® and Adoport® (IQR) patients were 9mcg/L (7-11) and 8mcg/L (6-11) respectively. The mean dose 1month post transplantation for Prograf® was 7.9mg/day (range=4 to 12) and Adoport® was 8.2mg/day (range=3 to 20). There was no significant difference in creatinine 3 months post transplantation in both Adoport® and Prograf® patients, however there was a strong correlation ($r=0.462; p<0.05$) between Adoport® dose and creatinine 3months after transplant.

Conclusion: Further studies are required to investigate these apparent differences in more detail, particularly in relation to creatinine at 3 months, where one would expect a "U-shaped" curve in relation to trough tacrolimus levels.

P70

Programmed switching of renal transplant recipients from branded to generic tacrolimus is safe, well-tolerated and cost-effective

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Background: There are currently 13 different oral tacrolimus brands available in the UK. Tacrolimus has a narrow therapeutic index and changes in formulations can cause a significant alteration in drug exposure, leading to rejection or drug toxicity. In order to reduce the risk of unsupervised switching, as well as reducing prescribing costs, we undertook a co-ordinated programme of monitored switching from Prograf® to Adoport® Tacrolimus, together with a home delivery service.

Methods: In June 2011, 598 kidney, pancreas and islet transplant recipients followed up at our centre were prescribed Tacrolimus Prograf®. As of November 1st 2012, we had successfully switched 484 (81%) to Adoport®. We retrospectively analysed 100 patients who had switched to generic Tacrolimus and established the dose and level of tacrolimus pre- and post-switch, number of extra visits, safety of monitoring, adverse events, and costs.

Results: The patients had a median age of 51.6 years, 62 were male and 38 female. Patients were 4.8 (0.7-23.3)yrs post-transplant, 52% DBD, 36% LD, 5% SPK, 5% DCD, 2% other. 98/100 were switched (2 did not consent), although 2 switched back at <1 week due to side effects. Post-switch, patients were followed-up for a median of 205 (range 78-471)days: 79/96(82%) had a level checked within 21 (12±24.6)days, neither mean levels (6.3±2 to 6.2±2ug/L, p=0.77), nor mean daily dose (4.7-4.8±2.8mg, p=0.61) changed significantly. 14/96(15%) of patients had a >40% change in level and required dose changes. Only 0.12 extra visits per patient were required. Headaches and dizziness were the most commonly patient reported adverse effect (n=4), 7 patients developed worsening hypertension (>20mmHg). Only 1 patient developed graft dysfunction: biopsy revealed eosinophilic tubulointerstitial nephritis, due to terbinafine. The conversion to Adoport Tacrolimus in these 96 patients led to an annual cost saving of £259,133 which equates to an estimated £1.3m annual saving for all 484 patients.

Conclusion: Conversion to a single generic formulation of tacrolimus is safe, well-tolerated and has the potential to provide the NHS significant cost savings.

P71

The effects of small bowel resection and reanastomosis on immunosuppression in a renal transplant patient

Oonagh McFerran, Angela Mitchell, Alastair Woodman

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A 39 year old male with a renal transplant was admitted to hospital with abdominal pain and vomiting. His baseline creatinine was 220µmol/L on a regimen of Rapamune (Sirolimus) 2mg PO OD and Cellcept (Mycophenolate mofetil (MMF)) 500mg PO TDS.

A CT scan of abdomen showed ischaemic large bowel. A laparotomy, ileocaecal resection and right hemicolectomy was performed. Two further surgeries followed, due to ischaemic small bowel, resulting in no large bowel and only 80cm of small bowel remaining. Initial post operative immunosuppression was established with iv Cellcept and iv Hydrocortisone, with no impairment in graft function.

The challenge facing the nephrology team was to achieve adequate immunosuppression to preserve graft function, despite the patient having only 80cm of small bowel. We decided to stop MMF, commence oral Tacrolimus and continue 10mg PO OD Prednisolone. The use of Tacrolimus also facilitated monitoring drug levels to ensure adequate absorption. The patient maintained a Tacrolimus trough level for months between 2-6µg/L on Tacrolimus 1.5mg BD until he underwent surgery to reverse the end ileostomy. After reversal surgery, Tacrolimus trough levels rose to 14-18µg/L and this warranted a reduction in dose to 1mg BD. He maintained stable trough levels (3.1-8.2µg/L) and his creatinine was stable (195-225µmol/L).

This case demonstrates that adequate Tacrolimus levels can be achieved with only 80cm of small bowel. This supports animal studies and the two other published case reports on the use of oral Tacrolimus to provide immunosuppression in short bowel syndrome. In addition, we have noted that with surgery to reverse the end ileostomy, trough levels rose significantly, supporting animal observations of further Tacrolimus absorption in the colon. We conclude that Tacrolimus can be used to provide immunosuppression in patients with short bowel syndrome.

P72

High intra-individual variability of tacrolimus clearance in renal transplant recipients on Prograf or Advagraf leads to increased graft loss

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Introduction: Recent evidence suggests significant variability for tacrolimus within individual patients, but there is limited data comparing the Prograf® and Advagraf® formulations. There are concerns that patients with high intra-individual variability are at higher risk of graft dysfunction or graft loss.

Methods: 103 renal transplant recipients who were converted from Prograf® to Advagraf® between 2008 and 2011 were included in this study. Tacrolimus variability was calculated before and after conversion using a previously described dose corrected method which determines the percentage variability from the mean. Patients were grouped as high or low variability for both preparations of tacrolimus and compared using a paired t test. Patients were also grouped as 'early' or 'late conversion' if converted <12 months or >12 months after transplant. Patient and graft survival were evaluated for high and low percentage variability of both tacrolimus preparations.

Results: The overall mean percentage variability was higher in patients taking Prograf® compared with Advagraf® (25.23±14.63% vs. 21.68±12.62%, p=0.043). The variability in patients converted early, was higher for Prograf® compared with Advagraf post-conversion (30.59±16.61% vs. 24.17±12.22%, p=0.038). There was no difference in variability between Prograf® and Advagraf® in patients converted 'late' (21.55±11.89% vs19.97±12.70%, p=0.447). Graft loss was significantly greater in patients with high percentage variability for both preparations of tacrolimus (18.75%) compared with patients with low variability of both preparations, irrespective of conversion time (6.25%), Log-rank p=0.034. Patient survival was unaffected by tacrolimus variability.

Conclusions: Tacrolimus variability is higher in patients taking Prograf® than Advagraf® however this is only significant in the first year post transplantation. Patients with high intra-individual tacrolimus variability are at increased risk of graft loss and may require consideration of an alternative immunosuppressive regimen.

P73

Five year outcome after a change from a ciclosporin based to a 'low dose' tacrolimus based regimen for kidney transplants

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Introduction: In January 2007 our kidney transplant centre changed from a ciclosporin (CyA)/azathioprine (Aza)/prednisolone (Pred) primary immunosuppression regimen (with basiliximab induction and mycophenolate mofetil [MMF] for those at immunologically high risk) to a Tacrolimus (low dose)/MMF/Pred regimen with basiliximab induction. The aim of this analysis was to assess the impact of this change on long-term patient and transplant outcomes.

Methods: Baseline and follow-up data were collected from the prospectively maintained electronic patient record for all consecutive kidney-only transplants from 01/01/2005 to 31/12/2008.

Results: 300 consecutive kidney only transplants were identified; 140 in the 2005-06 era and 160 from the 2007-08 era. The proportions of living donor transplant (37.5 v 22.9%; p=0.04) and donors after cardiac death (11.9 v 5.0%; p=0.03) were significantly higher in the 2007-08 cohort. The incidence of acute rejection in the first year was lower in the 2007-08 cohort (15.0; v 23.6%; p=0.06). 5 year actuarial patient survival was significantly higher in the 2007-08 cohort (96.8 v 87.1%; p=0.003) and there was a trend to higher 5 year transplant survival (84.7% v 76.3; p=0.08). eGFR was significantly higher in the 2005-06 era at 1 (53.5 v 44.5 ml/min/1.73m^2 ; p=0.0006) and 3 (50.9 v 43.4 ml/min/1.73m^2; p=0.02) years with a trend to higher eGFR at 5 years (41.8 v 49.6ml/min/1.73m^2; p=0.09). These differences were consistent when living donor and deceased donor transplants were analysed separately.

Discussion: A change from a CyA-based to a Tacrolimus (low-dose)/MMF/Pred immunosuppression regimen with basiliximab induction has been associated with better 5 year patient survival, transplant survival, improved transplant function and a trend to reduced acute rejection.

P74

Long-term tacrolimus dose-corrected concentration increases in non-expressers but not expressers of Cytochrome P450 3A5

Benjamin Sansom, Fu Ng, Michelle Moreton, Iain AM MacPhee

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Background: The calcineurin inhibitor tacrolimus presents a challenge in transplant patients, with a narrow therapeutic window and wide inter-individual variation. Tacrolimus is metabolised by two enzymes, CYP3A4 and CYP3A5. It is well established that CYP3A5 expressers have a higher dose requirement than non-expressers (1). Previous studies have shown an increase in tacrolimus dose-corrected exposure with time in CYP3A5 non-expressers but not expressers (2), but these studies have been limited to a 5 year period of follow-up. Here we establish if there is a difference in tacrolimus exposure over time in expressers and non-expressers of CYP3A5 over a 10 year period.

Methods: Retrospective data were collected from patients transplanted between 1995 and 2002 with 10 years of follow up at a single centre (St George's Hospital, SGH). Patient CYP3A5 genetics and dose and weight normalised tacrolimus concentration was collected for every year post transplantation.

Results: 124 patients were transplanted and followed at SGH. 62 patients (50%) remained on tacrolimus and had complete 10 year follow up data. Over a 10 year period a significant increase in dose-normalised tacrolimus concentration was seen in non-expressers (n=44, change year 1 to year 10= 78±14% $p<0.0001$) but not in non-expressers (n=18, change year 1 to year 10=45±16%, $p=0.11$). The gradient of tacrolimus concentration with time was 2.46±0.8 in expressers, and 8.8±1.5 in non-expressers ($p=0.001$)

Conclusions: These findings demonstrate the previously observed increase in dose and weight corrected tacrolimus concentrations in CYP3A5 non-expressers continues over 10 years. An increased tacrolimus concentration was also observed in CYP3A5 expressers, but at a shallower gradient that was significantly different from non-expressers. The reason for this trend is unknown, but it may be due to a progressive increase in drug absorption with reduced metabolism to which CYP3A5 expressers are less susceptible.

References:

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2. Kupyers et al. (2007). CYP3A5 and CYP3A4 but not MDR1 SNPs determine long-term tacrolimus disposition and drug related nephrotoxicity in renal recipients. J Clin Pharmacol. 82(6), 711-725.

P75

Single centre prospective study of conversion from tacrolimus suspension to modigraf ® tacrolimus in paediatric renal transplant recipients

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Introduction: Prescribing of medications in paediatric practice is problematic as many drugs remain unlicensed. This is especially true of immunosuppressive medications. However, there is now a licensed product for Tacrolimus called Modigraf ® with data available on bioavailability. We undertook a single centre prospective study of conversion to Modigraf ®, an oral liquid available in granule formulation (1mg and 0.2mg) that allows for dosing according to body weight.

Method: All paediatric transplant recipients under the care of a single centre were considered for conversion to Modigraf ® from their current Tacrolimus regimen. Inclusion criteria included all RTR under 18 years of age who were on Tacrolimus suspension. Exclusion criteria included recipients of multi-organ grafts, patients with lactose intolerance and patient choice to continue with their current suspension. Patients were then seen by the multi-disciplinary team. After equivalent dose conversion, patients were monitored with blood tests one week after conversion with subsequent doses adjusted accordingly. Patients continue to be monitored with blood levels over a 3 month period after conversion with renal allograft function, renal allograft loss and side-effect profiles recorded.

Results: Forty-three (27% of 158) RTR were considered for conversion to Modigraf ®. The families of four patients requested to stay on their current Tacrolimus suspension, three patients were deemed unsuitable due to lactose intolerance and three patients were excluded due to low doses (incompatibility with the granule dosing). Thirty-three patients were then converted to Modigraf ® and closely monitored. After blood level monitoring one week after conversion, 12% (4) patients had their doses increased due to lower than anticipated 12-hour trough tacrolimus levels. There was stable renal allograft function without renal allograft loss after conversion.

Conclusions: Conversion to Modigraf ® immunosuppression can be safely undertaken in paediatric RTRfuture, although regular monitoring in the immediate period of conversion is required to provide accurate immunosuppression dosing.

P76

Adoport –v- prograf in de-novo renal transplants: single centre experience.

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Adoport, a generic tacrolimus formulation was licensed for use in transplantation on the basis of demonstrating bioequivalence to Prograf. Use of the generic formulation could be associated with cost savings. We present our centre's experience in using Adoport in comparison to Prograf in de-novo transplants.

Methods: In August 2011, our transplant protocol was modified to allow prescription of Adoport instead of Prograf for de-novo renal transplants. No other changes were made to the protocol. We compared outcomes in sequential transplants (treated with Prograf) performed in the year prior to August 2011 (n = 51) against all transplants (treated with Adoport) in the year after August 2011 (n = 44). The outcomes of interest were mean/median daily tacrolimus doses, 12 hour trough levels, eGFR at 3/6 months, biopsy proven rejection episodes, graft/patient loss or other adverse events related to either medication at 90 days post transplant.

Results	N	Mean 3 months level	Mean 6 months level	Mean 3 months dose	Mean 6 months dose	Mean 3 months eGFR	Mean 6 months eGFR
Adoport	44	9	9	9	8	50	50
Prograf	51	9	12	8	6	59	63

	Patients with rejections	Rejection episodes	Low tacrolimus levels with rejection	CNI toxicity	Graft loss with low Tac level
Adoport	7	10	1	3	1
Prograf	13	14	3	4	0

Discussion: In our single centre experience, Adoport can be safely used in de-novo renal transplants with doses, safety and efficacy comparable to Prograf. Based on 2011 prices for both formulations, this has resulted in an annual cost saving of 2444 £/per patient. From our retrospective analysis we show that Adoport can be safely started in patients undergoing renal transplant. The levels are predictable and dose adjustments are similar to Prograf. By switching to Adoport in all patients significant annual savings of upto100,000 £ can be made.

P77

Intra-patient variability in tacrolimus trough concentrations and conversion of stable renal transplant patients from twice daily (prograf®) to once daily (advagraf®)

Toqa El-Nahhas[1], Joyce Popoola[1,2], Rajeshwar Ramkhelawon[1,2], Atholl Johnston[1,2], Iain MacPhee[1]

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Background: Tacrolimus is considered to have a narrow therapeutic window, with wide variation between individuals in the blood concentration achieved by a given dose (Borra et al, 2010). High intra-patient variability in tacrolimus exposure is a risk factor for allograft loss and late acute rejection (Prytula et al, 2012). There are very few studies that focused on comparing within-patient variability of tacrolimus formulations.

Objectives: This work was designed to study the impact of switching stable renal transplant patients from a twice a day formulation of tacrolimus (Prograf®) to a once a day formulation (Advagraf®) on within patient variability in tacrolimus trough blood concentration.

Methods: Sixty five patients aged between 21 to 76 years were included in this study. Switching from Prograf® to Advagraf® was made on a 1mg: 1mg basis. Tacrolimus trough blood concentrations (C0) were analysed over the periods before and after conversion and calculated tacrolimus trough concentrations variability using %CV. The data were analysed using analysis of variance (ANOVA).

Results: After the switch, there was a highly significant reduction in tacrolimus trough blood concentration (C0) ($p < 0.001$). The mean tacrolimus C0 concentration fell from 7.38 µg/L SD 1.4 to 6.49 µg/L SD 1.27 with a 12% reduction [90%CI 9 to 16%]. The within-patient percentage coefficient of variation (%CV) of tacrolimus C0 was not significantly different after switching. The mean within patient variability %CV of tacrolimus C0 was 25% SD 13.8 for Prograf® and 26.1% SD 9.6 for Advagraf® ($p > 0.05$). In addition, there was a significant change in the tacrolimus mean daily dose (mg/kg) after conversion ($p < 0.05$). The tacrolimus dose was reduced in 18 patients (27.7%) by a mean change of –27.9% and the dose was increased in 12 patients (18.5%) by a mean change of +30% with 53.8% of the patients continuing on the same daily dose.

Conclusions: Switching from twice to once release tacrolimus formulations in kidney transplant patients was associated with a significantly lower tacrolimus trough concentration (C0), confirming previously published reports but had no influence on within patient variability in contrast to published reports suggesting a reduction following conversion to Advagraf®. While many patients required dose changes, there was no overall increase in the amount of tacrolimus prescribed across the population.

Abbreviations: C0: Trough blood concentrations, ANOVA: Analysis of variance, %CV: Coefficient of variation and CI: Confidence interval.

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Prytula, A.A., Bouts, A.H., Mathot, R.A., van Gelder, T., Croes, L.K., Hop, W., and Cransberg, K.(2012) Intra-patient variability in tacrolimus trough concentrations and renal function decline in pediatric renal transplant recipients.Pediatr Transplant, 16(6):613-8.

Poster session

Wednesday 13th March

18:15 - 19:25

Immunosuppression - induction

P78

Steroid avoidance with alemtuzumab induction has comparable outcomes to a basiliximab based regime at three year follow up from a randomised controlled trial

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From December 2006 to November 2010 a randomised controlled trial comparing two steroid avoidance regimes was conducted in our centre. Alemtuzumab induction followed by tacrolimus (TAC) monotherapy was compared to basiliximab induction followed by tacrolimus / mycophenolate (MMF) maintenance. We present three year follow up data from the trial. At the time of renal transplantation, 116 adult patients were recruited and randomised to either the control group – basiliximab (BAS) followed by TAC and MMF, standard in our institution at the time, or induction with alemtuzumab (ALEM) and TAC monotherapy. At three years, the two groups were compared considering patient and graft survival, renal function, rates of infective, malignany and cardiovascular complications and rates of acute rejection.

Patient survival was 92.6% vs. 94.7% in the alemtuzumab and basiliximab groups respectively (p=0.64). Graft survival was 83.3% vs 87.7% (ALEM vs BAS, p=0.51). Renal function at three years was comparable between the two groups with mean eGFR 53±18ml/min (ALEM) vs. 50±19ml/min (BAS, p=0.45) and mean creatinine 138±51µmol/L (ALEM) vs. 151±55µmol/L (BAS, p=0.25). Four cases of post-transplant proliferative disorder were seen - two in each group. CMV disease was seen in two patients in each group over the three year follow up period. One case of BK nephropathy occured - in the basiliximab group. Cardiovascular event rates were comparable between groups. No differences were seen in urinary protein/creatinine ratios, haemoglobin, total white cell count, lymphocyte count or platelet count at 3 years. Latest follow up eGFRs are 56±22ml/min (ALEM) vs. 50±21ml/min (BAS, p=0.15), with median time to latest follow up of 4.3 years. Data was available for 111 patients at 3 years.

Steroid avoidance with alemtuzumab induction and tacrolimus monotherapy yeilds similar outcomes at 3 years to induction with basiliximab followed by tacrolimus / mycophenolate maintenance.

P79

Campath, calcineurin inhibitor reduction and chronic allograft nephropathy (the 3c study): baseline characteristics

Richard Haynes[1,2], on behalf of the 3C Collaborative Group[0]

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Background: Optimal immunosuppression strategies in kidney transplantation remain uncertain. Reducing exposure to calcineurin inhibitors (CNIs) with either potent induction therapy or elective conversion to sirolimus could improve outcomes, but robust evidence is lacking.

Aim: The 3C Study is a randomized controlled trial investigating two strategies: (i) whether induction therapy based on Campath (alemtuzumab, anti-CD52 lymphocyte-depleting antibody) is superior to standard basiliximab-based induction; and (ii) whether an elective conversion to sirolimus at around 6 months after transplantation is superior to remaining on long-term CNI-based maintenance therapy.

Methods: The 3C Study is being conducted at 18 kidney transplant centres in the UK. Eligibility criteria are simple to ensure a representative patient population. The primary outcomes are the incidence of biopsy-proven acute rejection during the first 6 months (induction comparison) and graft function at 2 years after transplantation (maintenance comparison).

Results: Since October 2010 the 3C Study has recruited 802 participants to date. Two-thirds of recipients are men. 4% are highly sensitized and 8% have had a previous transplant. About one-third of donors are DBD, DCD or living respectively (mean donor age 48 years). Mean cold ischaemia time (among deceased donors) is 13 hours. 278 participants to date have entered into the maintenance randomization (at about 6 months after transplantation) to date. Mean baseline eGFR is 53 mL/min/1.73m^2 and mean proteinuria is 14 mg/mmol.

Discussion: The 3C Study is the first large national collaborative trial in kidney transplantation and has demonstrated the ability of UK transplantation to recruit rapidly into such trials. These baseline data confirm that the study population is representative of UK recipients and the trial will provide reliable data to guide the choice of optimal immunosuppression to preserve long-term graft function.

P80

Live donor kidney transplantation and basiliximab induction are associated with a reduced postoperative inflammatory response

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Introduction: Major surgery is associated with a systemic inflammatory response that is reflected in altered serum levels of acute phase proteins, including c-reactive protein (CRP). Previous studies have shown that postoperative CRP levels correlate positively with the extent of surgical trauma and typically reach a peak on day two to three postop. As part of our interest in perioperative management in renal transplantation we have used retrospective data to further elucidate the inflammatory response in renal transplant recipients.

Methods: We reviewed serum CRP levels from the day prior to transplantation to the fifth postoperative day in 155 live and cadaveric renal transplant recipients from a single transplant centre. We compared patients who had induction therapy with basiliximab, a monoclonal antibody to the interleukin-2 receptor, to a historical control group who received transplants prior to the introduction of this therapy.

Results: There was no significant difference in CRP at baseline between live and cadaveric donors or between pre and post basiliximab groups. CRP peaked at day three in all groups. CRP response was significantly reduced at days one to three in patients from the post-basilixmab cohort. The reduced CRP response in patients receiving basiliximab was most pronounced at day two, when the mean CRP was 31.7 nmol/L lower than in the pre-basiliximab cohort (STD 8.6, $p<0.001$). There was no significant difference between these groups by day four. Live donor transplantation was also associated with a reduction in the postop CRP response. The observed effect was greatest at day two, when the mean CRP among live donor recipients was 41.3 nmol/L lower than among cadaveric donor recipients (STD 7.9, $p<0.001$). There was no significant difference by day three.

Discussion: Live donor recipient status and basilixmab induction are associated with a reduced CRP response early after kidney transplantation. This may reflect differing preop morbidity between our groups as well as the nature and timing of induction regimes. Further research is needed to determine whether suppression of the inflammatory response correlates with important clinical outcomes.

P81

Comparison of simulect to ATG induction in DCD Kidneys; a non randomised observational trial

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Background: DCD kidneys have a high incidence and suffer from a longer period of DGF compared to DBD kidneys. Avoiding early rejection in those patients might be even more important since it avoids additional injury and might also ameliorate the need for weekly biopsies during the duration of DGF.

Aim: of the study was to see if induction with ATG confers an advantage in terms of rejection in DCD kidneys compared to patients who received Basiliximab without increasing their morbidity.

Methods: This is a non-randomised observational study in patients transplanted in two different periods who received a DCD kidney and different inductions. Group A (n=77) received ATG induction for 5 days (1.25mg/kg/day). Group B (n=36) received Basiliximab (20mg on day 0 and day 4). Both groups received Tacrolimus to achieve levels of 4-8, Mycophenolate Sodium (up to 1g BD) or Mycophenolate Acid (up to 720mg BD), and 20 mg of steroids tapered down to 0 , 3months post transplant.

Results: The baseline characteristics were similar apart from total mismatches that were higher in the ATG group. Median CIT was 15 h in group A and 13h in group B. 1-year graft survival in group A of 95% was the same with group B (95.5%). 1 patient died in the Basiliximab and 2 in the ATG group. There were 7 rejections in group A in 77 patients (9%) and 10 rejections in group B in 36 patients (27.7%) [p=0.024, OR for rejection 0.33, 95%, CI=0.13-0.78]. DGF incidence was 72.7% in the group A compared to 77.7% in group B. There were no patients with CMV disease in the ATG group and 1 in the Simulect group. There were 2 cases of BK viraemia in group B, and 1 in group A. Creatinine clearance at 6 months and 1 year was 46 and 49.5 ml/min in group A compared to 41 and 40 in group B.,47.4% of the ATG group still received steroids at 12 months compared to 58% in the Simulect group.

Conclusion: ATG induction in DCD kidneys is safe and results in significantly lower rejection rate, same graft survival and marginally better 1 year Creatinine Clearance

P82

Campath mitigates the risk of early rejection associated with delayed graft function in deceased donor renal transplantation

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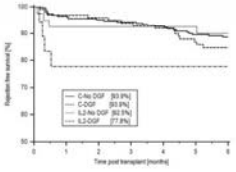
Delayed graft function [DGF] is associated with rejection [AR] and allograft loss. It is postulated that ischaemic injury up regulates the expression of allograft MHC leading to an increased risk of rejection. AR occurs later in patients receiving Campath(CAM) than with other induction agents and the aim of this study was to compare the impact of DGF on the incidence of rejection receiving either CAM or an IL2 receptor antagonist (IL2Ra).

We retrospectively studied 390 patients [m260,f130;mean age 48.8±13.7 yrs] who received a DDTx at our centre between 2005-2011. 332(85.1%) and 58(14.9%) patients received CAM and IL2Ra induction respectively. All patients received tacrolimus based maintenance immunotherapy with corticosteroids for one week only. The mean follow up was 41.9±19.8 months.

118(30.3%) of patients had DGF with no difference between the CAM and IL2Ra groups,p=0.99.There was no difference in patient survival at 3 yrs between the groups, being 97.3% and 89.7% in the CAM group with no DGF and DGF respectively;91.0% and 94.4% in the IL2Ra group with no DGF and DGF respectively,p=0.1.Allograft survival was inferior in the patients with DGF irrelevant of induction, allograft survival being 91.7%, 82.5% in the CAM group with no DGF and DGF respectively and 88.6%,82.6% in the IL2Ra group with no DGF and DGF respectively,p=0.02.Patients who received an IL2Ra were at highest risk of rejection in the first 3 months post transplant,p=0.03 as shown in figure 1.



This difference is subsequently lost and the 3 year rejection free survival is 79.6% in the CAM with no DGF, 75.1% in the CAM with DGF, 76.5% in the Il2Ra with no DGF and 70.7% in the IL2Ra group with DGF, p=0.4.This study shows that CAM mitigates the risk of rejection associated with DGF in the early post-transplant period but that this is not sustained.

Poster session

Wednesday 13th March

18:15 - 19:25

Immunosuppression - other

P83

Mycophenolate withdrawal in the first 12 months post renal transplantation (Tx) predicts worse graft function at 24 months

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Introduction: Mycophenolic acid precursors (MPAP) are widely used as first line anti-rejection agents after transplantation. However, many patients suffer intolerable side effects which are usually dose dependent, with reduction or cessation often reversing side effects, but with increased risk of rejection.

Method: This is a retrospective analysis of 153 Renal Transplant Recipients (RTR) from our Unit looking at graft function, MPAP dose alteration, multiple clinical, biochemical and graft factors in the first 24 months post-Tx. Primary outcome measure was the change in serum creatinine (SCr) from 12 to 24 months post-Tx.

Results: 61% of subjects were male, mean age at transplantation 47y (17-76), 79% cadaveric and 72.6% first transplants. 23% had biopsy proven rejection and 30% delayed graft function. Reasons for stopping / reducing MPAP were GI side effects (36.5%), leucopenia (36.5%), BKV or CMV infection (9% each) and other (9%). Participants were categorized into 3 groups: those remaining on full dose MPAP, those with a dose-reduction and those who discontinued MPAP in the first 12 months. Statistical analysis used ANOVA with P value <0.05. Stopping MPAP was found to be significantly associated with a deterioration in SCr from 12 to 24 months (162-202 umol/l) when compared to dose reduction (161-164) or no change (147-153)[P= 0.015 (95% CI 6.82 to 63.06) and 0.01 (95% CI 8.83 to 65.08) respectively]. Data was analysed for multiple potential confounding variables including biopsy proven rejection, type of transplant and CNI agent. None were significantly different between the groups and combined adjustment for all the variables made no difference to the significance observed.

Discussion: MPAP withdrawal in RTR within the first 12 months was an independent predictor of graft function at 24 months, regardless of the reason for withdrawal. MPAP withdrawal remained predictive of graft outcome when accounting for multiple factors which may influence graft function. We suggest that this is a result of chronic or subclinical rejection due to suboptimal immunosuppression in these individuals.

P84

Can we safely switch to a generic immunosuppressant?

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Background: Changes to transplant drugs for the patient can be stressful. With the introduction of a generic mycophenolate mofetil, the task was to convert all patients on denovo Myfortic (Novartis) and Cellcept (Roche) to Myfenax (TEVA). An audit was undertaken to identify patients with significant gastrointestinal (GI) symptoms and the process was evaluated.

Method: Our objective was to convert each eligible patient at their next delivery date of their immunosuppression. A letter was sent to all patients explaining the move to a generic drug. 2 months was initially supplied with a letter reiterating the change in brand and request to inform the transplant nurses on commencing Myfenax so that serum tests could be done 2 weeks later. A second instalment would be dispatched if results stable. After one year an audit was undertaken to determine how effective the transition to a generic medication had been. The successfully switched patients were sent a symptom questionnaire focussing on GI issues. Analysis was then undertaken of the questionnaires and evaluation of the process from a healthcare professional perspective.

Results: Of the 248 potentially suitable patients identified, 177 (71.3%) were successfully switched to Myfenax, 2 (0.8%) had not yet started Myfenax, 4 (1.6%) refused, 16 (6.45%) lost to follow up, 10 (4.0%) had other reasons for not converting and 39 (15.7%) experienced adverse events with Myfenax and had to come off this medication. Questionnaires were circulated to 177 patients. 113 (63.8%) responses. 45 (39.8%) had no GI symptoms, 39 (34.5%) had mild and 29 (25.6%) moderate to severe. There were 5 dose changes post switch, 3 decreases and 2 increases. Less than 50% followed the request to let the Transplant Nurses know that they had started Myfenax and hence didn't receive serum tests at the optimal time.

Conclusion: There were no major issues with a change of medication from a patient safety viewpoint. The next stage is to investigate all patients with significant symptoms identified on the questionnaire.

P85

The spectrum of transplant associated thrombotic microangiopathy and sustained reversibility of refractory disease with short-term eculizumab therapy

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Introduction: Transplant associated thrombotic microangiopathy (TA-TMA) affects approximately 1% of solid organ transplant recipients. Calcineurin inhibitor (CNI) -induced complement dysregulation is implicated in its pathogenesis. Management includes modified immunosuppression and plasma exchange, but due to the scarcity and heterogeneity of this condition there are no treatment guidelines. The potential role for complement inhibitor eculizumab is yet to be evaluated.

Methods: We performed a retrospective case note analysis of all cases of TA-TMA at our institution since January 2010.

Results: We identified 9 patients with TA-TMA, 5 female and 4 male, median age 41 (IQR 30-48) years who presented with Acute Kidney Injury (AKI), 6 following renal, 2 multi-visceral and 1 stem cell transplant. Diagnosis was made on renal biopsy (n=7) or peripheral blood film (n=2) at median 9 (IQR 4-28) weeks post transplant. 6 had renal limited disease, and all 3 non-renal transplant recipients had evidence of systemic disease (p=0.01). CNI was discontinued in all cases. Median peak creatinine was 250 (IQR 190-320) µmol/l and 2 patients were haemodialysis dependent. 3 recovered with cessation of CNI alone, belatacept was used as maintenance immunosuppression in 5 patients and 2 out of 5 patients recovered with plasma exchange. 4 patients had refractory disease and were treated with short-term eculizumab therapy: 900 mg weekly for 4 weeks and 1 patient received maintenance therapy for 4 months. No major adverse events were observed, and in particular there were no infective episodes attributable to this treatment. Mean creatinine in this group improved from 430 (range 180-600) to 136 (range 70-195) µmol/l (p=0.027) and no patients required ongoing haemodialysis.

Conclusions: TA-TMA tends to occur in the early post-transplant period. In our patients it caused significant renal impairment, which in all cases recovered with prompt diagnosis and appropriate management. Short-term eculizumab therapy is safe and offers sustained reversibility of refractory TMA.

P86

Advagraf and Myfortic in combination are associated with fewer gastrointestinal symptoms in kidney transplant recipients

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Introduction: Gastrointestinal (GI) complications may affect up to 64% of kidney transplant recipients. The causes may be multifactorial but are often associated with use of immunosuppression. Control of symptoms may only be achieved by dose reduction of this vital medication. This can lead to reduced exposure to the drugs in question resulting in an increased risk of acute and chronic rejection and subsequent reduced graft survival and increased morbidity and mortality. There is evidence that newer formulations of both tacrolimus (Advagraf) and mycophenolate (Myfortic) are associated with fewer GI side effects. Anecdotally we felt that the two in combination had an increased advantage in reducing GI symptoms above the individual benefits. The aim of this review was to explore the hypothesis that patients given Advagraf with Myfortic have a better GI profile than patients receiving twice-daily tacrolimus and mycophenolate mofetil.

Method: In this pilot study, 26 consecutive kidney transplant recipients receiving Advagraf and Myfortic were retrospectively reviewed from our prospective database, for GI symptoms, requiring a reduction in Myfortic dosage. All patients were commenced on Advagraf at a dose of 0.1mg/kg OD and a Myfortic dose of 720mg BD. Our target trough level for Advagraf is 5 to 10ng/ml.

Results: Out of the 26 patients, 18 (69.2%) were male with an overall mean age of 53.6 (range: 35-81). There were 21 deceased donor and 5 living donor transplants. The Myfortic dose was reduced in 8 of the 26 patients, within the first 3 months following transplantation. However, none of the patients in this cohort had a reduction of Myfortic because of GI symptoms. The dose was reduced due to either a reduced white cell count or non-GI viral infections.

Conclusion: This observational study suggests that patients on Advagraf and Myfortic, at standard therapeutic dosages, have fewer GI complications requiring dose reduction. Further comparative studies are needed to confirm this. If confirmed, this may have long-term benefits for graft survival.

P87

Experience of sirolimus conversion from calcineurin inhibitors in the chronic renal transplant setting

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Background: Mammalian target of rapamycin (mTOR) inhibition is potentially a less nephrotoxic form of immunosuppression than calcineurin inhibitors (CNIs). mTOR inhibitors have the advantages of being are less nephrctoxic, reduce progressive atherosclerotic injury and incidence of malignancies.

Methodology: Patient selection for conversion from CNI to SRL was based on the presence of chronic progressive graft dysfunction, CNI intolerance, malignancy and severe cutaneous viral warts. 29 patients were identified, 9 female and 20 male, 4 were LRTs and 25 cadaveric transplants of which 6 had a previous transplant(s). The population was predominantly Caucasian (86%).

Results: Seven patients failed to tolerate the switch due to complaints of; generalised swelling, acne, pancytopenia, diarrhoea, non-specifically unwell or a combination of the above. Six of the 7 were withdrawn within 2 weeks. No patient developed nephrotic range proteinuria and cholesterol values increased in 25% requiring additional therapy. The analysis of those patients that tolerated SRL for > 3months is as follows: age @ time of SRL conversion was 52.8 years with median 48.5 years; transplant duration was 9.6 years with median 6.3 years and the duration of SRL therapy was 2 years with median also of 2 years. The patients serum creatinine was documented 3 monthly over the 12 month period prior to and after conversion with the data presented as a scatter plot. In crude terms 9 patients deteriorated, 9 patients improved and 3 patients remained essentially unchanged.

Conclusions:

- Over 34% patients stopped SRL due to acute or chronic side effects
- For those patients who tolerated SRL the majority stabilised their RF
- Statistically there was no difference between pre-treatment group and post-treatment group which implies overall benefit.
- For selected patients SRL conversion has merit.

P88

Introduction of a home delivery service for immunosuppression: practicalities, pitfalls and prices

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Introduction: The availability of generic Tacrolimus (Tac) introduced the risk of inadvertent brand switching amongst community prescribed patients. In our local borough, 78% of GP Tac prescriptions were unbranded. The unsupervised switching of brands in the community has led to adverse effects, including rejection, infection and drug toxicity. We report the practical issues and cost benefits of introducing a home delivery service.

Methods: We introduced branded prescribing for all patients, initiated a home delivery system and repatriated immunosupression prescribing to secondary care. This was achieved by training the renal pharmacists to be Independent Prescribers and establishing them in all transplant clinics. Staff were educated in branded prescribing and a letter was sent to all patients and their GPs. All patients were interviewed by a renal pharmacist to review their medication, discuss switching to a generic brand of Tac, prescribe Tac and register for home delivery. Prescriptions are renewed at each clinic visit for delivery (usually every 2-4 months).

Results: All patients are now prescribed Tac by brand name. Prior to introducing home delivery, 73% of patients were on GP prescriptions, 27% hospital. Currently, 812 out of 1095 (85%) of our transplant patients receive their immunosuppression by home delivery, of whom 498 are on Tac: 91% Adoport, 9% Prograf. We have had no reports of failed or incorrect deliveries. There is a small cost for delivery but overall costs to the NHS are reduced, as the home delivery company can supply at hospital contract price and home delivery is VAT exempt. On average, switching from Prograf® to Adoport®, even with a 2 monthly delivery, saves approximately £2,500 per patient/yr.

Conclusion: Important logistic and staffing considerations are required for initiating home delivery of immunosupression and not all patients will agree to home delivery. Despite these issues, home delivery from secondary care allows consistency of brand supply and enables significant cost savings to be gained by switching to generic medication. A home delivery service is a safe and cost-effective way of ensuring the correct immunosuppressants are dispensed.

P89

Early sirolimus conversion as rescue therapy in kidneys with prolonged delayed graft function and slow graft function in deceased donor renal transplant

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Aim: Increasing rate of delayed graft function (DGF) and slow graft function (SGF) is seen with the use of DCD and ECD kidneys. Use of a CNI (cyclosporine, tacrolimus) may add to the insult by acute & chronic nephrotoxicity ultimately leading to PNF or premature graft failure. We report our experience of early sirolimus conversion in such cases in an attempt to salvage graft function

Methods: This was a retrospective study using hospital pharmacy records to analyse donor, graft and recipient data for patients with prolonged DGF and slow graft function who were converted to sirolimus between July 2003 - June 2012.

Results: 14 patients (9 males, mean age 53.6 ± 14.2 years) were identified who were converted to sirolimus for prolonged DGF and/or SGF. All the patients were established on dialysis (12 haemo and 2 peritoneal) with mean dialysis duration of 1393 ±72 days.7 patients received DCD grafts and 7 DBD grafts. Nine donors were ECD by UNOS criteria with mean donor age of 60±9 and pre-donation cGFR of 84 (± 28). Mean HLA mismatch was 3 and the mean cold ischaemic time was 1078 minutes (±259). These patients had prolonged DGF with a mean length of 42.3 days (±38.3). They were converted to sirolimus at a mean of 45.5 days (±21). The graft (patient) survival was 86% (86%), 73% (73%), 64% (64%) at 1, 3 and 5 years respectively. One graft never functioned (PNF) and the recipient died at six months post transplant. There were 4 graft losses 2 within first year and 1 each at 3 and 5 year follow up The mean eGFR (MDRD) for these patients were 26 (±11.3), 29 (±14) and 31 (±14.6) at 3, 6 and 12 months post transplant respectively. Six patients achieved sustained good graft function (mean creatinine at 1 year of 122mM/L).

Conclusion: Conversion to Sirolimus in patients with prolonged DGF and SGF may help salvage renal graft function & achieve long-term graft survival in some cases. We suggest a prospective study of this targeted group to validate such benefit.

P90

Early outcome data from an immunological risk stratification protocol for renal transplant immunosuppression demonstrates low rates of acute rejection and infection with preserved graft function.

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Introduction: The optimal long term immunosuppression (IS) regimen for transplantation remains uncertain. In June 2010 our transplant network implemented an IS protocol stratifying patients by rejection risk and using protocol biopsies at 3 months to guide and optimise long term IS.

Methods: Recipients of a 1st transplant with a population reactive antibody (PRA) <50% were assigned to the low immunological risk (LIR) protocol and recipients of a 2nd second transplant and those with PRA≥50% to the high immunological risk (HIR) protocol. All patients received induction methylprednisolone, basiliximab, tacrolimus and MMF. LIR patients received prednisolone until day 7 and HIR patients received long term prednisolone. We analysed patient outcomes from the first 2 years experience of our risk stratification protocol with minimum transplant follow-up of 3 months. ABO and HLA incompatible transplants were excluded.

Results: In the study period, 119 LIR and 54 HIR transplants were performed. DBD, DCD and LRD transplants were evenly distributed between the 2 groups. One year patient survival was 98% in the LIR and 100% in the HIR groups. Death censored 1 year graft survival was 97% in the LIR group and 96% in the HIR group. No grafts were lost to acute rejection. The mean MDRD eGFR at 6 and 12 months were 51.6±11.3mL/min and 51.8±10.4mL/min in the LIR group and 51.3±11.7 mL/min and 51.6±10.4 mL/min in the HIR group. Clinical rejection rates in the first 100 days were 7.6% (12.7% inc. borderline ACR) in the LIR and 9.3% (18.5% inc. borderline ACR) in the HIR groups. There was no difference in the severity of clinical rejection between the 2 groups. The overall rejection rates for months 1-6, (for-cause and protocol biopsies) were 16.4% for the LIR cohort and 13.5% in the HIR cohort. Infection rates were low with 4 cases (3.4%) of CMV, only in the LIR cohort, and two cases (3.8%) of BK nephropathy in the HIR cohort.

Conclusion: Our early outcome data with an immunological risk stratification protocol demonstrate low rates of acute rejection and IS related infection with maintained graft function at 1 year in both low and high risk patient groups.

P91

Switching from mycophenolate mofetil to azathioprine after 3 months post-transplantation is safe in tacrolimus based immunosuppression

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Mycophenolate mofetil (MMF) has been widely used in kidney transplantation after pivotal studies in the 1990s demonstrated superiority over Azathioprine (AZA) in Ciclosporin based regimes. However, there has been renewed interest in the use of AZA for maintenance immunosuppression using Tacrolimus.

This is a retrospective single centre analysis of a cohort of patients transplanted between July 2010 and June 2012. Patients classified as low immunological risk (1st transplant, kidney only, PRA <50%) received induction with Basiliximab and 7 days of oral steroids followed by Tacrolimus (trough level 10-15 month 1 reducing to 5-8 by month 3) and MMF (1g bd reduced to 0.5 g bd after 1 month). Protocol biopsy was performed at 3 months post-transplantation and patients without rejection or contraindications were switched from MMF to AZA (1.5 mg/kg).

55 low immunological risk patients were transplanted. Of these, following a normal protocol biopsy, 31 (57%) were switched to AZA. AZA was subsequently stopped in 3/31 (10%) due to adverse effects, and these patients were started on Prednisolone or returned to MMF. There were no serious adverse events and no rejection episodes following AZA switch. Graft function remained stable: median eGFR prior to AZA switch was 50 ml/min and following switch was 55 ml/min, 54 ml/min and 57 ml/min at 2-4 weeks, 6 months and 12 months respectively. With regards to cost, in comparison to generic MMF, switching these 31 patients to AZA saved £2500 per year which, assuming a mean 15 year graft survival would save £37,500 (cost saving of approx £80/patient/year). Now that generic MMF is available, these are modest savings and long term data would be required to justify this approach based on cost alone.

In summary, switching from MMF to AZA at 3 months post-transplantation in a Tacrolimus-based regime and following a protocol biopsy is safe, well-tolerated and associated with a favourable short-term graft outcome.

Poster session

Wednesday 13th March

18:15 - 19:25

Infection

P92

Re-audit of the use of valganciclovir for cytomegalovirus prophylaxis in high-risk renal transplant patients

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Background: Cytomegalovirus (CMV) infection is an important cause of morbidity and mortality in renal transplant recipients. Valganciclovir prophylaxis is indicated when a seronegative recipient receives a kidney from a seropositive donor (D+/R-). The recommended course duration changed from 3 to 6 months following the IMPACT study. We aimed to re-audit practice and CMV infection rates following this change in practice.

Methods: This was a retrospective audit of prospectively gathered data. All patients who received a renal transplant between May 2010 and October 2011 were included. Demographic data were collected along with donor and recipient CMV status, prescribing data, haematological data and renal function. Data were also collected on CMV viraemia and CMV disease.

Results: 27 of 119 transplants were D+/R-. 25 of 27 (93%) received prophylaxis correctly. Duration of prophylaxis was correct in 15 (58%) but truncated in 11(42%). Valganciclovir dose on discharge was correct in 8 (32%) patients, low in 3 (12%) and high in 14 (56%). At 60 days the dose was correct in 24 (96%) patients and high in 1 (4%). Out of the whole transplant cohort, 8 patients developed CMV viraemia (7 D+/R- and 1 D+/R+). Of these, 4 were treated for clinical CMV disease. Thus, of the D+/R- patients, 26% developed CMV viraemia compared to 46% in the previous audit cycle. CMV disease occurred in 15% of patients compared to 28% in the previous audit cycle. Most cases of CMV disease occurred after the 200 days of prophylaxis.

Conclusion: Overall, valganciclovir prescribing performance was good. CMV viraemia and disease rates dropped between audit cycles. These data are in keeping with the IMPACT study.

P93

Outcomes of thrimethoprim-sulphamethoxazole use in renal transplant recipients for Pneumocystis Pneumonia chemoprophylaxis following an outbreak

Nicos Mitsides[1], Darren Green[1], Kerry Greenan[2], Rachel Middleton[1,2], Elizabeth Lamerton[1], Jude Allen[1], Jane Redshaw[1], Paul Chadwick[1], Chinari Subudhi[1], Grahame Wood[1,2]

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Introduction: Following a clonal outbreak of Pneumocystis pneumonia (PCP) affecting transplant recipients in our tertiary nephrology unit, all transplant patients were offered chemoprophylaxis. Trimethoprim-sulphamethoxazole (T-S) 480mg daily was used as first line agent but a high rate of complications was noted. The aims of this study were to quantify the adverse events associated with T-S and evaluate its prophylactic benefit in their light. We also investigated potential risk factors for development of complications.

Method: This was an observational study of outcomes in 300 transplant recipients commenced on T-S prophylaxis in the 12 months from February 2011. End-points were adverse events due to the T-S, the additional medical burden as a result of these events, and diagnoses of PCP. Binary logistic regression was used to identify potential risk factors for the development of complications within the case group compared to the rest of the cohort.

Results: 300 patients commenced on T-S. 121 developed complications with most common being rise in serum creatinine (Cr)>15% from baseline (79%). 20% of complications led to hospitalisation. Most complications required unplanned medical review and many required extra investigations for allograft dysfunction including renal biopsy (6%). 92% of those affected had to stop T-S. Despite this, PCP incidence fell from 19 cases in 19 months to 2 cases in 12 months. The risk of rise in Cr with T-S was significantly increased with transplant age, lower baseline renal function, use of renin-angiotensin-aldosterone system blockade and use of Calcineurin Inhibitors, Prednisolone, Mycofenolate Mofetil and Sirolimus. The risk with immunosuppressive agents was dose dependant.

Discussion: Use of chemoprophylaxis reduced the incidence of PCP but led to a high number of complications. This was mainly due to raised serum Cr causing significant anxiety and leading to increase in investigations burden. We would recommend caution in T-S use, particularly in those with aging transplants, poor baseline renal function and high immunosuppression burden.

P94

Dapsone induced methemoglobinemia; increased prevalence in a cohort of renal transplant recipients receiving chemoprophylaxis for pneumocystis pneumonia.

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Introduction: Dapsone is the commonest cause of drug-induced methemoglobinaemia (MHb). The prevalence of MHb in patients on dapsone is reported to be up to 20%. Following an outbreak of pneumocystis pneumonia (PCP) in our tertiary nephrology unit, dapsone 50-100mg once a day was used as the second line chemoprophylactic agent. Because dapsone is renally excreted, we hypothesised that the rate of MHb would be even higher in this CKD population. We also aimed to describe their demographic characteristics, risk factors and presenting features of MHb in these patients.

Methods: This was a case series of 26 consecutive transplant recipients commenced on dapsone for chemoprophylaxis against PCP between February to September 2011. All patients had normal Glucose-6-phosphate dehydrogenase levels prior to treatment. Measurement of MHb level was triggered either by symptoms or drop in serum haemoglobin (Hb) and cases were diagnosed based on elevated MHb levels (>1.5%). MHb patient characteristics were compared against the rest of the cohort to determine potential risk factors.

Results: 46% of patients developed MHb (levels 6.4±4.1%). 50% of cases were symptomatic on presentation, with breathlessness most common (33.3%). Cases had a mean drop in Hb of 19±7.0%. Hb drop was associated with low albumin (correlation coefficient [cc] -0.805, $p=0.002$) and a baseline Hb (cc -0.715, $p<0.001$). MHb led to 5 admissions (median length of stay was 5 days, range 1-10 days) with MHb level showing a strong correlation with length of stay (cc 0.762, $p=0.002$). 17% of cases required blood transfusion. Following the high number of adverse reactions, the use of dapsone as chemoprophylaxis was stopped.

Discussion: This is the highest reported prevalence of MHb in patients receiving dapsone and its use led to significant morbidity in this renal transplant population. This study raises concerns to its use as chemoprophylaxis in this setting. As half the cases were asymptomatic on diagnosis, we recommend MHb levels be measured routinely in all patients.

P95

BK virus screening in transplant patients, do or not to do?

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Introduction: BK Virus can cause inflammatory interstitial nephritis (BKVN) or obstruction in kidney transplant patients. The incidence of graft loss has been reported 0-100%(mean =46.2%).Most of the cases happen in the first year of transplant. Screening for BK replication will enable to detect BK infection sooner and may improve graft survival. The Renal Association suggest screening transplant patients monthly for the first 6 months and then every 3 months until end of first year and also on patients that immusuppression therapy has been increased.

Aim of study: In our unit we do not routinely screen our transplant patients for BK virus. Historically the rate of BK infection and nephropathy has been low. The aim of this project was to identify the prevalence of BK nephropathy and outcome of our patients to see if our way of practice should change and we should start screening our newly transplant patient according to RA guidelines.

Methodology and results: We retrospectively reviewed the cases of BK positive tests in 2007-2012. 162blood and urine tests were checked on 58 kidney transplant patients.12 patients had positive tests. Prevalence of positive BK results at the end of observation was 4%(CI=1.8-6.3%). Nine patients had BK nephropathy(prevalence=3%,CI= 1.1%-5%). In 2011 we had 5 cases of positive serum BK PCR. All of these patients were newly positive and all of them developed BK nephropathy. At the end of observation all of them had functioning graft. 80% of our positive patients were male. The mean time between transplant and diagnosis of BK nephropathy was 14 months. The mean age of this group was 47.6 years. 20% of patients had had a ureteric stent. **Conclusion**: Each BK test costs £4.50.The RA suggests that every newly transplanted patient should have 8 tests in first year post transplant. In 2011 we had 70 adult kidney transplants that will have at least 560 tests in their first year. This would cost £2520 a year. The prevalence of BK nephropathy in our unit is 3% with no transplant loss after average 11 months follow up. We do check a serum BK PCR on all transplant patients with deteriorating renal function and biopsies are stained for BK .We may be missing undiagnosed BK but feel in our unit that this approach is sufficient. If the biopsy confirmed BK nephropathy then we will monitor BK PCR every 4 weeks till it became negative. Treatment involves reducing immunosuppression.

P96

Pneumocystis jiroveci pneumonia infection in renal transplant patients, a single unit review

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Introduction: Pneumocystis jiroveci is an opportunistic fungal pathogen. It can cause life-threatening pneumonia in immunocompromised patients. The majority of PJP occurs 3-6 months after kidney transplant. Over time the mortality of PJP has been declining from 38% in 1980 to 13% in the first decade of this century. Risk factors for PJP infections are rejection and intensity of immunosuppression. Concomitant infection with CMV is reported to be another risk factor, as is older age. Some studies suggest that low lymphocyte count could be another risk factor.

Methodology: A matched case-control study using a local database of kidney transplant patients (2005 to April 2012). Index cases of PJP were identified and matched in sex and year of transplant in 1 to 5 ratios with patients without PJP from the same database. Diagnosis of PJP was made with Polymerase Chain Reaction (PCR); either bronchoalveolar lavage (BAL) or blood.

Results: We had 5 cases of PJP in our transplant cohort compared which all occurred after September 2011; no cases in 2005-2010. The mean age of the PJP patients and 25 controls were 61±8.57 and 49.8±13.2 years respectively (p value= 0.087). The time between transplant and PJP infection ranges between 9 to 141 months (median and mean 55 and 61 months respectively).Three (60%) of patients presented with pneumonia and the rest presented with shortness of breath. PJP was mostly confirmed in BAL (80%). One case had positive blood PCR. None of the patients had been treated for acute rejection. At the time of presentation none of the cases had been on PJP prophylaxis. There was no statistical difference between the two groups in CMV infection rate, immunosuppression type, and lymphocyte count prior to PJP infection. After treatment, 3 patients had independent renal function, one patient died and one is now dialysis dependent.

Conclusion: There was no clear cause and pattern for PJP infection in our cohort. We did not perform genotyping; however previous attempts in other UK centres had not lead to the source of infection. We should be vigilant for the clinical signs and have a low threshold for investigating for PJP infection.

P97

Prospective BK virus screening protocol reduces BK Virus induced nephropathy (BKVAN) and subsequent graft loss

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Aim: Our study attempts to evaluate the utility of the BK virus screening protocol to prevent graft loss due to BKVAN.

Methods: 159 de novo kidney-only recipients were enrolled from Jan 2011.Standard immunosuppression with Alemtuzemab or Basilixmab and mycophenolate mofetil (MMF)/FK506 ± prednisone was prescribed. Quantitative BK virus (BKV) PCR surveillance in plasma was performed monthly for the first 6 months then every 3 months for 2 years. Patients with significant viremia (defined as >10,000 gEq/ mL) were treated with stopping MMF and 30% to 60% reduction in doses of FK506 without antiviral therapy. The target 12-hr FK 506 trough levels were lowered to 4 to 5 ng/mL in the significant viremia group, whereas the target levels remained unchanged at 5 to 8 ng/mL for all other groups. The renal biopsy was performed only if renal functions deteriorated.

Results: 41 (26%) developed BK viremia; 27 (16%) of whom had significant viremia. A total of 7 (25%) of the 25 (of 27) patients who underwent biopsy had BKVAN with positive SV 40 staining. The mean plasma BKV PCR reduced by 91% (range, 52%-100%) at 24 weeks after peak viremia. Acute cellular rejection seen in 02 (07%) of 27 patients, responded to bolus steroids. The median FK 506 level in patients with BK Virus nephropathy was 8.5 ± 1.2 ng/mL. The actuarial graft survival rate in patients with BKVAN was 100%, 98%, 96% at 6, 12, 18 months post renal transplant. The death censored graft survival rate in this group was 100%, 100%, 98% at 6, 12, 18 months post renal transplant. There was no significant decline in mean creatinine clearance at 1 month after transplantation to 1 year after peak viremia (P=0.67). There was no statistical correlation in development of BKVAN with CMV infection (p=0.81), Cold Ischemia Time (p=0.06) or Alemtuzemab induction (p=0.09).

Conclusions: BK viremia was controlled with reduction in immunosuppression in majority of patients. Nearly 10% patients had significant viremia, 4.5% patients had BKVAN and 1.2% patients had graft loss in the our screened population. Our BK viremia rate was similar to the majority of published reports.

P98

A single centre observational study of the prevalence and clinical implications of EBV DNAemia following adult kidney transplantation

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Aim: To investigate the prevalence of EBV DNAemia and compare baseline characteristics, clinical outcomes, quality of life (QoL) and symptoms between those renal transplant patients with persistent EBV DNAemia and those patients with no detectable EBV DNA.

Methods: Stable renal transplant recipients were screened for EBV DNAemia between February and September 2010 by PCR, using the gene target BNRF-1, with a threshold of sensitivity of 1000 copies/ml. Baseline data included age, time from transplant, rejection episodes and immunosuppression. Clinical outcomes included death, hospital admissions, cancer and PTLD rates, haemoglobin, white cell count, liver enzymes, and GFR. QoL was recorded using the SF36 questionnaire and included vitality, general health, physical function and mental health. Symptom scores included fatigue, night sweats, fever and weight loss.

Results: We recruited 499 patients to the study and serial samples (≥3) were obtained from 446/499 (89%) of participants over 1 year. At recruitment 90% were EBV seropositive and 153/499 (30%) had detectable EBV DNA in blood, including viral loads (copies/ml) of log 3: 94 (19%), log 4: 47 (9%) and ≥log 5: 12 (2%). Chronic high viral load (HVL) carriage (≥3 samples over 6 months with ≥10,000 copies/ml) was detected in 31patients, persistent DNAemia (PDNA) (≥75% samples with DNA detected) in 42, no detectable DNA (NDNA) in 234, and transient detection (<75% samples with detectable virus) in 139 patients. PDNA was associated with:

- increasing time from transplant (10.4 yrs vs 6.6 yrs, Student's t test, $p<0.0001$)
- no MMF in regimen (14% vs 56%, Fisher's, $p<0.0001$)
- reduced general health score (52.8 vs 60.1, Student's t test, $p=0.02$)
- a trend towards increased rejection episodes (clinical or biopsy diagnosed) (30% vs 19%, Fisher's, $p=0.058$)

Comparisons between PDNA patients and NDNA patients showed no significant differences in any other of the measured factors.

Conclusions: Persistent EBV DNAemia occurred in 16% of kidney transplant recipients and, interestingly, was not associated with B-symptoms. PTLD rates did not differ between the PDNA and NDNA groups.

P99

Outpatient parental antibiotic therapy in a renal transplant population: a single centre experience

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Introduction: Outpatient antimicrobial therapy (OPAT) has been established as a standard clinical treatment for a wide range of infections across different specialities. It not only allows patients to be treated in their home environment but is also cost-effective. The usability, effectiveness and outcome of OPAT in patients with immunosuppressants are not well reported. There is also little guidance regarding monitoring patients during OPAT. In this study we describe our experience of OPAT in our renal transplant patients.

Methods: Case records were studied retrospectively over a 10 year period in the South West Thames Renal Unit. Eight patients with functioning renal allografts received 614 episodes of antimicrobial therapy during 11 discrete OPAT courses. We recorded basic demographics; transplant functional data (eGFR and serum Creatinine) and indications for OPAT with its response, complications and outcomes.

Results: A successful outcome (cessation of infection) was achieved in 10 out of 11 courses (91%). Indications for commencement of OPAT were osteomyelitis (n=4, 36.4%), mycotic aneurysm (n=2, 18.2%), pyelonephritic sepsis (n=2, 18.2%), psoas abscess (n=2, 18.2%) and cytomegalovirus infection (n=1, 9.1%). Mean duration of OPAT was 27 days (Median 25 days, SD +/- 13.1). One OPAT course was terminated due to immunosuppressive related neutropenia. No patients were re-admitted to hospital due to failure of OPAT or adverse events. There was no significant impact of baseline allograft function during any of the recorded OPATs. No major line infections were noted.

Conclusions: We concluded that OPAT is safe and clinically effective in renal transplant recipients. During the OPATs no observed significant impact on graft function was observed in any of the patients. The incidence of adverse events, specifically related to line complications, was lower in our population than those reported in the general OPAT population. Future work should focus on the development of guidelines for the use of OPAT within renal transplant patients and aim to outline the degree of monitoring required.

P100

Incidence of infection in transplant patients followed up in a non-transplant renal unit

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Introduction: Infection is a major cause of morbidity and mortality in the renal transplant population. It is also a main reason for admission to hospital with associated cost to health service. We aim to evaluate the incidence and nature of infection in the post renal transplant population receiving follow-up care at the Derby Renal Unit.

Method: Data were collected retrospectively from 152 patients who had received follow-up care at Derby Renal unit. Patients underwent renal transplant at Nottingham city hospital and later transferred to Derby Renal Unit after initial follow up of up to 6 months. Data for demography, transplant status, pathology and microbiology was collected from renal and hospital database. Each episode of infection causing either a positive microbiological result or a hospital admission was analysed.

Results: Sixty five patients (42.76%) were identified to have at least an episode of infection. Fifty five percent were males with mean age of 54 $\pm$ 13 years. The 55.26% of patients were on triple drug immunosuppression on mycophenolate (41.13%) or azathioprine (13.81%) and 68% were on CNI. The median follow duration at the unit was 1.85 years (range 11.73 years to 1 month). One hundred and fifty nine infection episodes occurred in 65 (42.75%) patients. The incidence of post transplant infection was equivalent to 0.44 episodes per patient per year. Of the 159 infective episodes 70% were bacterial, 11.3% were viral, 2.5% were to fungal and 1.25% had PCP & BK virus. The majority of the bacterial infections were due to UTI from gram negative bacilli (coliforms). Twenty three episodes of AKI were documented. Of these only 1 patient had AKI stage 3. The median bed occupancy after hospitalisation following infection was 3.19 days per infection episode or 1.42 per patient per year. There was no graft loss. All patients recovered from infections except for one who died of atypical mycobacterial infection with a functioning graft. There were 2 rejections episodes equivalent to 0.006 Acute Rejection episodes / patient per year.

Conclusions: This was the first UK based study on infections in long term follow up at a non transplant unit. The incidence of infection may not be excessive compared to the one observed in other studies on epidemiology[1]. This may be due to lower rate of rejection and reduced exposure to excessive immunosuppression. However, prospective studies are needed to confirm the incidence rates and cost burden on non transplant hospitals.

Reference: 1. Infectious complications after kidney transplantation: current epidemiology and associated risk factors. Alangaden GJ, et al. Clin Transplant. 06 Jul-Aug; 20(4):401-9.

P101

Incidence and complications of CMV in transplant recipients receiving prophylaxis with valganciclovir: a single centre study

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Background: Cytomegalovirus (CMV) infection remains the most prevalent viral disease in renal transplant recipients and has a negative impact upon outcomes. Recipients at highest risk are those who are CMV naïve (R-) and receive a CMV seropositive donor organ (D+). In spite of a number of recent trials, the optimal duration of prophylactic therapy remains unclear.

Methods: We conducted a retrospective analysis of the incidence of CMV disease in our local renal transplant population over 7 years from January 2005 to January 2012.

Results: A total of 823 patients received kidney alone or simultaneous kidney pancreas transplant. All 257 D+/R- patients received 3 months of valganciclovir prophylaxis of which 50 (19.4%) developed CMV viraemia. 14 patients (28%) that developed CMV viraemia had been previously treated for rejection, 3 (6%) with ATG. Alemtuzumab induction was used for 33 (66%) of these patients. Of the 50 patients who developed viraemia, 11 (22%) were asymptomatic 35 (70%) developed invasive disease particularly colitis (51.4%) and 4 (8%) were symptomatic without evidence of tissue damage. 24 (48%) patients with invasive disease required intravenous treatment resulting in average hospital admissions of 21 days duration. There were 4 deaths directly associated to CMV disease in the first year post transplant. The majority of patients requiring CMV treatment were 4 or 5 months post transplant (34 and 30% respectively). As anticipated, CMV occurred much less frequently in the D+/R+ (10 of 282; 3.5%) and D-/R+ (9 of 284; 3%) categories of transplant recipients.

Conclusion: We report an occurrence of CMV disease in D+/R- recipients in our centre at 19.4% using a valganciclovir prophylaxis regimen of 3 months. Surveillance post completion of prophylaxis is essential to recognise disease and initiate prompt treatment.

P102

BK virus nephropathy in native kidneys post allograft bone marrow transplantation

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Introduction: Human Polyoma Virus (BKV) infects the majority of the immune-competent human population asymptomatically and remains latent. However, over recent years there has been increasing supporting evidence linking BKV to tubule-interstitial nephritis and ureteric stenosis in renal transplant recipients and late-onset haemorrhagic cystitis in Bone Marrow Transplant (BMT) recipients.Current treatment regimens involve reducing immunosuppressive medications. We report a case of acute kidney injury (AKI) secondary to BKV nephropathy in native kidneys following allograft BMT.

Case presentation and findings: A 47 year old female, diagnosed with acute myeloid leukaemia in 2008, initial treatment was FLAG chemotherapy leading to remission. There was a recurrence in January 2011 and few months later she had an allograft BMT from a HLA-matched unrelated donor. Following the BMT she developed diarrhoea and intense pruritus. A gastrointestinal tract biopsy confirmed graft versus host disease which was treated with extracorporeal photochemotherapy.

In September 2012 her eGFR dropped from a baseline of 68 (in May 2012) to 31mmol/l hence she was referred to us with AKI. Medications on admission included Posacarazole, Prednisolone, Aciclovir, Gaviscon, Sirolimus, Mycophenalate Mofetil. Initial investigations revealed, protein +1 on urinalysis, with a WCC of $<10^7$, RBC $< 10^7$, and mixed growth of organisms on culture. Urine PCR was normal at 38 mg/mmol. A renal USS showed bilateral echogenic cortex, with no evidence of hydronephrosis. Autoimmune profile was negative, serum electrophoresis showed no paraprotein and complement factor 4 was mildly raised.

Following initial investigations a kidney biopsy was performed, which revealed essentially unremarkable glomeruli. There were damaged tubules and patchy granulomatous inflammation. It also showed polyoma virus inclusions in the tubular epithelial cells which was confirmed on immunohistochemistry for SV40 T-Ag that demonstrated most extensive positivity within the medulla, which is a common finding in polyoma virus nephropathy. There was no evidence to support an immune complex mediated glomerulonephritis as has previously been associated with bone marrow transplants.

Discussion: BKV nephropathy is a common finding in renal allograft, however, it is rare in native kidneys. There is a single case report of PVN one year after chemotherapy for CLL (Van der Bij et al, J Clin Virol 2009; 45: 341), but to our knowledge this case is the first report of BKV Nephropathy in native kidneys following bone marrow transplantation. In terms of treatment her sirolimus was discontinued and renal function was closely monitored.

Conclusion: We suggest that BKV nephropathy of native kidneys should be considered in differential diagnoses of AKI following non-renal transplantation.

Poster session

Wednesday 13th March

18:15 - 19:25

Kidney outcomes 1

P103

Retrospective analysis of graft thrombosis in patients who underwent deceased donor renal transplant

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Introduction: This study was undertaken to analyse the possible etiological factors that caused renal graft thromboses after deceased donor renal transplant and led to early graft failure. We also tried to determine whether any pre-emptive steps can be undertaken to prevent or minimise such occurrences in near future. We wish to improve upon the current renal transplant success rates which should have positive clinical, financial and social impact.

Methods: A retrospective study was undertaken to analyse the patients who had graft thrombosis following deceased donor renal transplant between 1st April, 2006 and 1st April, 2012. Of the 363 patients who underwent deceased donor renal transplant during this period; ten patients suffered from graft thromboses. Nine were male and one was female. Mean age was 44.5 years (range 23-61 years). All patients underwent haematological and radiological investigations prior to and after the transplant. All these patients had kidney failure due to diseases like polycystic kidney disease, posterior urethral valve, congenital reflux nephropathy etc. They also suffered from overlapping medical conditions such as Diabetes Mellitus, Hypertension and/or hyperlipidemia. One of these patients was heterozygous for prothrombin gene mutation. Two patients were investigated for Anti-cardiolipin antibody and both were negative for them. All patients were on maintenance tacrolimus and mycophenolate mofetil in the post transplant phase. The data was subjected to statistical analysis by an independent analyst using Stata version 12 software. Results were declared as significant if two-sided p-value ≤ 0.05 was achieved; 95% confidence intervals were also provided.

Result: 2.75% of the recipients had renal graft thromboses within the given time period. Mean deceased donor age was 44 years (range 10 – 68 years). Mean warm ischemia time was 47 minutes (range 30-54 minutes). Mean cold ischemia time was 19 hours (range 11-28 hours). Renal Doppler ultrasound was performed to assess the status of the graft in post transplant period. Mean time interval between transplant and graft thromboses was 3 days (range 2-10 days).Renal vein thrombosis was the most frequent cause of graft thrombosis.

Discussion: Renal vein thromboses appeared to be the most frequent cause of early graft failure. More effort is required to look for possible etiological factors which could help reduce the current graft failure rate.

P104

Renal transplantation outcomes in elderly patients

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Introduction: The mean age of renal transplant recipients is rising, with age no longer considered an absolute contraindication. Outcomes in patients at the extremes of age have not, however, been clearly defined. This study's objective was to evaluate renal transplantation outcomes in the elderly at our institution.

Methods: All renal transplants performed at our centre from Jan 2001 – Dec 2010 were retrospectively analysed (n=762). Elderly patients (defined as those over 65 years old) were compared to those under 65. Outcome measures were: delayed graft function (DGF), primary non-function (PNF), biopsy proven acute rejection (BPAR), serum creatinine at 1 year and graft and recipient survival. Length of initial hospital stay and re-admission rates were also assessed. Student's T-Test was used to analyse continuous variables, Pearson's Chi-Squared test for categorical variables and the Kaplan-Meier estimator for survival analysis.

Results: Elderly recipients received proportionately more kidneys from elderly donors (27.1% vs. 6.3%; $p<0.001$). Such kidneys were more likely to have DGF (40.7% vs 16.9%; $p<0.001$). Graft loss at 1 year was higher in patients who received kidneys from elderly donors (15.3% vs 7.6%; $p=0.04$). There was no significant difference in overall patient survival at 1 year. Recipient age did not significantly affect DGF (16.9% vs 18.5%; $p=0.77$) or graft loss at 1 year (11.9% vs 7.8%; $p=0.28$). Elderly recipients were, however, more likely to die in the first year post transplant (6.8% vs 2.1%; $p=0.03$). BPAR was less common in elderly patients (6.8% vs 22%; $p<0.01$). Elderly recipients were more likely to be readmitted (31.8% vs 10.9%; $p<0.001$).

Discussion: Whilst kidneys from elderly donors were associated with DGF and earlier graft loss, elderly recipients were less likely to have BPAR and there was no association between elderly recipients and DGF or graft loss at 1 year. Elderly recipients were associated with higher readmission rates and death in the first year after transplant but this may reflect the higher prevalence of co-morbidities in elderly patients. Recipient age should not preclude renal transplantation.

P105

Is Waterlow score an independent predictor of outcome in renal transplantation?

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Introduction: The use of preoperative scoring systems to stratify risk, assist preoperative counselling and inform outcome is not proven in transplantation, largely due to variability in donor and recipient characteristics. The Waterlow score (composite analysis of age, gender, body mass index/BMI, nutritional state, tissue quality), initially developed in the 1980's, has been widely adopted as a tool to stratify risk of decubitus ulcer development. We aimed to assess this system as a surrogate marker to predict outcome in renal transplantation.

Methods: We performed a retrospective analysis of 109 consecutive renal transplant recipients at a single unit over 8 months (07/11 – 02/12). Patients were stratified based on preoperative Waterlow scores (<9 low, 10-14 medium and >15 high risk). Delayed graft function (DGF; dialysis requirement in the 1st week after transplant) was utilized as the primary endpoint. In addition, potential confounding factors including recipient age, BMI, ASA score, number of previous transplants, type of transplant, donor BMI, age and cold ischemic time were compared.

Results: 109 patients were included (62 males, 47 females; mean age 48.16; range 21-79, 75 deceased & 34 live donor transplants); 73 patients were low risk (47 and 26); 28 medium risk (19 and 9) and 10 high risk (10 and 0 respectively) Live donor patients demonstrated no differences in outcomes based on differences in Waterlow score. In the deceased donor group, DGF rates were 17%, 55% and 100% respectively ($p<0.005$ and $p<0.0001$ respectively; Fisher's exact test) There were also no significant differences in any examined potential confounding factors across the groups.

Conclusions: DGF is established as a surrogate marker of long term graft outcome. Accurate predictive models in transplantation have however proven difficult to validate. The Waterlow score, routinely collected on admission by nursing staff, is a useful modality of adverse outcome prediction in emergency surgery. It appears to offer the potential to similarly stratify outcomes in transplant patients, thereby ensuring optimal utilitarian use of donor organs.

P106

The effect of HLA mismatching on deceased and living donor renal allograft outcomes in paediatric recipients

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Introduction: Living donor kidney transplantation accounts for around half of all paediatric (<18 years) renal transplant recipients (PRTR) due to improved renal allograft survival, although there are no data comparing the effect of HLA-mismatching on outcomes. The 2006 Kidney Allocation Scheme prioritises children with good HLA mismatching (Level 1/2: 000 A,B,DR or [0 DR & ≤1 B]).

Methods: Data were obtained from the UK Transplant Registry on all PRTR who received a donation after brain death (DBD) or living donor (LD) kidney-only transplant between 2000 and 2011.

Results: In 1,333 PRTR; 779 (58%) received a DBD donor kidney. Table 1(a) shows the hazard of graft failure within five years of transplant has reduced over the period analysed (HR=0.93 p=0.001) and is 1.46 times as likely in children who receive a well-matched DBD donor kidney compared with those that receive a poorly HLA-mismatched LD kidney (p=0.04; 1(b)). The significance of this ratio is reduced when additionally accounting for transplant year (HR=1.40; p=0.06; 1(c)).

Table 1: Cox proportional hazard regression modelling of renal allograft survival

Factor	Level (Baseline)	n	Hazard ratio	(95% CI)	P
(a) Transplant year	Linear	1316	0.93	(0.88-0.97)	0.001
(b) HLA/Donor	Good/Live	178	0.84	(0.48-1.47)	0.54
	(Poor/Live)	**364**	**1.00**		
	Good/DBD	**599**	**1.46**	**(1.02-2.07)**	**0.04**
	Poor/DBD	175	1.65	(1.08-2.52)	0.02
(c) Transplant year	Linear	1316	0.94	(0.89-0.98)	0.01
HLA/Donor	Good/Live	178	0.84	(0.48-1.47)	0.55
	(Poor/Live)	**364**	**1.00**		
	Good/DBD	**599**	**1.40**	**(0.99-1.99)**	**0.06**
	Poor/DBD	175	1.47	(0.95-2.25)	0.08

Discussion: In children, well HLA-matched DBD donor renal transplants have inferior graft outcomes when compared with poorly HLA-matched LD grafts.

P107

Nephrectomy for the failed renal allograft in children: predictors and outcomes

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Background: The indications for removal of a failed renal allograft and its impact on subsequent dialysis and retransplantation remains uncertain.

Methods: We performed a 10 year review of allograft failure to review factors that determine a need for transplant nephrectomy, and patient outcomes in children with or without nephrectomy.

Results: 42 children developed graft failure over 10-years. Eight had graft failure within 4 weeks and were excluded. Of the remaining 34 children, 18 (53%) required transplant nephrectomy. The median graft survival was 1.1 [range 0.2-10.6] vs 7.5 [1.5-15.0] years in the nephrectomy and non-nephrectomy groups respectively; p=0.011. Children with graft failure within 1-year of transplantation were four-times more likely to require a transplant nephrectomy than those with graft failure after 1-year (p=0.04). Patients with a primary diagnosis of CAKUT were significantly less likely to require a transplant nephrectomy than those with glomerular disease (p = 0.006. Renal biopsy performed ≤8 weeks prior to graft loss showed Banff grade II acute rejection in 13/18 children who required subsequent nephrectomy vs 3/13 who did not need nephrectomy (p=0.01). Inflammation (fever, graft tenderness and raised CRP) was seen in 66% of nephrectomised children. Banff II rejection on biopsy, an inflammatory response and the time post-transplantation significantly and independently predicted the need for nephrectomy (p=0.008, R^2=67%). HLA antibody levels were increased in the nephrectomy group (p=0.0003) but there was no difference in the presence or class of donor specific antibodies. 82% required dialysis (61% hemodialysis) after graft failure and 35% have been successfully retransplanted.

Conclusions: Children with Banff II rejection, an inflammatory response and early graft loss are more likely to need transplant nephrectomy. Nephrectomy may be associated with higher circulating HLA antibody levels.

P108

Transplant nephrectomy – a single transplant centre experience

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Introduction: Of approximately 70,000 renal transplants performed worldwide annually an estimated 7 - 10% fail during the first year, and a further 3-5% fail every year thereafter. Allograft nephrectomy is associated with a significant morbidity and mortality and influences the outcome of subsequent renal transplantation. The aim of this study was to identify the reasons for allograft nephrectomy in a single transplant centre in the United Kingdom and to determine the complication rate and effect on relisting and retransplantation.

Methods: All transplant nephrectomies in a single regional transplant centre for a 11-year period (January 2000 – December 2011) were studied. Detailed information including donor characteristics, recipient gender and age at transplantation, duration of allograft function, cause of allograft failure and reason for transplant nephrectomy were obtained and entered onto an Excel database and analysed.

Results: Forty-two allograft nephrectomies were performed during this period (602 renal transplants) on 38 patients (24 men and 14 women). The median age of patients who underwent allograft nephrectomy at the time of transplantation was 57 years (range: 18 - 73 years) with majority of the kidneys (71%) being donated after cardiac death. The mean HLA mismatch for these patients was 2.3. The most commonly used immunosuppression was a combination of prednisolone, mycophenolate and tacrolimus in 50% of the patients. Eighteen (43%) of the transplant nephrectomies in this series were for kidneys failing in the first week of transplantation. Of the remaining, seven (17%) failed between one and 4 weeks; 10 (24%) between 1 month and 12 months; and seven thereafter. The most common indication for allograft nephrectomy was graft thrombosis (50%) with some of the other causes being hyperacute allograft rejection, pain, despite immunosuppression and infection. Overall in hospital mortality rate post procedure was 9.5% with severe haemorrhage, sepsis and pulmonary embolism as the causes. The morbidity rate was 33%, which mainly included infection and deep venous thrombosis. Eleven of the 17 patients listed for retransplant, underwent retransplantation with eight having a successful outcome. Four patients were lost to follow up due to transfer to other regional transplant centres.

Conclusion: Graft nephrectomy was largely limited to allograft failures in the early phase post renal transplantation. Though allograft nephrectomy is associated with risk of significant morbidity and mortality it does not preclude from listing for retransplantation. The limitations of study include lack of information about patients who moved out the area. The difficulty of access to complete information about transplant failures and allograft nephrectomy highlights the need for a national registry.

P109

Non-adherence is a major contributory factor to renal allograft failure

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Introduction: Maximising long term renal allograft survival depends on appropriate immunosuppression, with avoidance of opportunistic infections and drug nephrotoxicity. Non-adherence has been reported as a major contributory factor to graft failure.

Methods: Contributory factors to all grafts failing in the five year period 2007-2011 were determined, together with subsequent patient outcome.

Results: Seventy seven graft failures in 76 patients were identified. Seventeen early graft failures were excluded from subsequent analysis and the remaining 60 were analysed in detail.

Type of Transplant	# (%)	Mean age (yrs)	Mean graft survival (months)
DBD	39 (65)	44 ± 15	73 ± 43
DCD	2 (3)	58 ± 9	24 ± 31
LD	19 (32)	36 ±15	56 ± 53

56/60 (93%) patients underwent at least one graft biopsy. Biopsy proven acute cellular rejection > one year following transplantation occurred in 13 patients (22%). The most common causes of graft failure were chronic allograft nephropathy (biopsy proven in 14 patients and presumed in 2, 27%), antibody mediated or vascular rejection (20 patients, 33%) and recurrent IgA nephropathy (8 patients, 13%). Recurrent primary disease and non-compliance were the principle contributors to graft failure amongst recipients of LD transplants. Following graft failure and return to dialysis, 3 patients (3.9%) died within 3 months and a further 7 patients (9.1%) within 1 year.

Conclusion: Our study confirms that on-going immunological damage is a major factor leading to graft loss. Non-compliance is a significant contributor to this, and is a particular concern amongst younger recipients of LD transplants. It is imperative we identify, understand and appropriately counsel patients at risk to avert this unfortunate and potentially avoidable outcome.

P110

The incidence and risk factors for early kidney transplant loss

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Introduction: Kidney transplant outcomes are generally compared by long-term survival analysis, but the catastrophic nature of immediate graft failure warrants a separate analysis of the incidence and factors responsible.

Methods: Recipients of kidney-only transplants between 2002 and 2012 in our centre who suffered loss of their graft within the first 30 days were identified retrospectively. Factors associated with early graft loss were determined by multivariate comparison to the control cohort whose grafts survived beyond 30 days.

Results: During the study period, 1090 patients received a kidney transplant: DCD (435; 39.9%), DBD (366; 33.6%) and living donor (289; 26.5%). Early graft loss occurred in 49 (4.5%) recipient. Causes of graft loss included arterial or venous thrombosis (22; 44.9%), primary non-function (PNF - 14; 28.6%), haemorrhage (6; 12.2%), acute rejection (3; 6.1%) and other causes (4; 8.2%). Univariate analysis revealed that higher recipient and donor age, DCD donor and prolonged cold ischaemic time were associated with early graft loss. However, only DCD donor type was a significant risk factor for early graft loss on multivariate analysis (RR 2.71; p=0.015). Although PNF occurred slightly more frequently in the DCD than DBD group (2.3% vs 1.1%; ns), the principal difference between the two groups was the higher incidence of acute vascular occlusion in DCD kidneys (DCD 15 [3.4%] vs DBD 6 [1.6%]). This finding is suggestive that DCD kidneys are associated with increased technical complications; in support, one year graft survival of DCD and DBD kidneys was comparable (89.9% vs 93.2%; ns). Notably, 14 of 48 patients with early graft failure died (RR 8.8; p<0.0001).

Discussion: Early graft failure occurs more frequently among DCD recipients, and is associated with a reduction in patient survival. Addressing technical complications related to implantation may reduce its incidence.

Poster session

Wednesday 13th March

18:15 - 19:25

Kidney outcomes 2

P111

Recipients of South Asian ethnicity and risk for mortality 1-and 5-years post kidney transplantation

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Introduction: The risk of mortality post kidney transplantation for recipients of South Asian ethnicity is unclear. We sought to determine risk of mortality at 1- and 5-years post kidney transplantation in England over the last decade to ascertain whether there was any disparity in mortality risk between South Asians versus other ethnic groups.

Methods: Data was obtained from Hospital Episode Statistics (HES), an administrative data warehouse containing admissions to all National Health Service hospitals in England. Data extraction was facilitated utilising codes on procedural classification (Office of Population Censuses and Surveys Classification of Interventions and Procedures [OPCS-4]) and medical classification (ICD-10). We obtained data on all kidney transplant procedures performed in England between April 2001 and March 2010 with patient demographics obtained at time of transplant including age, sex, ethnicity, donor type (living versus deceased), medical co-morbidities and social deprivation (Index of Multiple Deprivation 2007). The primary outcome measure was mortality 1-year post kidney transplantation (HES data linked to Office for National Statistics to identify all mortality events), with 5-year mortality (for recipients between 2001-2006) the secondary outcome measure. Logistic regression algorithms were performed (R stats package) to identify independent factors associated with mortality ($p < 0.05$ considered significant).

Results: Data analysis was performed on 15,218 kidney transplant procedures performed in England between 2001-2010 (adult and paediatric). Breakdown of patients by ethnicity were: white (72%, n=10,975), South Asian (8%, n=1265), black (5%, n=698), chinese (< 1%, n=58), mixed (1%, n=127), other (2%, n=273) and unknown (12%, n=1822). 471 deaths occurred within the first year post kidney transplantation. 1-year patient survival post kidney transplantation based upon ethnicity was: white (97.0%), South Asian (95.3%), black (97.0%), chinese (98.3%), mixed (99.2%) and other (97.8%). Compared to white recipients (reference category), South Asian recipients had increased risk of mortality at 1-year post kidney transplant (OR 1.41, 95% CI [1.03-1.92], $p<0.030$). Despite similar pre-transplant cardiovascular co-morbidities, South Asians were more likely to die from cardiovascular events (cardiac, cerebrovascular and/or vascular event) compared to white recipients (37.9% versus 25.8%, p=0.043). South Asians were less likely to die from cancer compared to whites within the first year (0.0% versus 9.4%, p=0.005). No difference was observed in 5-year mortality post-transplantation amongst the ethnic groups.

Conclusion: South Asians have greater risk of mortality at 1-year, but not 5-years, post kidney transplantation compared to white recipients due to excess of cardiovascular events. Our results suggest robust pre-transplant cardiac evaluation for South Asians is merited, but long-term outlook is comparable to other ethnic groups.

P112

Managing patients with failing kidney transplants: what matters?

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An increasing proportion of incident dialysis patients have a failed kidney transplant. It has been reported that CKD complications are sub-optimally managed in this group and anecdotally, that they have a rapid decline in graft function prior to commencing dialysis. The mortality of this population exceeds that of transplant-naïve dialysis patients. This study aimed to quantify the rate of decline of eGFR prior to graft failure, assess management of CKD complications and investigate what factors impact long term survival in this population.

Methods: All recipients who underwent deceased donor kidney transplantation in Belfast between 1986 and 2005 and had a functioning transplant at 12 months were included. Information on clinical outcomes has been recorded prospectively. Laboratory information was obtained from patient notes, the regional nephrology database and the laboratory record system. The Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR; the rate of decline in eGFR was calculated by a least squares linear regression approach.

Results:

- 158 patients had death-censored allograft failure.
- Mean decline in eGFR was 7.9ml/min/1.73m^2 per annum prior to graft failure. This differed from transplant-naïve patients commencing dialysis ($p<0.001$).
- The majority did not meet Renal Association targets for anaemia and MBD.
- 36% of this group were re-transplanted.
- Re-transplantation had the greatest impact on survival (HR 0.12, $p<0.0001$).

Discussion: The management of patients with transplant failure is an increasingly common clinical challenge. This population have a rapid decline in graft function prior to end-stage renal disease and a poor prognosis on dialysis. Re-transplantation confers a significant survival benefit and should be considered at an early stage given the inevitable technical and immunological difficulties this presents.

P 113

Survival advantage from listing for elderly patients awaiting kidney transplant

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Introduction: Elderly patients (age over 65) now represent the largest population starting renal replacement therapy. However, their access to, and benefit from, transplantation remains unclear. This study examines donor profile and outcomes in elderly patients listed for renal transplantation at our centre, where twice as many DCD as DBD renal transplantations are currently performed.

Methods: A retrospective case review of all adult patients listed for renal transplant between 2002 and 2012. DBD were allocated according to a national allocation scheme; DCD were allocated locally using the same algorithm. For the analysis, elderly patients (>65yrs) were compared to a young cohort (<45yrs).

Results: 1491 patients were listed in total; 167 (11%) were >65yrs and 551 (37%) were <45yrs. The number of elderly patients listed per year increased from 8(6% of annual total) in 2002 to 25(17%) in 2012. Removal from the waiting list (death or development of comorbidity) occurred more frequently in the elderly (26%) than the young (5%, $p<0.01$). Only 5% of the elderly listed in the first six years remain active, compared with 31% of the young, with Kaplan-Meier analysis confirming that median time to de-listing is much shorter in the elderly (897 vs 2027 days, $p<0.01$). 49% of the elderly and 71% of the young was transplanted. Times from listing to transplantation were similar in both groups (elderly; median 424 vs young; 388days), but notably, the elderly received a much higher proportion of DCD kidneys (DCD/DBD/Living donation(%): 62/26/12 vs 35/34/31 (χ^2:$p<0.01$). The elderly generally received kidneys from elderly donors (median donor age 61 vs 43 years, $p<0.001$); this held true for DCD kidneys (68 vs 41, $p<0.001$). Graft survival was similar in the two groups (1yr 91 vs 98%, $p=0.66$), and in both, transplantation offered a significant survival advantage (92% 3 yrs from listing for those transplanted in the elderly group; cf. 85% those not transplanted, $p<0.05$).

Conclusions: The time frame for transplantation of elderly patients is limited. As numbers listed increase, greater use of elderly DCD donors may alleviate demand, yet still provide survival advantage.

P114

The impact of protocol biopsy and early steroid withdrawal on early renal transplant outcomes: a retrospective analysis

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We report our experience with a) 3 month protocol biopsies and b) early steroid withdrawal in low immunological risk patients. The study is a retrospective analysis of a cohort of patients from a single centre transplanted between July 2010 and June 2012 using a protocol that included classifying patients to low and high immunological risk and protocol biopsy at 3 months post-transplant. The data presented is for 87 of the 91 transplants performed over this period. 32/87 were treated as high immunological risk and 55/87 as low risk. All patients received tacrolimus, mycophenolate mofetil and prednisolone. In low immunological risk patients, prednisolone was stopped on day 7.

Three month protocol biopsy was performed in 54/87 patients (62%). 18/87 (21%) patients experienced rejection Banff 1A or above; two patients had 2 episodes of rejection. 7/20 rejection episodes were in protocol biopsies (sub-clinical rejection). Excluding protocol biopsies, the rejection rate was 13%. Of the 7 patients who had sub-clinical rejection (Banff 1A or above) on protocol biopsy, eGFR was $\leq$60 in 5 and >60 in 2 at the time of biopsy. Median 1 year eGFR was comparable in patients treated for early rejection and in those without rejection (median 56 v 58 ml/min). There was no difference in rejection rates between high and low immunological risk (early steroid withdrawal) patients (high 7/32, 22% vs low 11/55, 20%; OR=0.6; 95% CI=0.13-2.89, p=0.54). Subgroup analysis showed comparable 1 year eGFR in low and high immunological risk groups (55 vs 50 ml/min).

In summary, 3 month protocol biopsy detects sub-clinical rejection in approx 13% of patients biopsied, or 8% analysed on an intention-to-treat basis. Early steroid withdrawal (day 7) is safe in low immunological risk patients and is not associated with increased rejection rates or reduced 1 year graft function. This study supports the use of routine protocol biopsies and early steroid withdrawal in a selected group of transplant recipients.

P115

Outcomes of renal transplantation in sickle cell patients: a pan-Thames study

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Background: Sickle cell patients have a high prevalence of End stage renal failure. It has already been shown that patients with end stage sickle cell nephropathy (SCN) benefit from renal transplantation. However the long term results remain unclear.

Methods: We contacted all transplant units across London and we requested data for Sickle cell patients that received a renal transplant during the last 20 years. We received data from the Royal Free Hospital, GSST, KCH, Royal London, St. Helier Hospital and St George's Hospital.

Results: Twenty patients with End stage Sickle cell nephropathy (17 HBSS, 3 HBSC) underwent renal transplantation since 1990. Seven patients (35%) received live donor kidneys (1 in India, 1 in Pakistan), whereas 13 had cadaveric kidneys implanted (65%). The median follow up was 1734 days (range 21- 2928days). Delayed graft function was encountered in 66.7% of cadaveric transplants. There was no delayed function in live donor transplants from the available data. Multiple sickle cell painful episodes were documented in 35% (7/20) of patients. Infections accounted for death in 5 patients (5/6, 83.3%- the cause of death the 6th patient remains unknown). These patients died from septicemia 86 to 3580 days after transplantation. Only one of the deaths occurred during the first year after transplantation (septicemia at day 86- post ALG). Three patients died with working grafts. Two patients that were given ALG have died of sepsis. The patient and graft survival at 1 year was 95% (19/20) and 90% (18/20) respectively; at 5 years the patient and graft survival were 85% (17/20) and 50% (7/14) respectively. Two patients who were on exchange transfusion pre and post transplantation maintain good graft function without painful episodes at 6 and 7 years. Two patients have commenced exchange transfusion for acute sickle nephropathy post transplantation and both have currently stable renal function at 4 and 6 years.

Discussion: Sepsis is the leading cause of death in SCN patients post transplantation. Recurrent sickle cell painful episodes post transplantation are common in patients not receiving exchange transfusion. Previous studies have shown that the initial results of renal transplantation in patients with end-stage SCN are comparable to those of age-and race-adjusted renal transplant recipients with different cause of ESRD. The long term patient and allograft survival are still lagging behind those of other ESRD patient groups. However, it has been shown that transplantation offers a far better survival than dialysis alone (56% vs. 14% at 10 years).

Conclusion: This is the largest case series study on renal transplantation for End stage SCN. It is our belief that pre and post transplantation exchange transfusion offers a significant benefit in patient and graft survival with significantly fewer sickle cell episodes.

P116

Renal transplantation in light chain deposition disease; a case series

Jennifer Pinney[1,2], Simon Gibbs[1], Helen Lachmann[1,2], Ashutosh Wechalekar[1], Sanjay Banypersad[1], Jason Dungu[1], Carol Whelan[1], Philip Hawkins[1], Julian Gillmore[1,2]

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Light chain deposition disease (LCDD) is due to deposition of monoclonal light chains in a non fibrillary form. It is a rare disease which predominantly affects the kidneys. Patients frequently progress to end stage renal failure (ESRF). Persistence of the underlying clonal disorder has been associated with rapid recurrence of disease within renal transplants and early allograft failure such that patients with LCDD are felt to be poor transplant candidates.

Among a cohort of 43 patients diagnosed with LCDD, 23 (53%) progressed to ESRF. Four patients received renal transplants; three from live donors and one from a deceased donor. All transplant recipients had markedly elevated free kappa light chains with <20% kappa restricted clonal plasma cells on bone marrow trephine.

One patient was diagnosed with LCDD on a renal transplant biopsy at the time of graft loss two years after renal transplantation; the cause of ESRF had been thought to be hypertension. The same patient subsequently achieved a complete clonal response with autologous stem cell transplantation (ASCT) and is active on the deceased donor transplant waiting list. Three patients were diagnosed with LCDD prior to renal transplantation. Two such patients achieved complete clonal responses (CR) with ASCT prior to renal transplantation, and both remained in CR 4.5 and 7 years after ASCT. One patient received a renal transplant prior to achieving a partial clonal response with chemotherapy. This patient has subsequently required treatment with dexamethasone for clonal relapses on three occasions over a period of 7 years. All grafts are functioning well (median eGFR 51 ml/min, range 41-53) without evidence of disease recurrence after a median follow-up from renal transplantation of 2.7 years (range 2.6-7.1).

Renal transplantation is possible in LCDD and graft outcome can be excellent in patients whose underlying clonal disease is maintained in remission.

P117

Renal transplantation in the over 70s is safe and successful

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Background: The end stage renal failure (ESRF) population is ageing as a result of demographic changes and improving survival. Accordingly it is important that the safety and efficacy of renal transplantation in the elderly is carefully evaluated.

Methods: We performed a retrospective case note analysis of every renal transplant performed in a patient in their 70s at our institution since January 1st 2000. A control group was identified comprising the recipient of the paired kidney or the subsequent cadaveric transplant recipient.

Results: Since 2000, 26 patients have received a renal transplant after their 70th birthday; 14 from cadaveric non-heart beating donors, 9 cadaveric heart beating and 3 living donors. Median age was 72 (range 70-74) vs 57 (range 41-68) years. There were no significant differences between duration of renal replacement therapy, nor time spent on the transplant waiting list. There was a trend towards older patients receiving organs from older donors: 63 (range 57-71) vs 58 (range 52-63) years (p=0.051). Neither graft nor patient survival were significantly different between study and control groups: 1 year graft and patient survival 84 vs 95% (p=0.60) and 100 vs 95% (p=1.00) respectively and to date: 87 vs 90% (p=1.00) and 96 vs 90% (p=0.60) with a median follow up period of 34 (range 5-117) months. Current levels of graft function were similar: median creatinine 151 vs 170 µmol/l (p=0.42) and eGFR 36 vs 37 ml/min (p=0.97). Surprisingly delayed graft function was significantly more common in the control group: 90 vs 48% (p=0.003) despite comparable cold ischaemic times. Acute rejection episodes (30 vs 19%, p=0.49), length of stay (10 vs 10 days, p=0.13) and re-admission rates at 3 months (22 vs 14, p=0.20) were not significantly different. There were no significant differences in the frequency of acute and late complications between groups though there was a trend towards older patients having more urological issues post-operatively and more frequent infectious complications.

Conclusions: Renal transplantation in the over 70s is safe and successful. Longer term follow up is required to better assess graft and patient outcomes.

P118

"For cause" renal biopsies are heterogeneous irrespective of clinical presentation

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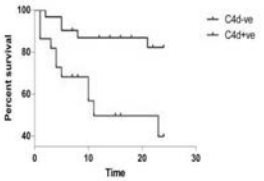
Deteriorating renal allograft function as evidenced by either a rise in serum creatinine or proteinuria remains the most important indication for a late transplant biopsy. Over the last 4 years we have performed 148 "for cause" biopsies at our centre.

In this study we analysed the histology of the biopsies in relation to the presenting indication. We have also collected serum samples for the detection of Donor Specific Antibody (DSA). The allografts were classified into those with acute dysfunction (AD, n=15), creeping creatinine with no proteinuria (CC, n=29), isolated proteinuria (P, n=46) and proteinuria with creeping creatinine (P+CC, n=58). Creeping creatinine was defined as a slope >0.35 and P<0.05 on the regression analysis of 1/creatinine values over 2 years prior to the biopsy. Proteinuria assessment was made on a cut-off value of >0.5g/day (minimum of 3readings).

We have found that the histology was quite heterogeneous with no relation to the indication (Table). In 116 patients with IFTA/microcirculation damage (MCD=g/cg/ptc≥1)/late T cell rejection BANFF scores were largely similar. In 53 patients with MCD, c4d deposition in the peritubular capillaries remained the single most important predictor for outcomes over a 2year follow-up period (P=0.004, figure). There was a trend towards worse survival in patients with higher degree of scarring with clinical presentation not having any impact on the outcome.

In summary, we propose that the histology of late "for cause" biopsies is heterogeneous irrespective of the indication and key histological features rather than clinical presentation affects the short term outcomes. Histological parameters rather than clinical presentation should be considered in the clinical decision making for these patients

	GN %	OTHERS%	MCD%	IFTA%	TCMR %
AD	7 (N=1)	13 (N=2)	20 (N=3)	47 (N=7)	13 (N=2)
CC	10 (N=3)	7 (N=2)	38 (N=11)	38 (N=11)	7 (N=2)
P	15 (N=7)	4 (N=2)	39 (N=18)	28 (N=13)	14 (N=6)
CC-P	14 (N=8)	12 (N=7)	36 (N=21)	33 (N=19)	5 (N=3)



P119

Management of the failing transplant on a dedicated care pathway

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Introduction: Patients with failing transplants (PfT) represent a unique group due to immunological, non-immunological and psychological factors, which impact on patient co-morbidity/mortality. In 2005 we reported outcomes of our failed transplants over a 10-year period. Renal replacement was initiated mean eGFR of 7mL/min/1.73m^2. A number were poorly adjusted psychologically & had significant co-morbidity. We now have a well-defined intercalated pathway for their care.

Methods: Between 2008-2012, 27 transplant patients reached ESRF. Patients found to have grafts with progressive irreversible worsening renal function were cohorted as low clearance patients in a dedicated clinic for intensified management. Patients were 'flagged' to increase team awareness. Multidisciplinary approach: targeted medical, nursing, psychology and dietary input were made available early & at a single visit where required (one-stop-shop). General practitioners were alerted early on to support transition & update hepatitis-B-vaccinations.

Results: Age range 32-71 years, male: female ratio (70%: 30%), 70.9% Caucasians, 7% Black, 7% Asians and 11.1% others. The aetiology of primary renal disease was variable, not necessarily related to cause of failing transplant. Transplant age range: 3 to >15 years, eGFR on establishing therapy 12.1+/-3.12 mLs/min/1.73m^2, haemoglobin10.8+/-1.41g/dL. Potential donors had been identified by 41%, 55% of these received transplants either pre-emptively or within one year of reaching ESRF, 9 peritoneal dialysis, 1 conservative care, 13 haemodialysis, 6 with functioning fistulae & 3 with planned tunnelled lines, 2 unexpected failures & 1 excluded as lost to follow-up.

Discussion: These patients have special needs & often require psychological input alongside management of diet/biochemistry/anemia/medical co-morbidities. Our special focus clinic enables us provide care, which meets general Renal Association guidelines for managing ESRF. We support development of guidelines for managing this unique growing patient population.

Poster session

Wednesday 13th March

18:15 - 19:25

Kidney transplantation - surgery

P120

Urine output and central venous pressure are widely used to define perioperative haemodynamics of renal transplant recipients in the UK

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Introduction: Despite progress in the immunological management of renal transplant recipients, there is limited literature to guide other areas of perioperative care for these patients. Published data suggest that perioperative recipient haemodynamic status influences graft outcome but there is no widely accepted standard of care for the haemodynamic management of transplant recipients.

Methods: We surveyed the lead clinician in all 23 adult renal transplant centres in the United Kingdom, using an online data collection tool. The survey asked clinicians to specify their standard operating procedures with regard to the haemodynamic management of transplant recipients preoperatively, intraoperatively and up to 24 hours postoperatively.

Results: 17 units responded to our survey (74% of UK units). In addition to non-invasive blood pressure (NIBP) and pulse, 15 of the responding units (88%) routinely use central venous pressure (CVP) monitoring intraoperatively and 12 (71%) use CVP postop. Only a small minority use other invasive measures of cardiovascular status including calibrated cardiac output monitors, oesophageal doppler or mixed venous oxygen saturations intraop and no units used any of these postop. 17 units (100% of respondents) use a standardised regimen for intravenous fluid postop. 15 respondents gave details of their fluid regimen: all 15 (100% of respondents to this question) use urine output (UO) as the primary target determining the volume of fluid infused in the postop period. Regimens range from UO + 30mls/hour to UO + 50mls/hour.

Discussion: Our UK survey shows CVP and UO are widely used to augment NIBP and pulse in the perioperative fluid management of renal transplant recipients. Other invasive cardiovascular monitoring is uncommon. Despite this clinical consensus, a UO-based fluid regimen in transplantation is not supported by the available literature and the utility of CVP for fluid balance assessment is controversial. Further research is needed to determine appropriate cardiovascular targets to use in this context and whether their use can influence graft outcome.

P121

Retention of transplant ureteric stents: an audit of practice and outcomes

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Introduction: Ureteric stenting is a temporising measure to facilitate healing of the ureteroneocystostomy. Although the incidence of urine leaks is reduced by stenting, it is important that stents are removed in a timely fashion. Retention of a ureteric stent increases the risk of urinary tract infection and this might jeopardise graft function. This audit sought to determine compliance with our unit protocol to remove ureteric stents by six weeks after transplantation.

Methods: A retrospective audit of patients receiving a kidney transplant in our centre between 1/1/2012 and 31/5/2012 was conducted. Transplant to ureteric stent removal interval was calculated and the reason for stent removal being delayed was determined. Data were compared with a previous years audit (1/1/2011 to 1/8/2011).

Results: Fifty seven patients were transplanted in the period studied. All received a single transplant JJ stent. The median time to stent removal was 67 days (range 15 to 102 days) compared to 68 days during the previous audit period. Eleven recipients (19%) had their stent removed within the 6 week protocol period (23% in the previous audit). Those exceeding the 6 week threshold had delayed removal due to patient morbidity (n=32), unknown reasons (n=10), lack of theatre capacity (n=3) and patient cancellation (n=1).

Conclusion: Sequential audits in our unit have highlighted deficiencies in the timely removal of transplant ureteric stents. The majority of recipients exceed our 6 week threshold for removal. A high proportion of stent removals are delayed due to patient morbidity, possibly arising from stent related complications. A policy of default listing of patients for stent removal has been adopted; rather than a 'reactive' policy requiring recognition of the presence of a stent. It is hoped that this will improve adherence to our 6 week protocol, reduce the burden of stent related morbidity and reduce the number of delayed stent removals.

P122

WHO surgical check list in renal transplant: is it another tick box exercise?

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Background: Estimated 234 million surgical procedures are carried out globally. Nearly half of all surgical complications are potentially avoidable. The evidence of quality teamwork achieving reduction in adverse events is overwhelming. The World Alliance for Patient Safety initiated WHO Safe Surgery Checklist in January 2007. The Check list was aimed to improve communication and safety pre-op; Intra-op and immediate post op.

Aim: We aim to perform a snap shot survey to determine if the present WHO Surgical Check-list is followed at renal transplant and vascular access lists. We aim to establish that checklist information is utilized optimally for patient safety.

Methods: Theatre staff including surgeons and anesthetists were randomly asked question about the patient and staff information intra and post operatively as discussed in the WHO Check list in last 30 operative sessions with the renal transplant team. The staff was unaware of the snap shot survey, in order to minimize Hawthorne phenomena.

Results: The Check Lists were religiously read in 100 % operations (N= 35) in all domains (Before anesthesia induction- ***Check in***; Before skin incision – ***Time out***; Before patient leaves theatre – ***Sign out***).

Question	Aware	Not Aware
Name of the Patient	12/30 (40%)	18/30 (60%)
Name of Surgeon	11/21 (52%)	10/21 (48%)
Name of the First Surgical Assistant	07/16 (43%)	09/16 (57%)
Name of Anesthetist	09/15 (60%)	06/15 (40%)
Name of Scrub Nurse	17/22 (77%)	05/22 (23%)
Side/site of operation (asked post operatively)	9/11 (81%)	02/11 (19%)
Name of the operation	17/21 (81%)	05/21 (19%)
Sponge count	22/22 (100%)	-
Labeling of the specimen	19/21 (90%)	02/21 (10%)

There was 01 episode of lost needle but no other adverse event was noted.

Conclusions: Even though the checklist was read in 100% operations, the information was not retained by the staff. The non-recognition of patient name is worrisome. This study should be done in all theatres randomly to assess the validity of our findings.

P123

Module based operative surgical training in renal transplantation setting at a University Teaching Hospital

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Aims: To assess safety and efficacy of module based operative surgical training in renal transplantation setting

Methods: The technique of renal transplantation was divided in 5 segments. A training program was designed, where the trainee learned the procedure in a mentor-defined schedule. During each educational renal transplant, the trainee only performed the operative steps corresponding to his acquired skill level. The mentor performed the remaining part of the transplant operation. Trainees were trained on various modules in 60 cadaveric renal transplants between August 2011- August 2012. The operative data was retrospectively retrieved from the trainee ASGBI operative logbooks

Results: There were N=4 ST3-ST8 trainees and were mentored by N=3 Consultants. The renal transplant surgery segment 1(Bench Dissection), N=45/60; Segment 2 (Incision & Exposure of vessels) 40/60; Segment 3 (Venous & Arterial Anastomosis) 25/60; Segment 4 (Neo-Ureterocytoplasty 40/60 and Segment 5 (Incision Closure and documentation) 45/60 patients were operated by trainees respectively. There were missed arterial & venous injuries in 02/45 bench dissections performed by the trainees but were managed successfully. The median anastomosis time in cases operated by trainees was 55 (45-76) min compared to 40 (25-50) min in cases operated by the mentors. There was no renal vein thrombosis/ renal artery thrombosis in cases operated by the trainees. 02/45 neo-ureterocytoplasties performed by trainees had ureteric stenosis. 03/45 incision closures performed by trainees had minor wound infection and 02/45 had incisional hernias. Documentation was deemed appropriate in all transplants.

Conclusions: This study demonstrates that a formal modular training program can efficiently and safety train the juniors with in service constraints. The complication rate in cases performed by trainees in comparable to global complication rates in renal transplant surgery.

P124

A national survey of perioperative care in deceased donor renal transplantation

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Introduction: Goal-directed fluid and inotrope therapy and Enhanced Recovery After Surgery protocols improve outcomes in patients undergoing major surgery. We sought to establish what national practice is with respect to the perioperative care of deceased donor renal transplant recipients.

Methods: A national survey of practice was undertaken. Senior members of clinical staff from all 24 adult renal transplant units in the UK were approached and asked to complete a validated questionnaire exploring the perioperative care of deceased donor renal allograft recipients.

Results: There was an 80% (19/24 units) response rate. Despite most (84%) units employing written protocols, perioperative care varied widely: thromboprophylaxis, intra-operative diuretic use, maintenance and bolus fluid choice and modality of haemodynamic monitoring differed particularly. 2 (8%) units described protocol-driven fluid and inotrope therapy guided by arterial and central venous pressure. 1 unit employed non-invasive cardiac output monitoring to guide therapy, although this was not protocol-driven.

Discussion: Perioperative goal-directed therapy does not appear to have been widely adopted in deceased donor renal transplantation. Although the exact reasons for this are unclear, it may be because of an absence of a clear evidence base for this approach. Further research, including a randomized controlled trial, would help to clarify the role of goal-directed therapy in renal transplantation.

P125

Dedicated theatres help reduction of cold ischaemic time for kidney transplants at a UK centre

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Prolonged cold ischaemic time (CIT) has adverse effect on the outcomes of kidney transplantation. It is associated with higher incidence of DGF, and may have negative impact on the long term outcomes. A local CQUINN target was agreed with the specialised commissioners. The target is to have 90% of kidney transplants have cold ischaemic time of < 16h. The Trust decided to invest in providing a dedicated theatre for kidney transplantation.

Methods: CIT of all kidney transplants of the twelve months after implementation of the dedicated theatres was compared to the previous 12 months. The causes of prolonged CIT was further analysed to establish whether the cause is related to theatre delays or other factors, such as delayed offering, transport, cross match etc. We also compared the CIT between locally retrieved kidneys and imported kidneys.

Results: The target of 16 hours was achieved in 91% of the transplants. The average CIT was 15.6h after implementation compared to 17.3 h.

Conclusion: The provision of dedicated theatres help to reduce CIT in kidney transplantation.

P126

Third and fourth kidney re-transplants – a single centre experience

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Introduction: The demand for kidney re-transplantation following graft failure is rising. Re-do renal transplantation is often associated with poorer outcomes due to a combination of immunological and surgical challenges.

Methods: We retrospectively analysed 66 living renal transplants performed between 2005 and 2011. 3rd and 4th transplants were case-matched with 1st and 2nd transplants. This series includes some antibody incompatible patients. In this centre living transplants are performed synchronously with laparoscopic retrieval and subsequent transplantation in adjacent theatres by a consultant-led team of transplant and vascular surgeons.

Results: Twenty two third and fourth grafts were matched with 22 first and 22 second grafts. Operative time (1st grafts: 198.3±15.0min, 2nd grafts: 212.1±9.9min, 3rd/4th grafts: 238.1±17.0min; p=NS) and anastomotic time (1st grafts: 38.4±2.5min, 2nd grafts: 32.2±0.82min, 3rd/4th grafts: 35.4±2.8min; p=NS) were equivalent between the subgroups. Length of stay was equivalent (1st grafts: 8 days (7.9-14.8), 2nd grafts: 10.5 days (9.2-15.5), 3rd/4th grafts: 8 days (8.0-14.0); p=NS). There was no significant difference in graft function up to 6 months. Complication rates were low in all groups.

Discussion: It appears 3rd/4th kidney transplants can be performed safely with similar outcomes to 1st/2nd transplants. A number of factors relating to the combined surgical/medical approach may contribute to these results.

Poster session

Wednesday 13th March

18:15 - 19:25

Live donation

P127

What is the implication of pre-donation weight loss to the post-donation weight and outcome of living donors?

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Background: A large proportion of potential living donors are overweight but a number of those lose the weight required in order to donate. There is a worry that regaining this weight might represent a risk for long-term complications.

Aim: To study whether obese potential donors are at greater risk of regaining the weight they lost post donation, and evaluate the risk factors for post donation weight change, hypertension and worse kidney function.

Results: There were 121 donors who were worked up and donated over 6 years in a single centre. 63 additional donors of the same period who were worked up and followed up in other centres were excluded from analysis. There was a minimum donor follow up of 2 years. Median BMI at preassessment was 26.8 with 25% of patients having a BMI over 30.3 and 14% a BMI over 32. Patients with BMI at preassessment of greater than 30 lost 4.5% of their weight to donate and their loss in weight at donation was statistically different (from BMI 30.5 to a BMI of 27.7, p=0.005) from the rest of the patients. *Patients weight change at 1 and 2 years is inversely related to the change of weight between preassessment and donation (p=0.002)* and is independent of BMI group at preassessment and donation, gender or age. Univariate analysis shows that the change in the 2 yr weight depends on the weight at pre-assessment (p=0.002) and donation (p=0.002), the weight change (0.08), smoking habit, R2=0.5.Regression analysis showed that the donor's systolic BP at 2 years was predicted by the initial systolic BP, the change of weight at donation, the donor age, the donor weight at donation and preassessment, the weight change at 1 year compared to both preassessment and donation weight. The change of creatinine at 2 years was dependent on the gender (0.03) and the weight gain at 2 years compared to donation (p=0.004) but not on the initial weight, the loss of weight to donate or the BP at either the preassessment or at 2 years.

Conclusion: This is the largest complete follow up study of the impact of predonation weight to medium term outcomes of those donors. It seems that obese donors lose the weight required to donate but some of it is regained with adverse impact on systolic and diastolic blood pressure and serum creatinine. Aggressive weight management is equally important post donation as it is to make live donation both feasible and safe.

P128

An assessment of potential living donors with persistent non-visible haematuria

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[1]University of Liverpool, Liverpool, UK, [2]Royal Liverpool University Hospital, Liverpool, UK

Introduction: In the UK, approximately 2600 kidney transplants are performed annually and 30% of the kidneys are from living donors.[1,2] In 2011, the British Transplant Society (BTS) published new guidelines on the assessment of potential living donors (PLD) with persistent non-visible haematuria (PNVH).

Objectives: To evaluate whether the BTS guideline is followed in Liverpool, the appropriateness of the guidelines, and also to ensure the service is performed in a timely manner.

Method: A retrospective audit of the medical records of 28 PLD with PNVH from 1997 to 2012. Information on the urinalysis results, waiting time to investigations, investigation results and, outcome after assessments was collected.

Result: The majority of the PLD had 'trace' or '+' haematuria on urinalysis. Thirteen (46%) have donated their kidneys or are proceeding to donation and four (14%) were unsuitable for donation. Two declined further investigations. Fifteen out of sixteen had normal cystoscopies. The median waiting time from for a cystoscopy was five weeks. Six out of twelve had normal kidney biopsies. The median waiting time for a kidney biopsy was five weeks, and three months for electron microscopy results. No complications from cystoscopy or kidney biopsy were recorded.

Conclusion: The BTS guideline is well adhered to and the majority of the PLD found the investigations acceptable. However, there was an unacceptable long delay for the result of the EM sample. A multidisciplinary meeting has taken place to identify ways to reduce this delay. Of those patients who underwent kidney biopsy 30% had a significant abnormality precluding transplantation. This investigation is therefore justified for this indication in our PLDs.

P129

Live donor evaluation. Why do potential donors not proceed?

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Introduction: Live donation represents 38% of Kidney transplants in the country. Live donation has become a treatment of choice. Donor welfare is paramount. Vigilant donor care and management is essential to inspire public confidence. We evaluated the reasons for unsuitability and outcomes following live donor assessment.

Patients and methods: We retrospectively analysed data on 109 donors who were referred to the consultant led live donor clinic following initial assessment in the Nurse lead clinic between the year 2009 and 2011. 49 of these donors (45%) were found to be unsuitable for donation. We evaluated donor demographics, relationship to recipient, past medical history and reasons for unsuitability. We also evaluated recipient eGFR and change in modality during this period.

Results: The average donor age was observed to be 47 years and majority of them were Caucasians (91%). Majority of the volunteers were family members. Hypertension (19%) was the commonest past medical history followed by mental health issues (11%)and high cholesterol (10%). 31% of the recipients were in the pre-dialysis group and 69% were on RRT. The average eGFR among the pre-dialysis group was observed to be 12ml/min. 6% changed modality form pre-dialysis to requiring RRT during the assessment period. The average time interval for assessment was observed to be 6 months. Low isotopic GFR was observed in 45% of the donors. 7% of the donors had high BMI. 5% of the donors were found to be hypertensive. 4% of the donors either had high cardiovascular risk, high risk of developing Diabetes or renal calculi. History of malignancy was observed in 4% of the donors. Following the assessment of these unsuitable donors 8% were placed in the CKD register, 4% were referred to the Geneticist and 2% of the donors were either referred to Cardiologist, gastroenterologist, gynaecologist or psychologist due to abnormal findings discovered during this live donor assessment period.

Conclusion: In our cohort of donors we found low isotopic GFR (45%) to be the commonest reason for unsuitability followed by high BMI (7%) and hypertension (5%). Hence isotopic GFR can be used as an effective screening and a cost saving tool. Incidental findings discovered among the unsuitable donors during this assessment period were appropriately investigated and managed.

P130

Genetic testing in autosomal dominant polycystic kidney disease (ADPKD) - a cost-benefit analysis for living kidney donor transplantation

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder. Approximately 50% of patients progress to end stage renal disease. In 2011/12, 9% (248) UK kidney transplants were in ADPKD patients, of which 34% were from Living Kidney Donors (LKD). For family members at risk of ADPKD, a negative renal ultrasound result has a low negative predictive value below the age of 40. However, this age group represents the majority of potential LKD. Genetic testing to identify the causative mutation in an affected proband has high clinical utility, permitting the predictive testing of any potential familial donors. Published recommendations state familial DNA testing should be pursued in candidates less than 40 years with fewer than 3 renal cysts, and older patients with equivocal imaging results.

Methods: We established the first UK-based comprehensive molecular diagnostic service for ADPKD using DNA sequencing and deletion/duplication analysis of PKD1 and PKD2 genes in April 2010. Since then we have performed genetic testing in more than 120 probands and predictive tests for more than 35 at-risk family members.

Results: The average cost for haemodialysis is £24,000pa, with peritoneal dialysis £17,000pa. In comparison, the cost of a living relative donor kidney transplant is £18,000 including first year follow-up, plus an additional £5,000 for donor loss of earnings. For subsequent years, the follow up costs are £4,000pa. The median waiting time for a kidney only transplant is 3.2 years.

Discussion: Based on this data, the estimated cost-saving of receiving an early LKD compared to dialysis is £38,000 per case over the 3.2 years. For a single early LKD transplant this equates to the cost of full genetic testing of PKD1 and PKD2, plus predictive testing of 2 at-risk relatives in an additional 14 ADPKD families. This does not include the £17,900pa savings for every subsequent year on dialysis. The 5yr survival is better for LKD transplants (96% vs 88% deceased donor); increased LKD would also release cadaveric kidneys for other patients.

P131

The use of magnetic resonance angiography in the living donor renal transplantation

Thilini Abeygunaratne, Santhanakrishna Balasubramanian, Richard Baker, Tony Nicholson

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Introduction: During the preoperative evaluation, the radiological evaluation is vital to determine the suitability of a donor. MRA is employed in many renal transplant centres to assess the vasculature of the donor. The aim of the study was to evaluate whether MR angiography results provided adequate preoperative information to the surgical team.

Method: We conducted a retrospective study of all live donors at our centre that underwent a MRA over a 67 month period, from January 2007 to August 2012. The data included demographic data of the donor, number of arteries, veins and ureters reported on the MRA scan. Using the donor operative notes data was collected for the number of arteries, veins and ureters found during the operation. Following the collection of the data the discrepancies between the MRA and the operative notes for the donors were recoded.

Results: Amongst a total 110 donors, there were 108 who underwent MRA study and 2 were identified to have CT angiograms. The mean age of the donors was 44.5 (min 19 and max 69) years. The total number of discrepancies for renal arteries between the MRA and operative findings were 18 (16%). The number of discrepancies for renal veins and ureters identified were 10 (9%) and 3 (2.7%) respectively. Our study demonstrated that there are discrepancies between MRA and operative findings. Though there are no national recommendations, we believe that the discrepancies identified are high in numbers. The discrepancies may be a result of operator bias or modalities of imaging therefore further studies are needed to evaluate this further.

P132

Can any of the eGFR formulae reliably predict the mGFR of healthy prospective living kidney donors?

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Background: Accurate measurement of GFR is useful in many different clinical settings. Estimated GFR (eGFR) measurements, derived from manipulations of plasma creatinine concentrations in different ways, have become the cornerstone for screening for chronic kidney disease (but not without some controversy). Measured GFRs (mGFR) are done in fewer situations, but one still extant is the accurate measurement of renal function in people potentially able to donate a kidney. We wanted to see the level of agreement between three commonly-used formulae for eGFR and the mGFR in this group.

Materials and methods: 508 people were evaluated between 2008 and 2012 for potential kidney donation by undertaking mGFR. mGFR was derived from ^{51}Cr-EDTA plasma clearance using blood samples taken at 2, 3 and 4 hours. The slope-intercept GFR was corrected for body surface area (BSA) using the Haycock formula and for the fast exponential using the Brochner-Mortensen equation. For each person with an mGFR and a contemporary plasma creatinine value we calculated the Cockcroft-Gault creatinine clearance, the 4-variable MDRD eGFR, and the CKD-Epi eGFR. We then explored the relationships between these different derived variables

Results: The mean mGFR for this population was 92.0 +/- 14.1 mls/min (range 38.6 – 166.7). Age range was 21 to 84. Racial / gender distribution was thus: White Female: 205; White Male: 193; Black Female: 32; Black Male: 28; Others Female: 27; Others Male: 22. Pearson correlation coefficients were poor between mGFR and MDRD eGFR (r=0.53), CG (r=0.54) and CKD-Epi (r=0.42), $p < 0.001$ all. However, Bland-Altman plots showed substantial bias: mGFR to MDRD bias -0.14 (SD 15.9), 95% limits -31 to +31 mls/min. mGFR to CG bias 21.3 (23.7), -25 to +67 mls/min. mGFR to CKD-Epi bias 12.2 (19.3), -25 to +50 mls/min.

Conclusions: The level of agreement between mGFR and all three sets of eGFR values was poor, with MDRD faring least badly, but eGFR values were of no clinical utility at all in this setting.

P133

Study of living kidney donor-recipient relationships: variation with socio-economic deprivation in the white population of England

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Socio-economic deprivation is associated with higher renal replacement therapy acceptance rates in the UK but lower rates of living kidney transplantation. This study examines donor-recipient relationship patterns with socio-economic deprivation in the white population of England.

Demographic characteristics of all white live renal transplant donors and recipients between 2001 and 2010 in England were analysed. Patterns of donor-recipient relationship were analysed to see if they differed according to an ecological measure of socio-economic status (Index of Multiple Deprivation). Group comparisons were performed using chi-squared tests and multivariable logistic regression.

Sources of living kidney transplants differed with deprivation ($p<0.001$). Recipients living in poorer areas were more likely to receive a kidney from a sibling, child and 'other relative' donor and less likely from spouses/partners. Logistic regression suggested differences seen with spouse/partner donations with deprivation were explained by differences in the age and gender of the recipients.

The source of living kidneys differs by level of area deprivation. Given the disparity in rates of living kidney transplants between the most and least socio-economically deprived there is a need to understand the reasons behind these observed relationship differences, with the aim of increasing transplantation rates in the most deprived.

P134

Altruistic kidney donation – one centres experience

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Background: NHS Blood & Transplant (NHSBT) – the body responsible for blood and organ transplantation in the UK wants to increase the number of living kidney donors. This is to meet the increased demand and because there is a significantly better outcome when an organ from a living donor is transplanted. Set against this background, the issue of altruistic donation becomes increasingly relevant. Legal in the UK since 2006, it is a phenomenon that can elicit strong feelings. Living Donor Kidney Coordinators have become increasingly involved in the altruistic donor programme even though it may go to a patient on the national waiting list. Altruistic kidney donation has become increasingly more complex to coordinate and can involve altruistic non-directed donation, short altruistic donor chains and also long altruistic donor chains.

Method: Altruistic donation was commenced within the transplant centre in 2006 and data has been collected subsequently to show the activity that result from this form of donation

Results: There have been 75 enquiries regarding altruistic donation since 2006. Of the 75 enquiries, 28 who were sent further information didn't follow up whilst 12 were declined for medical or psychological reasons. The transplant centre was the 2nd to carry out an altruistic donation in the UK with the oldest donor being 82 and the youngest 22.There have been 15 successful altruistic donations to date and the centre is the 3rd highest for altruistic donation. Of the 15 donations 1 has been a short donor chain with another one planned for January 2013. The centre has exported 14 of the 15 kidneys that have been altruistically donated and 1 local patient has benefited. The centre has received 2 altruistic donated kidneys from other centres.

Conclusion/discussion: Altruistic donation is an increasing work load for the Living Donor Kidney Coordinator which from the evidence collected does not necessarily benefit the patients listed locally. In order for this to be reciprocal more shared learning needs to happen to promote altruistic donation so all centres are participating in the programme. The results show that donors can vary in age although they need careful screening to assess suitability. Future developments are planned to carry out psychological assessment and follow up of the donors.

P135

Dynamics of improvement in residual renal function following living kidney donation

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Introduction: Living kidney transplant donors undergo a careful pre-donation assessment and post-donation follow up is recommended to confirm a favourable long term outcome. The purpose of this study was to examine the kinetics of change of renal function following nephrectomy, and whether this was influenced by age or the presence of hypertension.

Methods: Two hundred and eighty kidney donors (126 male, 154 female) were identified over a 10 year period. Blood pressure, Body Mass Index (BMI) and renal function (MDRD eGFR) were determined at baseline and subsequent follow up appointments.

Results: The baseline characteristics at time of donation were – age (years): 48.7±11.6; BMI: 27.2±3.4; blood pressure: mean 135/77, 17 patients (6%) were receiving anti-hypertensive therapy; eGFR (ml/min): male: 86.0±15.1, female: 79.7±12.2.

Table 1: Pre-donation eGFR by age, % change over time post-donation

Age	Pre-donation	2 wks	1yr	3 yrs	5 yrs	8 yrs	10 yrs
<40	88.4±13.6	-34	-25	-23	-20	-12	-5
40-59	81.8±14	-36	-31	-23	-21	-13	-11
>60	78.0±11.9	-36	-35	-26	-24	-9	-8

There were no deaths and no donor required dialysis over the period of follow up. The improvement in renal function over time was paralled by the proportion of donors assigned to CKD stage 3 or lower (pre-donation 3%, 2 weeks 81%, 3 months 75%, 1 year 72%, 3 years 54%, 5 years 55%, 8 years 22%, 10 years 20%). Twenty five patients (9.5% age 51.7±10.5 years) required initiation of treatment for hypertension following donation, but this did not impact on the recovery of their renal function.

Conclusion: This study confirms the long term safety of kidney donation. A consistent improvement in renal function continues for several years following donation in all age groups and is not influenced by the presence of hypertension.

P136

Socioeconomic status and access to renal transplantation on Teesside

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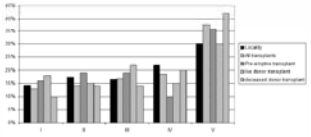
For patients who require RRT, transplantation offers improved quality of life and survival over dialysis. Previous studies have demonstrated superior patient and graft survival in live donor transplants and for pre-emptive kidney transplant recipients. It is therefore important that all patients have equitable access to live donor and pre-emptive kidney transplants.

A recent study based on UK renal registry data demonstrated socioeconomic inequity in live donor kidney transplantation in this country. Patients from lower socioeconomic backgrounds were less likely to receive a live donor renal transplant, a result that was found not to be confounded by ethnicity.

We therefore set out to evaluate the access to live donor and pre-emptive transplantation across the socioeconomic spectrum in our own unit. This was done on a background of a five year programme at our unit, aimed at improving rates of live donor and pre-emptive transplantation for all patients with severe CKD.

Methods: Social deprivation data was collected for all patients from our unit who underwent renal transplantation between 2008 and 2011, using the Index of Multiple Deprivation 2010. Locality data was collected for our catchment population and expressed as IMD quintiles.

Results



165 patients were transplanted between 2008 and 2011. Data is expressed in terms of IMD quintiles, where I is the least deprived and V the most deprived quintile. Our data show that the socioeconomic spread of all transplant patients reflects the locality population, indicating that socioeconomic deprivation is not a barrier to transplantation on Teesside. Both pre-emptive and live donor transplant rates are similar to the locality population, again indicating that socioeconomic deprivation is not a barrier to either of these types of renal transplant.

Conclusions: This data is contrary to UK wide registry data. Socioeconomic status does not appear to be a significant barrier to renal transplantation on Teesside, including access to live donor and pre-emptive renal transplants. This supports the principle that within a majority white ethnic group a pro-active approach to transplantation can negate the effect of socioeconomic inequity.

Poster session

Wednesday 13th March

18:15 - 19:25

Live donation - surgery

P137

Biomarker changes in hand assisted laparoscopic donor nephrectomy

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Introduction: Laparoscopic living donor nephrectomy (DN) exerts systemic effects causing transaminitis and increased urinary NGAL excretion [1]. Whether a hand-assisted laparoscopic donor nephrectomy (HALDN) would produce similar changes or might offer a less systemically stimulatory alternative to total laparoscopic donor nephrectomy is unknown.

Methods: Serial urine and serum samples were collected from 10 patients undergoing HALDN. Samples were analysed for NGAL and KIM-1 levels pre-operatively and 24hrs post-surgery. Data relating to ALT, creatinine and eGFR was also analysed in 48 live donors pre-operatively and at 24 and 48hrs post-surgery.

Results: Expected changes to creatinine and eGFR were seen in the donors. With comparison to the pre-operative levels ALT levels showed a significant decrease at 24hrs ($p= 0.004$) and were not significantly different from baseline levels at 48hrs ($p=0.08$). Serum KIM-1 and NGAL levels remained unchanged ($p= 0.79$ and 0.20) at 24hrs following donation. Similarly urinary levels of KIM-1 and NGAL were not statistically significantly different following donation. Mean operating time for this cohort was 1hr 36min.

Conclusions: In contrast to other published data our cohort did not exhibit changes to liver function tests or biomarker changes. This could be because of the lower operative time (96min vs. 216min) or because of the intermittent release of the pneumo-peritoneum in the hand assisted method which may exert less of a systemic inflammatory response.

1. Yap, S., et al., *Cytokine elevation and transaminitis after laparoscopic donor nephrectomy.* Am J Physiol Renal Physiol, 2012. **302**(9): p. 1104-11.

P138

Total laparoscopic retroperitoneal approach for living donor nephrectomy: first report of comparative study from Europe

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Background: Total Laparoscopic Retroperitoneal Donor nephrectomy (TLRDN) implies direct access to kidney without interfering with the intraperitoneal organs. Liverpool transplant Unit in the UK is the first European centre to commence this procedure in June 2011. We report our initial experience of TLRDN and compare the results with standard Hand assisted donor nephrectomies (HADN) done during the same period.

Methods: 44 Laparoscopic live donor nephrectomies performed in last 18 months at our centre were retrospectively reviewed and results of (TLRDN) group were compared to HADN group. Patient demographics, donor kidney laterality, intra and perioperative outcomes and recipient graft function were compared.

Results: Left donor nephrectomies were included in the study.15/41 patients underwent TLRDN. In both TLRDN and HADN groups, the median age was 36yrs vs 39yrs, BMI was 26 vs 27, operative time was 146 vs 141min and warm ischemia was 2.6 vs 2.5min (p=0.7) respectively. There were no major intra and post-operative complications and conversions in TLRDN, however there was one conversion to open due to bleeding from lumbar vein. Minor complications (wound infection and ileus) occurred in 2/14 TLRDN and 3/26 patients of HADN group. Median hospital stay was 2.5 days v/s 3.3 days, p=0.08). None of the donors needed readmission. Median creatinine clearance of recipients at month 1 and month 3 was 76 ± 2.4, 82 ± 1.6 v/s 72 ± 2.1, 79 ± 1.8 (p=0.7) in TLRDN and HADN groups respectively. **Conclusions:** In our initial experience TLDRN has no adverse impact on donor outcomes and early graft function in recipient. For its potential benefits, it's an attractive alternative to transperitoneal techniques. We feel that the learning curve is comparatively shorter and should be able to demonstrate in the subsequent report.

P139

Does stress affect wound healing as measured by high-resolution ultrasound in living kidney donors? A pilot study

Hannah Maple[1], Shanique Simmonds[2], Mary Tran[2], Joseph Chilcot[3], John Weinman[3], Nizam Mamode[1]

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Background: Stress is implicated as a factor that negatively affects wound healing. Living kidney donors are free from major physical or psychosocial co-morbidity and therefore provide an ideal group on which to assess the impact of stress on surgical wounds. The aim of this study was to use a new technique to assess the impact of stress on wound healing in living kidney donors.

Methods: 20 donors undergoing hand-assisted laparoscopic donor nephrectomy were included. Stress was assessed using the Perceived Stress Scale (PSS; max score = 16) and was measured 10-14 days pre-operatively. Two surgical wounds were scanned using the Episcan© High-Resolution Ultrasound machine with a 20MHz probe on days 1-3 and at follow up. Normal skin was also scanned to compare each participant to their own baseline. Image analysis included change in wound width and median colour intensity; a value calculated to reflect residual tissue oedema (lower median intensity indicating increased oedema).

Results: Median PSS score was 4.5 (range 0-10; sd 2.86). Stress did not correlate with age, gender, length of stay, donor-recipient relationship or pre-operative day on which the questionnaire was completed (mean 13 days; sd 4.01). Increased stress correlated negatively with wound healing as demonstrated by lower median intensity scores (and therefore increased tissue oedema) at follow up across two separate wounds (Hand port: r=-0.739, p=0.001; Lap port: r=-0.523, $p<0.05$). Stress was poorly correlated with net reduction and rate of reduction in wound size ($r < 0.2$, $p>0.05$). Inferior wound healing was not associated with age, BMI or the post-operative day on which the follow up scan was performed.

Discussion: The results of this pilot study show that pre-operative stress is strongly correlated with poor post-operative wound healing. High-resolution ultrasound is an effective way of quantitatively assessing wound healing in surgical patients. A larger longitudinal study is necessary to assess the relationship between ultrasound changes and immediate and long-term clinical outcomes.

P140

Peri-operative psychosocial factors and wound healing in living kidney donors

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Introduction: Research investigating factors which influence wound healing and recovery have identified a role for psychological stress and patient mood. Thus far, these findings have been mainly demonstrated using wounds specifically created for research purposes. Living kidney donors are selected due to their lack of major physical or psychosocial co-morbidity, making them an excellent group to study the effects of psychosocial factors on wound healing. This study investigated the extent to which preoperative stress, anxiety and depression impacted on surgical wound healing and a number of indices of recovery.

Methods: Living kidney donors completed a number of psychosocial outcome measures pre- and post-operatively. These included the Perceived Stress Scale (PSS), the Hospital Anxiety and Depression Scale (HADS) and the State-Trait Anxiety Inventory (STAI). Post-operative pain, fatigue and physical functioning were assessed by the Numeric Rating Scale-101 (NRS-101), Identity-Consequence Fatigue Scale (ICFS) and Short Form-36 (SF-36), respectively. The Wound Assessment Inventory (WAI) was used to measure wound healing.

Results: 15 donors were included in the study. Preoperative stress was positively associated with postoperative anxiety ($r=0.72$, $p<0.05$) and impaired physical functioning ($r=0.73$, $p<0.05$). Preoperative anxiety was positively associated with postoperative anxiety ($r=0.70$, $p<0.05$), fatigue ($r=0.61$, $p<0.05$) and impaired physical functioning ($r=0.61$, $p<0.05$). Wound healing was not associated with any psychological factors or the measured indices of recovery.

Discussion: This is the first study assessing the effect of psychological factors on wound healing and recovery in living kidney donors. Despite the small sample size preoperative stress and anxiety were found to be significantly associated with postoperative anxiety, fatigue and physical functioning; identifying a possible requirement for psychological interventions prior to surgery. A larger study using more objective measures of wound healing is necessary to further investigate the link between psychological factors and wound healing.

P141

Seroma formation following hand assisted retroperitoneoscopic donor nephrectomy

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Introduction: Hand Assisted Retroperitoneoscopic Donor Nephrectomy (HARDN) is an established technique for the purpose of live renal graft donation. The creation of the retroperitoneal space confers advantages over conventional laparoscopic methods by potentially reducing intraperitoneal complications, improving post-operative bowel recovery and the overall risk of localised bleeding. The aim of this study was to observe the incidence of seroma formation following kidney donation before and after the institution of a localised wound treatment. This consists of a superficial vacuum drain inserted above the fascia of the Pfannenstiel wound at the end of surgery.

Method: A retrospective review was undertaken of all live donor cases performed during a one year period June 2011-12. A comparison of 2 distinct groups was made. Group 1 comprised of HARDN cases performed during the first 6 month in which no drain was inserted. Group 2 were the latter 6 months patients in which a 10 fr Redivac drain was routinely inserted, with output monitored and removed on discharge (day 2 post operatively). Seromas were diagnosed on clinical suspicion and/or confirmed using Ultrasound imaging.

Results: In Group 1 there were a total of 24 patients, mean age of 49 (range 24-77) and mean BMI of 26.9 (range 19-34). There were a total of 6 seromas diagnosed in outpatients (mean BMI 29.9) and confirmed on USS imaging. Three patients required the seroma to be aspirated in outpatients (mean volume 40ml). The remaining patients underwent radiological drainage (mean volume 123ml). Two patients experienced delayed wound healing following spontaneous partial wound opening. In Group 2, there were a total of 24 patients with a mean age of 49 (range 30-69) and mean BMI of 26.6 (range 22-33.8). There was only one documented seroma whose BMI was 27.3.

Conclusion: The reduced incidence of seroma formation in Group 2 favour localised wound treatment in patients undergoing HARDN. It is now routine practice at our unit to insert a superficial operative drain in all live kidney donors.

P142

Adopting the retroperitoneal approach to live donor nephrectomy - confessions of a converted surgeon!

Nicos Kessaris[0, 2], Sarah Heap[1]

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Becoming trained and established in laparoscopic donor nephrectomy can be challenging as there have been few fellowships in the UK. The aim of this study was to review the development of a Live Donor BTS fellow, who had been trained in transperitoneal techniques, in adopting a retroperitoneal approach to donor nephrectomy at a single centre as a newly appointed consultant.

Method: A prospectively maintained donor database and operative logbook was reviewed from August 2011 to November 2012. There was a single senior surgeon training the new consultant in the Hand Assisted Retroperitoneal Donor Nephrectomy (HARDN) technique.

Results: There were a total of 57 donations of which 32 were from men. The mean age was 50 years (range 24 – 71) with a mean BMI of 29 kg/m^2 (range 18 – 33.8 kg/m^2). The training surgeon assisted in 3 full procedures and a further 3 to mobilise the vessels. In a further 8 procedures the training consultant required minimal help with either mobilisation or vessels dissection. From the 15th case no further assistance was required. Nephrectomy side was decided in a multidisciplinary team meeting. 50 were left sided, and 33 had simple anatomy. 13 cases had 2 arteries, two cases 3 arteries and one had 4 arteries. Mean operating time was 199 mins (range 129 – 358mins). Blood loss was recorded as < 200mls for 50 cases. One right sided procedure required a further incision to accommodate a gel port to help mobilise the upper pole of an adherent kidney. The mean post-operative stay was 2 days. There were 2 chest infections requiring antibiotics and 1 prolonged wound discharge. 2 patients required a post-operative CT scan to investigate unexplained abdominal pain and a raised CRP. These showed no abnormal features and the donors were discharged on day 4.

Conclusion: HARDN is a safe technique to train a surgeon with previous live donor nephrectomy experience. Additional help may be required to mobilise the vessels in the more confined space early on.

P143

Survey of chronic pain following laparoscopic-assisted donor nephrectomy

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Introduction: Several trials have shown superiority of laparoscopic nephrectomy when compared to open donor nephrectomy in terms of acute post-operative pain, hospital stay, patient satisfaction, cost-benefit ratio and early return to work. Our unit has previously shown the rate of patient recorded chronic pain to be as high as 26%.We investigated the effect of change of practice to minimal access donor nephrectomy on chronic post-operative pain nephrectomy in the same demographic population.

Methods: Chronic pain was defined as pain persistent at least 6 months post hand-assisted laparoscopic donor nephrectomy (HALDN). 49 patients from 2008 to 2011 were surveyed. Identical methodology to the units published study on open donors was used: Anonymous, validated pain assessment questionnaires (sf-BPI, EQ-5D and s-LANSS) were collated including the incidence of chronic pain, pain severity, type of pain and any treatment. Results for minimal access donors were compared to the earlier, open group.

Results: 32 of 49 patients responded but only 29 met the criteria to be entered in to our study. 17.2% reported to having chronic pain following the procedure with 7.4% of the group stating that they had pain affecting daily living. Of these 6.9% of patients were classified as having neuropathic pain. When compared to previous open-nephrectomy studies no patients in our cohort reported having extreme pain. Whilst reduced by almost half, the reduction of incidence of chronic pain following change from open donor nephrectomy to HALDN did not reach statistical significance (Fishers exact test p=0.2099).

Conclusion: The incidence of chronic pain and severe chronic pain is reduced in this series of minimal access donor nephrectomy compared to the unit's previous cohort of open donors. This difference did not reach statistical significance in the relatively small group analysed which may be a function of limited sample size. Ongoing audit will establish whether the reduction in chronic pain observed is real or a statistical sampling error.

P144

The feasibility and applications of non-invasive cardiac output monitoring (NICOM) and transit-time flow measurement (TTFM) in living-related renal transplantation surgery: results of a prospective pilot observational study.

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Introduction: Renal transplantation represents gold-standard renal replacement therapy, with significant survival and economic benefits over dialysis. We purport a role for NICOM and TTFM in prediction of immediate and early complications of surgery.

Methods: 10 consecutive living related renal transplantation recipients were prospectively studied. Non-invasive cardiac output monitoring (NICOM) was applied for the perioperative period. Transplant renal artery transit-time flow measurement (TTFM) was performed at reperfusion and following ureteric anastomosis using a doppler flow-probe. The results of pre- and post-operative blood tests/imaging were also collected.

Results: Median transplant-arterial bloodflow at reperfusion: 430ml/min (95%CI: 351-472) for routine cases c.f. 228ml/min noted in a case of partial transplant-arterial thrombosis, facilitating immediate revision and salvage. Cardiac index increased following transplant-reperfusion (mean CI-clamped: 3.17±0.29L/min/m^2, post-reperfusion: 3.50±0.35L/min/m^2; $p<0.05$) mediated by a reduction in total peripheral resistance index (mean TPRI-clamped: 2240±251dynes.sec/cm^5/m^2, post-reperfusion: 1985±166 dynes.sec/cm^5/m^2; $p<0.05$) and associated with a reduction of systolic blood pressure (mean SBP-clamped: 126±6.7mmHg, post-reperfusion: 116±4.3mmHg; $p<0.05$). These characteristic haemodynamic trends were abrogated in an individual later experiencing delayed graft-function.

Conclusions: Perioperative NICOM and intraoperative TTFM for living-related renal transplantation are technically feasible. Our data may support application of these techniques in the detection of significant immediate/early complications of transplantation, warranting further research.

P145

Total laparoscopic *versus* open donor nephrectomy: experience from a single centre focusing on donor safety

Syed Soulat Raza[1], Abdul Hakeem[1], Hannah Weston[1], Dhakshinamoorthy Vijayanand[1], Joe Barwick[1], Andy Lewington[2], Niaz Ahmad[1], Lutz Hostert[1], John Cartledge[3], Magdy Attia[1], Krish Menon[1]

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Aim: Laparoscopic donor nephrectomy (LDN) is considered as the current standard for living donor nephrectomy and can be performed as a total laparoscopic or hand-assisted procedure in a transperitoneal approach. LDN has replaced the traditional open donor nephrectomy (ODN) which involves long flank incision and resultant post-operative pain, poor cosmesis and longer convalescence. The aim of this single centre study was to compare donor outcomes between the total LDNs (tLDNs) and ODNs.

Methods: Consecutive tLDN (transperitoneal) and ODN performed at St James's University Hospital from 2000-2011 were retrospectively reviewed. Donor demographics, length of hospital stay, post-operative morbidity and mortality were compared between the tLDN and ODN groups. Continuous variables were expressed as mean±SD and categorical variables as percentages. P value was calculated using Fisher's exact or Chi-square for categorical and t-test for continuous variables.

Results: 151 tLDNs and 225 ODNs were performed over the study period. 95.3% of tLDNs and 54.2% of ODNs were performed after 2004. 5conversions were seen in the tLDN, all whilst retrieving left donor kidneys. Mean donor age, female gender and BMI were no different in 2 groups. Majority of the tLDNs (n=141,) were left kidneys, whilst 53.3% (n=120) of the ODNs were left kidneys (p<0.001). The mean length of hospital stay was shorter for the tLDN group, when compared to ODNs (p=0.020). The post-operative complications for tLDN *vs.* ODN: re-exploration for bleeding (1.9% *vs.* 0.8%, p=1.000), deep vein thrombosis (0.0% *vs.* 0.4%, p=1.000), pulmonary embolism (1.3% *vs.* 0.0%, p=0.160), wound infection (3.9% *vs.* 2.7 %,) and incisional hernia (1.9% *vs.* 4.0%, p=0.745). There was 1 death in the ODN group 3 years following nephrectomy.

Conclusions: Results suggest that tLDN done transperitoneally is a safe procedure and has similar profiles in comparison to ODN. Donor recovery and hospital stay were significantly shorter for the tLDN group, favouring tLDN.

P 146

Graft outcomes in living donor kidney transplant recipients: a comparison of laparoscopic *versus* open nephrectomy

Syed Soulat Raza[1], Abdul Hakeem[1], Olivia Posser[1], Louise Moore[1], Dhakshinamoorthy Vijayanand[1], Georgina Speak[1], Magdy Attia[1], John Cartledge[2], Adrian Joyce[2], Lutz Hostert[1], Stephen Pollard[1], Niaz Ahmad[1], Krish Menon[1]

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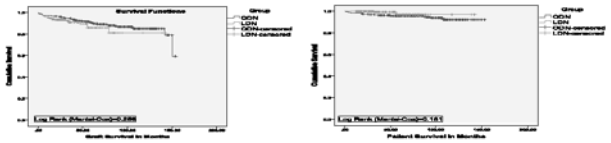
Introduction: Laparoscopic donor nephrectomy (LDN) is becoming the gold standard technique for retrieval. The method of retrieval of the kidney varies between the open and laparoscopic techniques. The aim of the current study was to compare graft and recipient outcomes between LDN and open donor nephrectomy (ODN) from a single centre.

Methods: Data were collected retrospectively from Jan 2001 to Dec 2011. Recipient and donor characteristics were collected between the two groups and graft and recipient outcomes were reported. P values were calculated using Fisher's exact or Chi-square test for categorical and t test for continuous variables. Kaplan-Meier survival curves with log-rank comparison was used for death-censored graft and patient survival.

Results: 376 living donor renal transplants were performed over eleven years. 59.84% (n=225) transplants were done following ODN and 40.16% (n=151) following LDN. The recipient outcomes comparing ODN *vs.* LDN were: Primary non-function (none in either groups), delayed graft function (6.6% *vs.* 2.6%,p=0.095), re-explorations for bleeding (3.1% *vs.* 2.6%, p=1.000), early graft loss due to vascular thrombosis (0.8% *vs.* 0.6%, p=1.000), renal artery stenosis (2.6% *vs.* 3.3%, p=0.761), ureteric stricture (2.6% *vs.* 3.3%, p=0.761), acute rejections (16.0% *vs.* 14.5%, p=0.771), chest infections (6.2% *vs.* 5.9%, p=1.000), wound infections (5.7%*vs.* 9.9%,p=0.161), incisional hernia (5.7% *vs.* 5.3%, p=1.000) and post-transplant lympho-proliferative disorder (0.4% *vs.* 0.0%, p=1.000). The median Creatinine at 6 months (131 *vs.* 120 mmol/L, p=1.000) and 12 months (130 *vs.* 119 mmol/L, p=1.000) were no different for ODN and LDN respectively. 1,3 and 5-year death-censored graft survival was 98%, 94% and 90% for ODN and 94%, 92% and 85% for LDN (log rank p=0.258). Similarly, 1,3 and 5-year patient survival was no different between ODN and LDN (98%, 94% and 94% *vs.* 100%, 99% and 98%, log rank p=0.181).

Conclusion: Early, mid and long-term recipient outcomes were similar for the total laparoscopic donor nephrectomy *versus* the open donor nephrectomy groups in our centre. Total laparoscopic donor nephrectomy approach for retrieval of kidneys can be safely offered with good graft and recipient outcomes.



Poster session

Wednesday 13th March

18:15 - 19:25

Liver transplantation 1

P147

The additive effect of pre-transplant obesity, diabetes and cardiovascular risk factors on outcome after liver transplantation: a 10-year national experience

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Background: The effect of pre-transplant obesity and other metabolic risk factors on outcome after liver transplantation (LT) is controversial. Questions have been raised over the appropriateness of the body mass index (BMI) for assessing obesity in these patients. Both issues have implications for organ allocation. Using gold-standard dual-energy x-ray absorptiometry (DXA) scanning for measuring % body fat (%BF) we examined the relationship between BMI and true %BF in LT patients, and evaluated the independent and additive risks of pre-transplant obesity, diabetes(DM), hypertension(HTN) and coronary artery disease(CAD) on post-LT outcome.

Methods: Retrospective study of consecutive adult patients undergoing LT at our national centre in New Zealand between 2000-2010. BMI and %BF were used to assess obesity immediately prior to LT and the kappa level of agreement between the methods determined. The influence of pre-transplant risk variables (including obesity, DM, CAD, HTN) on 30-d post-operative event rate, complication-type and length of hospital stay were analysed using regression models. 30-day, 1- and 5-year patient survival was modelled using Kaplan-Meier curves.

Results: 202 patients were included. There was agreement between BMI and %BF methods for determining obesity in 86% of the study population (kappa coefficient = 0.73). Obesity was an independent risk factor for post-operative event rate (counts ratio 1.03, $p<0.01$), as was DM (CR 1.4, $p<0.01$). Obesity with concomitant DM however was the strongest predictor of post-operative event rate (CR 1.75, $p<0.01$), cardiorespiratory and infective complications and longer hospital stay (15.8 vs.10.0 days, $p<0.01$). Obesity had no effect on 30-day, 1- or 5-year patient survival.

Conclusions: This study has demonstrated that BMI is an adequate tool for assessing obesity-associated risk in patients listed for LT, where DXA is not available. Interestingly, we found that post-LT outcome was poorest in patients with concomitant obesity and DM, highlighting the importance of looking at overall metabolic risk. Obesity did not influence early or late recipient survival, and should not on its own be considered an absolute contraindication to LT.

P148

International benchmarking in liver transplantation in Europe

Marco Carbone[1,2], Alexander Gimson[1], Alessandra Nardi[2], Tania Marianelli[2], Kerri Barber[1], Alex Hudson[1], David Collett[1], Mario Angelico[2], James Neuberger[1]

[1]Organ Donation and Transplantation, NHS Blood and Transplant, Bristol, UK, [2]Tor Vergata University, Rome, Italy and Italian Association for the Study of the Liver (AISF), Rome, Italy

Background: Differences in donor quality and recipient selection for liver transplantation (LT) in European countries may lead to differences in outcome. Comparing outcomes after LT internationally might stimulate cross-national learning. Aim of this study was to compare outcomes in LT recipients in the United Kingdom (UK) and in Italy.

Patients and methods: Data on 2,339 deceased donor LTs performed in adult recipients from June 2007 to May 2009 in the UK and Italy were obtained from the UK Transplant Registry (n=859) and the Italian 'Liver Match' database (n=1480). Follow-up data were available for 2335 patients with a median follow up of 2.8 years.

Results: Hepatitis C (HCV) and hepatocellular carcinoma (HCC) were more common as primary indications for LT in Italy compared to the UK (HCV: 22.8% vs. 16.1%; HCC: 42.4% vs.5.8%). Compared with their UK counterparts, LT recipients in Italy had lower MELD (median: 15 vs.16, p<0.0001), lower BMI (median:25.1 vs.26, p=0.0001), shorter cold ischaemic time (436 min vs.568 min, p<0.0001), were more likely to receive grafts from older donors (median age:56 vs.47, p<0.0001) and donors died for trauma (25.8% vs.13.1, p<0.0001). Risk factors for graft loss at Cox multivariate regression were different in the two countries: in Italy, risk factors consisted of donor age (HR=1.007), donor HBcAb status (HR=1.5), aetiology (HR for HCV=2.2), bilirubin (HR=1.18), creatinine (HR=1.3), portal vein thrombosis (HR=2.03); in the UK, risk factors consisted of national vs. local allocation (HR=1.5), recipient creatinine (HR=1.6) and donor BMI (HR=1.03). While 90-days unadjusted graft survival was similar in the two countries, differences were observed at 3-years (78% in Italy vs.84.4% in UK, p=0.0001). However, after adjusting for donor, graft and recipient significant factors, disease-specific survival was significantly different only in LT alcoholic liver disease (ALD) (HR=3.95; 95% C.I., 1.8-5).

Conclusions: Risk adjusted-survival analysis provides similar results in both countries, except for those transplanted for ALD; this requires further exploration. Given significant differences in aetiology, donor, recipient characteristics and risk factors, international comparison of LT outcomes must be approached with caution. These data suggest that predictive models developed in one country may not be valid in another.

P149

Poor predictive ability of the American donor risk index in orthotopic liver transplantation in Europe

Marco Carbone[1,2], Alexander Gimson[1], Sally Rushton[1], Alex Hudson[1], Alessandra Nardi[2], Tania Marianelli[2], David Collett[1], Mario Angelico[2], James Neuberger[1]

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Background: The Donor Risk Index (DRI), developed within the Organ Procurement and Transplantation Network (OPTN), is a continuous scoring system which predicts graft-failure based on donor and transplant characteristics. The DRI has been shown to be an important risk factor for liver transplantation (LT) in the Eurotransplant region; however, its ability to predict outcome has not been assessed. The aim of the study was to validate the DRI and to assess its predictive ability in another, more heterogeneous, European cohort.

Methods: Data on 2,339 deceased donor LTs performed in adult recipients (June 2007-May 2009) in the United Kingdom (UK) and Italy were obtained from the UK Transplant Registry (n=859) and the Italian 'Liver Match' database (n=1480). The relationship between DRI and graft survival was investigated using the Kaplan-Meier method. Cox proportional hazards models were used to investigate the risk-adjusted effect of DRI. A concordance statistic of Gönen and Heller was calculated to assess the predictive ability of the models. Follow-up data were available for 2,335 patients with a median follow up of 2.8 years.

Results: The mean DRI was higher in the European cohort (1.54±0.35) than in OPTN (1.45) in the same time frame. The Kaplan-Meier curves showed reasonably good discrimination between different DRI categories, with inferior graft survival associated with increased DRI (log-rank test: p=0.005). This effect remained apparent after adjusting for recipient creatinine, bilirubin and diagnosis; the change in the log likelihood statistic was highly significant on adding DRI to this Cox model. However, the predictability of the model including DRI and significant recipient factors was poor (c-statistic: 0.60) and there was only a small reduction after the exclusion of DRI (c-statistic: 0.58). Country-specific sub-analysis showed similar predictive ability in both countries.

P150

The utility of time-zero biopsy scoring of ischaemia/reperfusion injury after liver transplantation

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Introduction: The utility of time-zero biopsies after orthotopic liver transplantation (OLT) remains unclear. The aim of this study is to evaluate histological grade of ischaemia/reperfusion injury (IRI) on time-zero biopsy as a prognostic indicator.

Methods: Between February 2000 and 2010, 647 OLT were performed at our centre. Time-zero biopsies were available for 474 patients. Patients were divided into four groups based on histological grade of IRI: nil (50), mild (280), moderate (124) and severe (22) and clinical data compared for each.

Results: Biopsy score severity was strongly associated with recognised risk factors for IRI, including donation after cardiac death, donor age, donor BMI and allograft steatosis ($p<0.001$). Higher IRI grades also correlated closely with markers of an ischaemic insult, such as the incidence of post-perfusion hyperkalaemia ($p=0.01$) and peak ALT in the first seven post-operative days ($p<0.0001$). Interestingly, neither cold nor warm ischaemic times were significantly different between groups ($p=0.27$ and 0.38 respectively). The degree of IRI on biopsy correlated closely with graft outcome. In particular, a severe IRI grade was associated with significantly greater post–transplant morbidity compared to the other 3 groups, with markedly higher rates of primary non-function (9.1% vs 0.9%; $p=0.006$), early graft dysfunction (55% vs 21% $p<0.0001$) and the need for re-transplantation within 90 days (14% vs 2.6%; $p=0.02$). One year graft survival in nil, mild and moderate groups were significantly better than in the severe group (88%, 87%, 89% and 55% respectively; $p<0.0001$).Notably the degree of steatosis on biopsy did not correlate with graft survival ($p=0.37$), re-transplantation within 90 days ($p=0.82$) or PNF rate ($p=0.07$), suggesting severity of IRI to be an independent predictor of graft outcome.

Discussion: Time-zero biopsies have value in predicting adverse clinical outcomes following OLT and allow identification of patients at risk of a complicated post-operative course. Our analysis suggests that early re-transplantation should be considered for recipients whose time-zero biopsy reveals severe IRI.

P151

Time spent in hospital in the first two years after liver transplantation

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Introduction: Patient survival is the primary outcome used in liver transplant research. However, the time a patient spends in hospital after transplantation also reflects the success of transplantation.

Methods: A linked UK liver transplant (UKT) registry – Hospital Episode Statistics (HES) database of patients who had a first liver transplant between 2002 and 2007 was analysed. The time patients spent in hospital in the first two years after transplantation was compared between patients who had a super-urgent or an elective transplantation. The time spent in hospital was expressed as a percentage of 2-year patient post-transplant survival: i.e. time between date of transplantation and date of death or two years whichever is shorter.

Results: Our analysis included 2,126 adult liver transplant patients from the linked UKT-HES database. In the first two years after liver transplantation, patients spent on average of 52 days in hospital comprising 16.4% of their total 2-year survival time. Patients who had a super-urgent transplantation spent 62 days in hospital (24.3% of survival time) and those who had an elective transplantation spent 50 days (15.0% of survival time). Corresponding figures for super-urgent patients who survived two years were 64 days and 9.1%, and for those who died within two years were 56 days and 91.7%. For elective patients, these figures were 48 days (6.7%) for those who survived and 66 days (65.2%) for those who died. The observed differences of percentages of time spent in hospital between super-urgent and elective patients and between those who died within two years and those who survived were all statistically significant (all p values < 0.001).

Conclusion: Super-urgent patients had a higher 2-year mortality rate and they also spent more of their survival time in hospital than elective patients. Patients who died within two years, irrespective of whether they had a super-urgent or an elective transplantation, spent most of their life after transplantation in hospital.

P152

Incidental portal vein thrombosis: does it impact the surgical outcomes following liver transplantation

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Introduction: Complications arising from Portal vein thrombosis (PVT) necessitates appropriate graft selection; generally those with PVT are considered to carry higher surgical risk following liver transplantation (LT). Previously undetected PVT encountered at LT may impact the outcome as the graft selection has already been made. The objective of this study was to review if the incidental finding of PVT had any implications on the outcomes.

Method: Retrospective analysis of LT database from January 2000 - August 2012 and case notes review. Patients were classified into Diagnosed PVT (DPVT) and incidental PVT (IPVT) and Control group with no PVT. Control group was matched for age, sex, year of transplant and diagnosis. Statistical analysis done with Wilcoxon Signed Ranks tests, McNemar test & Kaplan Meier graphs for survival.

Results: Of total 1491 transplants during study period 41 patients were known to have PVT before transplant (DPVT), 85 patients found to have PVT at the time of transplant (IPVT); overall prevalence of PVT was 126 patients (8.4%). They were compared with matched control of 126 patients. The extent of thrombosis was mild (Yerdel's Grade I/II) in both DPVT and IPVT groups. Donor risk index was 1.63, 1.79 and 1.8 in DPVT, IPVT and Control group respectively ($p<0.05$). PVT group in total required longer theatre time (40 minutes longer approx), more blood products at the time of surgery and had higher incidence of post-operative bleeding [DPVT (n=8;19.5%), IPVT (n=10;11.7%) and control (n=7;5.5%); $p<0.05$]. There was no significant difference in ITU stay (Median of 4, 3 and 3 days respectively; $p=0.52$) or overall hospital stay (Median of 13, 14 and 12days respectively; $p=0.75$) or overall graft/patient survival ($p=0.66$). The risk of recurrent thrombosis was 2.3% in overall PVT group.

Conclusions: Care should be taken when using marginal grafts in the presence of PVT because of the longer operative time and its impact on graft ischaemic time. In the current era of expanding use of marginal grafts, we should consider effective preoperative imaging protocols to minimise the incidence of IPVT.

P153

Do arterial conduits in liver re-transplantation result in a worse outcome?

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Introduction: Establishing arterial inflow to Liver re-transplants (LrT) using arterial conduits (AC) could result in inferior rates of graft survival. We therefore sought to investigate the long-term outcomes of LrT using AC for arterial reperfusion.

Methods: 710 Adult LT procedures were retrospectively analyzed utilizing a prospectively maintained database from a single UK centre. LrT were divided into 2 groups either LrT+ AC or LrT direct hepatic artery reconstruction (DHA). Various donor and recipient variables including arterial complications and survival were analyzed.

Results: 76(10.8%) grafts were LrT. 72 were first LrT and 4 had a third graft, all were DBD transplants, 2 were split and none were multi-organ. 41 LrT had AC and 32 had DHA. 3 LrT were excluded from analysis because of limited operative details. Median follow up was 3y (range 6 months - 16.8 yrs). There were no significant differences between the 2 groups in terms of age, sex, MELD score, recipient BMI, CIT, WIT or DRI. Significant differences were found between DHA vs AC groups for peri-operative blood transfusion 13 (11) vs 24 (19) units (p=0.003), fresh frozen plasma transfusion 18 (13) vs 34 (27) units (p=0.009) and duration of surgery 7.1 (1.6) vs 8.4 (1.9) hours (p=0.023). Overall 7/76 (9.2%) LrT developed HAT (3/41 AC, 4/32 DHA p= 0.69). All of the HAT's in the conduit group occurred within 30 days while only 1 (out of 4) occurred in the DHA group (p=0.149). Hepatic artery stenosis was seen in 5 recipients (AC n=3 and DHA n=2). All these were identified after 30 days of LrT and were treated by angioplasty apart from one further re-transplant. Biliary reconstructions 54/76 (71%) were either HJ (X) or duct-to-duct (n=18); Only 4 PV reconstructions required iliac vein conduits. There was no difference in patient survival (mths 95% c.i.) between DHA or AC groups of 82.3 (53.8 – 110.8) and 101.6 (72.4 to 130.8) (log-rank p=0.43) respectively.

Conclusions: AC are often necessary in patients undergoing LrT. Their use does not appear to impact on long-term outcome in our series. Nevertheless they appear to be associated with an increasing trend of HAT during the first 30 days of LrT.

P154

Significant response to local ablative bridging treatments facilitates acceptable rates of survival following Liver transplantation for HCC in a UK centre

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Introduction: Liver Transplantation (LT) is a well-recognised treatment option for selected patients with hepatocellular carcinoma (HCC). There is always concern regarding tumour progression whilst on the waiting list and there is no consensus on how to reduce this. UK guidelines recommend local ablative therapy for all HCC patients being considered for LT. We have sought to review this practice and evaluate its benefit.

Methods: All consecutive patients with HCC who have undergone LT between 2001 to 2010 were identified from our prospectively maintained database. All patients are discussed at our LT assessment meeting and also at a separate HPB MDT for consideration of bridging treatment. Our imaging protocol includes 1) triple phase CT, 2) MRI for atypical lesions or 3) CEUS. Patients undergo either trans-arterial chemo-embolisation (TACE) and/or percutaneous/ laparoscopic radio frequency ablation (RFA) whilst on the LT waiting list.

Results: 55 HCC patients underwent LT (M:F = 43:12), Childs-Pugh A (n=9), B (n= 30) and C (n=16). Bridging treatments were either TACE n=31, RFA n=28, or both treatments n=4. TACE treatments per patient were 1 (n = 12), 2 (n = 12), 3 (n = 6) or 4 (n=1). Six patients did not undergo any form of bridging treatment as they rapidly progressed to LT. The response to bridging treatment was complete (n=8), good (n =10), moderate (n = 18), poor (n = 4) or no response (n =15). There were 2 deaths within 100 post-operative days. At last follow-up, 28 patients had died due to recurrent disease, stable recurrent disease n=4 or disease free n= 21. Overall survival [median (95% CI)] was 62 (53 -71) months. For those with a good response to bridging treatments it was 67 (55 – 79) months whilst for those with poor/no response it was 53 (42 – 64) months (log-rank p=0.059).

Conclusion: This study demonstrates the feasibility of various bridging treatments for patients with HCC who await liver transplantation in the UK. In combination with careful patient selection and surveillance acceptable rates of survival can be achieved.

Poster session

Wednesday 13th March

18:15 - 19:25

Liver transplantation 2

P155

Halploidentical stem cell therapy to restore haematopoiesis in liver transplant associated graft versus host disease

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Background: Graft versus host disease (GVHD) is rare following orthotopic liver transplant (OLT) occurring in < 2%. Allo-reactivity is presumed due to CD8+ donor T-lymphocytes overcoming the recipient's immunological resistance. Pancytopenia and loss of mucosal barrier function lead to sepsis and death once donor alleles reach >20%. Established GVHD is almost invariably fatal. A radical approach is required to remove allo-reactive donor T-cells.

Methods: An 18-year-old girl received OLT for paracetamol-induced acute liver failure. Falling peripheral blood counts were noted. On day 22 she developed diarrhoea and rash consistent with clinical grade III GVHD. Bone marrow (BM) aspirate was severely aplastic. Skin and colonic biopsies confirmed GVHD. Whole blood showed 50% donor HLA alleles. On day 27, steroids and Alemtuzumab were given. Her rash improved but profuse diarrhoea continued. We turned to haplo-identical transplant to deliver a temporary allo-immune hit to eliminate liver-derived T cells and restore stem cell function either from the haplo-identical donor or recipient. The patient's family were approached regarding a stem cell transplant (SCT). Her father donated and shared no HLA antigens with the liver donor.

Results: Chimerism testing demonstrated transient engraftment of the haplo-identical donor of 51%. By the time of neutrophil regeneration, recipient haematopoiesis was 89% with 11% stem cell donor detectable. At days 17-20, skin and liver contained 14-17% liver donor leukocytes and skin was also engrafted with the stem cell donor at 14%. The patient improved with restoration of haematopoietic function. On day 42, BM was 100% recipient containing normal megakaryocytes. She remains alive and well.

Conclusion: Prevention of transplant-associated GVHD by early detection of donor alleles and cessation of immunosuppression has proven efficacy and should be implemented in all organ transplant programmes. This case demonstrates that T-replete haplo-identical SCT can effect rapid, life-saving reversal of T-cell allo-immunity.

P156

Ischaemic complications associated with arterial reconstruction methods in patients undergoing orthotopic liver transplantation

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Introduction: Ischaemic complications such as hepatic artery thrombosis (HAT) and biliary strictures account for some of the major causes of graft failure, morbidity and mortality following orthotopic liver transplantation (OLT). These risks were assessed based on the method of arterial reconstruction performed.

Methods: 1364 whole graft OLTs were assessed over a 12-year period for HAT and biliary strictures. Patients were classified according to methods of arterial reconstruction.

Results: Of the patients receiving a graft requiring a single arterial anastomosis (n=1122) ischaemic complications occurred in 14.3% of cases, whilst those undergoing multiple anastomoses (n=242) had a risk of 21.5% ($p<0.05$). Those recipients with a longer native hepatic artery preserved, including native gastroduodenal artery (GDA), developed fewer complications (9.6%), with a gradual increase in risk as the preserved length decreased (16.1% mean risk) with greatest risk when divided at the celiac trunk (18.2%); This may be attributed to the corresponding long residual donor artery, which conferred a risk of 18.4% compared with those divided above the splenic artery bifurcation (14.4%). Preservation of a long donor and short recipient artery gave a risk of 11.3%, compared with 19.9% when a short recipient and long donor artery were used. Use of a patch to aid in the anastomosis formation conferred a risk of between 13.8 and 16.5% when a patch of either GDA or splenic artery were used.

Discussion: It is clear that the integrity of the arterial tree of the transplanted liver plays a major role in the development of ischaemic complications. The risk of complications can be limited when planning the method of arterial reconstruction.

P157

Recurrent PSC in liver transplant recipients with inflammatory bowel disease: a multicentre epidemiological analysis over 20 years

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Introduction: The association between Primary Sclerosing Cholangitis (PSC) and Inflammatory bowel Disease (IBD) is well recognised. However, the relationship between IBD and recurrent PSC (rPSC) in the liver allograft is less well understood. We aimed to assess the rate and risk factors for rPSC and the impact of IBD and its management on rPSC.

Methods: This is a UK multicentre study across 5 Liver Transplant Units of all patients undergoing LTx between 1990 and 2010 in the United Kingdom. NHSBT provided LTx data. Individual units provided colitis data.

Results: 7726 patients underwent a liver transplant of which 556 (7.2%) were for PSC. Of these, 260 (56.8%) were diagnosed with colitis (UC 223, Crohn's 25 and Other 12) and 76 (29.2%) patients with colitis underwent colectomy. Of these, 40.8% patients underwent colectomy before LTx, 3.9% during LTx and 47.4% after LTx. 6% of patients had recurrent PSC. Of these, patients who had their colectomies post-LTx had a higher risk of developing rPSC.

Conclusion: In this large cohort, the majority of patients underwent a colectomy after LTx. This study demonstrates that a colectomy before or during- LTx appears to have a protective effect against rPSC.

P158

Ischaemic cholangiopathy following liver transplantation from DCD donors: a single centre study

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Background: Donation after Cardiac Death (DCD) liver transplantation represents approximately 20% of UK liver transplant activity. However potential benefits of expanding the donor pool must be balanced with the potential for inferior outcomes with DCD allografts. The rates of ischaemic cholangiopathy (IC) reported in the literature vary widely (2-50%). The aim of this study was to compare development of IC & graft and patient survival between DCD and matched-DBD recipients.

Methods: A single centre retrospective review of electronic and paper records was undertaken of outcomes for all adult recipients who underwent an OLT from DCD donors (Maastricht Cat 3) and a contemporaneous cohort of OLT recipients of DBD donors between 12/5/2007 – 10/9/2012. The primary outcome measures were development of IC, primary non-function, graft and patient survival.

Results: 38 patients underwent DCD OLT during the study period. Patient survival was significantly reduced in DCD compared with DBD recipients; 30-day, 1-, 2-, and 3-year survival rates in DCD group were 86.7%, 72.5%, 72.5% and 72.5%, and 98.3%, 93.2%, 93.2%, and 90.2% within the DBD group. PNF occurred in 2 cases in each cohort (DCD 5.2%v DBD 3.3%). Rates of IC were significantly higher in the DCD group than DBD group: 9/38, 23% versus 0/59, 0% ($p<0.001$). 3/9 patients with IC died, 1 has been relisted and 5 have had endoscopic intervention. No association was demonstrated with regards to cold ischemia times, sequence of reperfusion or donor demographics within the DCD cohort. No differences were observed in the DCD cohort between those who developed IC in terms of time from withdrawal to asystole or asystole to cold perfusion.

Conclusion: Ischaemic cholangiopathy is a significant cause of morbidity and mortality after OLT but no parameters in this cohort were asscciated with IC. Analysis of data regarding donor management, withdrawal and assessment of functional warm ischaemia is ongoing.

P159

Venous complications after primary and liver re-transplants - a comparison of different caval reconstruction techniques.

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IVC reconstruction in OLTx is traditionally performed by caval replacement (CR). Side to side longitudinal cavoplasty (LC) is becoming increasingly popular as it is thought to reduce caval complications, reduces the extent of caval dissection and is a single anastomosis. We sought to investigate short-term outcomes between these 2 techniques in terms of venous complications including re-transplants

Between 2005 and 2010, 205 OLTX were performed, 79 with CR versus 126 with LC . We also compared IVC reconstruction at re-transplantation (LrT n=76) performed between 1995 to 2011.

For primary LT both CR or LC were similar in terms of mean (SD) recipient age 50 (11) vs 51 yrs (12) (p=0.566) , recipient weight 72.8 (14.5) vs 76.5 kg (19.6) (p=0.015), MELD 21(6) vs 24 (11) (p=0.5), DRI 1.49 (0.43) vs 1.46 (0.35) (p>0.05), CIT 665 (215) vs 715 (185) mins (p=0.46), packed red cell transfusion 10u (8) vs 11 u(10) (p=0.77) and hospital stay 31(19) vs 31 days (20) (p=0.98).

However warm ischemia time (to portal reperfusion) was 66 mins (18.7) vs 57.8 (15.8) p=0.02 and total duration of surgery 608 (137) vs 568 (94) mins (p=0.015) were longer in CR compared to LC groups respectively. IVC stenosis was seen in 4/126 (3%) and 4/79 (5%) of CR and LC respectively (p=0.48). However there appeared to be an increasing trend of venous complications in those patients having CR versus LC for re-transplants although this did not reach statistical significance (6.5% versus 11.6% p=0.48).

Conclusion: IVC replacement be it CR or LC has similar venous complication rates after primary liver transplants but larger studies are needed to confirm if LC has lower venous complication rates for re-transplants.

P160

The adverse effect of RRT on survival after liver transplantation for acute liver failure

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Acute kidney injury is associated with a poor prognosis in acute liver failure. However, little is known about the outcomes of patients undergoing super-urgent liver transplantation who have a requirement for renal replacement therapy (RRT).

A retrospective analysis of the UK Transplant Registry was performed (1 January 2001 – 31 December 2011). Graft and patient survival were determined for patients receiving RRT compared with those who did not using Kaplan-Meier methods. A Cox proportional hazards model was used in a multivariate analysis and included Monte Carlo simulation of outcomes at given covariate levels.

Of 5753 liver transplants were performed, 925 were for acute liver failure. In patients receiving RRT (502), 3 year graft and patient survival were 79.8% (95% CI 76.0-83.8) and 77.0% (73.3-81.0) compared with 86.0% (82.6-89.6) and 87.1% (83.9-90.5) for those not requiring RRT (log-rank test, $p<0.001$). In other univariable analyses of graft and patient survival, aetiology of liver failure, recipient age, haemoglobin level and the use of mechanical ventilation were significant predictors. In a multivariable analysis of graft survival, only the use of RRT was significant, hazard ratio (HR) 2.18 (95% CI 1.07-4.47), $p=0.03$). Significant predictors of patient death were RRT (HR 2.25, 1.21-4.20, $p=0.01$) and recipient age (HR 1.02, 1.00-1.03, $p=<0.01$). Even after accounting for interaction with RRT, serum creatinine at time of transplantation was also an independent predictor of patient mortality (HR 1.55, 1.08-2.14, $p=<0.01$, for creatinine = 100 umol/L vs. 300 umol/L). This finding was robust in sensitivity analyses.

Patients requiring super-urgent liver transplantation who are on RRT have a significantly worse graft and patient survival than those who do not. The finding that creatinine independently predicts mortality warrants further investigation, but consideration should be given to the timing and duration of RRT.

P161

Time alone should not be used in assessing the agonal phase in liver donation

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Background: The agonal phase varies both in duration and in donor physiology. National guidelines on the agonal phase comment only on its duration, however time is unlikely to be the most important feature. The aim of this study was to determine which agonal phase characteristics influence the decision to stand-down from liver donation using a novel method that takes account of the duration and severity of a physiological impairment.

Methods: For liver donors and for donors where stand-down from liver donation occurred prior to asystole, the following physiological parameters were plotted against time from withdrawal of life support: peripheral SaO_2 (<100%), heart rate (<60 BPM), respiratory rate (<8 breaths per minute), systolic (<90mmHg) and diastolic (<60mmHg) blood pressure. Area over the curve (AOC) was calculated to show the duration and extent of impaired physiological parameters (exemplified in Figure 1).

Results: The time to either asystole for liver donors (n=31, 18.2 mins ± 7.4) or stand-down for potential liver donors (n=40, 51.7 mins ± 31.6). Only the AOC for SaO_2 was significantly different ($p<0.01$, see Figure 2) between either group. Similarly only the AOC for SaO_2 correlated with agonal phase duration ($r^2 = 0.35$).

Figure 1.

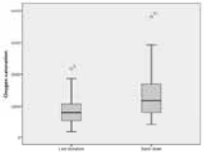

Figure 2.

Conclusion: These data suggest that SaO_2 is used to determine an 'unfavourable' agonal phase and therefore in the decision to stand-down. However, agonal phase duration remains the most critical factor. As AOC of the parameters examined correlates poorly with time, time alone needn't be a reason to stand-down during the agonal phase.

P162

Long term results of aorto-hepatic conduits in adult cadaveric orthotopic liver transplantation

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Background: Early graft loss secondary to arterial inflow problems remains a major challenge in liver transplantation. Revascularisation of the liver using donor iliac artery conduits is a well-recognised procedure.

Aim: This study analyzes the impact and long term results of aorto-hepatic conduits in adult cadaveric orthotopic liver transplantation (OLT).

Methods: This is a retrospective review of 452 OLTs from January 2003 to August 2009. The data on indication, type of graft, complications and survival were obtained from the transplant database and patient case notes.

Results: Aorto-hepatic conduits were required in 46(10.1%) patients. The median age of the recipients was 52 (Range: 27 – 68). The male to female ratio was 1.4:1. Three out of the 46 (6.5%) recipients received the liver from a non-heart beating donor. In 24 patients the conduit was created at the time of the first liver transplant. The indications were multiple hepatic arteries needing reconstruction (11), atherosclerotic / unsuitable recipient artery (9) and unsuitable donor vessel (4). In 21 patients the conduit was created during re-transplantation following acute hepatic artery thrombosis (HAT). The 30- day mortality of the aorto-hepatic conduits was 6(13%). Five out of 6 deaths were following HAT and re-transplantation. The conduit patency at three years for the primary and re-transplantation were 89% and 67% respectively. On median follow up of 38 months, the three-year graft survival were 72% and 53% respectively.

Conclusion: The primary aorto-hepatic conduits have good long term results and has no negative impact on graft survival.

Poster session

Wednesday 13th March

18:15 - 19:25

Marginal donors

P163

Deceased polycystic kidney donors – should they be considered to expand the donor pool?

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Introduction: Renal transplantation is the best modality for treating end stage renal disease (ESRD). Extended criteria (ECD) donors are often considered to expand the donor pool. Kidneys from polycystic kidney disease donors are generally not considered suitable for transplantation. We present the use of a pair of polycystic kidneys with a literature review, which reveals a very limited worldwide experience.

Methods: A case note review was carried out on two patients each receiving a kidney transplant from a 34 year old deceased donor assessing serum creatinine and estimated glomerular filtration rate (eGFR). In addition, a literature review was carried out using various data bases to create a brief evidence based document.

Results: Donor: 34 year old female, DBD (donation-after-brain death), Serum creatinine of 81, eGFR 90 ml/min and cause of death: intracranial haemorrhage. Recipients: The first Recipient was 58 years old received the left kidney (13cms) with cold ischemic time (CIT) of 16 hours. The second recipient was 44 years old and received the right kidney (15cms) with CIT of 22 hours. Renal function: Both recipients developed immediate graft function. At 6 months recipient 1 maintained a serum creatinine of 176µmol with a eGFR of 38, while recipient 2 became dialysis dependant at 4 month after a biopsy proven episode of graft pyelonephritis.

Conclusion: The data presented and available literatures support the option of using deceased polycystic kidneys from young donors with normal renal function at time of retrieval. The organs transplanted may yield adequate renal function and should be considered as part of the ECD donor pool.

P164

Deceased donor urinary kim-1 as an adjunct to predict outcome from organ donation

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Introduction: We studied whether urinary biomarkers had the ability to help predict which donated kidneys had already sustained damage that would impact on graft function within the recipient.

Methods: Urine samples from 182 cardiac donors were analysed retrospectively using a panel of biomarkers to identify urinary analytes with the ability to inform on post-transplant outcome. Levels, determined by an in-house multiplexed microsphere platform, were correlated to the outcome of the renal transplant. The most promising biomarker was also analysed using a point-of-care lateral flow device (LFD) (Renastick™). Renal transplant outcomes were: undamaged donors (both transplanted kidneys showing immediate function (n=133)), or damaged donors (both grafts showing delayed graft function (n=32) or one of the transplanted kidneys showing non-function (n=17)).

Results: Analysis demonstrated KIM-1 levels were statistically different between the damaged and undamaged donors (p=0.011). These findings were then confirmed using a Lateral Flow Device Assay (Renastick™) demonstrating mean urinary KIM-1 in the no damage group 6.1ng/ml and in the damage group of 8.0ng/ml (p=0.03) with an AUC of 0.63. Binary logistic regression was undertaken using those factors that were statistically different between the damage and no damage groups (age, creatinine and history of hypertension) and demonstrated that KIM-1 level outperformed creatinine in terms of identifying those donors defined as damaged.

Conclusions: Levels of KIM-1, as assessed by two different assays, were significantly different between the two groups of donors. Following regression analysis KIM-1 may outperform creatinine in determining damaged deceased donors which may allow better optimisation and lead to overall better organ outcomes.

P165

Should we transplant kidneys from very old DCD donors?

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Introduction: Kidney transplantation from elderly donors is still a very controversial topic. In recent years, we have seen an increase in the number of elderly DCD donors. From all DCD donors in the UK, 35% were older than 60 in 2011.

This reality has had an impact on our practice in Cardiff. Nowadays, we routinely transplant kidneys from elderly DCD donors aged far beyond 70. Therefore we analysed the effect of donor age on the graft function and graft/patient survival.

Method: Between 1/Jan/2010 and 22/Oct/2012 we transplanted 69 kidneys from DCD donor older than 60 years [44 transplants from donors age 60-69 years (≥60); and 25 transplants from donors more than 70 years old (≥70)]. We compared early outcomes between these two groups.

Results: The average donor age in ≥60 group was 65.27±2.88 (mean; SD) and 73.77±2.22 (mean; SD) in ≥70 group. There was no difference in recipient age (62.7±8.3 vs. 63.9±7.8, p=0.58), donor creatinine (69.5±20.9 vs. 65.8±11.1, p=0.41) and CIT (12.4±4.4 vs. 13.5±5.1, p=0.38); between ≥60 and ≥70. We found no difference in incidence of functional DGF, between ≥60 and ≥70 group (84 % vs. 72 %, p=0.23). Also, the glomerular filtration rate after one, three, six, twelve and 24 months was not statistically different between these two groups (≥60 vs. ≥70); 1-month 29.3±13.5 vs.33.7±10.3 p=0.16; 3-months 32.6±12.1 vs. 37.4±10.8, p=0.12; 6-months 36.1±11.9 vs. 37.6±11.0, p=0.64; 1-year 36.2±9.9 vs. 35.6±12.3, p=0.853; 2-years 31.2±7.7 vs. 38.4±19.2, p=0.25). Furthermore, there was similar graft survival in 1 and 2 years.

Conclusion: The results of our study showed that early outcomes of kidney transplantation from ≥70 DCD donors yielded satisfactory results comparable to kidney transplantation from DCD donors in their 60s. This fact encourages us to increase the kidney transplantation from elderly DCD donors.

P166

Early outcomes of dual cadaveric renal transplantation using clinical acceptance criteria

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Introduction: The shortage of organs available for transplantation and rapid increase in the waiting lists has led to alternate strategies to expand the donor pool. Transplantation of two marginal kidneys into a single recipient (dual renal transplant) can increase organ utilization.

The aim of this study was to evaluate the early outcomes of dual renal transplants in our institution with a view of expanding the acceptance criteria for marginal donors.

Methods: We retrospectively reviewed the data on all recipients who had cadaveric dual renal transplants from February 2011 to October 2012. A total of 13 transplants were carried out, with 11 from DCD donors and 2 from DBD donors. Data included donor/recipient demographics and co-morbidities, graft and implantation variables, DGF and current serum creatinine as the outcome end points. The selection criteria were based on the institutional guidelines, which include donors less than 75 years with multiple co morbidities, an eGFR between 40 and 60, cold ischaemic time (CIT) less than 24hours and primary warm ischaemic time less than 40 minutes. The donor and recipient were roughly age-matched to avoid placing marginal kidneys into young recipients.

Results: 11/13 pairs of kidneys were declined by 2 or more centres. The follow up period ranged from 2 weeks to 18 months. The mean CIT was 12.43 hours for the first kidney and 14.44 hours for the second kidney. 46% experienced delayed graft function but became dialysis independent between 4 and 56 days after transplantation. There has been 1 graft failure due to focal segmental glomerular sclerosis (FSGS). There is a 100% patient survival and 92% graft survival where 12/13 grafts still functioning. The mean 3 months serum creatinine is 180.5 µmol/l. 1 year results are not available yet.

Conclusion: We conclude that transplanting two marginal kidneys, otherwise destined to be discarded is an appropriate option for selected recipients. When donors are considered unsuitable as single kidney donors, dual kidney transplant should be cautiously considered. Previous authors have suggested using pre-implant histology scores to guide decision making, but this data demonstrates that clinical criteria may be sufficient.

P167

The impact of national sharing of DCD kidneys on transplant outcomes

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Background: DCD kidneys represent an increasing proportion of transplant activity. There have been concerns that wider sharing of these kidneys increases the cold ischaemic time (CIT) and leads to poorer outcomes.

Methods: DCD kidney transplantation was introduced in Scotland in 2005, each centre transplanting both locally donated DCD kidneys. A national sharing scheme of DCD kidneys has been introduced in 2007, sharing kidneys between the two renal transplant centres. A single multi-organ team provides the retrieval service and kidneys are shipped directly to the two units. Donor and recipient demographic data, CIT and outcome data have been prospectively collected. Outcome and CIT were compared within each centre and between centres pre-and post-introduction of the sharing policy.

Results: 152 DCD kidney transplants have been performed in Scotland between February 2005 and January 2012. 68 kidneys were shared as pairs since 2007. Recipient demographics were comparable before and after the introduction of sharing. The CIT was significantly higher in Glasgow (14.30±3.79 hours) compared with Edinburgh (10.72±2.99 hours), ($p < 0.001$, ANOVA) prior to the introduction of the sharing scheme. Following the implementation of kidney sharing, the CIT in Glasgow and Edinburgh has been comparable (10.50±3.34 vs.10.53±2.71 hours). Furthermore, a significant reduction in the CIT in Glasgow, from 14.30±3.79 hours to 10.50±3.34 hours ($p < 0.001$, ANOVA) was noted after sharing was instituted. Patient and graft survival, delayed graft function and incidence of acute rejection were not significantly affected by the sharing scheme and were comparable between centres. One-year creatinine was comparable between Glasgow and Edinburgh and was unaffected by national sharing.

Conclusion: Wider sharing of DCD kidneys should be encouraged as it does not compromise clinical outcomes. Furthermore, a transparent and well established sharing agreement, with no delays in the offering of DCD kidneys, has shown an improvement in cold ischaemic time in one of the centres.

P168

First evaluation of a novel 'traffic light' scoring for deceased donor kidney offer acceptance

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Introduction: Deceased donor kidney offers are accepted by consultant nephrologists/surgeons on-call with some inter-individual variability in the type of offers accepted or rejected. To improve the consistency of organ offer acceptance, a 'traffic light' scoring system was introduced. We present the one year analysis.

Methods: A literature review investigating donor factors influencing graft survival informed the creation of a scoring protocol. Through NHSBT we actively contacted Renal units that accepted kidneys that we have rejected. Presence or absence of relevant donor factors resulted in a 'traffic light' system of scoring: Green (un-conditional acceptance of kidney), Orange (sub-optimal graft function and hence equipoise in offer acceptance) and red (mainly for un-conditional refusal). We audited all the kidney offers from August 2011 to July 2012 and their outcome (accepted by us / elsewhere). Outcomes of interest were patient & graft survival, & graft function at 3 months post transplant.

Results: The table below shows the graft function for the kidneys transplanted.

Colour	eGFR	N	
Green	61.5	19	P for trend
Orange	45.7	65 (37 in our unit + 28 elsewhere)	<0.00001
Red	29.5	22	

During the study period, 57 kidneys (19 Green, 37 orange) were accepted for transplantation in our unit. Other units across UK transplanted 24 (out of 41) orange and 19 (out of 26) red deceased donor kidneys turned down by our unit.

Conclusions: The 'traffic light' scoring model appropriately risk stratified outcome in terms of graft function at 3 months. To a significant extent, kidneys classified as 'red' on our scoring system were also turned down by other transplanting units. Further modification of the scoring system in the light of the above findings may help strike the appropriate balance between achieving acceptable transplant outcomes and maximising transplant activity in the unit.

P169

Short-term graft function and allograft survival is not affected by Kidneys from DCD donors more than 70 years

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Royal Liverpool University Hospital, Liverpool, UK

Aim: DCD donors more than 70 years are now not uncommon. Liverpool was amongst the first UK centres to liberally accept donor offers more than 70 years.

Method: We performed a retrospective analysis of all DCD recipients between Jan 2009 and Aug 2012 receiving kidneys from donors >70 years. We analysed outcomes for donor age as measured by delayed graft function and creatinine clearance and incidence of graft failure.

Results: 121 DCD transplants took place since 2009, 17/128 were kidneys from donors >70 years. Median donor age in this sub-group was 76.6 years (70-83), Median recipient age was 63 years (36-76). Median CIT was 13.5 ± 1.89 hrs. (10-19). Prior to year 2010 induction immunosuppression was simulect and post 2010 campath was given as unit policy. All recipients received maintence immunosuppression as FK506 and MMF. 3/17 received steroid in addition. Only one patient had > 10% PRA, rest were non-sensitized. The donors were age matched only if mis-match was equivalent. 58% recipients were > 60 years and 30% recipients were >70 years. The Mean Creatinine Clearance in >70 year DCD donor kidneys at 1, 6 and 12 months was comparable to the standard DCD recipients. The actuarial allograft survival rate at year 1, 2 and 3 were 95%, 89%, 83%, the death censored graft survival rate at year 1, 2 and 3 were 100%, 100% and 94%. The rejection free graft survival rate in first year in simulect group was 86% compared to 91% in campath group (p=0.7). CIT was correlated to creatinine clearance at 1 month (p=0.02). Recipients >70 years had similar outcomes compared to Recipients <70 years. There was no evidence of increased graft failure in our experience.

Conclusions: Nearly 14% of our DCD donors were >70 years. There were excellent short-term outcomes in our study.

P170

Outcomes of super-expanded criteria deceased donor renal transplantation

Kerem Atalar, Jonathon Olsburgh, Chris Callaghan, Georgios Vrakas, Nizam Mamode, Martin Drage, Francis Calder, Rajinder Singh, John Taylor, Geoff Koffman, Nicos Kessaris

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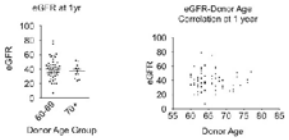
Introduction: Expanded criteria deceased donor (ECD) renal transplantation has been established as a framework to increase the donor pool. ECD donors are donors aged over 60 and donors aged 50-59 with two of the following comorbidities: hypertension. death from cerebrovascular cause or terminal serum creatinine >1.5mg/dL (132 µmol/L). At our centre, we recently expanded our use of organs from deceased donors aged 70 years and over. Data are limited for outcomes from these donors. We analysed recipient outcomes for these donors, which we refer to as super-Expanded Criteria Donors (sECD), compared with donors aged 60-69 (here referred to as ECD).

Methods: Data for renal transplants from deceased donors aged 60 and above at our centre (January 2006 to December 2011) were collected. Recipients of pancreas transplants were excluded. Outcomes were: graft loss; eGFR (4 variable MDRD); and creatinine at 1 and 3 years.

Results: 69 patients were included; 13 (19%) received kidneys from sECD. 2 sECD recipients (15%) had graft loss at 1yr compared with 5 (8.9%) ECD recipients. Median eGFR (ml/min/1.73 m^2) at 1 year was: ECD 39; sECD 37; and at 3 years was: ECD 38; sECD 36 (both not significant, p=0.52 and 0.85 respectively, Mann Whitney U test). Spearman rank correlation revealed no significant correlation between donor age and eGFR at 1 or 3 years.

Conclusion: The data show no significant difference for sECD donors compared to ECD donors at our centre and no significant correlation between donor age and eGFR in this cohort. These data are encouraging for our sECD program.



P171

Solid organ donation from paediatric donors less than 2 years of age: an under-referred and under-utilised source for deceased organ donation in the United Kingdom

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Introduction: Paediatric organ donation in general and those under two years of age, including neonatal donors (less than 1 month) remain an under-utilised resource for organ donation. There is a lack of consensus and often a degree of reluctance among transplant community in using certain organs from these young paediatric donors. We report the referral, donation and subsequent utilization of organs from these donors.

Methods: A retrospective review of NHSBT data from January 2001 till December 2010 was undertaken. All paediatric donor referrals under the age of 2 years were included in the review. Data collected for the entire pathway from referral to utlisation/discard of organs procured from these donors. All continuous variables are expressed as mean ±SD and percentages.

Results: During the study period (10 years, from January 2001 to December 2010) 34 paediatric donors less than 2 years of age were referred for donation (median 3 per year, range 0-8). These included 26 DBD and 8 DCD donors. 27 consented and proceeded to donation (22 DBD and 5 DCD). Maximum donation referral was seen in year 2010 where 8 potential donors were referred but the maximum donation occurred in 2004 where 5out of 7 potential donors proceeded to donate at least 1 solid organ per donor. No donor referrals were made in the years 2006 & 2007. Of 27 donors that proceeded to donation 68 solid organs were procured (10 hearts, 25 livers, 30 kidneys and 3 pancreas) and 62 were used (10 hearts, 21 livers, 28 kidneys, 3 pancreas). Procurement and utilisation rate was the best for livers (21/27) followed by kidney (28 /54, resulting in 14 en-bloc renal transplant) and heart (10/27). Pancreas was the least utilised organ (3/27).

Conclusion: Paediatric donors less than 2 years of age seem to be under-referred for solid organ donation. Utlisation of organs from those donors proceeding to donation remains sub-optimal. Paediatric donation in general and those under 2 years of age remain an under-referred and underutilized resource for organ donation in the United Kingdom.

P172

Outcomes of kidney transplants from DCD donors declined by the primary regional centre

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Introduction: The expansion in donation after circulatory death (DCD) kidney transplantation has raised questions regarding donor suitability, particularly relating to the evaluation and use of kidneys from elderly donors. Although national sharing was not obligatory initially, an NHSBT policy change in 2009 advised national offering of DCD kidneys refused by the regional centre. Here we report our experience using DCD kidneys declined by other centres.

Methods: A retrospective review of all DCD kidney offers to our centre from April 2008 to March 2012 was performed. Donor characteristics, reasons for non-acceptance by regional centre and graft outcomes for those transplanted (primary non-function (PNF), delayed graft function (DGF), 1 year estimated GFR and graft survival [censored for death with functioning graft]) were analysed.

Results: 343 DCD kidneys were offered from outside our region. We accepted 104 (30%) kidneys, which had been declined by the primary centre for reasons including: donor age, past medical history and logistical problems. Of these, we subsequently declined 51 (49%) for reasons including: failure to reach asystole in the donor, damage and evidence of significant chronic baseline disease. The median (range) donor age was 58 (1-77) years. Two deaths were trauma-related. Median (range) terminal donor creatinine was 88 (26-191). Despite transit (median [range] distance: 93.2 miles [58.9-166.8]), acceptable cold ischaemic times were achieved (median; range: 17h28m; 6h 46m – 24h 21m). Both kidneys from 5 donors were implanted into single recipients. There were 2 cases of PNF and 2 cases of early graft loss due to vascular complications. DGF occurred in 29 cases (60%). Estimated median (range) GFR at 1 year was 41 (6->60). Three deaths occurred during follow up, all from sepsis. Graft survival at 1 year was 94%.

Conclusions: Our results demonstrate acceptable outcomes for kidneys accepted from outside our region, despite further transit distance. We suggest that there is potential for widening the donor pool and reducing discard rates by using a national sharing scheme for DCD kidneys.

P173

A comparative analysis of short and long term outcomes of kidney transplants from different donor pools: a single centre experience

Rajinder Singh, Francis Calder, Nizam Mamode, Nicos Kessaris, Jonathan Olsburgh, Christopher Callaghan, John Taylor, Martin Drage, Sara Hayek, Kerem Atalar, Fred Compton, Sadia Anam, Mariam Aqueel, Rachel Hilton, Geoff Koffman

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Introduction: The purpose of our study was to evaluate the short and long-term comparative outcomes of kidney transplants from DCD (donation after circulatory death), DBD (donation after brain death) and LD (living donor) kidney transplants (KTx) performed at our single centre.

Methods: During the period from 01/1989 to 07/2012, a total of 2995 adult KTx were performed at our single centre. Follow-up data were available on 2427 patients, and these comprised of 230 DCD, 2197 DBD and 866 LD KTs.

Results: Comparison of donor, recipient and transplant characteristics showed that the mean donor age was significantly greater in the LD group (45 yrs) compared to the other 2 groups (42 yrs), whereas mean recipient age was significantly greater in the DCD group (50 yrs vs. 44 yrs in the other 2 groups). Cold ischaemia time was significantly shorter in the LD group (2.6 hours), compared DCD and DBD KTx (16 and 18 hrs respectively), all $P<0.05$). There were significantly greater number of female donors in the LD group (56%) compared to the DD (deceased donor) group (44%), whereas the recipient gender distribution was similar. There were significantly lower proportion of black recipients in the LD group (6.4%) compared to 15% in the DD group. The proportion of retransplants (30%) was similar in the 3 donor groups. The use of mycophenolate mofetil and tacrolimus was significantly greater, and of azathioprine was significantly lower in the LD group compared to the DD groups. Comparison of the kaplan meier actuarial total (uncensored) kidney allograft survival showed no significant differences between the DCD, DBD and LD KTs during 1, 5, 10 and 20 yrs post transplant (95%, 89%, 77% and 51% for DCD vs. 92%, 88%, 75% and 44% for DBD vs. 99%, 94%, 85% and 44% for LD KTx respectively). Actuarial patient survival analysis during the same periods showed that there was no significant difference between the DCD and DBD kidney transplants during 1, 5, 10 and 20 yrs post transplant (94%, 88%, 72% and 48% for NHB vs. 95%, 86%, 72% and 42% for DBD KTs), whereas LD group had significantly improved patient survival (98%, 91%, 84% and 69% respectively) compared to the 2 deceased donor (DD) groups. The rates of 1st year biopsy proven acute cellular (11%, 6% & 2%) as well as vascular rejections (5%, 3% & 1% respectively) were significantly greater in the DBD compared to DCD and LD groups respectively. The rates of delayed graft function were significantly greater in the DCD compared to the DBD and LD groups.

Conclusion: The intermediate and long-term patient survival of DCD and DBD KTx are similar to each other but inferior to that of LD KTxs. The long-term total kidney graft survival rates are similar in the 3 donor groups.

Poster session

Wednesday 13th March

18:15 - 19:25

Miscellaneous

P174

Understanding medical students' views on organ donation and transplantation: a cross sectional survey

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Background: The UK's organ donation system is currently under scrutiny. Changes to increase donation rates and streamline the donation process have been proposed, potentially posing ethical dilemmas to individual clinicians and society in general. Undergraduate medical students, "tomorrow's doctors", may be required to implement such changes.

Methods: We performed a cross-sectional questionnaire study of undergraduate medical students (of all stages) at the School of Medicine, University of Glasgow. We have, thus far, received 185 responses with a completion rate of 88.6%. We present an interim analysis of these responses.

Results: 98.2% of students agree with solid organ donation, yet only 82.8% have signed up to the donor register. 98.2% of students understand that there is a relative deficit of organ donors. A number of proposed changes were supported by a majority of students: opt-out system (78.4%); compensation for loss of earnings or other expenses incurred by live donor nephrectomy (70.8%); uncontrolled donation by non-heart-beating donors (64.3%); elective ventilation (59.1%); aggressive ITU donor management (55.0%). Informed donor consent was a recurring theme in free text comments and categorisation of these points may increase these majorities. A majority of students also expressed disagreement with: financial remuneration (in excess of expenses) for live donor-nephrectomy (79.5%); prioritisation of individuals already on the organ donor register (69.0%); and financial incentivisation of staff involved in the donation-transplantation process (62.0%).

Conclusions: Early data suggest that medical students support a range of measures to increase donation rates but this is tempered by a clear demarcation of boundaries to maintain an ethical regulatory framework.

P175

Paediatric live solid organ donors: yes or no?

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Introduction: Solid organ transplantation is the treatment of choice for a variety of diseases in children and adults. The major limitation in transplantation remains the availability of organs from suitable donors and the system is becoming increasingly reliant on living donors. The generosity of living donors is heavily dependent upon trust that the systems in place are fair, just and ethical. The ethical complexities of living donation are made more so by the controversial discussion of children as potential living organ donors. The key ethical, legal and practical issues relating to paediatric solid organ donation are discussed here.

Discussion: For a minority of recipients a living donor transplant from a paediatric donor may provide the only feasible opportunity for transplantation. Circumstances may include the recipient's blood group or sensitisation; both reducing the chances of receiving a kidney from the deceased donor pool. Paediatric donation is most advantageous within the context of sibling kidney donation where the tissue type match is of significant benefit to the recipient. For the donor, the "best interests" argument is most commonly referred to whereby the likely deterioration and/or death of the recipient would result in a significant detrimental effect on the child. In spite of the potential benefits of paediatric living donation to both parties, minors who are being considered as potential donors are likely to be very emotionally vulnerable and potential risk of harm is extremely high. Psychosocially, cases will be complex with possibly complicated family dynamics. The consequences in the event of making an erroneous decision are significant. Due to the limitations in previous experience and available data, an international consensus is essential to assist in the management of such cases and should be agreed as a matter of urgency.

P176

Vitamin D supplementation with monthly bolus oral cholecalciferol is both safe and effective in Vitamin D deficient renal transplant patients.

Antos O'Rourke-Potocki, Nathan Gauge, Hugo Penny, Antonia Cronin, Sharon Frame, David Goldsmith

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Background: Vitamin D insufficiency (> 25 < 50 nmol/L) and deficiency (< 25 nmol/L) are common in stable ambulant renal transplant patients (RTx).This has been associated with adverse skeletal, renal, cardiovascular and cancer outcomes in this population, but a formal repletion RCT with hard end-points has never been completed. We undertook vitamin D repletion using oral Dekristol ™ chole-calciferol in a group of long-term renal transplant survivors, all of whom had demonstrated sustained vitamin D deficiency, to assess both efficacy and safety of this intervention.

Methods: Out of 360 long-term RTx patients we found 57 subjects with sustained low (< 25 nmol/L) serum vitamin D concentrations, and either or both of raised PTH or bone/muscle pain. We prescribed all of these patients 40,000 IU Dekristol ™ cholecalciferol for 6 months (total dose 240,000 IU) and then interrogated the biochemical changes in plasma vitamin D, PTH, alkaline phosphatase, calcium, phosphate and creatinine (eGFR) over the course of the repletion period.

Results: Three patients did not complete the course of vitamin D repletion (two died from unrelated causes, and one developed cancer necessitating major surgery). This left 54 completed (per protocol) repletion courses to examine for efficacy and safety outcomes. Mean age 54 +/- 17 years. Mean time post -transplantation 14.4+/- 3.5 years. Mean eGFR (at start) 58+/-9 mls/min.

Conclusions: All 54 patients completed their repletion course. In all cases plasma vitamin D concentrations rose to > 25 mmol/L and in 80% to > 50 nmol/L. Two patients experienced a > 20% rise in plasma creatinine (biopsy proven rejection in both cases). Rremaining patients had a < 10% change in plasma creatinine. Only 5 patients experienced a plasma calcium concentration of > 2.60 mmol/L and in no case was it necessary to discontinue vitamin D treatment. The fall in plasma PTH concentration was significant (138 to 106 pg/mL; $p < 0.05$). Monthly bolus oral cholecalciferol seems a safe and effective means by which to render RTx patients vitamin D replete.

P177

Seasonal variations in plasma vitamin D concentrations, and vitamin D status, are functionally relevant to renal transplant patients' health status

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Background: Vitamin D insufficiency (> 25 < 50 nmol/L) and deficiency (< 25 nmol/L) are common in stable ambulant renal transplant patients (RTx) in the UK. This has been associated with adverse skeletal, renal, cardiovascular and cancer outcomes in this population, but a formal repletion RCT with hard end-points has never been completed. We recently described a significant seasonal variability in plasma vitamin D concentrations in this RTx population (1), despite the strongly re-enforced proscription of sun (UV-radiation) exposure without ensuring adequate skin sunblock application. We wanted to confirm these findings in a much larger population sample, and also see if there was any functional (skeletal/renal) consequence of this vitamin D variability.

Methods: Results from all blood samples drawn from outpatient-attending RTx patients sent for vitamin D measurements (2010-2012) wer analysed. Any plasma PTH, calcium, phosphate and alkaline phosphatase values which coincided with the vitamin D estimations were also retrieved. Note was made of any vitamin D supplementation. Paramater seasonality was examined in four discrete three-month periods. T-test, ANOVA, Spearman correlations.

Results: 856 vitamin D values from 449 patients (age mean 53, median 55, IQR 44-65, range 18-89 years) were located. There were 660 PTH, 801 Calcium, 812 Phosphate, 825 eGFR , 827 ALP, 531 urine creatinine 531, and 408 urine protein values.Seasonality was shown for vitamin D, PTH and urinary protein.

Conclusions: A highly significant seasonal variation in plasma vitamin D concentration was seen with highest values in the summer (20.6% sufficiency) and lowest in the winter (8.2% sufficiency). The opposite pattern was seen for plasma PTH concentrations: lowest in the summer in counterpoise to vitamin D. Urinary protein loss (irrespective of the use of ACE/ARB) was also reciprocally variable in relation to vitamin D concentrations (lowest urinary protein loss in the summer with the highest vitamin D concentrations). This makes a good case for fluctuations in vitamin D status being physiologically relevant in RTx patients.

P178

Visualising rejection: characteristics of abdominal wall rejection after combined intestinal and abdominal wall transplantation

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Aim: To report our experience of post-transplantation abdominal wall rejection.

Method: A retrospective case notes analysis was performed of all patients undergoing combined intestinal and abdominal wall transplant in our centre. We documented cause of intestinal failure, pre-transplant abdominal wall quality, operative method and immunosupression regime. Visual and histological characteristics of rejection along with method of treatment were recorded.

Results: Three patients underwent an isolated intestine with abdominal wall transplant from the same donor. Causes of intestinal failure were radiation enteritis, ischaemic colitis and necrotising enterocolitis respectively. All 3 patients had reduced abdominal domain size with low quality overlying skin. Two doses of Alemtuzumab (Campath) were given intravenously (IV) at induction and 24 hours later. Maintenance was with Tacrolimus (Prograf). At post-transplant day (PTD) 60 and 68 respectively, 2 patients presented with a peri-follicular, micro-papular pink rash limited to the abdominal wall graft, preceded by neutropaenia. Histology revealed grade II-III rejection in each case. Neither patient had evidence of rejection in the transplanted bowel. Treatment was with a single dose of 20mg Basiliximab IV, 500mg pulsed methylprednisolone IV for 3 days, and Tacrolimus ointment plus low dose azathioprine added to the maintenance regime. At a median follow-up of 6 months, both patients with rejection are alive and well. The third patient died from sepsis at PTD 62 with a functioning abdominal wall graft.

Conclusion: The highly antigenic nature of skin means rejection of the abdominal wall is expected, with a high-risk period around PTD 60. Basiliximab combined with methylprednisolone was effective in treating the acute rejection. Abdominal wall grafts appear to reject whilst underlying bowel remains healthy. Further studies with larger numbers will determine if skin is a herald of intestinal rejection.

P179

Mesenchymal stromal cells promote bowel regeneration after intestinal transplantation: myth to mucosa

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[1]The Oxford Transplant Centre, Churchill Hospital, Oxford, UK, [2]Department of Medicine, Imperial College London, London, UK, [3]Department of Cellular Pathology, John Radcliffe Hospital, Oxford, UK

Introduction: Mesenchymal stromal cells (MSCs) are a heterogeneous group of cells that have the ability to differentiate to many mesodermal lineages. They possess the dual properties of tissue repair and immunomodulation. We report the first case of use of MSCs to promote mucosal regeneration in an isolated intestinal transplant recipient who had significant bowel dysfunction following Candida and Noroviral infection.

Methods: Fresh MSCs were obtained from a bone marrow donor and one-million cells/kg were infused via a central vein over a period of 15 minutes. Clinical parameters including stoma output and serum citrulline levels were recorded pre- and post- administration of MSCs. Endoscopic imaging of the transplant graft was performed before and after MSC transplantation and histological findings were compared.

Results: Prior to administration of MSCs, stoma output was measured at 40mls/kg/24hours. The patient was receiving total parenteral nutrition (TPN) and showed no evidence of absorption of immunosuppressive drugs. Effluent and histology from the stoma showed Candida and Noroviral infection with loss of absorptive surface epithelium. Serum citrulline levels ranged between 5-9micromol/l. Infusion of MSCs was well tolerated with no immediate or late side effects. At 4 days following MSC infusion, the patient's GI output decreased to 25mls/kg/24hours and her serum citrulline increased to 15.4micromol/l. An endoscopy performed 11 days post- administration of the cells demonstrated marked macroscopic improvement with rudimentary villi. The histological findings demonstrated significant regeneration of epithelium, villi and lamina propria. Enteral feeding was recommenced with improvement in nutritional parameters. At 30 days following administration, the patient continued to have reduced GI output and was clinically well with a serum citrulline level of 45micromol/l.

Conclusion: We have demonstrated that MSC therapy in the setting of inflammation from Candida and Noroviral infection was effective in triggering a regenerative process. It was well tolerated and early results are promising.

P180

Evolution of transplantation in the UK seen through the eyes of the British transplantation society - a 15 year review

Omar Masood[1], Hitesh Khanna[2], Alexander Lomax[2], Hani Riad[1], Afshin Tavakoli[1]

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

Introduction: The British Transplant Society (BTS) is the professional voice of transplantation in the UK, representing all the varied disciplines in transplantation. Furthermore, the annual meeting is widely regarded as the forum to discuss topical issues faced by the transplant community. It has both documented the progression of transplants since 1972 as well as led to the development of nationally accepted guidelines for clinical practice. The past two decades has revealed significant changes in the field of transplantation in the UK and this review aims to assess if the last 15 years of the BTS annual meetings reflect these changes.

Aim and method: To help illustrate the key changes a review of the last 15 years of abstracts presented at the Annual British Transplant Society (BTS) Congress was carried out. A total of 2439 abstracts, presented between 1997 and 2012 were reviewed by 2 investigators. A simple method was designed to separate each abstract to organ and further sub-classified into the following categories: human or animal, organ rejection / immunological, pharmacological, ethical issues, organ procurement / donor process and outcomes. This data set was analysed to provide a trend, comparing mean data at five year intervals (MD1, MD2, MD3) for the percentage component from each category over time. Further more the evolution in the organisation (members of the Executive, Council and Committees) as well as the quality and the source of the study abstracts were analysed.

Results: Total abstracts (TA) was 2439 (MD1 96, MD3 217.8, trend revealed 227.9% increase in the number of abstracts ($p<0.0001$)). Kidney was the most prominent featured organ at 53.22% (TA 1298), followed by liver 10.13% (247), pancreas 6.03% (147) with the lowest proportion: intestine 0.49% (12). Heart: 3.98% (TA 97; MD1 6.4%; MD3 3.2%), a 50% decreasing trend was seen ($p<0.01$). Lung: 1.15% (TA 28; MD1 3.6%, MD3 0.88%), which showed a 409% decline ($p<0.001$), Kidney subcategories analysis revealed: Outcome (28.27%, TA 367), Donor/Recipient process (21.96%, TA 285), Pharmacology (18.18%, TA 236). However, Ethical issues 10.63% (TA 138, MD1 3.87%, MD3 12.11%), a 313% increase ($p<0.0001$).

Summary: With regards to individual organs; studies relating to kidney remain the most prevalent. Deeper analysis of the trends reveals that the largest individual components have become studies pertaining to the donor process and logistical issues involved. This may reflect that the need to improve organ availability has emerged as the area of most topical interest. The proportion of abstracts regarding heart and lung transplantation has dropped significantly, which may reflect either the abstract submission or acceptance rate.

P181

Should children with methylmalonic acidaemia undergo isolated renal transplantation?

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Introduction: Children with methylmalonic acidaemia (MMA) develop progressive renal impairment and neurological dysfunction. No specific therapy is available. Several case reports suggest that isolated kidney transplantation (iKT) improves metabolic control though does not prevent further neurological deterioration. However, other series have reported high mortality rates with iKT, isolated liver and combined liver-kidney transplantation

Methods: Supraregional centre experience of iKT (2 live donor) in 5 boys (median age 10.8 yrs) with stage 5 CKD secondary to MMA between 2008 and 2011.

Results: Four received antiCD25/tacrolimus/MMF with rapid steroid withdrawal and one tacrolimus/azathioprine/steroids. There were no instances of immediate metabolic decompensation or perioperative complications. One developed severe haemorrhagic pancreatitis on day 5 and died with a functioning graft due to septicaemia on day 48. Another developed bacterial endocarditis at 2 months and had gradual deterioration of graft function (GFR 11ml/min/1.73m^2 at 12 months). He developed pancreatitis at 13 months and then became dialysis dependent and had further neurological deterioration. At parental request care was withdrawn. The remaining 3 children remain well with reduced requirement for electrolyte and bicarbonate supplements and a reduction in hospital admissions 12-54 months following iKT. Plasma MMA levels were lower following iKT. Allograft biopsy performed in 3 children showed tubulointerstitial inflammation (TI) consistent with MMA; this was unresponsive to pulse steroids.

Discussion: In this, the largest series of iKT in MMA, whilst some children with MMA achieved better metabolic control following iKT, the procedure was associated with a high risk of mortality, often due to pancreatitis. Monitoring graft function is difficult as plasma creatinine is a poor marker of renal function and on biopsy acute rejection is difficult to distinguish from MMA induced TI. Parents of children with CKD secondary to MMA remain keen for transplantation to be performed, though opinion amongst healthcare professionals remains divided.

P182

Assessing the relationship between future renal allograft survival, cost and the transplant waiting list in the UK

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Introduction: The UK has an ageing and growing population and the prevalence of renal replacement therapy (RRT) has grown by 5.0% annually since 2000. RRT accounts for over 2% of the current NHS expenditure. Transplantation increases survival, improves quality of life and maintenance costs are less than dialysis. Despite increasing rates of transplantation, an estimated 7,000 patients remain on the waiting list. The objective of this study was to quantify the relationship between graft survival time, total estimated cost and the number of projected patients on the transplant waiting list.

Methods: We utilised a population based simulation model with published disease progression, incidence and prevalence parameters specific to the UK. We evaluated the number of years of functioning graft required for transplantation to remain cost saving compared to dialysis; the number of future transplants or improvement in graft survival required to avoid the transplant waiting list increasing. The study utilised UK costs and both future costs and benefits were discounted at 3.5%

Results: Over a 10-year projected time horizon the total per-patient cost saving associated with remaining on dialysis compared to transplant was £276,330; however, a cost saving was conditional upon achieving at least 3-years of functioning graft. In order to maintain the transplant waiting list at approximately 7,000, the number of annual transplants conducted would need to increase from 2,645 in 2010 to 3,640 by 2022 (a 37.6 % increase). At current activity levels the transplant waiting list is projected to increase by approximately 1,983; improvement in graft survival could potentially reduce this by 941.

Discussion: For kidney transplantation to be cost saving recipients must maintain at least 3 years of functioning graft. As early graft failure also impacts on future transplant waiting time, management strategies that maximize graft survival will reduce costs and improve service delivery targets.

P183

Student exposure to transplantation surgery; an analysis and action

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Introduction: Awareness of transplantation, as a treatment option, is an important part of medical training. We noted a knowledge gap existed amongst medical students and endeavoured to investigate and rectify this discrepancy.

Methods: An online questionnaire was sent to all final year medical students at our institution to establish awareness and attitudes towards transplantation. To raise awareness we designed and ran a session for first year medical students incorporating with their early clinical exposure programme that coincided with National Renal Day. We focused on the clinical, psychological, ethical and holistic impact of transplantation. Participants included an expert renal patient, renal psychologist, general practitioner and transplant surgeon. In addition exerts from a TV documentary, "transplant", were screened. We evaluated the session with questionnaires immediately after and subsequent focus groups eight months after the event to look at longer term impact.

Results: We received 161 complete responses to the final year questionnaire. Only 15% had seen a renal transplant, 30% had had exposure or would get exposure to transplantation by the end of their final year. Of those interested in a surgical career only 20% had had exposure to transplantation. 80% stated they would have been interested in exposure to the speciality. After the education session 330 feedback forms were completed these showed greatly increased awareness of the difficulties of renal failure and the positive effect of transplantation (95%). The focus groups (n=24) were analysed thematically and showed an awareness in particular of the effects of renal failure and transplantation, suggesting good retention and impact.

Conclusions: The results of our survey suggest a low exposure to renal transplantation in our institution by the final year. Whilst clearly not all medical students, including those with a surgical intent, will be aiming for a career in transplantation, an awareness of transplantation as a treatment option for renal failure is important. This is not only from the point of view of the surgery, but also in expanding the donor pool. We have attempted to do this by introducing the concept to our first year medical students, in a novel manner, showing not only the impact that renal failure has, but also the positive effects that transplantation and organ donation can have.

P184

An exploration of the psychosocial problems of patients who have received a kidney transplant

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Background: Patients with Chronic Kidney Disease (CKD) report a high degree of symptom burden, a decreased quality of life, and significant levels of psychological distress. Following a kidney transplant some patients experience medical and psychosocial problems. Psychosocial problems can include a high degree of anxiety and depression, adjustment difficulties, and a limited health quality of life (HQOL). NICE guidelines (2011) recommend that all patients with CKD should have access to psychosocial support.

Objectives: 1. Assess whether kidney transplant patients at different stages in their post operative care (< 12 months and > 12 months) have psychosocial difficulties 2. Explore whether the patient group have psychosocial support to manage psychosocial difficulties 3. Explore whether a psychosocial group would help kidney transplant patients manage psychosocial problems.

Method: 108 patients completed a demographic information sheet, the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety Disorder scale (GAD-7), Transplant Effects Questionnaire (TxEQ) and the Kidney Disease and Quality of Life scale (KDQol).

Findings: Males made up 56.5% of the sample, 86.1 % were White British, with a mean age of 50.1 years. Participants concerns included physical health (40.7%), coming to terms with the transplant (17.6%), family difficulties (9.3%) and work (19.4%). Depressive symptoms were common (41.7%), as well as anxiety (32.4%). There was no statistical difference between the groups in terms of their levels of anxiety and depression. All participants reported difficulties with their HQOL. There was no significant difference between the group's levels of worry, guilt, adjustment, disclosure and adherence. Only 57.4% had adequate psychosocial support, 37% said they would attend a psychosocial group. The data supports the view that renal services should provide more targeted psychosocial support to this group.

P185

A single center experience of pregnancy in women with renal transplant

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Introduction: Fertility is usually restored in women with renal transplants. Pregnancy is then common, occurring in 12% of women at childbearing age in one study.

Method: We undertook a retrospective review of pregnancy in women with renal transplant from 2007 to 2011. All patients are cared in a multidisciplinary team involving comprising nephrologists, obstetricians, midwives, dietician and transplant nurses from the antenatal period to delivery and beyond.

Results: There were 5 patients with confirmed pregnancy during this period. Average age of patients was 28.4 years. 3 had live donor and 2 had cadaveric transplants. Average time to pregnancy post transplantation was 24 months (range (25-36) and two patients were on ACE and ARB at time conception which was subsequently stopped. Average creatinine was 118 $\pm$ 30 and proteinuria was 0.28 grams (range 0.6-0.88).

Table below features of 5 patients

	Medication	Renal function (Pre-Pregancy)	Renal function (3 months post pregnancy)	Outcome
1	Tac/Aza	126	102	Miscarriage at 17 weeks
2	Ciclo/Aza	165	155	Birth at 33 weeks
3	Tac/MMF	85	99	Birth at 38 weeks
4	Tac	106	99	Birth at 38 weeks
5	Tac/Pred	108	88	Birth at 33 weeks

Average tacrolimus level was 1st trimester was 6.7, 2nd was 5.1 and 3rd was 3.9. MMF was stopped was replaced with azathioprine. Average booking BP was 131$\pm$10.1 and 3rd trimester BP was 128 $\pm$. There appear to be no reduction in creatinine in at 3 months post pregnancy. Average proteinuria was post 3 months was 0.55 grams. Although, one patient had miscarriage at 17 weeks but she was pregnant again. Average birth weight was 2854 grams.

Conclusion: Pregnancy in transplants is associated better foetal and maternal outcome due to careful monitoring of blood pressure, urine protein, renal function and drug therapy.

Poster session

Wednesday 13th March

18:15 - 19:25

Pancreas & islet 1

P186

Low level pre-transplant dsas are frequent but are not associated with a rejection diagnosis in pancreas transplant biopsies

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Our group has shown previously that pancreas biopsy is safe, has a high diagnostic yield.

Aim: To study what the incidence of Luminex DSA pre and post-transplant is, and their association with rejection in patients biopsied for potential pancreas rejection.

Patients and methods: 37 pancreas biopsies performed were interpreted by a single pathologist. All biopsies were stained for C4d. Recipients had their pretransplant sera investigated for the presence of antibodies to HLA by Luminex LABScreen Mixed. Mixed positive sera were tested by LABScreen Single Antigen for determination of HLA specificity. LABScreen Single Antigen was used to test for DSA during each rejection episode.

Results: 37 biopsies were performed on 26 patients out of the 108 pancreas transplants performed in the centre. 14 biopsies showed ACR whereas 3 biopsies showed AMR (1 mixed). The biopsies that showed no rejection were performed at a median of 321 days post transplant. 9 of those patients (34.6%) had positive pretransplant DSA whereas 13 (50%) had positive DSA at the time of Biopsy. 15.4% had Luminex DSA with MFI over 2000 pre compared to 30.8% at the time of biopsy. These figures compare with our kidney only transplant population pretransplant DSA of 24.8% (p=0.18), out of which 8% had MFI over 2000. There was no difference in the percentage of patients expressing pretransplant DSA between those who had biopsy proven rejection and those that did not (but still had a biopsy). 57% of those with rejection had positive DSA posttransplant compared to 41% of those without rejection. Interestingly rejection was the same or less common in patients with MFI over 2000 at the time of transplant or the time of biopsy compared to those without DSA. Only 1 case out of 3 with AMR had preformed DSA, and although they all expressed DSA at the time of rejection in 1 of them was less than 2000 MFI.

Conclusion: Low-level Luminex DSA pretransplant are common in the pancreas transplant population. They do not seem to be associated with frequency of rejection. A pretransplant DSA MFI level of 2000 in the absence of cytotoxic antibodies does not seem to be associated with more frequent rejection diagnosis at the time of a pancreas Biopsy.

P187

Pancreatic transplantation: revealing trauma in patients with type 1 diabetes

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Background and aims: To date, psychological research on the impact of pancreatic transplantation has lacked direct exploration into patient experiences, rendering it impossible to identify specific issues requiring psychological intervention. This study was undertaken to try to better optimize psychological support for patients post pancreatic transplantation.

Methods: Individual semi-structured interviews with 15 individuals with T1DM (8 women, 7 men). Time since transplantation varied from 7 weeks to 3 years. Interviews were recorded, transcribed verbatim and analysed using inductive thematic analysis.

Results: A variety of themes were identified some of which were related to the experience of traumatic stress. **Transformation** was a major theme associated with many subthemes, for example, **new beginning** described how the transplant enabled a fresh start; while **different person** described how the transformation following transplantation was comprehensive. This latter theme included references to disturbing changes in personality and emotional sensitivity as well significant periods of insomnia and changes in energy levels. The major theme of **Adjustment** described the complexity of life post transplant. **Powerful memories,** one of the subthemes of adjustment, included participants incredibly detailed memories of the morphine dreams and hallucinations they experienced in hospital as well as the strong feelings associated with their memories of uncontrolled, unpredictable hypos prior to transplantation.

Conclusions: The change following transplant is instant and dramatic for most patients, but it does involve negotiating complex changes in identity as well as adjustment in every aspect of life. Some patients may require extra psychological support to address traumatic stress.

P188

Intravenous or subcutaneous octreotide for pancreatic graft fistula?

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Aim: Pancreatic exocrine leaks after pancreas transplantation constitute a major source of morbidity and mortality. We use octreotide as part of a multi-modal strategy to treat pancreatic graft fistulas (PGF). Our aim was to evaluate the use of either high dose (IV) or low dose octreotide (SC) in management of PGF and graft outcome.

Methods: We retrospectively analysed 59 patients (Male 48% mean age 42 range 30-51yrs) who underwent PT in a single centre during a 13 yr period. Patients with and without PGF were compared along with those that received either IV (1200-2400 µgm/24hr) or SC (200-1500 µgm/24hr) octreotide to control their fistula.

Results: 15 patients developed a pancreatic leak (25%). The majority presented with either graft pancreatitis or intra-abdominal sepsis (80%). 8 patients were treated with high-dose and 7 with low-dose octreotide. PGF patients demonstrated a prolonged hospital stay (median PGF 21 days vs. no PGF 13 days, p= 0.04) but demonstrated no difference between those treated with high or low dose octreotide (21 days vs 22 days). Those with leaks had more re-operations (leak 86% vs. no leak 13.6%, p=0.035) however there was no difference between high or low dose octreotide groups (87.5% vs 85.7%). Those with leaks had more radiological interventions (leak 80% vs no leak 18%, p =0.04) but again no obvious difference between high or low dose octreotide groups (75% vs 85%). Furthermore, there was a trend towards lower rates of 1 year graft survival between patients with PGF and those without (73% vs. 82%, p=0.5).

Conclusion: PGF after pancreatic transplantation remains a source of considerable morbidity, prolonging hospital stay and may reduce 1 yr pancreatic graft survival. Treatment with different doses of octreotide does not appear to change the clinical course of a PGF.

P189

Management of an arterial mycotic pseudoaneurysm following simultaneous pancreas and kidney transplantation

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Introduction: Arterial mycotic pseudoaneurysms are rare but potentially catastrophic complication seen following pancreas transplantation with a high risk of mortality. It usually presents with life threatening haemorrhage as a result of rupture into adjacent bowel or bladder but are also rarely incidentally identified. Management is often complicated by the extensive defect in the arterial wall. Vascular techniques using synthetic tube graft or endovascular stents frequently fail due to graft infection whilst primary repair may result in vascular stenosis. We present a case of a simultaneous kidney pancreas (SPK) recipient presenting with catastrophic gastrointestinal bleeding secondary to an ilio-enteric fistula.

Case: A 41 year old male, who had a 38 year history of type 1 diabetes mellitus with associated end stage renal failure, underwent successful SPK transplantation (Donor 48 F; HLA mismatch - 2:1:2; CIT 13hours 57minutes). This resulted in good primary function. He presented, 9 months following transplantation, with copious fresh rectal bleeding secondary to a mycotic pseudoaneurysm located at the anastomosis between the native common iliac artery and Y-iliac conduit to the graft pancreas. This was successfully managed with a bovine pericardial patch repair of the arterial defect and enteric diversion following graft pancreatectomy. He remains well with no vascular insufficiency 12 months following the procedure.

Conclusions: Mycotic pseudoaneurysms following transplantation are a clinical challenge as conventional therapies employing synthetic vascular grafts are contraindicated due to the infected field. A bovine pericardial patch provides a surgical innovation, with good handling technique, excellent haemostatic properties and a favourable profile of infection risk in comparison to traditional synthetic patches. Its use in arterial reconstruction in infected fields has been previously reported. This case highlights its use as a treatment for a post transplant mycotic pseudoaneurysm in pancreas transplantation.

P190

A United Kingdom pancreas donor risk index for predicting outcome after deceased donor pancreas transplantation

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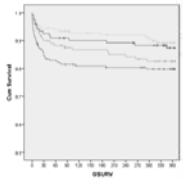
Background: Pancreas graft early attrition rates remain significant, leading to markedly more conservative allograft acceptance behaviour compared to other solid organ transplants. Identification of donor risk factors for poor graft outcome will inform organ utilisation decisions.

Methods: Data were obtained from the UK Transplant Registry on 1265 deceased donor, whole pancreas transplant recipients between 1st April 2004 and 1st July 2011. The dataset was randomly divided in modelling and validation datasets. The modelling dataset was used to investigate donor factors potentially influencing one-year graft survival using Cox regression, adjusting for significant recipient and transplant factors. A United Kingdom Pancreas Donor Risk Index was derived from the model and validated.

Results: Significant variables in the recipient model included transplant type (SPK, PTA, PAK), transplant centre and cold ischaemia time (p<0.001). Significant donor factors predicting poorer pancreas graft outcome were found to include donor age, donor type (DBD vs DCD), donor serum sodium, evidence of pancreas inflammation, cerebrovascular cause of death and donor ALT. In a multivariate model, pancreas inflammation emerged as the most predictive of one-year graft failure (HR 3.081, p=0.001) with donor sodium 146-150mmol/L(HR 1.985, p=0.04), donor ALT (HR 1.195, P=0.044) and cerebrovascular cause of donor death also highly predictive (HR 1.892, p=0.04). Other donor factors including donor gender, ethnicity, BMI, biochemistry, serology and past medical history were not significant predictors of graft outcome. A Donor Risk Index was derived and calculated. Kaplan-Meier plots comparing PDRI quartiles confirmed calculated PDRI to be prognostic of one-year graft survival in a validation cohort (p=0.041).



Conclusion: We have developed a simple tool that is applicable to UK practice. This UKPDRI will be clinically useful in guiding organ allocation and enabling informed consent. This may lead to more efficient organ utilisation and improved pancreas graft outcomes.

P191

The Waterlow scoring system: a robust method to predict length of hospital stay in pancreas transplantation

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Introduction: Pre-operative scoring systems to assess peri-operative risk and inform patient choice are valuable but have not been validated in Simultaneous Pancreas Kidney (SPK) transplantation. The Waterlow Scoring system, initially developed to assess patients for decubitus ulcer risk, may have utility as a potential surrogate marker to predict outcome in pancreas transplantation.

Methods: A prospective analysis of SPK recipients at a single unit was performed (Nov 2011-Nov 2012). Waterlow scores were collected for all patients (incorporating scores for age, gender, body mass index, nutritional state and tissue quality). These were correlated with other prospectively collected risk scores (Multiple Organ Dysfunction Score, P-POSSUM, Charlson Score, Revised Cardiac Risk Index and ASA) for each recipient. These scores were correlated to Intensive Care, High Dependency Unit and total length of hospital stay, which are important surrogate markers of patient progression and outcome. Potential confounding factors in donors and recipients were also calculated.

Results: 23 SPK recipients were analysed (10 female, 13 male; mean age 43.5 (range 32- 62); 2 excluded - early graft loss; no late losses, no mortalities). The cohort had no statistical difference in any confounding factor. The Waterlow score had a high correlation to total hospital stay for all patients ($p=0.0006$; Spearman Correlation). None of the other scoring systems had any correlation on analysis.

Conclusions: Outcome prediction in SPK transplantation is notoriously difficult due to patient co-morbidities. Systems designed for emergency surgery are used, with limited applicability in a transplant cohort. The Waterlow Score, with known applications in general surgery appears to have suitability in transplantation. It is traditionally stratified into risk categories, but for SPK recipients, where all are at least high risk, there appears to be a strong correlation between length of stay and actual score and it is therefore a useful surrogate marker of outcome. Further prospective studies to incorporate the Waterlow score as an important component of pre-operative patient and graft outcome prediction are required.

P192

Thrombosis in pancreas transplantation - single centre, 5 year experience

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Introduction: Simultaneous Pancreas Kidney (SPK) and Pancreas Transplant Alone (PTA) transplant are now standard treatment for patients with Diabetic Nephropathy and those with severe hypoglycaemic unawareness. Thrombosis is one of the leading non-immunological causes for early graft loss often resulting in graft loss.

Methods: This was a retrospective single centre study reviewing patients who had SPK or PTA transplants between 2007 and 2012. All patients received a Thromboelastogram (TEG) directed anticoagulation which comprises of intravenous low molecular weight Dextran, subcutaneous Heparin and 75mg of Aspirin. Cross-sectional imaging of the pancreas was only carried out in the setting of graft dysfunction or sepsis. Patients who had post-operative thrombosis were identified using an electronic data storing system. Clinical notes and flow charts were reviewed. All those with proven thrombus on imaging were started on therapeutic anticoagulation.

Results: 462 patients underwent pancreas transplantations between 2007 and 2012. 73 (15.8%) were reported to have thrombi in the pancreatic blood vessels. 19 (26%) were identified incidentally, however, 54 (74%) cases had demonstrated clinical manifestation of pancreatic insufficiency such as fluctuating blood sugars, failed oral glucose tolerance test, or decrease in urinary amylase for those with bladder drainage pancreas transplant. Thrombosis was reported in the following vessels; 41 (56%) were arterial, 20 (27.4%) were venous and 12 (16.4%) were mixed.

Conclusion: Thrombi formation after pancreas transplantation has been widely reported in the literature. These are seen in spite of an anticoagulation protocol. Some are detected in the background of graft dysfunction, whereas others are identified incidentally when patients are scanned for other causes. Our data suggests that imaging helps detect thrombi in most settings and therapeutic anticoagulation after thrombus detection results in graft salvage in 74% cases.

P193

Outcomes of simultaneous pancreas - kidney transplantation from DCD donors

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Purpose: Organs from donation after circulatory death (DCD) donor are increasingly being used to expand the donor pool. What are the outcomes of simultaneous pancreas-kidney transplants (SPKTx) utlizing DCD donors?

Methods: A single centre, retrospective study was performed of 240 consecutive systemic venous drained SPKTx performed from 12/08/2006 to 30/04/2012, which included 24 (10%) from DCD donors and 216 (90%) from DBD donors. Before 18/2/06, the mode of exocrine drainage was exclusively bladder drainage (n=92) after which, all except 1 were enterically drained. For the study comparison purpose, all systemic venous, exocrine enteric drained SPKTx (n=146) since 18/2/2006 were included, and this comprised of 23 (16%) transplants from DCD and 123 (84%) from DBD donors. The median follow-up was significantly shorter in the DCD group compared to the donation after brain death (DBD) group (15 vs. 45 months). Therefore, actuarial survival analysis was done, and 2 year outcomes are reported.

Results: Comparison of donor, recipient and transplant characteristics between the DCD and DBD donor SPKTx groups showed that DCDs had a significantly greater proportion of donors whose cause of death was trauma (47% DCD vs. 22% DBD, p=0.02). DCD donors were slightly younger compared to DBD donors (mean 28 yrs DCD vs. 36 yrs DBD), and slightly lesser proportion with donors having BMI > 30 (0 vs. 8%). DCD SPKTx had significantly lower proportion of pre-emptive (not on dialysis) recipients (44% vs. 65%, p=0.04) and a slightly greater proportion of non-white recipients. Other characteristics were similar. Comparison of actuarial survival analysis showed that there was no significant difference between the 2 groups in the 2 year actuarial patient survival (100% DCD vs. 97% DBD), death-censored kidney allograft survival (100% DCD vs. 92% DBD, all p=NS). There was no significant difference in the incidence of graft thrombosis (0 DCD vs. 2% DBD), peripancreatic fluid collections (17% DCD vs. 18% DBD), duodenal stump leaks (0 DCD vs. 9% DBD), early (1st week) graft pancreatitis (22% DCD vs. 33% DBD), major bleeding episodes (9% DCD vs. 7% DBD) or 1st year biopsy proven acute rejections of either kidney or pancreas (22% DCD vs. 31% DBD, all p=NS). The overall infection rates were similar (52% DCD vs. 54% DBD). The rates of urinary tract infections (UTI), abdominal sepsis, bacteraemia and wound infection were similar. There was a slightly greater incidence of enterococcal UTI in the DCD compared to DBD SPKTx group (0% DCD vs. 17% DBD, p=0.08).

Conclusion: The outcomes of DCD SPKTx are excellent and comparable to the DBD SPK transplants. There is a slightly increased incidence of infected intraabdominal collections in the DCD group, which could possibly be related to contamination from the rapid retrieval process involved in the DCD retrieval process.

Poster session

Wednesday 13th March

18:15 - 19:25

Pancreas & islet 2

P194

Key components of the human islet double basement membrane are differentially digested during islet isolation

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We have incomplete understanding of how collagenase blends digest components of the extracellular matrix (ECM) at the islet: exocrine interface during human islet isolation. The interface contains two basement membranes (BM), one associated with the islet capillary and the second integral to the islet itself. Maintaining integrity of BMs may be critical for optimal islet survival post-isolation. This study aimed to characterize digestion of key islet BM components in human pancreas and purified islets in culture prior to transplantation. Human pancreases were retrieved with appropriate consent and ethical approval (n=7, age 44-59, BMI 23-32, CIT 5-10h). 0.5cm^3 tissue biopsies were snap-frozen, then cryosectioned. Sections were treated ± Serva collagenase-NB1 and neutral protease-NB for 2 or 5 minutes at 37°C. Following double immunolabelling for insulin and collagen-IV, pan-laminin, laminin-511 or perlecan, expression was semi-quantified by morphometry. Following islet isolation, islet samples were collected after purification and at 24h, 48h, 72h and 7 days in culture. Islet BM proteins were identified by immunofluorescence labelling and western blotting. Collagen-IV, laminin and perlecan were identified as major islet BM components and were considerably digested after 5 minutes enzyme treatment. Complete dissolution of laminin-511 occurred within only 2 minutes. In purified islets laminin-511 and perlecan expression was absent. Collagen-IV and pan-laminin expression was present, yet markedly decreased during the first 24h of islet culture. Collagen-IV expression stabilised over the proceeding 48h and was present up to 7 days in culture, whereas laminin expression was lost after 72h. Key components of the islet double BM: collagen-IV, laminin and perlecan, are substantially digested by clinically-used collagenase. Importantly, laminin-511 (the only laminin isoform found in both layers of the duplex BM) and perlecan are lost entirely, indicating extensive BM disruption. Incomplete BM may compromise islet function and survival, as destruction of ECM can trigger integrin-mediated cell death, thereby contributing to the reduction in islet yield commonly seen following culture.

P195

Utility of serum markers in evaluating graft pancreatitis following simultaneous pancreas - kidney transplantation

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Introduction: Graft pancreatitis remains difficult to diagnose using clinical assessment alone, leading to indiscriminate use of cross-sectional imaging. We seek to correlate the presence of radiological features of graft pancreatitis to biochemical markers of inflammation and to clinical outcome.

Methods: A retrospective analysis of 109 simultaneous pancreas-kidney transplants performed at our centre between January 2005 and December 2010 was undertaken. All 299 post-operative CT scans performed on this cohort were blindly scored by 2 independent radiologists for features of pancreatitis – graft enlargement (normal=0; enlarged=1), graft perfusion (normal=0; heterogeneous =1), ascites (absent=0; present=1) and peri-pancreatic fat changes (mild=0; moderate=1; severe=2). CT score was correlated to the length of post-operative stay and to levels of candidate serum inflammatory markers measured within 24 hours of each scan.

Results: A CT score ≥ 2 in the post-operative index admission correlated with a significant increase in median length of stay (26 vs. 19 days, p=0.044). Mean serum CRP levels were significantly higher in patients with positive CT findings (p<0.001) including enlarged vs. normal graft size (114±74 vs. 76±80 mg/L) heterogeneous vs. normal perfusion (132±81 vs. 82±76 mg/L), presence vs. absence of ascites (125±81 vs. 74±73 mg/L) and mild vs. moderate vs. severe peri-pancreatic fat changes (23±34 vs. 53±59 vs. 107±80 mg/L). Serum CRP correlated closely with the CT score (p<0.001), and the median length of stay was significantly longer (26 vs. 17 days, p=0.005) in patients with a CRP > 50. Mean serum white cell counts were also significantly higher in patients with enlarged grafts (10±5.1 vs. 8.7±5.5 $x10^9$ cells/L, p=0.013) and CT-detectable ascites (11±5.2 vs. 8.7±5.6 $x10^9$cells/L, p=0.006), and correlated linearly with the CT score (p<0.001). In contrast, serum amylase and lipase levels had no significant correlation with radiological grading of pancreatitis or effect on length of post-operative patient stay.

Conclusion: CRP and white cell count are useful markers of graft pancreatitis and as such may allow avoidance of repeated radiological investigations to assess graft inflammation.

P196

Age and BMI impact on different human pancreatic peri-islet collagens

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Objectives: Donor variables may affect the protein structure of the peri-islet extracellular matrix (ECM) and influence enzymic digestion of ECM. We have previously reported that peri-islet laminin increases with age and is more susceptible to Serva Collagenase blend digestion whereas age and BMI has no significant impact on peri-islet collagen VI. We have extended these studies to include peri-islet collagen I, III and IV.

Methods: Frozen specimen slides of pancreatic samples (appropriate consent and ethical approval obtained) from 17-18 donors (ages 20-63 years, BMI 20-37 kg/m^2, CIT < 12 hours) were thawed and incubated in HBSS (control) or with Serva Collagenase NB1 ± Neutral Protease for 5 minutes. Digestion of the islet-exocrine interface was detected by double immune-labelling for insulin and each collagen isoform (I, III or IV). Collagen was semi-quantified by morphometry. Statistics were performed using linear mixed modelling.

Results: Peri-islet collagen I increased with donor age ($P = 0.014$), but not BMI. Peri-islet collagen III increased with both donor age and BMI ($P < 0.02$). Peri-islet collagen IV decreased with donor BMI ($P = 0.022$), but not age. However, undetermined donor factors, independent of age and BMI, significantly impacted on the quantities of peri-islet collagen types I and IV ($P < 0.02$). Collagens I and IV were susceptible to treatment with Serva Collagenase blend ($P < 0.02$) while collagen III was not. The extent of digestion of collagens I and IV did not appear to be affected by age or BMI.

Conclusions: Donor factors, including age and BMI, impact on the quantities of different peri-islet collagens. These factors do not appear to affect their digestion by Serva Collagenase and Neutral Protease. These results suggest that these particular peri-islet ECM proteins do not majorly influence the outcome of islet isolations.

P197

An economic analysis of pancreas transplant; a single centre's experience

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Introduction: In a growing population health demands continue to exceed finite national resources. By 2014 the NHS is predicted to have a £10 billion shortfall. Pressures on state commissioning and budget management inevitably impacts on clinical practice. To counteract escalating discrepancy PCT's and health care trusts have ever increasing responsibility to analyse the costs of services. This is a review of a single centres pancreas transplant programme. In particular it is an analysis of the logistical components and outcomes and how this translates into cost.

Aim and method: Resource use data were collected on all 266 Pancreas Transplants (combined Pancreas and Kidney as well as Pancreas Only) in our institute from June 2001 to August 2012. The data collected contained information regarding operation time, in-patient stay (Transplant ward, HDU, ITU), pharmacological therapy, infection treatment, reoperations and readmissions. Median and mean values were obtained for each category. Each component was then priced according to the most recent costing schedule obtained from the trust accounting department. The average inpatient cost per patient undergoing pancreas transplantation (up to 1 year excluding follow-up and maintenance immunosuppressant drugs) was calculated. This cost was then compared to the nationally allocated funds for the procedure. There was a protocol change to routinely admit all patients to the ITU post-op (April 2008 on ward). The cost was therefore compared for pre and post April 2008 era (140 v 126 patients respectively). The main caveat to the data is that all costs were calculated as per elective operating sessions which clearly will be higher as many are performed on unplanned lists. Also the cost of preparation of pancreas for transplantation was not included.

Results: Median theatre time was 5hrs 4 minutes (anaesthetic + operating). The data revealed that there was a significant increase in critical care services cost post 2008: £11,119.38 (pre) £14,489.66 (post), this coincides with a protocol change to routinely admit all patients to ITU post-op (April 2008 on ward). Mean cost for surgical re-exploration pre and post 2008 was £5664.75 and £3427 respectively. The mean cost of induction immunosuppressant per patient in the two period was £1518 and £1026 respectively (this was reduced to only £300 in the last 60 patients following change from Simulect to Campath). Median hospital stay per patient was 18 days and prolonged hospital stay was directly associated with factors such as age, donor BMI and Cold Ischemic Time. Total minimal mean inpatient cost per patient pre 2008 changes was 32352.08 whereas the mean cost post 2008 changes were £32621.99 in our series.

Summary: The data revealed a significant increase in critical care cost post 2008 however this did not translate as a significant increase in the overall cost per patient. This may be explained by the increased re-exploration rate /cost pre 2008 and higher cost of induction immunosuppressant medication. Re-exploration and re-admission post pancreas transplant has a significant cost implication which is often excluded from initial estimations and initial costs.

P198

Allocation of donation after cardiac death pancreas allografts: impacts on kidney transplantation?

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Introduction: Allocation of donation after cardiac death (DCD) pancreas and associated kidneys is currently a source of dispute. This has altered, mandating that the kidneys travel to enable implantation of DCD pancreata as simultaneous pancreas kidney (SPK) transplants if possible. Some kidney only units (KTA) have postulated that this may bias their patients due to perceived 'loss of organs'. This is because if the pancreas isn't used, increased cold ischaemic time (CIT) may preclude repatriation of the kidney to its original allocated centre. We assessed sources of DCD pancreata in our unit and correlated this with patient origin.

Methods: Retrospective analysis was performed of all DCD pancreas transplants since the programme's inception (SPK and pancreas alone (PA); 07/05 - present) The geographical origin of all DCD transplant allografts (local or zonal) and recipients was correlated to examine any potential mismatches in terms of equitable organ allocation for recipients.

Results: 267 pancreas transplants (215 SPK (80.5%), 52 PA (19.5%)) have been performed at our centre (27 (12.5%) - DCD donors (17 SPK, 10 PA)). 7% of the SPK's are from DCD donors and more in PA's (17.5%; p=0.04, Fisher's exact test.) Of the 17 DCD SPK's, 6 were implanted into local recipients (within our KTA catchment area) and 11 into imported recipients (zonal – outside our KTA area). We have used 10 DCD donors from our local area compared to only 7 imported DCD donors. Our current SPK waiting list (active (47) and suspended (56)) comprises of 30 (16 active) local recipients and 56 (31 active) imported recipients.

Conclusions: We currently implant more SPK's into imported recipients than organs received from outside region. Despite concerns, our centre is in debit regarding DCD organ usage ultimately lessening the load on local waiting lists at KTA units. KTA unit's historical desire to keep both DCD kidneys also does our PA recipients a disservice, as they receive more DCD organs. Outcomes in DCD PA allografts, coupled with donor shortages, a national resource, mandates strict adherence to the current utilitarian allocation of kidneys with DCD pancreata.

P199

The role of surgical drains in simultaneous pancreas kidney transplantation: a single centre retrospective analysis

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Surgical drains are often used in simultaneous pancreas kidney transplantation. These are placed in order to detect abdominal bleeding and decrease the incidence of intra-abdominal collections. However, there is increasing evidence that drains can increase the risk of infections following abdominal surgery. In this retrospective study, we analysed the correlation between the use of drains with postoperative intra abdominal collections.

195 consecutive patients, who underwent simultaneous pancreas kidney transplantation at Oxford Transplant Centre between March 2004 and April 2009, were included in this retrospective analysis. 141 (72.3%) patients had drains placed at time of surgery and 54 (27.7%) did not have a drain. Drains were placed at the discretion of operating surgeons. All patients had enteric drainage of exocrine secretion. There was no difference between groups regards donor (age, gender, BMI and donor type) and recipient characteristics (age, gender and BMI). However, the drain group had a significantly longer cold ischaemia (619 min Vs 474 min, p=0.009). Drain insertion practice varied by year (61.5% of transplants had drains in 2007 compared to 100% in 2004 and 2009, p=0.043). 86.5% patients had a drain for less than 5 days, 11.3% had a drain for more than 5 days. Postoperative events were as follows: relaparotomy (22.1%), intra abdominal sepsis (10.8%), sterile intra abdominal collection (13.8%), 30-day pancreas graft loss (4.62%); kidney graft loss (1.03%). In a univariate and multivariate analysis, use of a drain was not predictive of intra-abdominal sepsis, sterile collection or 30 day graft loss.

In conclusion, use of abdominal drains did not increase the complications following simultaneous kidney pancreas transplantation. However drains were also not shown to be beneficial. These results justify the need for a randomized controlled trial to examine the precise role of abdominal drains following simultaneous kidney pancreas transplantation.

P200

Anti-islet cell antibodies as predictors of graft loss in simultaneous pancreas-kidney transplantation

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Introduction: Type I diabetes is an autoimmune disease characterised by destruction of pancreatic -cells, which culminates in a failure of insulin production. The resulting chronic hyperglycaemia leads to diabetic nephropathy and end-stage renal failure in some patients. Kidney-pancreas transplantation is an effective treatment for type I diabetes complicated by nephropathy. Recurrent type I diabetes in the pancreatic graft is a recognised complication, leading to loss of functioning -cells. In *de novo* type I diabetes there is a pre-clinical phase in which autoantibodies to -cell antigens are detectable, and highly predictive for disease development.

Methods: We performed a single centre, retrospective study to assess anti-islet antibody status in 140 consecutive patients (96 male and 44 female) undergoing simultaneous pancreas-kidney (SPK) transplantation from January 2002 – May 2011. Testing for islet autoantibodies was performed during routine clinic visits.

Results: 20 patients had either a pre or post-operative, positive (weak or definite) anti islet cell antibody (AICA). Thirteen patients had a weakly positive AICA, none of whom went onto have pancreatic graft dysfunction. Three patients developed recurrent type I diabetes, presenting with elevated blood glucose and had selective I -cell loss confirmed by pancreas transplant biopsy. All three of these patients had detectable definite AICA on two or more occasions at least 1 month apart prior to the onset of graft dysfunction.

Conclusions: Persistent detectable AICA post-SPK transplantation has some predictive value for recurrent type I diabetes. Weakly positive AICA pre or post transplantation does not appear to be predictive of recurrent disease.

P201

Improvements in systolic and diastolic function post kidney-pancreas transplantation are maintained over the long-term

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Introduction: There is a high prevalence of diastolic dysfunction amongst patients with type 1 diabetes. It has been well established that the improved glycometabolic control achieved by pancreas-kidney transplantation improves systolic function and causes reversal of diastolic dysfunction. The aim of this study is to evaluate whether the improvement in diastolic dysfunction in kidney-pancreas transplant patients is maintained over time.

Method: Left ventricular systolic and diastolic functions were evaluated using echocardiography in 53 kidney-pancreas transplant patients. The patients were grouped according to time from transplant into less than 3 years post op and more than 3 years post op. Both patient groups had similar baseline characteristics. Systolic and diastolic function was compared between these two groups. A Mann – Whitney test was performed to detect any significant differences between groups. Left ventricular wedge pressure was estimated based on the Nagueh formula.

Results: Complete echocardiograms were performed in 53 patients. 27 patients were less than 3 years post pancreas-kidney transplant (average time from transplant 18 months), and 28 patients were more than 3 years post-transplant (average time from transplant 56 months). In the less than 3 years post-transplant group, 15 patients had normal diastolic function, 6 patients mild diastolic dysfunction, and 6 patients moderate diastolic dysfunction. In more than 3 years post-transplant group, 16 patients had normal diastolic function, 2 patients had mild diastolic dysfunction, 7 patients moderate diastolic dysfunction and 1 patient severe diastolic dysfunction. These two groups had no statistically significant difference in diastolic function ($p = 1.0$). There was no difference in LV systolic function in the two groups: LVEF 61% vs. 63% ($p = 0.29$). There were similar rates of LVH amongst the two groups ($p = 0.347$). LVH in the less than 3 year's post-transplant group: 6 mild, 1 moderate, 5 severe. LVH in the more than 3 year's post-transplant group: 5 mild, 4 moderate, 4 moderate. Left atrial size was similar between the two groups ($p = 0.06$). There was no statistical difference between the estimated left ventricular wedge pressures in the two groups 11.3mmHg vs. 13.8mmHg ($p = 0.05$).

Discussion: The initial improvement in diastolic and systolic function identified in kidney-pancreas transplant recipients is a long lasting effect that is seen up to eight years post surgery. This is likely to be the result of insulin independence, an improved glycometabolic pattern and hypertension control.

Poster session

Wednesday 13th March

18:15 - 19:25

Pancreas & islet 3

P202

Pancreas retransplantation in the United Kingdom

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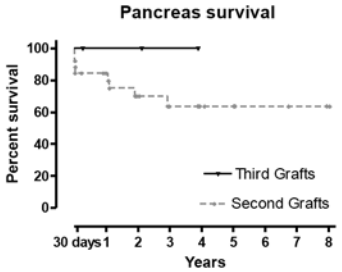
Background: Pancreas transplants are susceptible to failure through thrombosis, acute and chronic rejection and recurrence of autoimmunity. It is often unclear which disease process has predominated when the graft fails. Listing patients for re-transplantation is based on patient wishes without good evidence to guide surgeons which patients are likely to get the most benefit.

Methods: We performed a univariate analysis of the UK Transplant Registry data (1998 to 2010) to identify factors which were associated with success as defined by 2nd pancreas graft survival.

Results: 62 patients were re-transplanted with a second pancreas graft in the time period studied. 4 patients received a third graft. Second transplants were a median of 3 yrs (range 0 - 15) after the original transplant. The original graft was SPK in 38 (2nd graft: 32 PAK, 6 SPK), PAK in 14 (2nd graft: 2 SPK, 12 PAK) and PTA in 10 (2nd graft: 9 PTA, 1 SPK). One year pancreas 2nd graft survival was 85% which compares favourably with all UK first SPK graft survival at 87% (2007-2010, n=552, 95% confidence intervals 84 – 90%). The majority of re-transplant patients lost their original graft in the first year (56%). Timing of first graft failure (<30 vs. >30 days) had no effect on second graft survival. Similarly analysis of 2nd graft type, panel reactivity, HLA mismatch (B and DR), immunosuppression and exocrine drainage failed to find factors predictive of early re-transplant pancreas graft failure.

Conclusions: Pancreas retransplantation is associated with excellent 1yr patient and graft survival and can be considered in all representing patients independent of the original graft type and when the graft failed.



P203

The role of nutritional assessment for simultaneous pancreas kidney transplant candidates and early enteral nutrition

Sally Finlay, Argiris Asderakis, Elijah Ablorsu, Dawn Chapman, Jane Dursley

University Hospital of Wales, Cardiff, UK

Introduction: There is limited research into the role of nutrition within Simultaneous Pancreas Kidney Transplant (SPK) candidates, pre and post-operatively. Malnutrition is considered one of the late complications of chronic kidney disease. Furthermore, type-1 diabetics frequently suffer from impaired nutritional status. Therefore, it is important to actively manage these patients prior to transplantation and provide adequate and intense nutrition after surgery. Early Enteral Nutrition (EEN) has been proven to improve the postoperative course after major surgery.

Method: Prospective data was gathered from 23 consecutive SPK recipients who underwent transplantation between Jan-2010 and Jul-2012. All candidates received nutritional assessment prior to activation on the WL and post-transplant nutrition was planned, according to their nutritional status (early oral intake with supplementation [O] or early jejunal feeding, via surgically placed NJ tube [J]). The end-point was to assess nutritional intake between the two groups: achievement of ≥60% energy requirements by day-7 (7d-60%) and by discharge (total-60%).

Results: From 23 recipients, 13 received J-feed and 10 O-feed. We found no difference between the groups in CIT, recipient-age, donor-age, donor-creatinine, LOS. However J-group had lower BMI (24.17 vs. 24.9, p=0.14) and lower pre-transplant Albumin (30.4 vs. 35.1, p=0.05). Despite features of malnutrition in J-group, these patients reached 60% energy requirements significantly faster (7days vs.15days, p=0.02); with higher 7d-60% 87% vs. 60%, p=0.31, and shorter period of reinstitution of pre-transplant albumin levels (56days vs. 69days, p=0.55). Only one patient in each group required TPN.

Conclusion: Results suggest that both types of EEN provide sufficient nutritional intake; and minimize need of TPN. Furthermore, careful pre-transplant nutritional assessment helps to identify malnourished candidates and recommend early jejunal feeding.

P204

The benefit of early enteral nutrition after simultaneous pancreas and kidney transplant

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Introduction: Early post-operative enteral nutrition is an important part of perioperative management, including transplantation; and strongly supported by ESPEN Guidelines. However, there is limited evidence into the use of Early Enteral Nutrition (EEN) after Simultaneous Pancreas Kidney Transplantation (SPK). We know malnutrition in type-1 diabetics with ESRF is a common problem and significant risk factor. Therefore, we introduced EEN in our patients.

Method: We monitored and recorded nutritional data on 21 SPK recipients who underwent transplant between 2007-2009, without active nutritional feeding *[Monitored Group (MG)]* and on 22 SPK recipients between 2010-2012, who received EEN (NJ feed or oral intake with supplementation, according to their nutritional status) *[Fed Group (FG)]*. The end-point was to assess nutritional intake: achievement of ≥60% energy requirements by day-7 (7d-60%) and at the time of discharge (total-60%).

Results: There was no difference between MG and FG; in CIT, recipient-age or donor-age. Both groups had similar Length of Stay (30.8±23.7 vs. 24.6±12.3, p=0.29), day-0 albumin levels (35.29±4.9 vs. 32.43±5.7, p=0.085), donor-creatinine (86.3±31.4 vs. 64.1±20.9, p=0.01), re-operation rates (1 vs. 0.83, p=0.56).

However, FG group more frequently achieved 7d-60% (72.7% vs. 23.8%; p=0.02) and total-60% (95.2% vs. 71.4%; p=0.047). Furthermore, FG patients with early pancreas-graftectomy achieved target intake compared to MG patients with pancreas-graftectomy: 7d-60% 100% vs. 50%; p=0.4 and total-60% 100% vs. 75%; p=0.667. But MG patients achieved it only with TPN support. There were only 2 FG recipients on TPN (8.7%) compared to 5 MG (23.8%; p=0.17).

Conclusion: EEN is a safe method and helps to deliver adequate nutritional intake early after SPK transplant and it is paramount in recipients experiencing major post-transplant complications. Furthermore, it minimizes the need for TPN and its complications.

P205

Outcomes following pancreas transplantation in patients with a raised c-peptide

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Introduction: Simultaneous pancreas and kidney (SPK) transplantation is a recognised treatment for Type I diabetes mellitus (DM) but suitability as a treatment for Type II DM remains controversial. C-peptide levels are used to aid differentiation between Type I and II diabetics. We identified patients with a raised c-peptide prior to pancreas transplantation and assessed post- transplant outcomes for this demographic.

Methods: All patients undergoing pancreas transplantation at a single centre between January 2008 and September 2012 were identified. Patients with a pre- operative c-peptide greater than 0.02ng/ml were extracted from this group and further analysed. Patient demographics and pre-operative data specific to diabetes mellitus (DM) were recorded. Standard post- operative outcomes including incidence of complications and short and long term graft and recipient survival were also assessed.

Results: A total of 365 pancreas transplants were performed during the study period. Twenty five (6.8%) patients had a pre- operative c-peptide >0.02ng/ml with a median level of 0.49ng/ml (range = 0.04-4.51ng/ml). All of these patients underwent simultaneous pancreas and kidney (SPK) transplantation. Median age at diagnosis was 16 years (range = 2-51 years) and mean body mass index (BMI) was 24.6kg/m^2. Two (8%) patients were not on insulin therapy at time of transplantation and of the remainder, median daily insulin requirement was 40 units/day (range = 20-130 units/day). In the immediate post-operative period, 3 (12%) patients developed vascular complications and 2 (8%) patients developed infected pelvic collections requiring surgical and percutaneous drainage. One (4%) patient required a laparotomy for small bowel obstruction and 1 (4%) patient died 66 days post-operatively following graft pancreatectomy and cardiac arrest secondary to hypoxic brain injury. Twenty four (96%) patients had a functioning graft at time of discharge and at last follow-up (range 0.25-4.5 years), 22 (88%) patients had functioning grafts.

Conclusion: We report favourable early and late outcomes in this patient population that are comparable to patients without pre-operative c-peptide production.

P206

Alemtuzumab or basiliximab as antibody induction for simultaneous pancreas kidney transplantation

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Objectives: The goal of induction therapy is to reduce acute rejection and early graft loss. Both the interleukin 2 receptor blockers (Basiliximab (BAS), Simulect™) and the CD52 specific antibody (Alemtuzumab (AZB), Campath-1H™) have been used for this purpose. At the inception (1998) of our PT program BAS with triple maintenance (Tac/Pred/Aza or MMF) therapy was the preferred regimen. From 2009 induction therapy was changed to AZB with a dual maintenance regimen. The aim of this study was to compare patient and graft outcomes between these different immunosuppressive protocols.

Methods: We analysed a prospectively maintained database of 58 SPK transplants performed between 1998-2011. Since 2009 maintenance immunosuppression was with Tacrolimus (Prograf™) (0.05 mg/kg BD target 8-10 µg/L) and mycophenolate mofetil 500-750mg mg BD.

Results: 21 SPK patients received AZB and 37 BAS, demographic data was comparable. More patients had bladder drainage after AZB than with BAS (86% vs. 60%, p=0.04). At 1 year there was no difference in either pancreas graft (81% AZB vs 82% BAS, p=NS) or patient survival (94% vs 93%, p=NS). There was a difference in renal graft function at 1 month (serum creatinine AZB 122 ± 10 vs BAS 175 ± 25, p<0.001), which normalised at 1 year (serum creatinine AZB 122 ± 7 vs BAS 120 ± 5, p=NS). Rates of biopsy proven rejection (AZB 23% vs BAS 24% , p=NS) were similar. A trend towards lower leak rates in the AZB grafts (AZB 9.5% vs AZB 13.5%,p = NS) was noted.

Conclusions: In this study there was little to choose between the two induction agents in terms of patient and graft outcome. However, at 1 month renal function was better in the AZB group. This may reflect differences in the pancreatic exocrine drainage and lower leak rates in the AZB group.

P207

Quality of life after pancreas transplantation

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Aim: There is limited evidence currently available to explain the psychosocial aspects of pancreas transplantation especially after graft failure. The aim of this study was to investigate different aspects of patient well being relevant to pancreas transplantation.

Methods: Questionnaires were sent out to patients who had undergone Simultaneous Pancreas Kidney (SPK) transplantation along with those on the waiting list (W/L). Questionnaires included The Hospital Anxiety and Depression Scale (HADS), Clinical Outcomes in Routine Evaluation (CORE-10), Generalised Anxiety Disorder Assessment 7 (GAD-7), Roland Morris Pain/Disability Questionnaire Abbreviated (RMDQ-A), work and social adjustment scale (WSAS) and WHO Quality of Life- BREF (WHO-QOL BREF) within four domains. Results are expressed as mean ± SD and p value ≤ 0.05 (ANOVA) was considered significant.

Results: Overall response rate was (45%) including those on the W/L (n=6), functioning SPK (FSPK) (n=24) and non-functioning SPK (NFSPK) (n=6). The HADS responses did not reveal any significant difference between the three groups (p values of 0.078 and 0.079 for anxiety and depression scores respectively). The scores for CORE-10 questionnaires revealed significantly higher levels of psychological distress in patients with NFSPK (17.83±3.0) compared to FSPK group (9.44 ± 6.5) (p=0.014). Similarly, there were higher levels of disability (pain) with the RMDQ-A questionnaire in the NFSPK group (14.4±3.2) compared to the FSPK group (6.1±6.0) (p=0.028). Scores were similar in all groups for GAD-7 (p=0.069), WSAS (p=0.061) and Domains 1, 2 and 3 in WHOQOL-BREF (p=0.054, 0.066 and 0.087 respectively) with better indices in the post transplant group for domain 4 (p=0.001)

Conclusion: Although these numbers are small, this study demonstrates that despite the correction of uraemia those patients with a failed pancreas graft do experience significantly reduced impairment in some aspects of their quality of life which should be addressed during their rehabilitation.

P208

Amylase and lipase in the monitoring of whole organ pancreas transplantation

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Introduction: Serum lipase and amylase are routinely used for graft surveillance following whole organ pancreas transplantation, however the threshold at which graft pancreatitis is diagnosed is not clear. We report the diagnostic ability of different threshold criteria in the prediction of graft failure

Methods: Patients with whole organ pancreas transplants under follow-up at a single centre were identified using an electronic database. All available serum lipase and amylase levels were collected, along with outcome measures of patient death, prescription of any hypoglycaemic agent and glucose tolerance. Episodes of graft pancreatitis were defined using different criteria: elevation above the normal range, twice the population mean, twice the individual patient mean and twice the running mean for an individual patient. The contribution of elevations of serum lipase and amylase to the diagnosis of these episodes was recorded. The number of episodes was used to predict graft failure using receiver-operator characteristics.

Results: Sixty nine patients were identified with a total of 3314 serum lipase and amylase levels. Mean serum lipase across the whole population was 18 IU/L, mean amylase 40 U/L. The mean of individual patient's mean lipase and amylase were 52.1 IU/L [95%CI 37.6-66.6] and 81.4 U/L [72.1-90.8] respectively. Eighteen instances of graft failure were recorded. Mean lipase or amylase alone were poor predictors of graft failure (AUROC 0.58 for lipase, 0.54 for amylase). Graft failure was best predicted by number of episodes where lipase was greater than two times the running average level for an individual patient (AUROC 0.70 [0.57-0.83]). Episodes defined by population mean and laboratory normal ranges were less sensitive (AUROC 0.62 [0.48-0.75] and 0.52 [0.38-0.67]).

Discussion: These data suggest that an individualised serum lipase based on previously recorded levels has the best sensitivity to diagnose clinically relevant episodes of graft pancreatitis.

P209

How should we use urinary amylase as a marker for rejection in pancreatic allografts?

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Introduction: For pancreas transplantation alone (PTA), an early, graft-specific marker for rejection remains elusive. Exocrine bladder drainage of the graft has the advantage of providing a means to monitor for rejection through the measurement of urinary amylase (UA). However, gold standards for sample collection and interpretation have not been well defined. We studied the correlation between UA measured as 24 hr collections and spot urine samples, estimation of a standard range for UA and the use of UA to predict clinical events.

Methods: From January 2011 to October 2012, 21 patients underwent a bladder drained PTA. During their in-patient stay and follow-up, values for UA were determined. Clinical pancreas graft events were defined as thrombosis (proven radiologically) or by rejection based on duodenal segment biopsies. Significant drops in UA were defined as a decrease of greater than 25% from baseline. Daily values for UA and urine creatinine concentration were determined in both urine spots and 24-hours collections.

Results: We found a large inter-patient variability for UA (median 24,862 IU/L, range 5,432 to 88,102 IU/L). UA values increased from transplant and reached stable level by 15 days. Therefore, we defined baseline as the median UA concentration after day 15. There was a strong correlation between urinary amylase concentration from 24 hr collection and spot urine samples ($r=0.88$, $P<0.001$). The UA/ creatinine ratio showed less variation during episodes of impaired renal function, and may be a useful method to assess changes in UA. There were 15 clinical events in this cohort. A >25% fall in UA predicted 10/15 (67%) whereas a >50% fall was less predictive.

Conclusion: There is a large inter-patient variability in UA, requiring comparison to each patient's individual baseline, which should be set once the values have stabilized. Spot urine amylase correlated well with 24 hr collection concentrations, and may be used rather than 24 hr samples. A reduction should be defined as a decrease of greater than 25%. We conclude that no urine collections but spots should be taken to determine UA values as a marker for events in pancreas transplantation alone. If used appropriately, UA could provide an early detection system for significant pancreas graft events.

Poster session

Wednesday 13th March

18:15 - 19:25

Preservation/IRL 1

P210

Ischaemia reperfusion injury in human hand veins: a new model relevant to patients with kidney disease

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Background: In patients with CKD, ischaemia-reperfusion (IR) injury contributes to tissue damage that complicates vascular occlusion, including perioperative injury to the allograft after transplantation. Modelling IR injury in patients will likely allow novel interventions to be validated at an early stage in drug development. Existing human models include IR injury to the arterial vascular bed. However, the venous vascular bed offers certain advantages as a model system, being less likely to be affected by vascular disease (including hypertension, atherosclerosis and calcification), and more accessible to pharmacological interventions, especially in CKD. We set out to establish a model of venous IR injury that might be used to investigate interventions to reduce IR injury.

Methods: Healthy volunteers (age 22-50) were recruited. A butterfly needle was inserted into a dorsal hand vein and the Aellig technique used to measure venous diameter by recording the vertical displacement of a probe placed on the summit of the vein. Noradrenaline (NA; 20-160 pmol/min) was infused to assess venous constriction, and the endothelium-dependent dilator bradykinin (1-8 pmol/min) was used to assess venous endothelial function. IR injury was induced by inflating an upper arm cuff to 200 mmHg for 20 minutes followed by 20 minutes reperfusion. The response to drugs was measured by calculating the area under the dose-response curve (AUC).

Results: IR injury reduced the vasodilator response to bradykinin (AUC 265.4±51.8 vs 65±66.3 units; n=10; p=0.0098), but had no effect on the response to noradrenaline.

Conclusion: In healthy subjects, IR injury causes venous endothelial dysfunction, but smooth muscle responses are preserved. This model, which allows local infusion of drugs at much lower doses than would have systemic effects, might be useful in investigating effects of novel therapies that protect against IR injury in CKD.

P211

Does hypothermic machine perfusion improve outcomes of kidney transplantation from elderly DCD donors?

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Induction: Advanced donor age is recognised to have a negative impact on outcomes of kidney transplantation. However, persistent organ shortage has led us to use kidneys from elderly donors, including those over the age of 70. Based on published data and our positive experiences with Hypothermic Machine Perfusion (HMP), we employed this technique to routine practice; LifePort© kidney transporter from Organ Recovery System™. In this study we are investigating the impact of this storage type on kidney transplant outcomes from elderly DCD donors.

Method: In the period between1/Jan/2010 and 22/Oct/2012 we performed 47 kidney transplants from DCD donors aged more than 65 years. 21 of these kidneys were preserved on HMP (HMP65) and 26 in CS (CS65). We compared the transplant outcomes between HMP65 and CS65 group. The end-point of this study was to evaluate incidents of DGF, early graft function and graft survival.

Results: Overall, there was not a difference in donor characteristic between HMP65 and CS65 group: recipient age (63.2±7.2 vs. 63.3±8.1), donor creatinine (68.19±18.1 vs. 68.6±18.9). But CIT was significantly longer in HMP65 (15.8±4.5h vs. 11.7±4.6, p=0.003). Incidence of functional DGF was similar between groups, as well as GFR after 1, 3, 6 and 12 months (29.7±10.0, 35.8±11.3, 36.4±9.9, 34.3±11.2 in HMP65 compared to 30.34±13.2, 32.4±11.9, 35.5±12.6, 35.2±11.6 in CS65; p=0.86, 0.35, 0.79, 0.83, 0.65). In correlation analysis there is significant correlation between CIT and DGF only in HMP65 group (p=0.029), whereas in the CS65 group this correlation was not significant.

Conclusion: Our results showed that HMP neutralises negative impact of long CIT on elderly DCD kidneys and improves early graft function. In addition there is evidence that CS alone is a strong risk factor for DGF in DCDs above 65.

P212

The relationship between NO3 and NO2 post perfusion is pivotal in DCD kidneys in the context of reperfusion injury

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Reperfusion injury (RI) is an important factor in DCD organs due to warm and cold ischemia. The importance of nitric oxide (NO) in the generation of reperfusion injury is pivotal. The role of NO2 and NO3 is probably different to each other and varies in phases of the RI. NO produced in both the kidney and systemically might be important.

Aim: Study the changes of NO (NO2 and NO3) following RI in DCD kidneys. Associate those changes to known risk factors for DGF.

Methods: NO3 and NO2, were measured by the Griess and Ozone-based chemiluminescence methods, starved preoperatively, post induction, at 30 min, 2h and various times points thereafter. Here we present the initial results analysis.

Results: Median (mean) NO3 base line values measured by Griess reaction (gNO3) were 27 (30) μmoles/l. The respective median NO2 and NO3 values measured with the chemiluminescence method (cNO2, cNO3) were 0.50 and 38.6μmoles/l. The baseline cNO3 was somewhat correlating with the patient age (Spearman cc=0.55, p=0.09). There is a tight correlation between 2h cNO3 and gNO3 (cc=0.9, p=0.0001). The changes of cNO2 and cNO3 at 2h are independent of recipient age or each other but they are affected by their respective baseline values (p=0.02 for cNO2 and p=0.03 for cNO3). Univariate analysis shows that recipient age (0.007), donor age (0.025), first WIT (at donor) [p=0.01], second WIT (at recipient) [p=0.02], but not CIT affect the cNO3/cNO2 ratio at 2h post perfusion. Regression analysis showed that the level of cNO3/cNO2 ratio is dependent on the age of the donor (p=0.02), age of the recipient (p=0.004), the 1st WIT (p=0.02), and the 2nd WIT (p=0.018) but not CIT and the baseline values of cNO3 and cNO2 (p=0.05). Interestingly the 30 min cNO3 and ratio is also affected by CIT (p=0.04) but not primary WIT.

Conclusion: The ratio of NO3 to NO2 post perfusion might be more strongly associated with the RI in DCD kidneys. These early results show that the change of NO3 and NO2 levels post perfusion (at 2h), are strongly associated with risk factors for RI, ATN and DGF namely donor age, CIT, primary and secondary warm ischemia but also the recipient age. The latter might reflect the ability of producing IFN-γ, known to be the strongest trigger for iNOS upregulation, which changes with age.

P213

Hypothermic machine perfusion improves outcomes in DCD kidneys

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Background: To overcome organ shortage, utilization of kidneys from DCD donors has increased. Those kidneys have comparable long-term outcomes as DBD kidneys, however they have higher incidence of DGF and worse initial graft function. Published data supports favourable impact of pulsatile Hypothermic Machine Perfusion (HMP) on DCD kidneys. Aim of this study was to assess the effect of HMP on the early function of controlled DCD kidneys.

Methods: We analysed prospectively collected data of 130 consecutive controlled DCD kidney transplants performed in a single centre between 1 January 2010 and 22 October 2012. Subsequently we compared DCD kidneys preserved on HMP (N=52), using the LifePort© (from Organ Recovery Systems) to DCD kidneys stored in Cold Storage (CS) (N=78). We excluded DCD kidneys transplanted in combination with pancreas and those performed as double transplants.

Results: The mean donor age in HMP group was 59.09±1.83 years (mean±SD) and 56.26±11.14 years in CS group (p=0.28). There was no significant difference in recipient age 59.65±19.84 years in HMP group vs. 57.85±12.13 years in CS (p= 0.40); however Cold Ischaemia Time (CIT) was significantly longer in HMP group (14.73±4.3 hours) compared to CS group (11.32±4.5 hours), p<0.001. We found no difference in the incidence of functional DGF, 65.4% and 74.4% in HMP and CS groups respectively (p=0.27). Also, the eGFRs were similar at any time point. In a logistic regression analysis, we found that higher donor age (Exp(B)=1.029, p=0.038), longer CIT (Exp(B)=1.114, p=0.031) and CS as the type of storage (Exp(B)=2.5, p=0.043), were significantly increasing the risk of DGF. In linear regression analysis the donor age, CIT, and type of storage showed significant correlation with the eGFR at 1, 3 and 6 months. At 1 and 2 years only the donor age correlated significantly with the eGFR.

Summary: HMP, in DCD kidneys with long CIT, can neutralise the adverse effect of cold preservation, leading to at least equivalent early graft function and similar incidence of DGF compared to kidneys preserved by static CS for significantly shorter preservation time.

P214

Preservation solutions for static cold storage of liver allografts: a systematic review and meta-analysis

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Introduction: Static cold storage of livers for transplantation requires the in situ and/or extracorporeal flush out of blood with a chilled preservation fluid. The liver is then stored on ice in a bag of preservation fluid. Preservation solutions have been designed to counteract the effects of the retrieval process, graft cooling and reperfusion injury. Our aim was to appraise the evidence for the efficacy of the currently available preservation solutions, which differ in composition and cost.

Methods: We performed a systematic literature search using Ovid MEDLINE, EMBASE, the Cochrane Library and the Transplant Library from the Centre for Evidence in Transplantation. The International Clinical Trials Registry Platform was also searched. No language limits were applied. Inclusion criteria specified any randomised, comparative study of preservation solutions for liver allografts from deceased donors. Studies were assessed for methodological quality using the Cochrane Collaboration risk of bias tool, Jadad score and intention to treat analysis. Outcomes analysed are: early dysfunction, primary non-function, re-transplantation rate, patient survival, graft survival, and peak serum ALT in the first week.

Results: 3,364 unique abstracts were retrieved and from these, 16 RCTs met the full inclusion criteria (1,620 liver transplants). Overall the quality of RCTs was poor and individually studies were underpowered. No reliable differences were demonstrated between Celsior, HTK and UW in terms of the outcomes of interest.

Conclusions: The best available studies show no evidence for a superiority of Celsior, HTK or UW Solutions. The quality of available studies also means that meta-analysis to deal with the problem of individually underpowered studies is based upon at best, moderate quality RCTs. We therefore have only moderate evidence of equivalence of these fluids. An adequately powered and well conducted RCT is required to establish the most cost effective solution for liver preservation, this would require large numbers.

P215

A phase IIa, multicentre, double-blind, placebo-controlled safety and efficacy study of the complement inhibitor APT070 as an ex-vivo flush prior to renal transplantation

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Ischaemia reperfusion injury, mediated in part by complement, is a significant contributor to donor kidney damage. APT070 is a low molecular weight, membrane-targeted complement inhibitor that has shown a favourable side effect profile in pre-clinical and Phase I studies. We performed a phase IIa, multicentre, double-blind, placebo-controlled safety and efficacy study in 16 human subjects, using APT070 as an ex-vivo flush. There was no difference in baseline characteristics, cold ischaemia time or anastomosis time between the study and control groups. There were 16 serious adverse events in the study group and 6 in the control group. There was one cardiac arrest in the placebo group, otherwise the SAEs were routine post-operative complications. The overall adverse event profile was mild and similar between the groups. There was one death in the trial which occurred in the study group at 32 months post transplant following several months' admission with sepsis. One patient in the study group developed BK virus infection at 4 months. One patient in the study group had a TIA at 24 months; one placebo patient had a stroke at 10 months post transplant. No malignancies were reported during the study. In a 9 patient subgroup from one centre there was no significant difference between groups in the level of serum NAG, urinary GST, urine protein, anti-APT070 antibody, total complement activity, C3 activity or C4 activity at any timepoint. The pharmacokinetic profile of APT070 was favourable. Three patients in the study group and one in the placebo group had DGF. After 60 months there had been 3 graft losses, all in the study group; one patient suffered primary non-function as a result of FSGS in the donor kidney; in one patient the kidney thrombosed during a septic illness at 24 months post-transplant; one patient suffered resistant acute cellular rejection at 6 months post transplant. There were no graft losses in the placebo group. The MDRD eGFR was significantly higher in the placebo group than in the study group at 12 months (p=0.028), 36 months (0.0027), 48 months (0.0143) and 60 months (p=0.0373) post transplant. We believe APT070 deserves further investigation.

Poster session

Wednesday 13th March

18:15 - 19:25

Preservation/IRL 2

P216

The truth about the relationship between flow rates from machine perfusion and transplant outcome for kidneys from Donors after cardiac death

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The relationship between parameters determined from kidneys before transplant and their subsequent outcome continues to be controversial with advocators for and against. We initially used machine perfusion to determine which kidneys were 'viable' and we found this useful for Maastricht II donors where the warm ischaemia was particularly protracted.

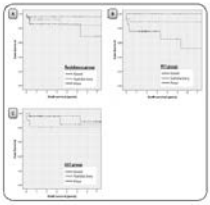
However the majority of DCD's utilised now in the UK are Maastricht III where the relevance of machine perfusion characteristics are more controversial.

We have reviewed the outcome of 94 single kidneys transplanted from MIII DCD's where the flow characteristics and GST perfusate levels were known at 3 hours after commencing machine perfusion. Follow up data was available for these kidneys up to 7 years post transplantation.

The parameters were divided into thirds (good, satisfactory and poor) and these groups compared for glomerular filtration rate, graft and recipient outcome.

Findings: there was no correlation with perfusion characteristics or GST with recipient survival. However for both graft function and graft survival there was a significant correlation between flow and outcome particularly flow/mmHg- perfusion flow index ($p<0.0005$). No such correlation was found with perfusate GST.

In a separate analysis of PFI with donor age there was a 2 tailed correlation between the two ($P<0.01$), though the correlation coefficient was only 0.154. Therefore the flow parameters which correlated with outcome for Maastricht III donor kidneys are likely to be explained by its cause namely donor age (and presumably donor hypertension) which is known to influence graft outcome.



P217

Hypothermic machine perfusion to optimise the timing of renal transplantation

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Background: Conflict has always existed between Cold Ischaemic Time (CIT) and safe, timely transplantation. This study pilots the use of Hypothermic Machine Perfusion (HMP) to extend CIT and permit cadaveric renal transplantation to occur at times when resources and expertise are optimal.

Methods: Between December 2011 and October 2012 cadaveric kidneys arriving during normal working hours were transplanted from Static Cold Storage (SCS). Kidneys at risk of being transplanted out-of-hours were placed on HMP and surgery arranged for the following morning on the dedicated transplant list. Relevant data were gathered prospectively.

Results: Seventy cadaveric renal transplants were performed; 35 kidneys were transplanted from SCS and 35 underwent HMP. Selected data are shown below.

	SCS(n=35)	HMP(n=35)	P value
Mean CIT (hours)	14.97	24.09	<0.0001**
Transplanted out of hours	17	5	0.002*
Functional DGF (fDGF)***	18	8	0.01*
Cardiorespiratory Complications	7	1	0.02*

*Chi squared 2-tailed test **Unpaired 2-tailed t-test ***Defined as the absence of a 10% reduction in creatinine for 3 consecutive days in the first post-op week

Conclusions: HMP extended CIT without increasing fDGF allowing more renal transplants to be performed at times when appropriate resources and expertise were available. This may have contributed to fewer cardiovascular complications.

P218

Novel biomarkers of oxidative stress in a porcine DCD model of Renal warm ischaemia

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Introduction: The use of donation after circulatory death (DCD) kidneys for transplantation is increasing in the last decade. Subsequent delayed graft function is related to warm ischaemia (WI) exposure. Potential molecular markers of renal WI, are limited to small animal and cell line reports. The identification of a biomarker of WI may enable future viability assessment or therapeutic development. Total RNA microarray and 2-dimensional gel electrophoresis (2-DE) were used to identify potential candidate biomarkers of WI in a large animal DCD model.

Methods: 6 large white pigs were terminated, with sequential open renal wedge biopsies taken at 30-minute intervals up to 180 minutes of WI. Biopsies were divided for RNA and protein extraction and flash frozen in liquid nitrogen, prior to storage at -80oC. Total RNA was copied and cyanine dye labelled to enable hybridisation to custom one colour 44k microarray slides (Agilent technologies, Kent, UK). Slides were scanned and quantification of gene expression analysed using in house feature extraction software. Subsequent ANOVA analysis was performed using Genespring v9.0 software (Agilent technologies, Kent, UK). Protein extracts were subjected to 2-DE using differential in-gel electrophoresis technology (DIGE). Resulting protein maps were analysed with Progenesis SameSpots and differentially expressed proteins ($p < 0.05$) were excised for identification via tandem mass spectrometry.

Results: Gene expression of CCL5, HSP-70, PCD-1 and TUB2A were significantly differentially expressed over all time points, compared to control biopsies ($P<0.01$, one way ANOVA). Protein expression of PRX-4, -6 and HSP-70 were identified as significant over all time points following tandem mass spectrometry.

Conclusions: Several apoptotic upstream markers of WI were identified using microarray with oxidative stress biomarkers revealed in down stream proteomics. HSP-70 showed significant increased expression both in its gene sequence and protein marker. This is the first large animal model to confirm this finding.

P219

Sinusoidal endothelial injury in hypothermic machine perfusion (HMP) of human donor livers - single vs dual vascular perfusion

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Introduction: Liver HMP must avoid sinusoidal endothelial injury (SEI) from perfusion. This study was undertaken to assess SEI in human livers.

Methods: 16 human livers rejected for transplant by all UK centres with appropriate consent for research were randomised into 4 groups. Group1: 7 hours cold storage (CS) and one hour HMP through hepatic artery (HA) alone (n=4). Group2: 7 hours CS and 1 hour HMP through HA and portal vein (PV) (n=4). Group3: 7 hours CS and 1 hour HMP through PV alone (n=4). Group4: 8 hours CS. A pressure controlled prototype based on Lifeport Kidney Transporter was used (Organ Recovery Systems).Livers were perfused at 4 to 8 °C under sterile conditions using Belzer MPS. Electron microscopy of 3 liver biopsy samples taken before perfusion, were compared with 3 samples from adjacent areas after perfusion. The severity of damage was assessed by comparing the morphology of SE lining and cells.

Results: Pre-set HA pressure of 30 mmHg and PV pressure of 7 mmHg were maintained throughout the perfusion. Temperature was maintained between 4 and 8°C. No difference in sinusoidal endothelium ultrastructure was seen before and after machine perfusion, or between any of the groups. Sterility was maintained throughout the HMP.

Conclusion: HMP of human livers did not produce evidence of sinusoidal endothelial injury. Single or dual perfusion modes did not impact on vascular resistance or flow. The results suggest that further studies into HMP on human livers are warranted

P220

Normothermic perfusion of discarded human pancreases

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Introduction: Pancreas transplantation (solid organ or islets) is the most effective treatment for patients with progressive complications of diabetes, or patients with labile blood sugar control and hypoglycaemia unawareness. Increasing demand for transplants requires the use of more marginal donor organs, including those from DCD donors. However, the deleterious effects of cold ischaemia affect the viability of the organ and are exacerbated by prior injury. Currently there is no validated means to test the viability of the organ before transplantation. There is accumulating evidence of the benefits of a more physiological approach using continuous perfusion of an oxygenated, blood-based perfusate at normal body temperature. We describe here the practicality of normothermic ex-vivo perfusion of human pancreases.

Methods: Human pancreases that were turned down by all transplant units have been utilised. A cardiopulmonary circuit consisting of oxygenator, heat exchanger, centrifugal pump, reservoir, flow probes and gate clamp is primed with time-expired packed red cells and the temperature maintained at 38^{0}C. The arterial inflow of the pancreas is cannulated and venous outflow collected and recirculated. Effluent from the duodenal segment is collected and measured.

Results: Using this circuit, it is possible to achieve stable normal arterial pressures and flows. During preservation, physiological flows and pressures are maintained in the splenic artery and the superior mesenteric artery by controlling the pump head speed and adjusting the proportional pinch valve on the bypass circuit.

Discussion: This is the first demonstration of successful normothermic perfusion of the human pancreas. This has the potential to increase the viability, assessment and safety of donor organs in this expanding field.

P221

Changes in mitochondrial activity during non-oxygenated hypothermic machine perfusion in human livers

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Introduction: This study focuses on changes in the activity of mitochondrial respiratory chain complexes in human discarded livers during non-oxygenated hypothermic machine perfusion.

Methods: Human livers declined for transplantation were selected for this experiment (n=10). The livers were cold stored during transport from donating hospital to our labs. Upon arrival of the liver sample, the portal vein was cannulated and kidney perfusion solution (KPS) was used to flush the liver. The liver was then connected to the perfusion machine to deliver a continuous flow of KPS through the portal vein at a constant pressure. Hypothermia was achieved using a heat exchanger system. Samples for mitochondrial isolation were taken from two different liver segments, namely segment four and seven, both before and after perfusion. Spectrophotometric analysis was performed on all samples to illustrate the differences in mitochondrial complexes activity. The results for individual complex groups were compared using paired T test.

Results: Mitochondrial complexes activities varied among different groups. A statistically significant ($P<0.05$) drop in complex I activity in segment four was noticed. Another significant drop ($P<0.05$) in complexes II and III activity in segment seven was observed. This was not matched by a drop in the activity of complex I in segment seven, nor was there a drop in complex II and III activity in segment four. Complex IV activity did not show any statistically significant change for the samples collected.

Conclusion: Changes in complex activities were not consistent among groups; this could be due to uneven flow through different liver segments. Expanding the sample number and comparison with cold-stored, non-perfused livers would be the next logical step to ascertain our initial findings.

Poster session

Wednesday 13th March

18:15 - 19:25

Prognostic factors in transplantation

P222

National survey of cardiovascular workup for renal transplant recipients

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Introduction: Patients with chronic renal failure have an increased risk of cardiovascular morbidity and mortality. Coronary artery disease prevalence is estimated at 40% and left ventricular hypertrophy at 75%.Given there is pressure to reduce unnecessary investigations and associated delays in activation onto transplant waiting lists and a lack of national standardisation, we were interested in looking at current practice of the 23 UK renal transplant units.

Method: A telephone survey to the renal unit transplant co-ordinators was conducted, with the survey being sent by fax or email, if requested

Results: We had responses from 19 centres. 3 centres perform echocardiography on all patients (2 also routinely perform perfusion scanning). 2 centres preferentially use myocardial perfusion scanning. 1 centre refers all patients to a cardiologist. Indications for selective use of echocardiography (16 units) and stress testing (19 units) are shown below.

	Echocardiography	Stress Test
Poor exercise tolerance	9	13
History of IHD	15	11
LVH on ECG	12	3
Abnormal ECG	11	0
Murmur	10	0
Diabetics	10	8
Age > 50	7	0

Discussion: Practice varied widely between transplant centres, partly due to local access to specific tests. Differences in investigations may help to explain inter-unit variations in waiting list rates and patient outcomes following transplantation. Some questions maybe answered by the **A**ccess to **T**ransplantation and **T**ransplant **O**utcome **M**easures (ATTOM) study. Whilst we await the results of this ambitious 5-10 year study, is national guidance required or should it remain with individual units to have their own local protocols?

P223

Reduced functional measure of cardiovascular reserve identifies kidney transplant recipients at high risk of perioperative morbidity

Stephen Ting[1, 2], Hasan Iqbal[1], Thomas Hamborg[2], Rob Higgins[1], Chris Imray[1], Susan Hewins[1], Prithwish Banerjee[1], Rosemary Bland[2], Daniel Zehnder[1,2]

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Background: There is currently no effective preoperative assessment for patients undergoing kidney transplantation that is able to identify those at high perioperative risk requiring admission to critical care unit (CCU). We sought to determine if functional measures of cardiovascular reserve, in particular the anaerobic threshold (AT), could identify these patients.

Methods: Adult patients were assessed within the 4 weeks prior to kidney transplantation in a University hospital with a 37-bed CCU, between April 2010 and June 2012. Cardiopulmonary exercise testing (CPET), echocardiography and arterial applanation tonometry were performed.

Results: There were 70 participants (age 41.7 ± 14.5 years, 60% male, 91.4% living donor kidney recipients, 23.4% were desensitized). 15 patients (21.4%) required admission to CCU following transplantation. Reduced AT was the most significant predictor, independently (OR = 0.47; 95% CI 0.31 – 0.72; p < 0.001) and in the multivariate logistic regression analysis (adjusted OR = 0.27; 95% CI 0.13 – 0.59; p = 0.001) (Fig A). The area under the receiver-operating-characteristic curve was 0.93, based on a risk prediction model that incorporated AT, body mass index and desensitization status. Neither echocardiographic nor measures of aortic compliance were significantly associated with CCU admission.

Conclusions: To our knowledge, this is the first prospective observational study to demonstrate the usefulness of CPET as a preoperative risk stratification tool for patients undergoing kidney transplantation. The study suggests that AT has the potential to predict perioperative morbidity in kidney transplant recipients.

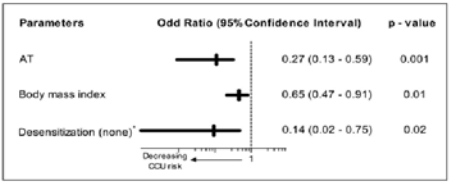

Fig. A: Final risk-prediction model on multivariate logistic regression analysis.

P224

High BMI is not a risk factor for rejection, graft loss or mortality following renal transplantation

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Obesity increases peri-operative complications in transplantation but effects on long-term kidney transplant outcomes remain controversial.

We analysed the U.K transplant registry data for the period from 1st January 2004 to 31st December 2010. A total of 13167 patients were listed for the first time during 2004-10; follow-up was until February 2012. 6365 (48%) patients received a first renal transplant; 4045 male, 2315 female with 5 missing data. BMI was available for 5203 (82%) and missing for 1162 (18%). During follow-up, 857 patients suffered rejection, 510 had graft loss and 205 patients died. Survival analysis was done using Cox PH modelling. Initial analysis showed no difference in mortality between transplanted patients if they had their BMI recorded or not.

We divided the patients into BMI bands of <=18, 18.1 -30, 30.1-35, >35.1 and missing BMI. The recipient variables analysed were age, gender, ethnicity, primary diagnosis, rejection episodes and duration of renal replacement therapy prior to transplantation and donor variables were age, gender, donor BMI band. Donor variables were not available for 1424, graft survival data were missing for 1428 and rejection data were missing for 1548 patients.

We analysed the data twice; missing BMI was included as a band on the first analyses and excluded on the repeat. The analyses was done using three different models. Model 1 included all variable plus interactions for age by gender and gender by ethnicity. Model 2 was as Model 1, but with interactions removed; no interaction terms were statistically significant. In Model 3 donor variables were excluded. Table 1 shows results using Model 2 for analyses.

Table 1- Results using Model 2

BMI Band	p Value	Hazard Ratio (HR)	N
<18	0.06	2.63 (0.95 to 7.28)	73
18.1-30	Ref	1	3021
30.1-35	0.31	0.79 (0.50 to 1.24)	679
>35	0.31	0.55 (0.17 to 1.74)	157
Missing BMI	0.29	1.24 (0.84 to 1.83)	693

All other analyses also showed increase in HR for BMI band <=18 and reduced HR for BMI bands 30-35 and >35, though not significant.

In conclusion, our study shows there is no increase in rejection, graft loss or mortality in patients transplanted with higher BMI. Also patients with lower BMI seemingly did worse, though of borderline significance.

P225

A simple cardiovascular health score predicts mortality in kidney transplant candidates

Christopher Lawrence, Sandra Cruickshank, Ananda Manoj, Shahid Chandna, Suresh Mathavakkannan, Sarah Fluck, Ken Farrington

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Kidney transplantation (KTx) confers improved quality and length of life but the survival benefit from KTx is limited by cardiovascular (CV) deaths. The ASTS/AST recently endorsed an American Heart Association (AHA) statement on CV disease evaluation in KTx candidates. This that patients asymptomatic of coronary artery disease (CAD) should undergo non-invasive stress testing based on the presence of risk factors such as diabetes (DM), previous cardiovascular disease, duration of renal replacement therapy (RRT) >12 Mths, left ventricular hypertrophy (LVH), age >60 Yrs, smoking, hypertension (HTN) and dyslipidaemia. We examined a large cohort of asymptomatic patients, without prior CAD, to devise a simple risk score and compared this against the AHA statement.

200 consecutive KTx candidates (135M:65F, age 53.8±11 Yrs, 43% diabetic, 56% current/ex-smokers) underwent coronary angiography (CA) between 2000-2012. A Cox model was constructed using AHA risk factors (except LVH but including ethnicity and gender). Only age, DM and current smoker status were significant predictors of death. Univariate analysis showed age <45 Yrs conferred a survival advantage ($p<0.05$). The Cox model was repeated with 3 risk factors (age >45, current smoker, DM) to establish the relative contributions of each (ExpB 3.6 ($p=0.006$), 2.2 ($p=0.014$), 2.1 ($p=0.047$). A risk score was constructed with 2 points each awarded to current smoker and DM and 3 points for age >45 Yrs. Patients were categorized as low risk (≤2), medium risk (3-4) or high risk (≥5).

Angiographically significant CAD correlated with increasing risk (12.2%, 18.6%, 34.7%, $p=0.01$). Overall 5Yr patient survival was worse with increasing risk (89%, 80% and 69%, $p=0.005$). Across all risk groups KTx patients had improved 5Yr survival (100 v 68%, 92 v 68%, 90 v 57%). Patient survival was poor in high risk patients who were revascularised but not transplanted ($n=16$, $p=0.07$).

In Cox modelling this simple risk score outperformed both the AHA model and CA findings as predictors of death. We suggest that this simple risk score has the potential to streamline CAD assessment and expedite transplantation.

P226

Who needs coronary angiography prior to kidney transplantation?

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Patients with end stage renal failure are at high risk of coronary artery disease (CAD). Death with function due to cardiovascular disease is an important cause of patient and graft loss. The role of screening coronary angiography (CA), and treatment of silent CAD, prior to kidney transplantation (KTx) is controversial.

Between 2000-2012 235 potential KTx candidates underwent CA. 200 patients (135M:65F, age 53.8±11 yrs, 69% HD: 14% PD: 16% Predialysis: 2% Failing KTx, duration of RRT 30.7 ±53.6 Mth, 43% diabetic, 56% current or ex smokers,) were asymptomatic and had no history of CAD. CA results were defined as 'Significant' in 46 (Diffuse or Obstructed 6, PCI 28, CABG 12) and 'Not-Significant' in 154 (Normal 82, Minor atheroma 72). In univariate analysis only predicted significant CAD (58.4 ±9.8 v 52.4 ±11.0, p=0.001) with a trend towards more CAD in diabetics. In multivariate analysis the absence of DM in patients <50 years was a strong negative predictor for CAD (2/34 vs 17/35, p=0.01). Patient survival (all cause mortality) was less good in asymptomatic patients with significant CAD, regardless of revascularisation (93.3 v 96.6% 1 year and 65.1 v 80.9% 5 year survival, p<0.05). Time to activation on KTx list was longer in patients with significant CAD, 21.9 v 65.2% by 1 year and 71.1 v 87.1% by 3 years (p=0.001). 16 (35%) patients with significant CAD (DD 12, LD 3, SPK 1), c.f. 66 (43%) without have been transplanted (DD 34, LD 21, SPK 11). Time to transplantation was not statistically significantly different in patients with significant CAD, however by 1 year, in patients without significant CAD only 29.4% of recipients of DD kidneys had been transplanted c.f. 71.9% of LD kidneys (p<0.05).

Screening 200 asymptomatic KTX candidates with CA resulted in 40 revascularisations (15 proceeded to KTx). It is likely that CA screening may have delayed listing for KTx and is of questionable validity (the majority of patients had not received a KTx within 3 years of CA). CA should not be a routine part of KTx work up for asymptomatic patients without a LD option and has no role in asymptomatic non diabetic patients aged 50 years and under.

P227

Pretransplant cardiac evaluation: is it worth the fuss?

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Introduction: The role of screening for coronary artery disease prior to renal transplantation is controversial. The purpose of this study was to assess the effectiveness of this in preventing post-operative cardiac events.

Methods: Demographic data, history of cardiac evaluation and post-op outcomes were collected prospectively from the day of transplant for 126 consecutive patients receiving renal transplant. The following conventional risk factors for IHD were assessed: diabetes, smoking, hyperlipidaemia, hypertension and family history. We classified 68 (54%) of the recipients as high risk on basis of age (>65 yrs), known IHD or the presence of >3 risk factors, and determined prior cardiac assessment for each group.

Results: The mean age was 51.5 (range 18-80) years and 32 (25%) were diabetic. Twenty seven patients were pre-dialysis, and the mean duration of dialysis for the remaining recipients was 28.6 (range 1 to 98) months. The median number of conventional cardiac risk factors per patient was 2. Fifty three recipients (43%) had undergone dynamic testing and/or a coronary angiogram. The mean interval between assessment and transplantation was 33.4 (range 2-56) months. There were no deaths in the immediate post operative period. Eleven recipients (8.7%) had a cardiac event within 30 days of transplantation. Four of these recipients were diabetic and five had a prior history of IHD. The high risk patients had undergone a more stringent assessment, but the event rate between the two groups was similar.

	Number	ECHO	ECHO + Other	Cardiac events
High risk	68 (54%)	61 (90%)	45 (76%)	**7 (10%)**
Low Risk	58 (46%)	41 (71%)	13 (32%)	**4 (7%)**

Conclusions: 1. Careful cardiac evaluation allows transplantation to be safely performed in a high risk population, with low incidence of post-op cardiac events. 2. The future rate of cardiac events will be determined by longer term follow up.

P228

What do patients on the kidney transplant waiting list want and need to know about transplantation? A pilot study

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Background: The demand for kidney transplants far exceeds the availability of organs, so organs from deceased donors not previously considered are being used. This development raises the question whether there are any donor characteristics that potential recipients would find unacceptable. In addition, would they like to be given information about "extended criteria" donors?

Methods: A pilot study using a questionnaire written specifically to explore the views of patients about organ donors was conducted. The questionnaire was initially trialled amongst transplant specialist nurses, clinicians and post-transplant patients to test validity and reliability. Inclusion criteria were adults over 18 years of age active on the deceased donor kidney transplant waiting list, attending a pre-transplant clinic or dialysis centre at one UK transplant centre. Exclusion criteria were candidates deemed as unable to consent, or unable to understand written English. Data was collected over 4 months.

Results: Of the candidates who consented to participate in the study, 22 out of 24 completed the questionnaire. More than half (59%) would like information about potential donors, in particular statistical information about the length of time a kidney would function by reference to the age of the donor and recipient. Over 60% of participants were willing to accept kidneys from extended criteria and older donors. They were pragmatic about the risks. Participants trusted the medical team and they were happy to leave the decision whether to accept a kidney to the clinicians. A small number (20%) did not want kidneys from extended criteria donors.

Conclusion: This pilot study had a good response rate, suggesting that this patient group are highly motivated and interested in increasing their knowledge about transplantation. The results indicated that a significant proportion would like more information about their organ donor. A minority did not want any information which demonstrates that it is important for clinicians to assess patients to find out how much information they want to receive.

P229

Routine myocardial stress imaging combined with selective coronary angiography for the assessment of patients undergoing simultaneous pancreas and kidney transplantation

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Introduction: Diabetics have a higher incidence of occult cardiovascular disease and warrant careful assessment prior to listing for simultaneous pancreas and kidney transplantation (SPK). We sought to assess our screening practice, and see whether it predicted post-operative cardiac events.

Methods: Patients assessed for SPK underwent cardiac magnetic resonance stress imaging (MRI), radionuclide myocardial perfusion imaging (MPI), or dobutamine stress echocardiography (DSE). Significant abnormalities were evaluated by coronary angiography. Prospectively collected assessment data were studied together with retrospective review of their post transplant records for cardiac events.

Results: 145 patients were transplanted between January 2001 and November 2012. 143 underwent stress testing of some sort, and 2 went to coronary angiography as first line investigation. 101 (71%) had satisfactory stress imaging and 42 (29%) had an abnormality and proceeded to angiography. Of these, 4 patients (3%) required stent(s) placement for a lesion discovered at angiography. In the same period, 7 (**5%**) patients had a cardiac event following SPK, 5 (**3.5%**) of which were myocardial infarction (MI). 3 (2 MIs) of these were in patients who had undergone angiography. None of the 3 patients with a history of MI had a cardiac event following SPK. None of the 4 patients who underwent stenting had a subsequent cardiac event. A further 29 patients were assessed for SPK transplantation in the same 11 year period and declined for a variety of reasons, but only 1 (**0.6%**) patient because of poor cardiac function.

Conclusion: A policy of screening by stress imaging combined with angiography when indicated is associated with a low cardiac event rate post SPK transplantation.

P230

Not recording BMI on patients' waitlisted for transplantation is associated with a significantly less chance of receiving a kidney transplant

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We analysed the U.K transplant registry data for the period from 1st January 2004 to 31st December 2010.

A total of 13167 patients were listed for the first time during 2004-10; including 8100 (62%) males and 5056 (38%) females, with data missing for 11 patients. 3241 (25%) patients had missing BMI. Survival analysis was done using Cox PH modelling.

There was significant variation in transplant proportion by centre, ranging from minimum 29.4% (170 of 578 pts) to maximum 70.45 (231 / 338 patients). At least one BMI measure was recorded for 75.4% of patients (9926/13167); there was significant variation in availability of BMI data between centres, ranging from 13.3 (116/875) to 99.5% (185/186). Also, inclusion of transplant centre in analyses had no significant impact on estimates.

We divided the patients into BMI bands of <=18, 18.1 -30, 30.1-35, >35.1 and missing BMI. The recipient variables analysed were age, gender, ethnicity, primary diagnosis, rejection episodes and duration of renal replacement therapy prior to transplantation.

Significantly fewer female than male patients received a renal transplant during the study period; 46% vs. 50%, P<0.0001. There was some variation in receipt of transplant between ethnicity defined groups, with white patients most and Asian patients least likely to receive a transplant, P<0.0001. BMI band of 18.1-30 kg/m2 was most likely to receive a transplant and BMI band of <18 were less likely. If no BMI was recorded there was a significant disadvantage in receiving a kidney transplant as shown in Table 1.

Table 1

BMI Band	p Value	Hazard Ratio (HR)	N
<18	0.0081	0.76 (0.62 to 0.93)	196
18.1-30	Reference	1	7435
30.1-35	0.44	0.97 (0.90 to 1.05)	1868
>35	0.78	0.88 (0.77 to 1.01)	417
Missing BMI	<0.0001	0.64 (0.60 to 0.69)	3240

In conclusion, our analyses show that if patients do not have BMI recorded whilst waiting for transplantation, they have a significantly less chance of being transplanted. As BMI is not included in the criteria for offering kidneys, further studies are needed to investigate this association.

Poster session

Wednesday 13th March

18:15 - 19:25

Rejection and DGF

P231

Does it really matter which definition of delayed graft function we use after renal transplantation?

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Introduction: Delayed Graft Function (DGF) is associated with graft nephropathy, rejection and loss after renal transplantation. A recent systematic review identified eighteen heterogeneous DGF definitions, none of which is universally accepted. Their relative value in predicting graft outcomes is unknown. The aim of this study was to compare different DGF definitions' sensitivity and specificity for predicting biopsy proven acute rejection (BPAR), graft loss and serum creatinine at 1 year.

Methods: All renal transplants at our centre from Jan 2001–Dec 2010 were retrospectively analysed (n = 762). Ten different definitions of DGF identified from the literature were evaluated. DGF definitions' sensitivity and specificity for BPAR and graft loss at one year was found and McNemar's test was applied to compare them. Student's t test was used to determine whether there were significant differences between DGF definitions' mean creatinine values at one year.

Results: There was no significant difference between DGF definitions' mean serum creatinine at 1 year (p=0.76). DGF definitions' sensitivity and specificity for graft loss at 1 year ranged from 63.5%-73.0% and 67.1%-85.7% respectively. DGF definitions' sensitivity and specificity for BPAR were 34.6%-46.3% and 80.5%-84.8% respectively. There were significant differences between the predictive value of "creatinine-based" and "dialysis-based" DGF definitions for both graft loss at 1 year (p=0.004) and BPAR (P=0.001), with "dialysis-based" definitions having higher sensitivity and specificity for graft loss and "creatinine-based" definitions having higher sensitivity for BPAR. There were no significant differences between the "dialysis-based" DGF definitions' sensitivities or specificity for BPAR (p=0.67, 0.54) or graft loss at 1 year (p=0.92, p=0.29). There was no significant difference between the sensitivities of "creatinine-based" definitions.

Discussion: There were significant differences between different DGF definitions' sensitivities for BPAR and graft loss at 1 year. The identification and adoption of a gold standard definition would reduce DGF misclassification, increase study comparability and aid the development of more reliable diagnostic tests for DGF.

P232

Circulating microRNAs as early biomarkers of acute renal allograft rejection

Joanna Willis[1], Espe Perucha[1], Irene Rebollo-Mesa[1], Sui Phin Kon[2], Christopher Farmer[3], Paramit Chowdhury[1], Maria Hernandez-Fuentes[1], Graham Lord[1]

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Background: MicroRNAs (miRs) are well-recognised as potential biomarkers in transplantation. Over-expression of miR142 (-3p & -5p) in human renal allograft biopsies was found to be highly predictive of acute rejection (AR) (Anglicheau et al, 2009). However, the potential of miRs as early (pre-biopsy) biomarkers of AR is as yet unexplored. We aimed to investigate the feasibility & utility of miR142 as a peripheral biomarker in the weeks leading up to an episode of AR.

Methods: RNA was extracted from plasma and PBMC samples from 9 patients with biopsy-proven AR, taken at 4 time-points (immediately pre-biopsy, 1 week, 3 weeks and 6 weeks pre-biopsy), 9 stable transplant recipients at matched time-points, and 3 healthy controls. Due to uncertainty in the scientific community regarding optimal plasma miR RT-PCR methodology, healthy control plasma samples were subjected to various methods of RT-PCR and normalisation (including spiking in a synthetic miR, fixed volume vs. fixed mass of RT input, and miR16 as an endogenous control) to determine the optimal method prior to testing patient samples, which were then reverse transcribed and subjected to RT-PCR.

Results: Median-normalisation to spiked in synthetic miR39 and the use of a fixed volume of eluted RNA as the RT input resulted in a reduction in the coefficient of variation on repeated measurement of the same plasma samples from 6% to <1%. Plasma miR16 expression was stable across patient groups (2 way ANOVA p=0.7) and time-points (p=0.8), suggesting it is a suitable endogenous control in this population. There was a trend towards patients with AR having higher circulating (PBMC and plasma) miR142-3p and -5p expression than stable recipients at 3 and 1 weeks prior to the episode of AR, as well as immediately pre-biopsy, although it did not reach statistical significance in this cohort.

Conclusions: Our data demonstrate a suitable method for measuring circulating miRs by RT-PCR in renal transplant recipients. Circulating miR142-3p and -5p show promise as early biomarkers, potentially even heralding AR prior to the onset of allograft dysfunction. A further cohort is being tested.

P233

CD68 positive glomerulitis predicts the development of transplant glomerulopathy in patients with cellular rejection

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Transplant glomerulopathy [TG] has a very poor prognosis and is almost always associated with eventual graft failure. The risk of TG is increased in patients who have experienced acute rejection or have had evidence of microcirculatory inflammation. The Banff classification stipulates that glomerulitis [GL] is a lesion predominantly associated with AMR; it may occur in ACR although its significance is not well described. The purpose of this study was to establish the significance of GL in patients with ACR.

147 cases of ACR [m104 (70.7%); 67LD (45.6%)] with predominant tubulo-interstitial rejection were analysed. Mean follow up post biopsy [bx] was 2.74 ±1.55yrs. All patients had received monoclonal antibody induction with a tacrolimus based, steroid sparing maintenance immunotherapy regime.

Patient and allograft survival was 94.2% and 82.5% 2yrs post bx. 27/147[18.4%] patients had GL. GL was not associated with allograft failure, HR 0.89, p=0.80; further episodes of TCMR, HR 0.93, p=0.83 or AMR, HR 0.64, p=0.48. GL was associated with subsequent TG, HR 10.67, p<0.001. Glomerular immunohistochemistry staining showed that 8/25(32.2%) cases had CD3+ cells alone, 6/25(24.0%) CD68+ alone and 13/27(48.1%) had both CD3+ and CD68+ cells. Only patients with CD68+ cells were at risk of developing TG, with TG free survival in the CD3+ group, CD68+ group and CD3+/CD68+ group being 87.5%, 44.4% and 45.5% respectively, p<0.01.Pure CD68+GL was strongly associated with the presence of donor specific antibodies [DSA] with 5/6[83.3%] having DSA.

This study shows the importance of determining the type of infiltrating cell in GL. CD68+ cells herald the development of TG and a pre-emptive increase in immunosuppression may be preventative.

P234

Delayed graft function in renal transplant patients receiving a steroid sparing regime

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Delayed graft function [DGF] is common post deceased donor renal transplantation [DDTx] and is associated with increased risk of allograft loss. The aim of this study is to determine the risk factors and outcomes of DGF in patients receiving a steroid sparing immunosuppressive protocol.

We retrospectively studied 427 patients who received a DDTx at our centre between 2005-2011. All patients received monoclonal antibody induction with tacrolimus based maintenance immunosuppression and corticosteroids for one week only. The mean follow up post transplant was 42.62 ± 19.96 months.

135[31.6%] experienced DGF. Patient survival was inferior in the DGF group at 90.6% compared with 69.2% in the non DGF group,p=0.0025. Allograft survival was also inferior in the DGF group at 73.8% compared with 90.2% in the non DGF group, p=0.0001. Rejection risk was not increased in the DGF group, with a rejection free survival of 67.8% in the DFG patients compared with 74.1% in the non DGF group, p=0.18.The table below shows the factors found to be associated with DGF at the time of transplantation by univariant analysis.

Factor		DGF	Non DGF	p value
Recipient age	Yrs	51.43 ± 12.19	47.45 ± 13.93	0.0046
Donor age	Yrs	51.56 ± 13.05	47.00 ± 15.99	0.0041
Recipient gender	Male	105 (77.8%)	178 (61.0%)	0.0009
Ethnicity	Black	35 (27.1%)	41 (15.5%)	0.0094
Time on RRT	Yrs	6.37 ± 5.44	5.00 ± 5.07	0.012
Donation type	DCD	45 (33.3%)	32 (11.0%)	<0.00001
CIT	Hrs	24.70 ± 7.82	21.29 ± 7.58	0.000023

On multivariant analysis black ethnicity, DCD kidneys, CIT, donor age and time spent on dialysis were associated with DGF and female recipients had a reduced risk of DGF. This study has identified risk factors for developing DGF post transplant in patients receiving a steroid sparing protocol.

P235

Luminex-based screening of T cell activation markers in the urine of renal transplant recipients correlates with graft rejection

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Background: Diagnosing renal transplant rejection depends on measuring serum creatinine, recognizing pathological changes in biopsies and detecting donor-specific HLA antibodies. The detection of lymphocyte associated chemokines in the urine of functioning grafts, potentially provides an early biomarker to predict long term transplant outcome and potential rejection episodes. We have therefore investigated the presence of osteoprotegerin (OPG), monokine induced by interferon- γ (MIG) and interferon-γ induced protein (IP-10) biomarkers in urine of renal patients with or without rejection. OPG is a secreted glycoprotein regulating bone resorption, a member of the TNF receptor superfamily and a marker of T cell activation. By contrast, MIG is a T-cell chemoattractant inducible by gamma interferon, while IP10 is a T cell and monocyte chemoattractant.

Methods and results: Using the Luminex platform for identification of chemokines, we analysed 106 mid-stream urine specimens from 45 renal transplant recipients at time of biopsy, for the presence and absence of OPG, MIG and IP-10. OPG was detected in 86/106 (81%) of urines (range= 1-1,200pg/ml; median = 16pg/ml). MIG was detected in 62/106 (58.4%) of urines (range = 4 -1603pg/ml; median = 37.9pg/ml). IP-10 was detected in 94/106 (88.7%) of urines (range = 9 – 3908pg/ml; median = 215pg/ml). 11/45 (24.4%) patients had biopsy proven episodes of cellular rejection and generated significantly higher median levels of OPG, MIG and IP-10 in their urine at or around the time of biopsy (IP-10, P=0.002; MIG, P=0.006; OPG, P=0.005, Student's t-test), when compared to rejection free patients.

Conclusions: Screening urine biomarkers in renal allograft recipients with Luminex is a rapid, sensitive and potentially informative adjunct to standard methods of diagnosing rejection. These biomarkers were not elevated in transplant patients who had impaired renal function due to non-immunological factors.

P236

Late acute rejection in adult renal transplant recipients: can we predict it?

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Introduction: High intra-patient serum tacrolimus variability is associated with increased risk of acute rejection (AR) and poorer outcomes. AR occurring beyond one year – late AR (LAR) – is linked to non adherence with medication; particularly in adolescent recipients. Rates of early (EAR) and LAR within our adult renal population were investigated with plans to pilot 'Transplant 360' as an educational and motivational tool to improve adherence.

Method: Data were collected retrospectively from the patient electronic records for adult kidney recipients from 03/01/2007 to 26/03/2010. Statistical analysis compared recipients with EAR and LAR for sex, age, eGFR at 1 yr and graft failure. Patients were then invited to watch the 'Tx360' DVD. Tacrolimus variability was calculated pre and at intervals post intervention.

Results: 242 recipients were followed for an average of 3.98 yrs (IQR 3.05 - 4.75), 14% (34/242) of recipients had EAR with only 5% (11/242) having LAR. However, 36% (4/11) of those with LAR experienced graft failure (9% with EAR). Sex, age and eGFR at 1 yr showed significance between EAR and LAR. A small number of patients watched the educational DVD and 4/6 showed improved tac variability.

Discussion: LAR affects a small proportion of our population with a significant increased chance of graft loss. Sex, age and eGFR at 1 yr may help us predict these high risk patients who would perhaps benefit from education to improve medication adherence and thus improve outcomes. Further research into risk factors or predictors associated with LAR is needed to enable the use of TX360 in a cost effective way.

P237

Eculizumab use in refractory acute antibody mediated rejection; short-term success and long-term concerns

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

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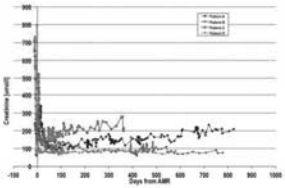
Introduction: Acute antibody mediated rejection [aAMR] is a common cause of renal allograft failure both in the short and long term. Eculizumab [Ec] has anecdotally emerged as a therapeutic option when allograft loss seems inevitable acutely, but little is known about reliability or sustainability of effect.

Methods: In this study we describe Ec therapy in 4 consecutive patients [2 antibody incompatible transplants] who had refractory aAMR, occurring at a mean time after transplantation of 6.5±4.8 days. Creatinine continued to deteriorate in spite of Methyl Prednisolone, ivIg and 5.0±5.5 plasma exchanges, with high and rising de novo anti-HLA donor specific antibodies [DSAbs]. 600mg of Ec was administered to each patient at weekly intervals for a total of 6 doses and plasma exchange stopped. Mean follow up was 16.9±5.7months.

Results: Patient and allograft survival is 100%. Creatinine after AMR is shown in the figure below. There has been a reduction in DSAbs in all but one patient, with disappearance in 2. All patients have undergone re-biopsy; 2 had ongoing alloimmune injury, 1 had acute cellular rejection [TCR] and 1 had BK viral nephropathy.



Conclusion: This is the largest study to show that Ec is 100% effective at preventing allograft loss from aAMR in the short term. However, treatment is not without subsequent rejection episodes or infective complications and 2 allografts are deteriorating with BKVN and chronic AMR. One of the 2 remaining cases with a stable creatinine may not have alloimmune injury on biopsy (TCR) but is the case with continuing and significant DSAbs. Consequently, longer-term outcomes may mirror the use of Ec as prophylaxis in HLA incompatible transplantation where continual Ec infusions can be required and Transplant Glomerulopathy is reported.

Poster session

Wednesday 13th March

18:15 - 19:25

Transplantation biology

P238

The cyto-protective role of autophagy in human hepatocytes during oxidative stress

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Introduction: The role of the cellular process of autophagy in human hepatocytes during oxidative stress remains unknown. Understanding this process may have important implications for the understanding of basic liver epithelial cell biology and the responses of hepatocytes during liver disease. In particular this would improve the understanding hepatocyte survival during and following liver transplantation.

Methods: To address this we isolated primary hepatocytes from human liver tissue and exposed them ex vivo to hypoxia and hypoxia-reoxygenation (H-R).

Results: We showed that oxidative stress increased hepatocyte autophagy in a reactive oxygen species (ROS) and class III PtdIns3K-dependent manner. Specifically, mitochondrial ROS and NADPH oxidase were found to be key regulators of autophagy. Autophagy involved the upregulation of BECLIN1, LC3A, Atg7, Atg5 and Atg 12 during hypoxia and H-R. Autophagy was seen to occur within the mitochondria of the hepatocyte and inhibition of autophagy resulted in the lowering a mitochondrial membrane potential and onset of cell death. Autophagic responses were primarily observed in the large peri-venular (PV) hepatocyte subpopulation. Inhibition of autophagy, using 3-methyladenine, increased apoptosis during H-R. Specifically, PV human hepatocytes were more susceptible to apoptosis after inhibition of autophagy.

Conclusion: These findings show for the first time that during oxidative stress autophagy serves as a cell survival mechanism for primary human hepatocytes.

P239

Indirect CD4 T cell allorecognition of MHC class II alloantigen is limited by adaptive immunity

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Introduction: We have previously described a partially-mismatched [bm12.Kd.IE (IA^{bm12}, IE^{d}, K^{d}, K^{b}, D^{b}) to C57BL\6] model of chronic rejection, demonstrating that indirect CD4 T cell allorecognition of donor MHC class II alloantigen occurred only transiently. This work aims to identify the factors limiting this response.

Methods: Indirect CD4 T cell allorecognition of donor MHC class I and II was assessed by quantifying proliferation of, respectively, CFSE-labelled TCR-transgenic TCR75 (H2-K^{d} peptide-specific) and TEa (I-E peptide-specific) CD4 T cells, adoptively transferred on day 0 or 28 following transplantation of bm12.Kd.IE hearts into either wild-type or RAG2KO C57BL/6 recipients. The role of donor DC's in priming indirect allorecognition was assessed by incorporating BALB/c.DTR donors, enabling ablation of donor DCs by diphtheria toxin, and by adoptive transfer of cultured bone-marrow derived dendritic cells (BMDC's).

Results: Extensive proliferation of TCR75 CD4 T cells was observed in heart-grafted recipients both early and late. TEa proliferation was detectable only immediately after transplant. We hypothesised that early termination of the class II response reflected rapid loss of donor DCs; in support, donor DC depletion attenuated the indirect class II response but only mildly reduced class I responses. Donor DCs were not killed by NK cells, because bm12.Kd.IE cells survive long-term in RAG2KO recipients. Equally, late anti-class II indirect responses in RAG2KO recipients were detectable, albeit weaker than the response immediately following transplantation, suggesting that donor DCs are instead lost to natural senescence and adaptive immune killing. Critically, transfer of donor BMDC's into RAG2KO recipients 28 days after heart grafting completely restored late TEa responses, but this was not seen in WT recipients, presumably because rapid killing of donor DC by primed adaptive alloimmunity prevents antigen presentation.

Discussion: The longevity of indirect-pathway CD4 T cell responses varies according to target antigen. The class II response terminates early, likely because donors DCs, the major source of MHC II alloantigen, are depleted rapidly.

P240

How to track adoptive Treg therapy in transplantation: a pre-clinical skin transplantation model

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Introduction: Regulatory T cells (Tregs) were identified several years ago and are key in controlling autoimmune diseases and limiting immune responses to foreign antigens. Tregs are being studied for adoptive transfer immunotherapy for various diseases such preventing transplant rejection. However, key questions such as where therapeutic Tregs go and how long they stay viable in patients remains unsolved. Here we are trying to answer these questions in a pre-clinical set up with the help of nuclear medicine imaging technology.

Methods: Imaging of the human sodium/iodide symporter via Single Photon Emission Computed Tomography (SPECT) has been used to image various cell types *in vivo*. This study addresses whether SPECT/CT imaging can be used to visualise the migratory pattern of Tregs *in vivo*. Murine Treg lines were retrovirally transduced with a construct encoding for the human Sodium Iodide Symporter (NIS).

Results: NIS expressing Tregs were specifically radiolabelled *in vitro* with Technetium-99m pertechnetate ($^{99m}TcO_4^-$) and exposure of these cells to radioactivity did not affect cell viability, phenotype or function. In addition adoptively transferred Treg-NIS cells were imaged *in vivo* in mice by SPECT/CT using $^{99m}TcO_4^-$. After 24-hours Treg-NIS cells were observed in the spleen and their localisation was further confirmed by organ-biodistribution studies and flow cytometry analysis. Moreover, we have demonstrated that this method of imaging can be utilised to image migration of Tregs with direct and indirect allo-specificity in a skin transplant model.

Discussion: The data presented here suggests that SPECT/CT can be utilised in preclinical imaging studies of adoptively transferred Tregs without affecting Treg function and viability thereby allowing longitudinal studies within disease models. Moreover, this technology has also the potential to be applied to human Treg studies in future.

P241

Renal transplant recipients (RTR) with chronic immune mediated graft injury display significant alterations within the peripheral B lymphocyte phenotype

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Phenotypic characterization of PBMCs constitutes part of the immune signature for operational tolerance in RTRs. Alterations of subpopulations in the PBMCs of patients with biopsy proven microcirculation injury are less well understood.

In this study, we analysed various Lymphocyte subsets in the peripheral blood of healthy volunteers and RTRs and assessed their relationship with graft function. A total of 110 healthy volunteers and RTRs were included in this study (Healthy volunteers (n=18); and RTR-stable graft function (n=45); GD-NI: graft dysfunction-non immunological (n=22); GD-I: graft dysfunction-immunological (n=25)). All RTRs also had serum analysis for Donor Specific Antibody using Luminex beads. Absolute numbers of lymphocytes in the peripheral blood were quantified using Trucount beads. Lymphocyte subsets within the T and B cell compartments were analysed and compared across the patient groups (Significant differences are shown in Table-1). There were no significant differences in the numbers of the recent thymic emigrants, naïve $CD4^+$T cells, and central or effector memory $CD4^+$ T cells. Within the GD-I group, 30% of the patients with no DSAs on serum analysis had significantly higher numbers of TRS cells along with a higher B-Naïve-memory ratio and a marginally higher proportion of Tregs. B lymphocytes which were found to distinguish the clinical subgroups of patients were further analysed by multi-colour flow cytometry. $CD19^+CD24^{hi}CD38^{hi}$ (TRS cells) cells which were

Cell type	HC (95% CI)	S (95% CI)	GD-NI (95% CI)	GD-I (95% CI)	P-value
$CD3^+$ T cells	1496 (1168-1824)	1144 (1011-1277)	1154 (874-1435)	1123 (921-1325)	<0.05
CD4+ T cells	878 (730-1025)	650 (563-738)	646 (461-831)	616(491-741)	<0.01
CD19+ B cells	349 (223-475)	257 (216-297)	136(101-171)	140 (93-188)	<0.01
NK cells	274 (218-330)	238 (201-275)	205 (154-258)	139 (91-187)	<0.01
T Regs	6.7% (5.8%-7.7%)	5.1% (4.6%-5.5%)	4.6% (4%-5.2%)	4.5% (3.6%-5.3%)	<0.01
$CD19^+CD24^{hi}CD27^+$ B cells	22.5% (17%-28%)	13% (9%-17%)	14% (9%-18%)	21% (15%-26%)	<0.05
TRS B cells	14% (11%-17%)	11% (9%-12%)	8% (6%-10%)	5% (3%-7%)	<0.01
TRS-T1/T2 ratio	0.3 (0.2-0.4)	0.22 (0.17-0.25)	0.2 (0.15-0.25)	0.09 (0.03-1)	<0.01
B Naïve/Memory ratio	3 (1.5-4.4)	7.6 (6-9)	9.6 (3.8-16)	3.8 (2-5.7)	<0.01

significantly reduced in patients with biopsy proven microcirculation injury were found to contain a significant number of the $CD19^+CD5^+CD1d^{hi}$ cells which correspond to regulatory mouse B-10 cells. In a separate series of experiments we demonstrated that these cells exhibit regulatory properties in vitro.

In summary we have shown significant differences within the B cell compartment with a t reduction in the circulating regulatory type peripheral B subsets in patients with histological evidence of immune mediated graft injury. Such a phenotype has to be studied prospectively to assess its clinical utility.

P242

Identifying dysregulation of the B cell compartment in patients with deteriorating renal graft function

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Introduction: B cells have multiple immunological functions. In transplantation their defining role has been the secretion of HLA antibody against the allograft. However more detailed analysis of these cells suggests additional factors may contribute to dysfunction in the B cell compartment. Here we investigate expression of the B cell activating factor (BAFF), a member of the tumour necrosis family essential for B cell selection, differentiation and survival. Excessive BAFF production has been associated with the development of autoimmune disorders and recent studies in renal transplant recipients have shown elevated serum BAFF (sBAFF) to be associated with rejection and the development of donor-specific antibody (DSA). In this study we measured sBAFF and its receptor (BAFF-R) to identify the relationships between differential expression and level of function of the allograft. In addition we investigated if the presence of regulatory B cells (Breg) would also differ depending on graft function.

Method: Peripheral whole blood was collected from renal transplant recipients with deteriorating (gp 1), stably impaired (gp 2) and well-functioning (gp 3) grafts a minimum of one year post-transplant. $CD19^+$ cells were isolated by positive selection and stained for CD19 & BAFF-R. $CD19^+$ cells were cultured for 5 days in the presence of CpG-B 2006 (3ug/ml) for Breg analysis. Post-culture cells were treated with PMA (50ng/ml), ionomycin (500ng/ml) and monensin (2mM) stained for surface CD19, CD24, CD38 and intracellular IL-10. sBAFF levels were measured by ELISA. HLA antibodies were assessed using Luminex technology and HLA Single Antigen beads.

Results: Patients in gp1 (n=20) had significantly higher sBAFF levels than those in gp 2 (n=10) and gp 3 (n=16) (mean values 1005.66, 681.74, 664.70pg/ml respectively; gp 1 vs. gp 2 $p=0.047$, gp 1 vs. gp 3 $p=0.125$). In addition, expression of BAFF-R on $CD19^+$ cells is downregulated in gp 1 patients (62.87%) compared to gp 2 & 3 patients (86.71 & 87.54% respectively; $p<0.001$). DSA with elevated sBAFF (higher than the overall mean; >784.03pg/ml) or low BAFF-R (lower than the overall mean; 79.03%) were only detected in gp 1 patients. Furthermore the rate of graft deterioration showed a significant correlation with elevated sBAFF level ($p=0.004$) but not with decreased expression of BAFF-R. In a smaller cohort of patients (n=5) there was an increase in IL-10 producing B cells in gp 3 patients compared to gp 1 (1.09% vs. 0.27%; $p=0.04$). In addition these cells were enriched in the $CD24^{high}CD38^{high}$ compartment (gp 1; 31.84 vs. 5.18% & gp 3; 30.66 vs. 5.51%).

Conclusion: These data show that expression of sBAFF and its receptor correlate with deteriorating graft function, suggesting an important role in regulating B cell homeostasis. In addition, preliminary data shows B cells with a regulatory phenotype are associated with stable graft function but further investigations are necessary to link these cells with down regulation of the immune response.

P243

Tregs of haemodialysis patients are phenotypically comparable to healthy controls: implications for cell-therapy in transplantation

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Background and objectives: Cell-based therapy to induce transplant tolerance is now a realistic possibility. Highly suppressive $CD4^+CD25^{hi}CD127^{lo}$ "natural" regulatory T cells (Tregs) are considered candidates as cellular products for clinical trials as they can be expanded from healthy controls (HCs) *ex vivo* under good-manufacturing practice (GMP) conditions while retaining their function. However, human Tregs are heterogeneous and there are suggestions that Tregs from patients on haemodialysis (HD) awaiting transplantation are functionally defective and that they are predominantly of memory ($CD45RO^+$) sub-types. In addition, memory human Tregs retain plasticity and can convert to the pro-inflammatory Th17 lineage under inflammatory conditions, as could be encountered in the HD environment, during transplantation or during infections post-transplantation. Here, we address the suitability of Tregs from patients on HD for clinical trials of cell-based therapy.

Methods: Tregs from 14 stable HD patients and 14 age- and sex-matched HCs were studied by flow cytometry to compare Treg sub-populations and phenotypic surface marker expressions. Their suppressive function and plasticity (capacity to produce IL-17) at baseline and following *in vitro* expansion in the presence or absence of Rapamycin were then compared using standard assays.

Results and conclusions: We show for the first time that Tregs from patients on HD have phenotypically comparable sub-populations to age- and sex-matched HCs, including a population of $CD161^+$ Tregs that have the capacity to convert to Th17. HD Tregs, however, were less suppressive and expanded poorly relative to healthy Tregs in the absence of Rapamycin. As predicted, they also retained significant Th17 plasticity. The presence of Rapamycin in the cell culture efficiently expanded HD Tregs to a highly suppressive cell product and abrogated their Th17 potential. These data argue that patients on HD have suitable Treg populations for use in clinical trials of cell-based immunotherapy for the induction of tolerance to renal allografts, and that Rapamycin-based protocols would be most suitable for such trials.

P244

Galectin-1^{+} T2 B cells isolated from mice housed in conventional facilities, but not SPF facilities, promote allograft survival *in vivo*

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In transplantation, B cells are generally thought to promote graft rejection through the production of alloantibody. However there is growing evidence that B cells can also contribute to the maintenance of tolerance both in animal models and in humans. Recently, spontaneous tolerance to kidney transplants has been associated with a B cell signature in patients' peripheral blood. Here we use a mouse model of MHC-class I mismatched skin transplantation to investigate the contribution of B cells to graft survival.

We demonstrate that the adoptive transfer of naïve transitional-2 (T2) B cells can prolong skin graft survival, but only when the B cells are derived from mice housed in conventional (cv) facilities and not in specific pathogen free (spf) facilities. The immunoregulatory function of the T2 B cells was shown *in vitro* by their ability to suppress alloantigen-stimulated CD4^{+} T cell activation. To confirm the involvement of bacteria in the acquisition of regulatory function by T2 B cells we demonstrate that antibiotic treatment of mice kept in cv facilities abolishes the regulatory function of B cells. We also demonstrate that IL-10 is not involved in their regulatory function. Finally we demonstrate that the expression of Galectin-1 (Gal-1), a molecule with immunomodulatory functions for B and T cells, was necessary for the acquisition of regulatory function by T2 B cells. The ability to prolong graft survival *in vivo* and to suppress T cell activation *in vitro* is lost when B cells are isolated from the spleens of Gal-1$^{-/-}$ mice.

These results suggest that T2 B cells can suppress the alloimmune response to prolong graft survival, but only when they are "licensed" *in vivo* under non-hygienic conditions and that the expression of Gal-1 is necessary for their function.

P245

Laminin-511 degradation is targeted by neutral protease and thermolysin, but not collagenase

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Objectives: Donor variables influence the protein structure of the peri-islet extracellular matrix (ECM) and may influence enzymic digestion of the ECM. We have previously reported that peri-islet laminin increased with age and was more susceptible to Collagenase blend digestion. Laminin-511 is an enzyme-digestible isoform found in both the outer endocrine and inner vascular basement membrane of the intra-islet vascular channels. However, no previous study has investigated how laminin proteins are digested. Here, we incubate recombinant laminin-511 with constituents of commonly used enzyme blends to determine which enzymes degrade which peri-islet ECM proteins during islet isolation.

Methods: Recombinant laminn-511 was incubated with Collagenase isoforms, Class I and Class II, Collagenase Class I fragment, Clc, Neutral Protease, Thermolysin or Clostripain (tryptic–like activity). It was also incubated with Class I and Class II isoforms in combination (60:40) ±Neutral Protease. Digestion of laminin-511 was assessed by gel electrophoresis for Western Blotting or Coomassie staining. Determination of laminin-511 cleavage sites was determined by proteomic tandem mass spectrometric methods.

Results: Recombinant laminin-511 was digested by Neutral Protease and Thermolysin, and to a lesser extent, Clostripain. Laminin-511 was not digested by Collagenase isoforms alone or in combination except in the presence of Neutral Protease. Cleavage sites of laminin-511 were localized to the "arms" of the individual peptide chains with Thermolysin being the most aggressive enzyme. Additionally, Thermolysin cleaved the Laminin alpha5 chain in the C-terminal globular domain, which interacts with islet integrins and other cellular receptors.

Conclusions: As age affected peri-islet laminin and its digestion by Neutral Protease is less susceptible in younger donors, we suggest that islet yields from younger donors could be improved by substituting Neutral Protease with the more aggressive Thermolysin in Collagenase blends.

P246

Regulation of transplant inflammation by the atypical chemokine receptor D6

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Introduction: The function of transplanted organs is limited by immunological processes. Chemokines are intimately involved with each stage of allograft inflammation, from ischemia reperfusion injury and acute T cell mediated rejection to chronic rejection. The pluripotent atypical chemokine receptor D6 is able to bind >11 proinflammatory chemokines and is thought to have a powerful capacity to regulate inflammation. Although we have previously reported strong D6 upregulation in human cardiac allograft biopsies, no previous studies have examined the role of D6 during transplantation.

Methods: Fifteen human renal transplant biopsies were examined by confocal immunofluorescence microscopy to quantify and phenotype D6 expression patterns. A murine model of skin and renal ischemia reperfusion injury was performed contrasting wild-type and D6 knockout mice; tissue inflammation was monitored non-invasively using the IVIS platform. Murine skin transplantation was performed to assess the rejection of fully MHC mismatched skin by wild-type and D6 knockout recipients.

Results: D6 was expressed by $CD45^{+}CD68^{+}$ infiltrate during acute kidney rejection, with significantly increased expression in more severe rejection ($p<0.05$). Skin and renal ischemia reperfusion injury was increased in the absence of D6 ($p<0.01$). Median survival of MHC mismatched skin was 6 days in wild-type and 10 days in D6 knockout recipient.

Discussion: D6 plays distinct roles in different types of transplant inflammation. D6 was protective against ischemia reperfusion injury however T cell driven acute rejection was significantly delayed in D6 deficient recipients. These data represent the first investigation of the role played by an atypical chemokine receptor in transplantation.

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Investigation into the role of B-lymphocytes and tertiary lymphoid tissue in a mouse model of renal chronic allograft damage

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Background: Nodular B-lymphocyte rich infiltrates have been identified in chronically rejected renal allografts and biopsies of acute transplant rejection, this has been associated with the development of tertiary lymphoid tissue (TLT). However their significance is unclear, with conflicting published data. We aim to investigate the role and significance of B-lymphocyte infiltrates and the development of TLT in a murine model of renal chronic allograft damage.

Methods: We have used congenic strains with donor C57BL/6-BM12 mice kidneys transplanted into C57BL/6 recipients, this being a single MHC-II mismatch. Using immunohistochemistry we investigated the presence of B-lymphocytes within the allograft. In addition we have investigated other markers of chronic allograft damage in this model including lymphatic expansion, micro-vessel rarefication and fibrosis.

Results: Nodular aggregates of B-cells appearing to be TLT develop over a 12-week period; however in some allografts we observed a scattered B-cell pattern. The B-cell infiltrate of the allograft cortex increased progressively with a significant increased density by 12 weeks compared to 5 days after transplantation. Micro-vessels were counted using a 25-point graticule and there was a significant difference between allograft and native kidney cortex ($p<0.01$) with both time and transplant kidney being responsible for affect. There was a significant difference in the number of lymphatic vessels at 12 and 8-weeks compared to 5-days ($p<0.05$). Similar to findings in human chronic rejection the expanded lymphatics were seen both in the tubulointerstitium and in the perivascular regions. The B-lymphocyte phenotype was explored and shown by immuno-fluoresence to form germinal centres with IgG+ CD138+ plasma cells.

Conclusion: We have shown that this strain combination closely models that of chronic rejection of the renal allograft; furthermore we have identified the progressive infiltration and expansion of the B-lymphocytes compartment within the allograft cortex. This work has provided the basis for further investigation of B-lymphocyte depletion and the prospects of identifying a regulatory B-lymphocyte.

Poster session

Wednesday 13th March

18:15 - 19:25

Access 1

P248

Novel approach to reduce the burden of neointimal hyperplasia in arteriovenous fistulae

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Introduction: The use of native arteriovenous fistulae (AVF) for haemodialysis access is hampered by a high failure rate, due to the development of early neointimal hyperplasia, in which haemodynamic factors are thought to play an important role. Given the seeming importance of the local flow, including its physiological three-dimensionality, our group wishes to determine whether the adoption of non-planar conformation at the anastomoses can reduce the burden of neointimal hyperplasia.

Methods: Perspex models of an AVF were created with planar orientation of the vessels at a range of anastomotic angles. A further, otherwise identical set of models, were created with 'offset' junctions, novel non-planar anastomoses, which mimicked the geometry at the origin of arterial branches and can improve flow characteristics by inducing swirling. Comparative observations were made under non-pulsatile (but otherwise physiological) flow conditions, using flow visualisation and computational fluid dynamics (CFD).

Results: Similar results were observed in the flow visualisation and CFD work. Flow separation occurred at outer walls of curvature in both planar and offset (non-planar) models, but appeared reduced in the offset case. It is suggested that flow disturbance (including separation, wall shear abnormality and instability) occurs in regions associated with neo-intimal hyperplasia development in humans and animal models. For certain anastomotic angles, the 'offset' configuration appeared to enhance mixing and reduce fluid residence time in separation regions.

Discussion: Flow visualisation and CFD allowed complementary assessment of vascular anastomosis models. Preliminary results suggest that alteration of anastomosis configuration may improve the peri-anastomotic and downstream flow fields. Further studies, including with animal models, will allow examination of the hypothesis that these changes affect the burden of neointimal hyperplasia, possibly mediated through wall shear stress and/or mass transport mechanisms. Concurrent observational studies in humans will increase understanding of how current practice correlates with clinical outcomes.

P249

Comparing efficacy of saphenous vein loop graft with ePTFE graft used in lower limb AV fistula

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Introduction: Lower extremity is used as an access site for haemodialysis patients as a last resort when no further upper extremity access is possible. A systematic review concluded that autologous access is associated with less infective complications, however at the expense of increased ischaemic complications rates[1]. There is however limited data available on the efficiency of the saphenous vein loop graft.

Objective: To study the differences in outcomes between autologous (saphenous vein loop graft) and prosthetic (ePTFE-Expanded Polyfluroethelene) graft use in lower limb AV fistula for haemodialysis.

Methods: A retrospective analysis of all the lower limb vascular access formed using either saphenous vein graft or ePTFE graft done in Salford Royal Hospital between 1st June 2008 and 31st December 2011 was performed. We collected data to examine patency rates, infection rates; thrombosis rates and failure rates between two forms of grafts.

Results: A total of 21 patients underwent 24 vascular access procedures on their lower limbs using these grafts in this time period. 15 (62.5%) grafts were made using PTFE and 9 (37.5%) using saphenous veins. The 6 months and 12 months patency rates for PTFE grafts were 46.7% and 40% compared to 77.8% and 33.3% for saphenous grafts. Infection rate was 53.3% for ePTFE and 11.1% for saphenous. Saphenous grafts underwent a total of 12 thrombosis episodes compared with 26 in PTFE grafts.

Conclusions: Lower limb ePTFE loop grafts are associated with early failure rate, high infection rates and high thrombosis rates when compared with lower limb saphenous vein loop grafts.

Reference: [1]Eur J Vasc Endovasc Surg. 2009 Sep;38(3):365-72.

P250

Flow monitoring to predict catheter dysfunction in haemodialysis

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Introduction: Access surveillance is advocated for arteriovenous fistulae and grafts with clear criteria for dysfunction. Despite the enduring prevalence of central venous catheter [CVC] use and associated high rates of mechanical dysfunction there are no equivalent studies with this access form. We therefore studied the role of flow monitoring as a predictor of CVC dysfunction.

Methods: We retrospectively studied all patients with CVCs on haemodialysis [HD] at 1 dialysis unit at our centre [Oct 2008-Feb 2011]. CVC function was assessed as the ratio of blood flow rate:outflow access pressure [BFR:AP]. CathRisk, an indicator variable, was positive when BFR:AP<0.9. Target BFRs were ≥350ml/min with dysfunction defined by consistent BFR <250ml/min and/or declining spKt/V [target ≥1.6]. All CVCs were locked routinely with heparin [5000U/ml]. 2-hour urokinase [UK] dwells, 5000U/ml, were used initially for dysfunction and infusions given in the event of treatment failure.

Results: We studied 40,333 HD sessions with 224 CVCs in 164 patients [mean age 62.7±15.1yrs, 45% diabetic] with 108,114 catheter days follow-up. 59% CVCs were the first such access type in the study cohort. Mean session length was 4.3±0.5hrs, mean BFR 402±53ml/min. The rate of CVC dysfunction was 5.5 / 1000 catheter days [95% CI 5.1-6.0]. UK locks elicited proportionally greater improvements in more advanced dysfunction [mean 4.7±0.6ml/min per 10ml/min BFR, p<0.001]. On multivariate regression the risk of CVC dysfunction was associated with greater dry weight [4% per kg, p=0.009], catheter vintage [2% per month, p=0.003], ultrafiltration rate [70% per l/hr, p=0.05] but the most significant risk factor was CathRisk positivity [OR 7.83, p<0.001].

Conclusions: In the first study of its kind to our knowledge we characterized the natural history of CVC function correlating it to a dynamic performance parameter [BFR:AP]. This novel framework for CVC monitoring can transform care with pre-emptive thrombolysis for incipient dysfunction as opposed to current reactive strategies.

P251

Comparison of Tesio and Lifecath twin permanent dialysis catheters - the vytes randomized controlled trial

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Background: Central venous catheters [CVC] for haemodialysis [HD] are designed to deliver high blood flow rates [BFRs] to achieve dialysis adequacy. Despite its good long-term function the TesioCath [TC] is reported to function poorly immediately post-insertion. We prospectively studied the performance of the TC and a similar twin-catheter CVC, the LifeCath Twin [LC].

Methods: This single-center randomized controlled trial [NCT 01022359] allocated adult incident patients 1:1 to receive either a TesioCath™ [MedComp] or LifeCath Twin™ [Vygon]. Patients were dialyzed to target spKt/V≥1.6 and target BFR 450ml/min and followed up for 12 months or until change of dialysis access, death or transfer out. The primary outcome was achievement of target BFR during the 1st HD session. Secondary outcomes included thrombotic dysfunction [BFR≤250ml/min] and CVC-related infection.

Results: 80 patients were randomized [mean age 61.0±16.1 yrs, 48% diabetic] with 24,179 total catheter days follow-up. More LCs reached the primary endpoint compared to TCs [44% vs. 10%, p=0.001] delivering a higher BFR [mean 383±82 vs. 277±79ml/min, p<0.001]. Significant differences in BFR persisted until the 4th session after which both CVCs delivered equivalent BFRs [mean 411±43 vs. 413±46ml/min, p=0.5] and adequacy [mean spKt/V 1.85±0.36 vs. 1.81±0.29, p=0.07]. Rates of CVC-related bacteraemia [0.40 vs. 0.51/1000 catheter days,p=0.7] and exit site infection were similar between groups [p=0.4]. Overall rates of catheter dysfunction were 2.8/1000 catheter days with no difference in UK lock use between groups [p=0.3] although the LC group required more UK infusions [6 vs. 0, p=0.01].

Conclusions: LCs initially deliver greater BFRs although this did not translate into long-term differences in performance, dialysis adequacy or complications. This data confirms that both CVC types can consistently deliver high BFRs and dialysis adequacy over an extended period of time.

P252

Presentation and complications of non-thrombus related fibrin sheath pulmonary embolus following tunnelled dialysis catheter removal

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Introduction: We report an unusual complication of tunnelled dialysis catheter removal. Fibrin sheaths have a reported prevalence of 60-100% in association with tunnelled dialysis catheters. Fibrin sheath emboli have previously only been reported following line stripping, or in association with catheter related thrombus, whilst a prospective study has suggested that fibrin sheaths alone do not directly embolise following line removal.

The case: A 25 year old male presented with headaches, severe hypertension and advanced renal impairment of unknown cause. Renal biopsy was non-diagnostic. Dialysis was commenced via an uncomplicated insertion of a tunnelled dual lumen Palindrome dialysis catheter. This remained his preferred choice of vascular access whilst transplantation was pursued. He received treatment for 3 exit site infections over the following months but declined offers of modality changes or alternative vascular access. After 9 months on haemodialysis he presented with sepsis attributed to his dialysis catheter. His line was removed without event and a temporary femoral dialysis catheter was inserted. 48 hours later he described left upper quadrant pain out of keeping with physical examination and observations. After several reviews, a CT pulmonary angiogram was performed; demonstrating left lower lobe pulmonary artery fibrin sheath embolus and no thrombus. With cardiothoracic advice he was managed conservatively and warfarinised. Within a week he complained of new breathlessness. Repeat imaging and investigation demonstrated an area of infarction, unchanged sheath emboli and an exudative pleural effusion. After a prolonged admission he recovered and is now established on CAPD.

Relevance: Non-thrombus related fibrin sheath embolisation has not previously been reported. It is believed to be a rare complication, or perhaps is rarely diagnosed or clinically apparent. We suggest that this unusual case highlights that consideration should be given to fibrin sheath embolisation in patients presenting with pleuritic chest pain, upper abdominal pain or new pleural effusions, who have recently had their tunnelled dialysis catheter removed.

P253

Accuracy of pre-operative fistula assessment and association with outcome

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Introduction: Planning for arteriovenous fistula formation depends on a number of factors, of which the size and quality of vessels are most important. The accuracy of pre-operative measurement of vessel size is unclear.

Methods: Blood vessels were scanned and measured pre-operatively with ultrasound in patients undergoing elective upper-limb fistula creation. The pre-operative measurement of artery and vein were compared with measurements taken intra-operatively, and clinical outcomes recorded.

Results: Fifty-eight fistulae (13 radiocephalic, 11 brachiobasilic, 34 brachiocephalic) were formed in 58 patients (age 18-79, 69% male). Pre-operative measurement was closely related to intra-operative finding for arterial diameter, but tended towards overestimation of size. The diameter was overestimated by more than 0.5mm in 43.8% of cases, was within 0.5mm of the finding at surgery in 47.9%, and underestimated by more than 0.5mm in 8.3%. For vein diameter the pre-operative measurement was much less accurate. The diameter was overestimated by more than 0.5mm in 65.3% of cases, was within 0.5mm of the finding at surgery in 30.6%, and underestimated by more than 0.5mm in 4.1%. In 36.7% the overestimate was by more than 1.5mm. The measurements taken intra-operatively were the best predictors of outcome, with primary failure occurring in only 6.5% of cases with an artery over 2mm and 7.9% of cases with vein over 2mm.

Conclusions: Pre-operative ultrasound is a good predictor of both artery and vein size, although overestimation of both is common. Vein measurement is the less reliable aspect, and substantial overestimation can occur. Measured intra-operatively, both artery and vein size are important predictors of outcome – further refinement of venous assessment would therefore be useful.

P254

Infectious complication rates in patients receiving buttonhole cannulation compared to standard needling in a maintenance haemodialysis population

Nicole Williams, Richard Hoefield, Eliazbeth Garthwaite

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Introduction and aims: There is growing evidence to suggest that buttonhole needling (BN) technique for arterio-venous fistulae (AVF) cannulation is associated with less complications and vascular interventions compared to standard rope ladder needling (SN). We have previously reported lower pain scores, aneurysm size and reduced access interventions in patients receiving BN compared to SN in our renal units. There is however growing concern that BN may confer an increased risk of infection compared to SN. The aim of this analysis was to describe infection rates in patients having BN or SN in a large maintenance haemodialysis (HD) cohort.

Methods: In this study we retrospectively assessed infection rates (bacteraemia) in 473 HD patients via BN (n=259), SN (n=129), arterio-venous graft (AVG) (n=12) or venous dialysis catheters (n=73), over an 8 month period.

Results: Rates of bacteraemia were similar in BN versus SN, 0.27 and 0.21 per 1000 HD sessions respectively (p=0.79). This equates to 0.0032 (BN) and 0.0026 (SN) infections per patient month. There were no reported infections in those patients receiving HD via an AVG. Rates of bacteraemia were significantly higher in those using venous dialysis catheters at 0.75 per 1000 HD sessions (0.06 infections per patient month).

Conclusion: This analysis demonstrates that buttonhole needling was associated with similar rates of bacteraemia in our dialysis population. Long term follow-up is required to assess the true infectious complication rates associated with BN in our HD cohort.

Poster session

Thursday 14th March

12:00 – 13:00

Access 2

P255

Likelihood of sustained av access use after first AV access creation – which patients never use av access?

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Introduction: The Renal Association guideline suggests that planning for AV access should commence when patients enter CKD stage 4. This strategy, which encourages relatively early access planning, will inevitably mean that some patients undergo creation of AV access that is never used for dialysis. The aims of this study were to determine the probability of sustained use of AV access for HD from the time of first AV access creation, and to see if a sub-population of patients with low probability of AV access use could be identified.

Methods: 1106 consecutive patients attending our centre who had at least one AV access procedure between 01/01/2000 and 23/08/2012 were identified from the prospectively maintained electronic patient record. The primary end-point was time to first sustained AV access use, defined as use of AV access for a minimum of 30 consecutive HD sessions.

Results: 3 year Kaplan Meier actuarial probability of sustained AV access use was 71.6% for all patients, higher in males than females (76.9 v 65.1%; $p<0.0001$), higher in those on renal replacement therapy (RRT) than those not (74.2 v 69.9%; $p<0.0001$) and lower with each quintile of age ($p<0.0001$). In the subgroup of patients not on RRT, higher eGFR and lower urine protein: creatinine ratio ($p<0.0001$) at the time of AV access creation were associated with reduced 3 year probability of sustained AV access use. By multivariate analysis age (HR 0.99; per year increase $p<0.0001$), male sex (HR 1.47; $p<0.0001$) and being on RRT (HR 1.43; $p<0.0001$) were independent predictors of sustained AV access use and, in patients not on RRT, eGFR (HR 0.86 per ml/min increase; $p<0.0001$) was also an independent predictor. Females >60 years with an eGFR of >15ml/min at the time of AV access creation (n=73) had a 3 year probability of sustained AV access use of only 48.8%.

Discussion: Our data suggest that refinement of the current guideline for timing of AV access creation in planning RRT may be justified to take into account factors that contribute to the likelihood of technical success and clinical need.

P256

Costing surveillance of problematic arteriovenous fistulae

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Introduction: The optimal method of surveillance for AVF is unknown. Although surveillance and timely re-intervention seems intuitively sensible, the benefit has never been demonstrated. The aim of this study was to evaluate the outcomes and costs of radiological surveillance after angioplasty of a stenotic AVF vs. clinical follow-up alone.

Methodology: All patients who received an angioplasty for stenotic AVF were followed up for 1 year (n=116). Patients with clinical follow-up (n=60) had repeat radiological intervention only if deemed clinically indicated. Patients undergoing radiological follow-up (n=56) had an ultrasound 12 weeks after angioplasty. If this was normal they were discharged to clinical follow-up; if significant stenosis, repeat endovascular intervention was performed; if mild residual stenosis, further surveillance ultrasound was performed every 12 weeks.

Results: In the clinical follow-up group, 6.5% failed initially; 60% had a good result with no further intervention; 33.5% had repeat fistuloplasty after symptoms developed (of whom the procedure failed in 50% (n=10)). Of those patients followed up radiologically, 25% had a satisfactory initial ultrasound; 15.5% remained under radiological follow-up; 32.5% underwent repeat interventional procedure (all successful). No patient in the radiological follow-up group required a salvage procedure. In the radiological follow-up group a total of 86 ultrasounds and 67 fistuloplasties were performed In the expectant group 30 fistulograms, 60 fistuloplasties, 12 thrombectomies and 8 ultrasounds were performed. 10 patients in the expectant group required TCVC insertion. The cost of radiological follow-up (excluding bed days) is £1518.30/patient/year whilst expectant management is £1626.25/patient/year .

Conclusions: Our results indicate that there is a benefit in ultrasound surveillance following angioplasty of a problematic AVF, permitting early detection of recurrence, timely intervention and ultimately a more successful outcome. Furthermore, radiological surveillance would appear to be cost effective.

P257

Evaluation of aggressive intervention to minimise TCVC usage: completion of the audit cycle

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Background: The aim of this study was to evaluate current reasons for TCVC usage in our population and identify patients who might benefit from definitive vascular access.

Methodology: This is a prospective audit of all patients in the West of Scotland dialysing via a TCVC in November 2010. Reasons for TCVC usage and complications of TCVCs were evaluated. Over the subsequent year, aggressive intervention was undertaken to achieve definitive access for any patient identified as suitable by the initial audit. The audit cycle was completed in November 2011.

Results: There was no significant difference in the proportion of patients dialysing via a TCVC in 2010 compared to 2011 (30.3% (n=193) vs 31.7% (n=201); p=0.56). As a result of the audit all patients now have a "vascular access plan'. Of the 193 patients dialysing via a TCVC in 2010, 37% had died by 2011 (only one the result of a complication of the TCVC), 22% remained on a long term line, 20% successfully had an AVF created, 1% had an AVG and 2% were transplanted. 34 patients were still in the process of trying to obtain definitive access. Of these patients, 10.4% had successful AVF created but it subsequently required tying off for complications. A further 6.5% died within 28 days of surgery to create an AVF. No improvement was seen in the number of patients commencing dialysis via an AVF (28.7% vs 30.4%; p=0.65).The incidence of culture positive *Staph. aureus* bacteraemia between 2010-2011 was 1.6 per 1,000 catheter days.

Conclusions: Aggressive strategies of AVF creation have resulted in one-fifth of patients on a long-term TCVC having successful creation of an AVF. This must be offset against a high failure rate and significant complication rate from AVF creation in this population. Additionally over one-third of patients dialysing via a TCVC died in the subsequent year. Correct patient selection for AVF creation is therefore essential. There is a sub-group of patients in whom the risk-benefit ratio may favour permanent TCVCs. These factors should be taken into consideration on an individual patient basis when considering vascular access options.

P258

A comparison of TCVCs and immediate access AVGs: bacteraemia rates and cost-effectiveness

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Background: TCVCs are associated with a higher rate of bacteraemia than AVF/AVG, however unfortunately may be necessary in incident HD patients due to late presentation/ referral precluding AVF creation/ maturation on time to allow initial dialysis. It might be that novel immediate access AVGs, which permit needling within 24 hours, can avoid TCVCs in this patient group.

Methodology: This "virtual study" enrolled all patients having TCVC insertion over a 6 month period and posed the hypothetical questions: i. Would an AVG have been an acceptable and practical alternative to TCVC? ii. What individual and service costs would be associated with the two management strategies? All patients were followed up for 6 months with complications including bacteraemia, hospital admission and occlusion recorded. It should be emphasised that the overriding aim was always to obtain definitive access via AVF and TCVCs/ AVGs were only used is a bridge to AVF creation/maturation if necessary.

Results: 101 TCVCs were inserted in 79 patients. The mean delay waiting for TCVC insertion was 7.5 days. This delayed discharge for 35 patients. A total of 471 additional hospital days were required for line complications during the 6 month period (bacteraemia rate 1.6 per 1,000 catheter days). 57 of 79 patients would have been suitable and agreeable to consent for AVG. AVG would have been the definitive access option for 1/3rd of patients. Assuming that all suitable patients had an AVF placed within 2 weeks of referral with a 60% maturation rate for AVF and first needling at 8 weeks, the initial additional costs of AVG insertion would be offset by a reduction in bacteraemia rates and immediate access AVGs as a bridge to AVF maturation would be cost neutral five months after insertion.

Conclusions: Immediate access AVGs are a practical, acceptable and cost effective alternative to TCVCs as a bridge to definitive AVF establishment in patients requiring urgent vascular access for HD. We now intend to undertake a prospective RCT to confirm this.

P259

Outcomes and patient satisfaction following excision of redundant arteriovenous aneurysmal fistulae

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Introduction: Aneurysms in disused upper limb arteriovenous fistulae can cause both symptomatic and aesthetic concerns. Our aim was to assess outcomes and patient satisfaction following excision of redundant aneurysmal fistulae.

Methods: Patients presenting with true aneurysms in redundant upper limb arteriovenous fistulae were identified from a prospectively maintained database. Aneurysmal arteriovenous grafts were excluded from this study. Patient demographics, aneurysm characteristics, symptoms, complications and follow-up were recorded. Satisfaction surveys were conducted in the follow-up clinic or by telephone. Both comfort and aesthesis before and after surgery were individually measured by subjective assessment using an ascending scale from 1 to 10.

Results: Seventeen patients underwent aneurysm excision of redundant upper limb arteriovenous fistulae, twelve men and five women. The mean age was 50 years (range 31-79 years). Eleven patients had a brachiocephalic fistula (65%); five had a radiocephalic (29%) and one brachiobasilic (6%). Thirteen patients (76%) who underwent surgical excision were symptomatic whilst the remainder had predominantly aesthetic concerns. In the symptomatic group, 2 patients presented with cardiovascular compromise, 3 with steal syndrome, 4 with pain, 2 with neurological deficit, 1 with skin breakdown and 1 with limb swelling. The median follow-up interval was 5.1 months (range 1.1-12.9 months). One patient developed a small haematoma and one developed a seroma post-operatively, both resolved without further intervention. Fourteen patients (82%) completed the satisfaction survey. Median comfort and aesthetic scores before surgery were both 3. Following surgical excision, patients reported a significant improvement in comfort and aesthetics with a median score of 8 and 9 respectively.

Discussion: Patients report a significant improvement in both comfort and appearance of the upper limb following excision of aneurysmal redundant arteriovenous fistulae with low associated surgical morbidity. Symptomatic aneurysms in redundant fistulae can safely be considered for excision.

P260

A single centre review of procedures to salvage thrombosed vascular access between 2008 and 2012

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Background: Our unit has a dialysis programme of approximately 400 pts, with <15% dialysing via tunnelled central venous catheters. Our vascular access surveillance programme using monthly measurements by Transonic© ultrasound dilution access flow monitoring, allows early detection of access problems and elective radiological intervention. Despite this, a small proportion of arterio-venous fistulae (AVF) and PTFE grafts (AVG) thrombose.

Methods: We retrospectively studied all vascular access thromboses between January 2008 and April 2012, interrogating our departmental databases and computerised hospital medical records to review outcomes of emergency intervention.

Results: 70 radiological interventions, on 51 AVF (39 brachial, 6 radial and 4 brachiobasilic) and 19 AVG were undertaken in 65 patients; mean age 59 years. The success rate was 84%. 90% underwent radiological thrombectomy with angioplasty; 10% required angioplasty alone. Four interventions occurred whilst patients awaited elective intervention. Five patients had stents inserted. Four patients subsequently underwent surgical intervention. During follow-up, 65% of access required re-intervention with 16% requiring a further emergency thrombectomy. Prior intervention had occurred in 54%. Only 29% had a recorded Transonic© flow rate <500ml/min pre-thrombosis. Pre-and post-access flow rates were available in 60% of cases; mean flow rate increased by 352mls/min. 91% were hospitalised due to their thrombosed access. Mean time from referral to procedure was <1 day (range 0-4). Their mean in-patient stay was 2.5 days. 83% of patients currently remain on the same vascular access.

Conclusions: Previous data from our unit reported that most radiological access intervention is performed electively. Nonetheless, a few of our patients' AVF and AVG clot requiring emergency intervention. Prompt radiological intervention results in an excellent success rate of >80%, minimising the need for central venous catheters and helping to maintain a high usage rate of native AVFs.

P261

Inferior vena cava filter insertion in patients with underlying renal disease

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Introduction: Inferior Vena Cava (IVC) filters are indicated in patients with venous thromboembolism (VTE) who are at risk of developing a pulmonary embolus (PE) where anticoagulation is contraindicated. In the renal unit we have observed additional indications for IVC filter (IVCF) insertion.

Aims: These were to: 1) review the indication for IVCF insertion in the renal unit and 2) to determine whether IVCF insertion is safe in patients with underlying renal disease.

Methods: We conducted a retrospective analysis of all patients under the renal unit who had an IVCF inserted between 2002 and 2012. Inclusion criteria were patients on the renal unit database with 'IVC filter' or 'IVC' in their problem list. Patients were excluded if insufficient information was available about their IVCF insertion. Underlying renal disease, renal replacement therapy, reason for anticoagulation, previous anticoagulation, target INR, indication for IVCF insertion, date of insertion and any complications were identified.

Results: Indications for IVCF insertion included Renal Biopsy (n=5, 21%), Concurrent bleeding leading to a contraindication of alternative forms of anticoagulation (n=9, 38%), Procedure (n=2, 8%) Thrombocytopenia (n=1, 4%) and other/unknown (n=7, 20 %). One patient developed PE's despite IVCF insertion. There were no other complications and no deaths resulting from IVCF insertion.

Conclusion: IVCF insertion is common in patients who are stopping anticoagulation for a renal biopsy (21%). IVCF insertion is safe in patients with underlying renal disease. There may be an argument for its increased use in order to reduce length of stay with potential cost savings to the NHS.

Poster session

Wednesday 13th March

18:15 - 19:25

Acute kidney injury 1

P262

Incidence and outcomes and characteristics of acute kidney injury presenting to a renal unit in a teaching hospital

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Introduction: Acute Kidney injury (AKI) is a common and serious condition affecting 5-20% of acutely ill patients; with mortality reported to be > 50% in patients with multi-organ failure requiring renal replacement therapy (RRT). Most of the currently available epidemiological data on AKI come from either intensive care units (ICU) or from all-hospital admissions data. This is because most AKI occurs on general wards and most RRT happens on ICUs. For example, in a previous study at our centre 70% of RRT for AKI was done on ICU. Therefore, there is lack of specific data on the incidence and outcomes of patients with AKI presenting with single organ failure to tertiary renal units in the UK.

Aim: To evaluate the incidence and outcomes of AKI presenting to our renal unit - large teaching hospital with a catchment population of 1.4 million.

Methods: We retrospectively collected data on AKI admissions between 1 Jan 2012 and 30 April 2012. We excluded patients stepped down from level 3 care. This included data on demographics, aetiology of renal disease, length of hospital stay and requirement and modality of RRT. The outcomes evaluated were patient and renal survival at six months from date of admission to the renal unit.

Results: 33 patients (69.6% males) with AKI stage III were admitted during that period, mainly through inter-& intra-hospital transfers. This gives an estimated annual incidence of 71 cases pmp per year. The average age was 69 years (SD=17). The aetiology varied with only 15% (5/33) representing pre-renal causes and 30% (10/33) due to GN and TIN. Of those, 51% required RRT (17/33) using intermittent haemodialysis, and 6% (2/33) required step-up of care to level 3 where they received CVVH. The average length of stay from date of admission to the renal unit was 17 days (15-19, 95%CI, *SD=18*). At six months 84.8% (28/33) of patients were alive and 78.6% (26/33) were dialysis independent, with average eGFR 35 mL/min/1.73m^2 (31-39 ml/min/1.73m^2, 95% CI, *SD=30*).

Discussion: While the risks associated with AKI may essentially be the same regardless of place of care, there is a difference in the severity of AKI and the underlying illness between those cared for on general wards, those admitted to renal units and patients admitted to ICUs. Therefore, data should be collected on these groups of patients separately to define best standards of care and to commission services appropriately. In addition to standard setting, such baseline data will help to evaluate the impact of interventions such as AKI care bundles and electronic alert systems.

Conclusion: We showed that mortality among our group was less than 20% & ESRD occurred in less than 25% of patients. This is in contrast to worse outcomes reported among AKI patients on ICU. We recommend that similar data are collected on a national level and be incorporated into the UK renal registry.

P263

Outcomes in patients with AKI in peripheral hospitals referred to tertiary services

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Leeds Teaching Hospitals, Leeds, UK

Introduction: The cost of caring for patients with acute kidney injury (AKI) has been estimated at £400-600M per year, with an incidence of 172-630 per million population per year. The Renal Association has recommended that local guidelines are used improve the recognition and management of AKI, and that sufficient critical care and renal beds are available for rapid transfer of patients to renal services when indicated. As a tertiary referral centre our unit receives referrals from six peripheral hospitals.

Method: In this prospective study, we aimed to assess the number of patients with AKI referred from 6 peripheral hospitals and whether they were transferred to renal services in a timely fashion. All patients referred with AKI from peripheral hospitals were included in the 1 month study period. Information regarding the patients' admission date, referral date, observations, imaging and blood results were recorded. The outcome, transfer date and time of transfer noted also.

Results: There were 15 referrals documented from 6 hospitals over a month. Nine patients were accepted for transfer, but only 7 patients were transferred. The average time from admission until referral was 6 days, with 9 of the patients being in AKI stage 3 at time of referral. No patient was transferred on the day of referral and 6 patients waited 3 days for transfer. All of the patients were transferred between 7pm and 11pm. Six patients were not accepted for transfer; 5 of these died within 4 weeks.

Discussion: All patients were referred at an advanced stage of AKI. The 5 patients who were not accepted for transfer were not discussed with the on-call consultant and experienced a high rate of mortality. Patient transfer occurred in the evenings when there was less staff available to assess and care for a new admission. It is hoped that the introduction of the West Yorkshire Acute Kidney Injury Patient Pathway will result in improved recognition and management of AKI. The pathway provides agreed referral criteria and aims to facilitate timely referral and transfer of patient within normal working hours.

P264

Risk factors of acute kidney injury in patients after coronary arterial bypass graft surgery

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Acute kidney injury following coronary arterial bypass graft surgery is one of the complications that worsens the outcome. Establishment of proper risk factors could aid early diagnosis and improve the patients condition preventing from the severe consequences. Determining the proper risk factors influencing the prognosis and occurence of acute kidney injury was our goal.

The prospective observational study included 291 patients after coronary arterial bypass graft surgery. Our study analysed influence of following risk factors on incidence of acute kidney injury. Patients parameters included age, ESL, illness duration, smoking duration, perfusion and reperfusion time, cross-clamp time, weight, height, BMI, number of anastomoses, CKMB, CRP, WBC, creatinine level, procalcytonin level, amount of fluid drainage, perioperative packed red blood cells transfusions, FFP, sex, NYHA, CSS, epinephrine usage, fever, TLR polymorphism, occurence of pneumonia, wound infection occurence. CRP, WBC, creatinine level, procalcytonin were measured at the day of surgery, at first and second day after surgery. Furthermore we analysed influence of AKI apperance on overall cost of treatment, hospital residence duration and mortality. Statistical analysis was performed using Student's *t*-test and Mann–Whitney *U* test. Results was considered statistically significant for $p < 0.05$

In this study we ascertained that there is statistical dependence between the occurrence of AKI after CABG surgery and factors such as patient's older age, higher ESL score, longer perfusion and reperfusion time, higher CKMB, CRP, creatinine, procalcytonin level, higher WBC, amount of fluid drainage, perioperative packed red blood cells transfusions and epinephrine usage. Higher overall cost of treatment, longer hospital residence duration, wound infection occurence and mortality was also correlated with apperance of AKI.

Incidence of AKI after CABG can be predicted by proper analysis of the above factors.

P265

Validation of a continuous very low dose Iohexol infusion (CIVLDI) to measure glomerular filtration rate (GFR)

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Aim: To validate a novel method of measuring GFR which can feasibly be applied in patients with acute kidney injury (AKI).

Background: There is currently no accurate method of measuring GFR in patients with AKI. Current definitions are based upon changes in serum Creatinine concentration and urine output, however, these have limitations in patients with AKI and diagnosis may be delayed if using these criteria alone. We have designed a method of continuous measurement of GFR with the intention of applying it in patients with AKI. The purpose of this crossover trial was to prove the concept and safety in volunteers over a range of GFR from normal to <30mL/min/1.73m^2.

Methods: 17 volunteers were allocated, via block randomisation, to measurement of GFR, either by measuring the plasma clearance of a single intravenous injection of Iohexol (gold standard), or by measuring the plasma clearance of a continuous infusion of very low dose Iohexol (CVILDI; 0.5mL/h for 12h). GFR was then measured by the other method after a washout period of 4-28 days. Iohexol was measured by HPLC-ms/ms at 10 time points and the time to steady state was determined by plotting on a two-phase exponential decay graph.

Results: Logarithmic transformation of data revealed no crossover effects (P=0.43). Mean GFR measured by the gold standard was 78.7±28.5mL/min/1.73m^2, and 78.9±28.6mL/min/1.73m^2 when measured by CIVLDI (P=0.82). Time to plasma steady state concentration was 155±84 minutes in subjects with GFR >60mL/min/1.73m^2 and 487±127 minutes in subjects with GFR <60mL/min/1.73m^2. Correlation between the methods was 0.98 (P<0.0001) and Bland Altman comparison revealed a bias of 2.2mL (3.5%), with limits of agreement -8.2 to 12.6mL/min/1.73m^2 when GFR was measured by CIVLDI. Plasma clearance overestimated renal clearance by 5.5±7.3mL/min/1.73m^2.

Conclusion: CIVLDI appears to be accurate and precise. In future, we aim to apply this method in patients with AKI. We predict changing GFR can be accurately measured earlier than conventional criteria.

P266

Symmetrical dimethylarginine (SDMA) is a more sensitive biomarker of renal dysfunction than creatinine

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Introduction: Symmetrical dimethylarginine (SDMA) is the structural isomer of the endogenous nitric oxide synthase inhibitor asymmetrical dimethylarginine. SDMA concentration increases in parallel with serum creatinine concentration (SCr). Currently, no formula exists to estimate GFR from SDMA concentration. Tubular secretion of SCr may be as high as 40%. SDMA may be a more sensitive biomarker of renal dysfunction than SCr if it undergoes less tubular secretion, however, the fractional excretion of SDMA (FeSDMA) is unknown.

Aims: 1) Calculate the tubular secretion of SDMA by measuring FeSDMA; 2) Derive a formula to estimate GFR from serum SDMA concentration.

Methods: 17 subjects with stable renal function had GFR measured twice via a) measurement of the rate of elimination of a single injection of Iohexol, and b) measurement of the plasma clearance of a continuous infusion of Iohexol given over 12 hours. 12 serum and 10 urine samples of SDMA and SCr were obtained from each subject during GFR measurement. SDMA concentration was measured by HPLC-ms/ms. FeSDMA and fractional excretion of SCr were calculated using Iohexol concentration as the denominator. SDMA concentration was plotted against measured GFR, and estimated GFR equations were derived from linear, quadratic and third order polynomial plots.

Results: Mean SDMA concentration (641±38 *v* 623±22nmol/L; p = 0.68) and GFR (78±28 *v* 79±29mL/min/1.73m^2; p=0.82) were similar on both occasions. Tubular re-absorption of SDMA was lower in subjects with GFR<60mL/min/1.73m^2 (12±8% *v* 18±8%; p=0.0002), and tubular secretion of SCr was higher (29% *v* 23%, p<0.0001). The third order polynomial equation (r =0.93) was a better estimate of GFR than quadratic and linear equations. Bland Altman comparison revealed no bias when the third order equation was used (precision: ±20mL/min/1.73m^2).

Conclusions: SDMA appears to be an accurate and precise estimate of GFR and a more sensitive biomarker of CKD that SCr. We predict SDMA will perform better than SCr as a biomarker of AKI. This forms the basis of a future study.

P267

Acute kidney injury requiring renal replacement therapy in a tertiary referral centre

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King's College Hospital, London, UK

Background: Acute Kidney Injury (AKI) is increasingly a focus for improving care. The National Confidential Enquiry into Patient Outcomes and Deaths (NCEPOD) recently identified deficiencies in clinical care at all levels, including referral to specialist renal services and rapid step-up to higher level care where appropriate.

Aims: To analyse the cohort of patients referred to a tertiary renal unit with AKI to determine referral patterns, predominant causes of AKI, renal outcomes.

Methods: Retrospective analysis of case notes pertaining to admissions to the Renal Unit between 1st January 2011 and 31st December 2011 with the clinical coding term "acute".

Results: 106 referrals were analysed. 52% of referrals were received from the same NHS trust whilst 25%, 11% and 10% originated between three main feeder district general hospitals respectively. The main referring specialities were General Medicine (42%), the Emergency Department (20%) and Intensive Care Unit (8%) with smaller but notable contributions from liver, renal and orthopaedic specialties 7% of patients had Stage 1, 9% Stage 2, and 84% Stage 3 severity of AKI according to AKIN Criteria. The most common causes of AKI were sepsis (12%), pre-renal failure (12%) and acute interstitial nephritis (10%). 30% of patients underwent renal biopsy. 49% of patients received renal replacement therapy; 58% received haemodialysis, 23% continuous veno-venous haemofiltration, 15% a combination of the two and 4% peritoneal dialysis. Renal outcomes were as follows; 16% died, 5% return to normal renal function, 9% Chronic Kidney Disease (CKD) Stage 1, 8% CKD Stage 2, 20% CKD Stage 3, 18% CKD Stage 4, 10% CKD Stage 5, 10% long-term haemodialysis, 2% long-term peritoneal dialysis,

Discussion: This single centre's experience is a valuable insight into the organisational, financial and longer-term management challenges resulting from AKI. The data has been used to plan services within a changing NHS structure. Prospective studies are needed and our centre is developing computational strategies to capture this data.

P268

Is ethnicity a predictor for renal recovery following acute kidney injury?

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Introduction: One of the most important questions in Acute Kidney Injury (AKI) is predicting recovery. It is not yet known whether ethnicity is an important prognostic predictor for renal recovery. At our institution, we are in the unique position of having one of the most ethnically diverse patient populations in the UK, putting us in a strong position to answer this question. Our aim was to examine the records of patients who had suffered AKI, and establish whether there was a significant difference in recovery depending on ethnicity.

Methods: Patient records coded as 'AKI' by the renal unit between August 2002 and October 2009 were examined. The following information was collected from a pre-existing renal database: age, gender, ethnicity, baseline creatinine, cause of AKI, severity of AKI (AKIN Stage), length of stay, follow-up creatinine levels were then recorded at day 30, day 90, year 1 and year 3.

Results: 1152 patient records were studied, 256 cases were discounted due to lack of follow-up data or incorrect coding; The mean age was 59.3 yrs; 40.6% were women; 72% were white, and 22% were black; There was no significant difference in the proportion of patients achieving AKIN stage 3 between Black and White patients (82.1% and 83.0% respectively); Full renal recovery (defined as returning to the baseline CKD stage by day 90 post AKI) was seen in 18% of White patients, and 20% in Black, this similarity was also seen at 1 and 3 year follow-up; At day 30 follow-up, 81 % of white patients had survived, in comparison with 88% of black patients. This trend continued to year 3 of follow-up with 63% survival in White patients vs 74% in Black patients; 16% of White patients required renal replacement therapy by 3 yrs compared to 24% in Black.

Discussion: Ethnicity is not a predictor for renal recovery following AKI, contrary to what some authors have hypothesised. Mortality was similar in Black and White patients. This study has provided useful epidemiological insight into mortality and renal recovery rates following AKI in an ethnically diverse UK population.

P269

Estimated GFR based on hospital discharge creatinine may significantly over-estimate renal function and under-estimate CKD in survivors of critical illness

Ivana Kolic, Jeremy Purdell-Lewis, Christopher Kirwan, John Prowle

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Introduction: Acute kidney injury (AKI) complicates over 50% of Intensive Care (ICU) admissions. Episodes of AKI are recognised as a major risk factor for development or progression of Chronic Kidney Disease (CKD), however methods of estimated glomerular filtration rate (eGFR) may be poorly calibrated to survivors of critical illness who often have reduced muscle mass. We hypothesized that eGFR may underestimate rates and severity of CKD in ICU survivors.

Method: Retrospective observational study of renal function in all patients admitted to a London teaching hospital ICU for ≥5 days and surviving to hospital discharge during 2011. Patients with current or new diagnosis of end stage renal disease or renal transplant were excluded. We assessed AKI in ICU by KDIGO 1 criteria and hospital discharge eGFR by the CKD-EPI equation. For comparison we assumed a normal GFR in a healthy individual of 120ml/min/1.73m^2 at age 20 decreasing by 0.8 per year over age 20.

Results: We identified 282 patients, 180 of whom had AKI (56 received RRT). Median age was 50 and 68% were male. Median hospital discharge serum creatinine was 57µmol/L (Range 16-654), median eGFR was significantly higher than predicted normal GFR for age at 115 vs. predicted 95 ($p<0.001$, median difference 16). In patients who had not had AKI discharge eGFR was 119 vs. normal predicted 98 ($p<0.001$, median difference 19) suggesting that eGFR could be over estimating true GFR in our population by at least a factor of 1.23 (Fig1). Applying this correction factor to eGFRs of patients who had recovered from AKI resulted in 44% more diagnoses of CKD (eGFR<60) at hospital discharge (36 vs. 25). **Conclusion**: eGFR may over estimate renal function in survivors of critical illness confounding identification of CKD in this at risk population. Prospective studies with measurement of actual GFR are required to assess the burden of CKD in survivors of critical illness.

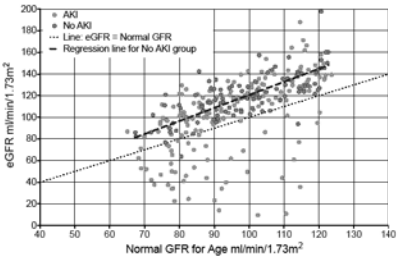

Fig 1: eGFR at hospital discharge vs. expected normal GFR for age in health in ICU survivors. A significant over estimate of renal function at hospital discharge is suggested, possibly related to loss of muscle mass in critical illness and poor pre-morbid condition. Given that a healthy normal GFR is a high estimate of true GFR a population of ICU survivors this effect may actually be larger than estimated and the extent of undiagnosed CKD greater.

Poster session

Wednesday 13th March

18:15 - 19:25

Acute kidney injury 2

P270

E-Alert AKI system – early experience and comparison with past practise in management and outcome of AKI at a University Hospital in UK

Azharuddin Mohammed[2], Krishna Appunu[2], Sunil Daga[1,2], Robert Higgins[1,2], Simon Fletcher[2]

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Introduction: Following UK NCEPOD report on Acute Kidney Injury (AKI), alert systems have been introduced in number of hospitals to identify and manage AKI earlier. This has increased the work load in renal unit but the potential benefit of such system has yet to be assessed. We looked into change in practice pattern and mortality outcome in era prior to and after introduction of e-AKI Alert system.

Methods: All inpatient AKI nephrology referrals at a single UK university hospital were audited in two different time period -2010 (10/2/2010 to 24/03/2010) and 2012 (11/9/2012 to 14/10/2012). In 2012, e-AKI alert system was introduced that alerted renal on call if the creatinine was over 200umol/L during the admission. Referrals were grouped in to early(ER < 48 hr) and late (LR >48hr).

Results: 43 cases from 2010 and 29 cases from 2012 were analysed. Overall 30 day mortality was 34.6% with 24 % Vs 46 % in ER: LR (RR = 1.9). Out of 29 cases, 25 were seen within 48 hours of development of AKI. Mortality in early referral group in 2012 was higher but in seven out of nine cases that died were cared for terminal illness.

	AKI-2010		AKI-2012	
	<48hr (ER)	>48hr (LR)	<48hr (ER)	>48hr (LR)
No	21	22	24	4
AKIN stage >3	10	9	9*	2
30 day mortality	6	11[a]	2*	1
2-yr mortality	8	14[b]	na	na

Table1: Comparison of pattern and mortality of cases with AKI in year 2010 and 2012

(cases on EoL excluded, a – p value 0.13 & b – p value 0.02)*

Conclusions: Late referrals following AKI carry significant long term mortality risk. E-Alert system allowed early intervention by renal specialist team. However, higher number of patient cared for terminal illness were alerted and excluding these cases, 30 day mortality was better following introduction of alert system.

P271

Effect of acute kidney injury on chronic kidney disease progression and proteinuria: initial results from a pilot study

Rebecca Packington[1], Robert Scott[1], Christopher McIntyre[1, 2], Nitin Kolhe[1], Richard Fluck[1], John Monaghan[1], Nicholas Selby[1]

[1]*Royal Derby Hospital, Derby, UK,* [2]*University of Nottingham, Nottingham, UK*

Introduction: There is an increasing recognition that episodes of AKI may have profound longer term sequelae on renal function and patient outcomes. However, the majority of studies in this area are retrospective and many only focus on specific patient groups. There is therefore a need to examine the long term effects of AKI on patient outcomes in a prospective, UK based study that includes general hospitalised patients from across the entire spectrum of AKI severity.

Methods: We report the baseline results from a pilot study performed to test the proposed methodology for a long-term, observational case-control study. Cases (patients with AKI) and controls (those screened for AKI but who did not sustain it) were identified from a hospital-wide electronic reporting system for AKI based on the AKIN criteria. Potential participants were contacted via post and invited to participate; all participants gave informed consent. The control group was matched to AKI patients on a 1:1 basis in terms of baseline eGFR (within the same CKD stage but as closely as possible) and age ± 5yrs. Renal function and proteinuria were measured at 3 months after AKI (or index hospital admission for controls) and will also be measured at 1 and 3 years. Baseline demographics, AKI data (baseline renal function, peak serum creatinine/AKI stage), co-morbidity and hospital stay data were extracted from electronic records. The Medical Research Information Service will be used to track survival data to five years.

Results: 266 cases and controls were included with a mean age of 69 ± 11yrs. 56% were male and 69% had a baseline eGFR of >60ml/min/m^2. There were no differences in age (69 ± 11yrs versus 70 ± 11yrs) or baseline CKD stage between cases and controls. Baseline eGFR was also similar between groups (p=0.22). At hospital discharge, serum creatinine was significantly higher in the AKI group (126 ± 72µmol/l versus 86 ± 33µmol/l, p<0.0001). At three months, this difference was maintained: eGFR was 61 ± 18ml/min/m^2 in AKI group versus 76 ± 24ml/min/m^2 in controls, p<0.0001. A significantly greater proportion of patients in the AKI group demonstrated an increase of at least one CKD stage (29.5% versus 5.8%, p<0.0001). Proteinuria was more common in the AKI group as compared to controls (OR 1.7, 95% CI 1.01-2.8, p=0.045); in a significant proportion of cases this appeared non-glomerular in origin (as evidenced by a disproportionately low ACR:PCR ratio).

Conclusions: These initial data confirm that episodes of AKI are associated with a decline in renal function in a significant proportion of patients that is seen at time of hospital discharge and persists to at least three months. Proteinuria was also more common in the AKI group; this may reflect renal parenchymal damage at the time of AKI or reflect a higher prevalence of pre-existing proteinuria that predisposed to AKI. These findings, along with longer term outcomes, will be further examined in a larger study following the successful pilot of the recruitment, consent and matching methodology.

P272

A prospective observational study in patients who are hospitalised with or develop hospital acquired AKI

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Acute kidney injury is a global public health issue, which remains a diagnostic and therapeutic challenge. The incidence and associated mortality of AKI varies between populations, and risk factors for poor outcomes associated with AKI have been poorly defined. In this study we aim to compare outcomes in hospitalised patients with AKI compared to a non-AKI cohort of patients over a 6-month period. Furthermore, we attempt to compare outcomes in community acquired versus hospital-acquired AKI, as well as compare patients referred and not-referred to nephrology services.

Methods: Electronic records of 16,000 patients admitted to 2 District General hospitals over 6-months were analysed. 1021 AKI episodes were identified and compared to 1000 randomly selected time-matched controls without AKI. Chi-squared & Man Whitney U tests were used to compare between groups and logistic regression used to assess 6-month mortality and readmission rates.

Results: The incidence of AKI was 6.4%. The AKI group were older than non-AKI controls (75 vs 62 years, $p<0.001$) and had greater pre-existing CKD (32% vs 10%, $p<0.001$), longer duration of inpatient stay (15 vs 5 days, $p<0.001$) and greater ICU admissions (6.5% vs 1.8%, $p<0.001$). AKI was an independent predictor of 6-month mortality (OR 4.1, 95% CI 3.2-5.3, $p<0.001$) but not of re-admission within 6 months. Hospital acquired AKI was associated with greater length of stay than community acquired (20.6 vs 12.6 days, $p<0.001$), less recovery rates (46% vs 55%, $p=0.005$), and greater mortality (37% vs 16%, $p<0.001$). 8.3% of all AKI's were referred to renal, 29% of which required RRT and 26% transferred for renal care. The referred cohort were significantly younger (69 vs 76years), had greater pre-existing CKD (58% cf 29%) and were more likely to have community acquired AKI (84% vs 66%) (all $p<0.001$). 10.5% of all AKIs were missed.

Discussion: AKI is an independent risk factor for mortality, and outcomes are worse in patients with hospital acquired AKI. The mechanisms for this remain unclear. However this highlights the importance of developing preventative as well as management strategies for AKI, especially in hospital.

P273

Emergency nephrostomy insertion: a single centre experience

George Greenhall, Zara Sayar, Arunraj Navaratnarajah, Vishal Kumar, Hugh Cairns, Jason Wilkins, Gordon Kooiman, Satish Jayawardene

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Introduction: Obstructive nephropathy is a common, reversible cause of acute kidney injury (AKI). Prompt recognition and intervention are paramount in order to salvage renal function. Little research has focused on the outcomes in patients undergoing emergency percutaneous nephrostomy (PCN).

Methods: A retrospective study of the clinical characteristics and outcomes of patients undergoing emergency PCN in a tertiary referral centre over four years.

Results: 112 patients (52% male) aged 18 to 91 (mean 60.2) included. 36% were hypertensive, 16% were diabetic, 24% had established chronic kidney disease (eGFR <60ml/min/1.73m2). Mean baseline serum creatinine (SCr) was 110.2µmol/L. 38% had bilateral hydronephrosis. The commonest causes of obstruction were calculus and malignancy (38% and 28% respectively). At presentation, 17%, 12% and 22% were in AKI stages 1, 2 and 3 respectively. After a mean interval of 5 days from diagnosis to decompression, this rose to 21%, 14% and 29%. 11% required renal replacement therapy (RRT) prior to intervention. 33% underwent bilateral decompression. Complication rates were low (one ureteric perforation). Patient and renal survival were 79% and 77% at 90 days; 63% and 60% at one year; 41% and 36% at three years. Of the patients with AKI (n=72), 61% fully recovered renal function (fall in SCr to within 20% of baseline, or GFR >60ml/min/1.73m2), 29% partially recovered renal function (fall in SCr but >20% above baseline, or GFR <60ml/min/1.73m2), and 10% had no renal recovery (no fall in SCr, or dialysis-dependence). Factors associated with a full renal recovery were an interval between diagnostic imaging and decompression of less than 48 hours (p=0.027) and age under 60 years (p=0.012).

Conclusion: Early decompression of obstructive nephropathy is important to stop progressive AKI. Following decompression, the chances of renal recovery are reasonable. The overall patient survival is poor, in keeping with its frequent association with malignancy.

P274

The impact of acute kidney injury on outcome and mortality in patients presenting with stroke

Ragunath Durairajan, Karan Lund, Tejpreet Kalra, Alarmeluvalli Sivaramakrishnan, Thayalini Loganathan, Ashish Kundu, Raja Shoaib, Devesh Sinha, Lucy Coward, Anthony O'Brien, Paul Guyler, Michael Almond

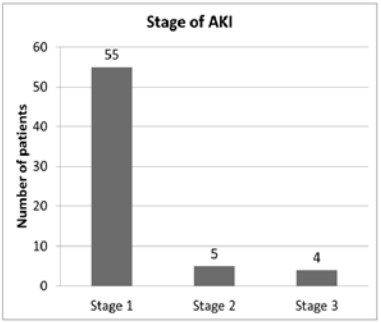
Southend University Hospital, Westcliff-on-Sea, Essex, UK

Introduction: Acute kidney injury (AKI) is associated with increased mortality and length of stay (LOS) across a broad spectrum of conditions. Moreover, outcomes are related directly to the severity of acute kidney injury, whether characterized by nominal or percentage changes in serum creatinine. There is little data in patients with acute stroke; we aimed to investigate this further.

Methods: We retrospectively analysed our stroke database to obtain data for 2151 patients admitted to the Acute stroke unit (ASU) from August 2009 to July 2011 with diagnosis of ischaemic or haemorrhagic stroke The cohort was followed up for 1 year after discharge.

Results: 64 patients had AKI according to Acute Kidney Injury Network definition. The mean length of stay was 15.38 days for overall admissions versus 24.78 days for AKI patients and mortality 15.21% versus 21.87% respectively. Five patients had AKI with creatinine in the normal range and none of them were recognised. The mean baseline creatinine was 117.55 with eGFR of 55.99 and 136.67 and 51.02 on discharge. Renal input was not sought as inpatient in any of the patients. 2 out of 64 discharge summaries mention the diagnosis of AKI during admission.

Conclusion: AKI in stroke is uncommon (2.97% patients in this cohort) and often not severe (the majority being stage 1) – which is therefore likely to be missed. The impact of AKI on mortality and morbidity is not recognised adequately by non-specialists. Patients with AKI showed longer length of stay in hospital, poorer functional outcome and increased mortality following stroke, similar to other conditions. AKI may not be recognised; serum creatinine does not return to baseline on discharge and it is not being communicated to primary care for follow up. Nephrologists are not being involved in management. Joint stroke/renal management of these patients may improve their outcome, although evidence for AKI/nephrology teams using AKI network guidelines are only just coming out as abstracts. We recommend further studies with regards to this.



P275

A retrospective audit of outcome for patients who have undergone continuous venovenous haemofiltration for acute kidney injury on the CICU

Alexandra Monkhouse[1], Hasita Patel[1], Chris Laing[1,2], Andrew Smith[1]

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Introduction: Acute kidney injury (AKI) requiring renal replacement therapy (RRT) is a risk factor for the subsequent development of chronic kidney disease (CKD).

Methods: Data was collected retrospectively for patients who had undergone RRT on the Cardiothoracic Intensive Care Unit (CICU) over a six month period. Those with documented pre-existing CKD were excluded. Data sets were collected for the remainder focusing on admission diagnosis, grade of AKI, outcome (discharge, transfer or death) and the quality of written communication to the General Practitioner (GP) including arrangements for renal follow-up.

Results: During 6 months in 2012 there were 30 patients, 19 men (63%) and 11 women (37%), who underwent RRT for AKI on the CICU. In terms of AKIN grade, 4 patients (13%) were grade 3, 8 patients (27%) were grade 2, 5 patients (17%) were grade 1 and 13 patients (43%) were not an AKIN grade upon entry to CICU. The outcomes were split evenly between discharge home (10 patients), death (10 patients) and transfer (10 patients) of which 3 were transferred to renal units. In regards to GP correspondence, 5 patients (17%) received an eDischarge letter, 5 patients (17%) received a following surgical letter and 12 patients (40%) received both. 8 patients (27%) did not receive any correspondence regarding their inpatient admission. Within the correspondence 18 letters (53%) reported renal impairment and/or RRT, 2 letters (6%) discussed renal follow-up and only 1 letter (3%) instructed to repeat creatinine.

Discussion: There is poor quality correspondence between hospital physicians and GPs regarding inpatients who have undergone RRT which needs to be addressed in order to aid in improving long-term outcomes for our patients with AKI.

P276

An acute kidney injury 'one-stop' clinic – a six month pilot

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Introduction: Acute kidney injury (AKI) complicates 20% of all emergency admissions to hospital. It is therefore impractical for all these patients to be under direct care of renal teams. In a large proportion of these patients the AKI resolves and patients are then discharged without further follow up by the renal unit. Multiple observational studies have now shown that AKI is a risk factor for future chronic kidney disease (CKD) and there is also strong evidence that early intervention from nephrologists can help slow CKD progression.

Objective: Our objective was to create a 'one stop' clinic to review patients who had had an episode of AKI. The aims of the clinic were to: ensure complete recovery from the episode of AKI, check there was no underlying renal pathology that would require specialist input and educate the patient. The diagnosis of AKI would be fully explained together with advice on basic prevention of CKD.

Methods: Twenty seven patients were reviewed in the pilot clinic over six months. The criteria for referral were: AKI, in hospital renal team review and creatinine <200 by discharge. The clinic letters were reviewed at the end of six months with the results of all blood tests and compared to the ward discharge summaries. Outcomes measured were: place of follow up (eg. primary care, general nephrology clinic) and number of risk factors identified as a result of hospital admission documented in the clinic letter compared to ward discharge letter.

Results: All patients with baseline creatinine <110 (n=13) made a full recovery and were discharged to GP follow up except one who had previously been under the renal Low Clearance Clinic. This patient had been lost to follow up and his creatinine had normalised in the intervening time. After this admission with AKI his creatinine had not returned to baseline so he was referred for follow up in general nephrology outpatients. Patients with baseline creatinine >110 (n=10) all needed referral on to the general nephrology clinic with the exception of four patients. Three had creatinine <150 with easily identified causes for chronic kidney disease (diabetes, renal artery stenosis, renovascular disease) and all of their creatinine fell back to baseline giving them a diagnosis of stage 3 CKD which could be appropriately managed in the primary care setting. The fourth was a 96 year old who had stable CKD and had been referred specifically for anaemia management. This patient made the decision to attend the anaemia clinic but did not want multiple hospital visits and so was not referred on to the general nephrology clinic. Four patients did not have recorded baseline creatinine levels. Patients with 1 or no documented co-morbidities (N=11) were all discharged to the GP. In patients with 2 or more co-morbidities (N=16) there was no correlation between number of co-morbidities and clinic outcome. Comparing AKI clinic letters with ward discharge summaries showed that the AKI clinic letters provided more information in terms of identifying risk factors for CKD, advice for regular monitoring and drawing attention to treatable co-morbidities such as hypertension and hypercholesterolaemia.

Conclusion: In a subset of patients with AKI whose baseline creatinine <150, 1 or fewer co-morbidities and whose creatinine is falling on discharge from hospital, there is a role for a one stop AKI clinic to provide high quality healthcare advice and raise awareness of the risk of CKD.

P277

Clostridium difficile infection and acute kidney injury, more than a casual relationship – single UK centre experience

Mohamed Kolpurka-Abdulsamad, Suresh Ramadoss, Dimitrios Chanouzas, Randula Haththotuwa, Jyoti Baharani

Heart of England NHS Foundation Trust, Birmingham, West Midlands, UK

Introduction: Clostridium difficile infection (CDI) and acute kidney injury (AKI) are frequent problems in hospitalized patients. The objective of this study was to examine the incidence of AKI in the context of CDI and its impact on outcomes.

Method: We carried out a retrospective analysis of 388 patients admitted with CDI in our hospital between January 2009 and December 2011. We identified the cases from discharge diagnostic coding. Analysis was carried out using SPSS. Categorical variables were analysed using the chi-square test whilst t-test was used for continuous variables. Kaplan-Meier analysis was carried out to examine post-discharge survival.

Results: 388 cases of CDI were analysed of which 46.4% (n=180) developed AKI. The mean age was 76.3+/-15.3 and 55.9% were females. Older people were more likely to develop AKI with a mean age difference of 5 years (P-0.001). Patients with a higher Charlson's index score were also more likely to develop AKI (AKI vs. Non-AKI- 5.76 vs. 5.09, P-0.007). Patients who developed AKI had longer length of stay (LOS) compared to those who didn't have AKI with mean difference of 7.4 days (P-0.016). There was a trend towards statistical significance for the presence of AKI to be associated with a higher mortality (AKI 41.1% vs. Non-AKI 32.2%; P-0.073). Kaplan-Meier analysis revealed no significant difference in 3-month survival after discharge between AKI and non-AKI groups in our study.

Conclusion: Older age and higher comorbidity are associated with a higher incidence of AKI in the context of CDI. This in turn is linked with a higher LOS although the post-discharge 3-month survival does not appear to be affected.

Poster session

Thursday 14th March

12:00 - 13:00

Acute kidney injury 3

P278

Multiple myeloma with and without acute kidney involvement: clinical comparisons and outcomes

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Introduction: Multiple myeloma (MM) is a neoplastic disorder that is frequently associated with acute kidney injury (AKI). The aim of this study was to analyze its clinical features and outcomes according to the patients' renal characteristics at presentation.

Methods: We studied the course of 170 newly diagnosed patients with MM.

Results: 94 patients (55% of the sample) presented with no form of renal impairment (NRI), 76 (45%) with AKI, defined and staged according to the K/DIGO guidelines. Mean age was 66±11.1 years, males were 55% of the cohort. The AKI group was more hypercalcemic (2.5±0.4 vs. 2.3±0.2 mmol/l, p<0.001), hyperphosphatemic (1.7±0.6 vs.1.1±0.4 mmol/l, p<0.001), proteinuric (1.8±1.7 vs. 0.8±1.3 g/24 hr, p<0.001) than NRI group. It also had a higher kappa/lambda ratio (385±962.7 vs.36.1±115.6, p=0.02), a higher percentage of plasma cells (PC) in the bone marrow (35.3±26.5% vs. 25.1±20.8%, p=0.01) and lower hemoglobin levels (90.7±16.2 vs. 116±20.7 g/l, p<0.001). During a median follow-up time of 2.8 years (IQR 0.9-6.2), 40 patients (23.5%) required renal replacement therapy (RRT). 92.5% were from the AKI group. 73 patients (43%) died of which 26 (36%) occurred in the AKI group. The factors associated with the need for RRT were: previous MGUS (OR=6, 95%CI 1.4-26.1, p=0.017), and higher levels of white blood cells (OR=2.6, 95%CI 1.5-4.4, p=0.0006). Those associated with risk for death were: percentage of PC (HR= 1.06, 95%CI 1.01-1.12, p=0.01), higher levels of serum paraprotein (HR= 1.05, 95%CI 1-1.11, p=0.037) and lower levels of proteinuria (HR= 0.28, 95%CI 0.09-0.93, p=0.037). 12-month mortality was higher in the AKI than NRI group (28 vs. 11% p= 0.003). We also found a higher 12-month survival in all the patients receiving chemotherapy vs. the untreated (84 vs. 74% p=0.022).

Discussion: Our study highlights that MM with AKI represents a more aggressive disease, being associated with worse hematologic features and increased risk for short-term death. Patients with MM-related AKI should then be considered for prompt institution of RRT and MM-directed therapy.

P279

Time to stop diagnosing hepatorenal syndrome in the emergency assessment unit?

David Foxwell[1], Andrew Yeoman[1], Arjun Sugumaran[1], Marek Czajkowski[1], Nick Mason[1], Gareth Roberts[1,2]

[1]Royal Gwent Hospital, Newport, UK, [2]Institute of Nephrology, Cardiff, UK

Introduction: Though hepatorenal syndrome (HRS) is a well defined pathophysiological entity, accurate diagnosis of this condition is often difficult. Renal dysfunction in cirrhotics is frequently poorly managed in the emergency assessment unit (EAU) with patients mislabelled as HRS when diagnostic criteria are not met. In addition, over-reliance on HRS criteria thresholds (such as a creatinine of 133μmol l^{-1}) leads to delayed treatment and the false belief that those who do not meet these criteria need less aggressive therapy. The use of more conventional AKI criteria may cause less diagnostic confusion and improve the recognition and management of renal dysfunction in hospitalised cirrhotics. The aim of this study was to asses the utility of the Acute Kidney Injury Network (AKIN) criteria in cirrhotics admitted with AKI

Methods: 158 consecutive admission episodes from a prospectively collated cohort of cirrhotic patients, was retrospectively analyzed.

Results: Within the cohort of hospitalised cirrhotics, 54% had AKI on admission. Of these at least 80% had clinical features that would preclude the diagnosis of HRS (no ascites, creat<133 μmol l^{-1}, a clear alternative explanation for AKI). Over 50% of those admitted with either stage 1 or 2 AKI progressed to stage 3. Clinical outcomes correlated with the peak stage of AKI reached, with 90 day mortality of 11%, 30% and 55% for Stages 1, 2 and 3 respectively. Overall cumulative inpatient mortality for cirrhotic patients with AKI was 40%, as compared to 7% in cirrhotics with no AKI ($p<0.0001$).

Discussion: Our study demonstrates that AKI is common in cirrhotics admitted to the EAU. The majority of AKI is not HRS, but still carries a poor prognosis, especially if it progresses beyond stage 1. As such early recognition and timely intervention is paramount. We believe that trainees should now be discouraged from using the term HRS on the admissions unit, so that they can focus instead on recognising and managing AKI in these often acutely unwell patients.

P280

Incidence of acute kidney injury in post surgical cyanotic heart disease patients – a retrospective case control study

Sheetal Bhojani, Chris Kidson, Ian Ramage

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Background: Acute kidney injury (AKI) is a potential life threatening complication of intensive care treatment especially after cardiac surgery. AKI causes renal dysfunction affecting electrolytes and extracellular water handling, and impacts upon the provision of medical therapies. The Acute Kidney Injury Network defined AKI as an acute absolute increase in serum creatinine (SrCr) of ≥ 26.4 mmol/L or a ≥50% increase from baseline. We studied AKI in cyanotic heart disease (CHD) patients in our tertiary referral paediatric intensive care unit (PICU).

Methods: We retrospectively identified all CHD patients admitted to PICU in 2010. Patients who met the diagnostic criteria for AKI (cases) were compared with those without AKI (controls). The demographic and clinical data was collected from the clinical information system.

Results: In 2010, 97 CHD patients were admitted to PICU of which 44 (45%) developed AKI. 4 cases (9%) required renal replacement therapy (3 cases required CVVH, 1 required peritoneal dialysis). In 32 (73%) cases, SrCr returned to baseline by the time of discharge from intensive care. Comparing the cases to the controls, the male female ratio and the underlying cardiac disease distribution was comparable. The cases were younger (p 0.007), with a longer PICU stay (<0.001), longer bypass (p 0.002) and X clamp time (p 0.017). The use of nephrotoxic drugs was more common in the cases (0.048). The 2 groups were comparable in their use of inotropes, diuretics and antibiotics. None of the cases had routine renal follow up post-discharge.

Conclusion: The development of AKI is common, especially in critically ill patients who also receive nephrotoxic drugs. Younger age, prolonged PICU stay, long bypass and X clamp time are known risk factors for AKI. The concomitant use of nephrotoxic drugs may be unavoidable, however with early identification of AKI, modification of therapy may minimise the duration of AKI. The long term renal outcome of AKI in the PICU population is unclear and warrants further investigation.

P281

A seven year retrospective analysis of the aetiology and severity of acute kidney injury in a tertiary referral centre

Robin Ramphul, James Ewer, Georgina Hicks, Nay Aung, Chris Jones, Satish Jayawardene

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Introduction: Acute Kidney Injury (AKI) is a common clinical problem with numerous aetiological factors. These factors will contribute to the severity of AKI and in turn to adverse outcomes but it is unclear which ones are most significant.

Method: We retrospectively studied patients admitted to our unit with a diagnosis of AKI between July 2002 and December 2009. Patient demographics, renal function, cause of AKI and severity of renal dysfunction were obtained from our renal database and electronic patient records. We assessed the degree of kidney dysfunction using the Acute Kidney Injury Network (AKIN) AKI staging criteria. We noted the incidence and severity of renal dysfunction in each ethnic and aetiological group.

Results: 895 patients with AKI were identified with 744 (83.1%) AKI Stage 3, 68 (7.6%) Stage 2, 36 (4%) Stage 1 and 47 (5.2%) did not meet the criteria for AKI based on serum creatinine. 415 (46%) of admissions required RRT.

Ethnicity	**AKI no. (%)**	**RRT no. (%)**	**Stage 3 no. (%)**
White	646 (72.1)	326 (50.5)	538 (83.3)
Black	196 (21.9)	93 (47.4)	161 (82.1)
Other	27 (3.0)	11 (40.7)	22 (81.5)
Diagnosis			
Obstructive Uropathy	59 (6.7)	26 (44.1)	47 (79.7)
Dehydration	60 (6.7)	27 (45%)	52 (86.7)
Glomerulonephritis	101 (11.3)	43 (42.6)	82 (81.2)
Perioperative	73 (8.2)	14 (19.2)	63 (86.3)
Sepsis	165 (18.4)	98 (59.4)	149 (90.3)

Conclusions: Similar proportions of White and Black patients reached AKI Stage 3 and needed RRT. The most common cause of AKI was sepsis, which also had the highest numbers of cases requiring RRT and achieving AKI Stage 3.

P282

Sepsis six bundle may prevent severe acute kidney injury in hospital

Edward Stern[1], Kelly Wright[1], Ben Caplin[1], Dorothea Nitsch[2], Nick Murch[1], Margaret Mary Davaney[1], Catriona Shaw[1], Sarah Crawford[1], Chris Shaw[1], Chris Laing[1]

[1]Royal Free London NHS Foundation Trust, London, UK, [2]London School of Hygiene and Tropical Medicine, London, UK

Introduction: Systemic sepsis is estimated to be a contributory cause in 47% of episodes of in-hospital acute kidney injury (AKI). There is limited evidence for interventions that reduce the incidence of sepsis-associated AKI. The Sepsis Six care bundle uses fixed physiological parameters (triggers) on the bedside observation chart to identify patients at risk of severe sepsis. The bundle specifies six mandatory interventions (oxygen, fluid balance chart, arterial blood gas, intravenous fluid, blood cultures, antibiotics) for these patients. We investigated whether compliance with the bundle was associated with improved renal outcome.

Methods: We identified 415 consecutive patients who triggered for Sepsis Six shortly after the introduction of the bundle to a large teaching hospital. We compared baseline with peak creatinine up to 10 days post trigger to classify renal outcome using KDIGO delta creatinine criteria. We compared outcomes between patients with complete and incomplete implementation of the Sepsis Six bundle.

Results

(number in group)	No AKI	AKI 1	AKI 2	AKI 3	Total
6 interventions	140	22	23	11	196
0-5 interventions	141	25	14	39	219
Total	281	47	37	50	415

We calculated relative risk ratio (RRR) for developing each stage of AKI (versus no AKI) with all six interventions completed and corrected for the presence of hypotension when triggering: AKI 1 RRR=0.9 (95% CI 0.5-1.7, p=0.73); AKI 2 RRR=1.5 (95%CI 0.8-3.1, p=0.24); AKI 3 RRR=0.3 (95%CI 0.1-0.6, p<0.01).

Discussion: AKI was common in this cohort of patients with sepsis. Full compliance with the Sepsis Six bundle of care was associated with a 70% reduction in the risk of developing AKI 3, compared with incomplete compliance. These data support the hypothesis that simple, protocolised interventions, performed early in the course of sepsis, may be protective against AKI.

P283

Acute kidney injury in paediatrics: incidence in a tertiary paediatric regional centre

Sally Feather, Ashley Garner

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The epidemiology of paediatric acute kidney injury (AKI) has changed considerably in the last two decades due to the increasingly successful management and survival of children in a range other paediatric subspecialities in which AKI is caused both by the underlying disorder and nephrotoxic treatment. Identification of cases of paediatric AKI is essential not only for optimum acute management but also planning appropriate long term monitoring for chronic kidney disease in survivors. Furthermore, the availability of a number of definitions of paediatric AKI has caused lack of consensus in collecting data. To date, there is limited UK data available on paediatric AKI incidence.

We have analysed serum creatinine results in all admissions to a tertiary regional paediatric centre with a range of paediatric subspeciality services in a single month, November 2011 using both RIFLE and AKIN criteria as per KDIGO guidelines. The results of patients meeting AKI criteria were then reviewed by a clinician and biochemist.

Results: 2257 paediatric patients were admitted in November 2011: 410/2257 had multiple serum creatinine measurements. 43/410 met KDIGO definitions of AKI (24 RIFLE, 9 AKIN and 10 both). Review of results by clinician and biochemist found that fewer patients 14/43 (8 RIFLE, 2 AKIN, 4 both) were considered to have AKI. Analysis of multiple serum creatinine results using KDIGO was a practical method to identify paediatric patients with AKI highlighting patients that required clinical consideration. Further work is needed to assess the sensitivity and specificity of KDIGO definitions of AKI in paediatrics.

P284

Outcome of acute kidney injury managed in a regional paediatric tertiary nephrology centre

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Introduction: Acute kidney injury (AKI) in children is associated with increased morbidity and mortality. This study reviewed the aetiology, treatment modalities and outcome of children with AKI managed by the paediatric nephrology department at the University hospital of Wales, Cardiff.

Method: Retrospective analysis of referral practices, aetiology and management of 38 children with AKI. Outcomes noted as complete recovery, residual renal injury, renal replacement therapy (RRT) dependency or death. Children primarily treated in intensive care were excluded.

Result: Out of the total 38 patients, 34 % were under 5 years of age. Haemolytic uraemic syndrome (HUS) was the commonest cause of AKI 18/38 (47.3%) with E coli 0157 accounting for most (15/18). Significant number of these cases required dialysis (10/15). Obstructive renal failure (5 cases) was second most common and renal function improved following relief of obstruction. Overall, supportive management sufficed in 23/38 cases and 15 received RRT. Most children on dialysis were oliguric (14/15). Peritoneal dialysis was the commonest mode of RRT used. Outcome was equally favourable irrespective of mode of RRT. At 3 months there were no deaths; 29 (76%) had completely recovered, one was dialysis dependant, 5 children had estimated glomerular filtration rate between 40- 60 ml/min/1.73m^2, 3 had mild to moderate proteinuria and two were hypertensive.

Discussion: Prognosis following AKI was excellent in children not needing intensive care probably because of lack of multiorgan dysfunction. HUS was the commonest cause of AKI. Those with oliguria are more likely to require dialysis and should be referred early to the nephrology team. All cases should have long-term follow up to ensure renal recovery and detect delayed complications.

P285

Acute kidney injury in urology patients: incidence, causes and outcomes

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[1]Royal Derby Hospital, Derby, UK, [2]University of Nottingham, Nottingham, UK

Introduction: Acute kidney injury (AKI) is common in hospitalised patients and is associated with high mortality rates. However, the epidemiology of AKI in urology patients may differ due to a higher proportion of post-renal causes and surgical procedures that result in the intentional removal of renal parenchyma. We performed a study to examine the incidence, aetiology and outcomes of AKI in a urological population.

Methods: Patients who sustain AKI at our centre are identified by a hospital-wide, electronic AKI reporting system, based on the Acute Kidney Injury Network (AKIN) criteria. This system populates a prospective database, from which all patients who sustained AKI and had urology as their primary speciality were retrieved for a 17 month period. Additional data on aetiology of AKI and surgical procedures performed were obtained retrospectively by manual searching of paper and electronic medical records.

Results: Between October 2010 and February 2012 there were 587 episodes of AKI in 410 urology patients (6.7% of all hospitalised urology patients within the same time period). 273 patients (66.6%) were non-elective admissions, whilst 137 cases (33.4%) sustained AKI during the course of an elective admission. In the elective group, 58 patients (42.3%) underwent nephrectomy (radical and partial) or nephroureterectomy; other procedures that were complicated by AKI included TURBT/cystodiathermy of bladder tumour (21 patients, 15.3%) and radical cystectomy (10 patients, 5.8%). For emergency admissions, obstructive causes and urinary sepsis accounted for the majority of cases. Overall 30-day mortality was lower than reports in other patient groups at 7.8% (32 pts). The severity of AKI retained an association with mortality (4.8% in stage 1, 9.1% in stage 2 and 14.9% in stage 3, chi square for trend $p<0.05$). Of those that did not survive, 22 (68.7%) were associated with urological malignancy. At the time of discharge, only 237 (57.7%) patients had achieved complete recovery of renal function.

Conclusion: AKI is common in urology patients but is associated with a lower mortality than other patient populations. This likely reflects the underlying aetiologies of AKI in this group, although it is important to note that the severity of AKI retains an association with mortality. However, the low rate of renal recovery suggests that urology patients who sustain AKI are exposed to a significant risk of chronic kidney disease and its attendant consequences for long term health.

Poster session

Thursday 14th March

12:00 - 13:00

Acute kidney injury 4

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Population based estimated reference creatinine value, a novel method of accurate electronic acute kidney injury alert

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Background: Acute kidney injury (AKI) is common, affecting 1 in 5 cases of hospital admissions with serious consequences. Despite the progress has been made in last decade, early identification of AKI cases remained a challenge. This highlights the clear clinical need for a robust, user-friendly electronic AKI alert system that allows early detection of the condition and improve patient outcomes. In recent years, electronic AKI alert system has been tested in some renal units. However, to produce electronic AKI alerts, it is essential to determine an accurate baseline creatinine value. But there is no consensus on a gold standard method in producing such alerts

Method: In our hospital, we have developed electronic AKI alerts with joint collaboration between nephrologist and clinical chemistry department. We have also produced a 'population based reference creatinine value age and sex matched from 137,000 serum creatinine values extracted from out-patient blood tests in general practice from our Telepath system . We have chosen GP requests as these usually exclude a large set of abnormal values from hospital based populations with AKI and end stage renal disease.

Results: Creatinine results were split by gender and then within each group the creatinines were stratified according to year of age. The median creatinine for each individual year of age was identified and plotted versus age to give separate graphs for males and females that gave excellent fits (R2) to cubic regressions. Median creatinines were chosen in preference to means as the data at each age point was non Gaussian and could not be adequately transformed (positive skewing caused primarily by prevalence of CKD, which increased with age). All statistical analysis was performed using SPSS v12.0.

Males: $y = 75.0758 + 1.0167x - 0.0298x^2 + 0.0003x^3$ $R^2 = 0.965$

Females: $y = 66.5047 + 0.0918x - 0.0065x^2 + 0.000098x^3$ $R^2 = 0.982$

Conclusion: Population based estimated reference creatinine measurement from community based clinic blood test results can be more robust and near accurate method in generating potential electronic AKI alerts to help early recognition and treatment of AKI cases leading to improved overall outcome.

P287

Staying alert: a simple e-alert for acute kidney injury

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An NHS Kidney Care survey identified IT issues and cost as barriers to AKI e-alerts. We set up an e-alert in 10 min that most laboratory IT systems could mimic.

A real-time automated delta-check flagged a >50% increase in creatinine from the most recent result within 90 days and automatically appended the comment '?AKI – creatinine increase >50% from previous' with a link to local AKI guidelines. In addition, results >300 μmol/L were reviewed twice daily and phoned if due to AKI.

From 11930 creatinine requests in 12 days, 90 (88 patients) triggered an e-alert for a >50% increase to >50 μmol/L (10 ITU, 24 A&E/AAU, 31 inpatient, 21 OP, 4 GP). In addition, 54 creatinine results >300 μmol/L were reported from 26 patients. Baseline creatinine was determined after review of patient records and AKIN criteria used for staging. 63 of 90 delta check e-alerts (70%) were due to 61 AKI episodes (35 Stage 1, 13 Stage 2, 13 Stage 3). 34 of 54 (63%) creatinine results >300 μmol/L were due to 14 AKI episodes (3 Stage 1, 2 Stage 2, 9 Stage 3), of which 4 (all Stage 3) had been identified by the delta check. Mortality 120 days after the first e-alert or creatinine result >300 μmol/L for each patient was 4/38 (11%) for Stage 1, 4/15 (27%) for Stage 2, 9/18 (50%) for Stage 3 and 3/39 (8%) for false positives.

For the e-alerts, the median creatinine rise (IQR; range) was 47 μmol/L (36-71; 18-666) at a median (IQR; range) of 9.3 days from the previous result (1.2–37; 0-77). The median (IQR; range) trigger creatinine was 120 μmol/L (78-152; 51-752). False positive e-alerts were more common at trigger creatinines <100 μmol/L; during a separate 12 day audit, there were no convincing episodes of AKI among 20 e-alerts where the trigger creatinine was <50 μmol/L.

This simple automated delta check detects and flags AKI 24/7 at little cost.

P288

Tramadol as a cytochrome P450 2D6 drug probe in the critically ill with acute kidney injury: pharmacologic and genetic evidence

Katie Lane[1,2], John Dixon[1,2], Denise McKeown[1,2], Atholl Johnston[1,2], Ron van Schaik[3], Iain MacPhee[1,2], Barbara Philips[1,2]

[1]St George's, University of London, London, UK, [2]St George's Healthcare NHS Trust, London, UK, [3]Erasmus Medical Centre, Rotterdam, The Netherlands

Introduction: We have demonstrated significant inhibition of hepatic drug metabolism by the enzymes Cytochrome P450 (CYP) 3A4 and 3A5 in critically ill patients with acute kidney injury (AKI)(1) . We are now investigating tramadol as a probe drug of CYP2D6, to test the hypothesis that CYP2D6 function is also inhibited by AKI in critical illness and to determine the influence of CYP2D6 phenotype on this relationship. In this preliminary study, we sought to determine whether tramadol metabolism reflects CYP2D6 function in critically adults, based on tramadol metabolite data and on newly available CYP2D6 genotype data.

Methods: 10mg tramadol was given IV to 10 critically ill patients in our hospital´s critical care unit, and serum taken at 0.5,1,2,3,4 and 8 h for determination of concentrations of tramadol ([Tramadol]) and its two main metabolites. Whole blood was collected for determination of CYP2D6 genotype.

Results: There was a strong correlation between area under the curve (AUC) of the [Tramadol]-time graph and t=4 h [Tramadol], $p< 0.0001$, $r= 0.983$, when all genotypes were examined together. [Tramadol] at other time points correlated less strongly with AUC.

When analysed according to genotype, initial inspection of the results suggests a clinical effect of genotype on [Tramadol]. This is preliminary data and numbers are currently too small to test for significance, yet represent our on-going research.

Conclusion: Single time point analysis of [Tramadol] 4 hours post-IV injection reliably predicts integral tramadol exposure in critically ill adults and may reflect CYP2D6 genotype and function. This requires confirmation in the larger study of the influences and interactions of AKI and CYP genotype on hepatic drug metabolism that is under way.

Reference: (1) Kirwan et al. Intensive Care Med. 2012 Jan;38(1):76-84.

P289

Assessing trainee doctor's knowledge of the diagnosis & management of hyperkalaemia

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[1]Institute of Nephrology, Cardiff, UK, [2]Royal Gwent Hospital, Newport, UK, [3]Cardiff University School of Medicine, Cardiff, UK

Introduction: Hyperkalaemia is a common, potentially fatal complication of acute kidney injury (AKI). Recently, a large AKI audit in our region demonstrated significant variation in the care received by patients with hyperkalaemia. Prior to implementing an education program, we first sought to asses the understanding of hyperkalaemia amongst trainee doctors.

Methods: We produced a questionnaire covering all key aspects of the diagnosis and management of hyperkalaemia. The highest possible score was 33.

Results: 191 doctors completed the study. The mean score for the group was 17/33. Medical and anaesthetic SpR's scored the highest 21 and 20/33 respectively whilst GP trainees scored the lowest (14/33). Most trainees had a relatively low threshold for IV treatment of hyperkalaemia (K>6.0mmol), very few trainees mentioned bicarbonate as either an investigation or treatment option (28% and 7% respectively) and few were aware of the need to monitor urine output in significantly hyperkalaemic patients. Of concern few trainees mentioned angiotensin receptor blockers (ARBs) as a cause of hyperkalaemia and 21% incorrectly stated that loop and thiazide diuretics cause hyperkalaemia. 10% of all trainees could not mention a single drug that caused hyperkalaemia. Whilst most trainees mentioned refractory hyperkalaemia as an indication for nephrology referral, very few mentioned that hyperkalaemia in the context of AKI/oligoanuria was an indication for nephrology referral.

Discussion: Our study has demonstrated that the variation in care observed for patients with hyperkalaemia is at least partly due to deficiencies in the knowledge base of the trainees. In light of these findings we are now developing an education program targeting trainees in all specialities; additionally we are in the process of writing local guidelines for the management of AKI and its complications, which will be easily accessible to all trainees on the health board intranet site.

P290

Long term outcome in patients with acute kidney injury in terms of kidney function and survival

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Introduction: Acute kidney injury (AKI) common in hospitalized patient with serious consequences in terms of mortality and morbidity. We conducted a retrospective audit on inpatients referred to Nephrology team with AKI to assess the short and long term outcome post AKI in terms of renal recovery, prevalence of Chronic Kidney Disease (CKD) and mortality. We used our Cheshire and Merseyside policy for AKI as reference standard.

Method: Total 78 cases were reviewed retrospectively between Oct 2009 to Jan 2012. We reviewed serum creatinine(CR) and eGFR (estimated glomerular filtration rate) value during admission, base line value prior to admission, follow up value at 6 and 12 months post discharge and also maximum CR rise value during AKI episode . We also looked at the number of patients who were deceased both in - hospital and post discharge. We used AKIN AKI classification and definition to stage the AKI cases[1].

Results: The age varied between 35 to 89 yr with mean age of 69 year. Mean serum CR values at baseline was 167mcmol/L and one year follow up mean CR was 196mcmol/L. There was a drop of mean eGFR by 14% from the baseline at 1 year follow up. A total of 32% (n=25) of patients died during 3 year period since AKI episode. Among deceased patients, 40% (n=10) died during hospital inpatient stay and 60% during post discharge period ; 64% of total deceased (n=16)were in stage 3 AKI.

Conclusion: There is higher risk of developing long term CKD post AKI episode contributing to long term CKD related co-morbidities and mortality. There is also high mortality risk during inpatient stay with AKI and higher with stage 3 AKI. It demonstrates the importance of early identification and management of AKI patients to prevent CKD and reduce mortality.

Mean Values of:	baseline	admission	Maximum rise	At 6 months	At 12 months
Creatinine(mcmol/L)	167	360	431	218	196
eGFR (mls/min/1.73m$^{2)}$	42	20	-	34	36

References: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury, Ravindra L Mehta et al. *Critical Care* 2007, 11:R31

P291

Survivors of acute kidney injury requiring renal replacement therapy rarely receive follow-up: identification of an unmet need

Chris Kirwan, Rachelle Taylor, John Prowle

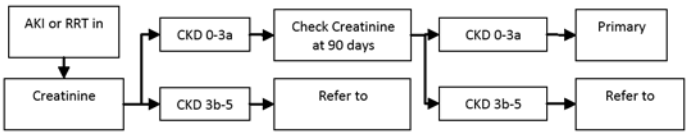
The Royal London Hospital, Adult Critical Care Unit, London, UK

Introduction: Acute Kidney Injury (AKI) occurs in more than 50% of ICU admissions, requiring renal replacement therapy (RRT) in around 10% of cases. There is now increasing evidence that AKI is a risk factor for the development and progression of chronic kidney disease (CKD) however when AKI occurs as a complication of critical illness appropriate follow-up may be neglected. Accordingly, we reviewed the follow up of renal function in all patients who received RRT on our ICU and survived to hospital discharge.

Methods: A retrospective audit of patients who received RRT in a central London Adult Critical Care Unit during 2011.

Results: Of 921 patients admitted, 203 received RRT with 109 surviving to hospital discharge. We excluded 52 patients who had end stage renal disease, renal transplant or known glomerular disease. Of the remaining 57 AKI patients median age was 60 (range: 18-77) and 37 (65%) were male. Median discharge creatinine was 74.5µmol/L (27-662). 42 (74%) were offered follow up, but in only 6 cases (11%) was this to nephrology services 28 attended follow-up (5 to nephrology) at a median time of 6 weeks, however creatinine was measured at in only 14 and in 6 of these it had risen (by median 16.5 µmol/L). In addition, 14 patients had creatinine measured 3-6 months post-discharge and in 8 it had risen (by median 31.5µmol/L).

Conclusions: Follow-up of patients who received RRT for AKI in the ICU was poor and they were rarely referred to nephrologists. Where renal function was measured after discharge, there was evidence of progressive renal dysfunction; however renal function was often not assessed. We propose an algorithm for clinicians to guide follow-up.



P292

A pilot study to determine the feasibility of training doctors and nurses in using ultrasound scans as part of an acute kidney injury assessment

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The Department of Health states that 'Ultrasound imaging in Acute Kidney Injury (AKI) should be performed within 24 hours of admission and if there is suspicion of an infected, obstructed kidney, within 6 hours'. Thus, we piloted an Ultrasound Scan (USS) training course to determine whether it is possible to train acute medical staffs (doctors and nurses) to be able to identify acute renal pathologies, in a single afternoon teaching session. By the end of the session trainees were expected to be able to: a) measure the size of native kidneys; b) identify the absence of a kidney; c) identify hydronephrosis and d) identify a normal bladder.

Four doctors and four nurses working in the Medical Acute Unit and in Accident and Emergency were recruited by open invitation. The afternoon comprised of three 30 minutes didactic lectures on AKI, basic ultrasonography and the anatomy of renal pathologies. Trainees were then split into pairs for 2-to-1 hands-on experience with live renal patients under the guidance of a Consultant Nephrologist or Radiologist. At the end of 2 hours and 30 minutes of hands-on training, trainees were assessed using a short Multiple Choice Questionnaires (MCQ) and an Observed Structured Clinical Examination (OSCE) on a new set of renal patients with the relevant renal pathologies. Trainees were encouraged to use their new skills and were re-assessed one month later to determine if the skills learnt were retained. On average trainees obtained 65% in the OSCE and 87.5% in MCQ in the first test. One month later trainees were examined with the same MCQ paper and an OSCE using a different patient cohort. The results of the re-test showed that skills and knowledge were not retained. However, only 2 out of the 7 trainees in the re-test gave feedback to the effect that they had been able to practice their skills. This project is innovative because it is the first pilot study to demonstrate that, it is feasible to train medical professionals with no prior knowledge of ultrasongraphy in one afternoon. However the pilot also demonstrated that regular training is needed for skills to be retained.

P293

Clinical outcomes of elderly patients on a renal HDU

Jia-hui Wang, Jen Joslin, Rebeka Jenkins, Phillippa Peto, Claire Sharpe, Satish Jayawardene, Sapna Shah

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Introduction: The ageing population is susceptible to acute kidney injury (AKI) and its sequelae. Previous studies examining the effect of age on AKI prognosis have mainly been derived from an ITU setting (Level 3 beds) with short follow-up periods leading to conflicting conclusions. We evaluated the outcomes in a cohort of patients admitted to a Renal HDU (Level 2 beds) over a three year period to assess the influence of age on survival and renal recovery in this clinical setting.

Methods: This was a retrospective observational study. All patients that were admitted to the Renal HDU from 2009 to 2011 requiring haemofiltration were identified. Patients who were previously dialysis dependent or had a renal transplant were excluded. Patient data was recorded at discharge, 3 months and 12 months from time of admission.

Results: 50 patients were identified. 60% were over 65 years of age, 60% were male and 74% Caucasian. Unadjusted Kaplan-Meier curves demonstrated decreased survival in those over 65 years of age at discharge ($p=0.03$) but no significant difference at 3 or 12 months was found. Cox regression analysis showed that only inotrope use was associated with survival at discharge ($P<0.01$). At 3 and 12 months, survival was associated with admission eGFR, inotrope and NIV use (all $P< 0.01$). Factors significantly associated with a lower discharge eGFR (MDRD) include female sex (37 ml/min in males v 22 ml/min in females, $P<0.01$), baseline eGFR ($P<0.01$) and younger age (26 ml/min in <65 years v 37 ml/min in >65 years, $P=0.01$). At 1 year, a lower eGFR was associated with diabetics (31 v 34 ml/min, $P<0.01$). The need for continued renal replacement therapy (RRT) at discharge was significantly increased in non-Caucasians ($P<0.01$) and females ($P=0.04$) though at 1 year continued RRT was more likely to be required in non-Caucasians alone ($P=0.02$).

Conclusion: Advancing age is not an independent factor associated with mortality, renal recovery or RRT dependence following admission to a level 2 bed up to 1 year after discharge. Therefore, we argue that chronological age alone should not be used to restrict access to a level 2 bed when haemofiltration is required.

Poster session

Friday 15th March

11:30 - 12:30

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Outcomes following ITU admission with AKI- 5 year single centre experience

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Aim: To assess outcomes in patients with Acute Kidney Injury requiring renal replacement therapy (RRT) in ITU.

Methods: We identified all patients requiring ITU care at Monklands Hospital between 01/01/2007 and 31/12/2011 including those who required RRT. We used the hospital and renal electronic patient records (EPR) to identify subsequent mortality and renal outcomes as well as those already receiving RRT. Statistical analysis was done using SAS v 9.3.

Results: The patients were divided into three groups for analysis; 202 patients required RRT and ventilation (group 1), 963 required ventilation alone (group 2) and 28 chronic RRT patients (group 3). Group 1 had a higher proportion of co-morbidity $p<0.0001$. This group also had a higher median stay in ITU (9 days v 1 day <0.0001) and in-hospital stay (17 days v 8 days $p<0.0001$) as well as higher in-ITU mortality 45% v 20.1% $p<0.0001$. In-hospital mortality was not significantly different between group 1 and group 2 (5.4% v 8.4% $p=0.1553$). For those surviving to be discharged from hospital the survival at one year was similar between the two groups at 88% and 88.37% for group 1 and 2 respectively ($p=0.914$). This was also shown to be not significant on Kaplan-Meier plot (log rank $p=0.9747$). Of the 100 survivors in the AKI requiring RRT group, 21 were left with some form of kidney disease, 2 failed to recover renal function and 17 were attending general nephrology clinic. In group 3 of the 28 patients who were already receiving some form of long-term RRT, 14 died in the first 15 days with the rest surviving at 1 year.

Conclusion: Patients who require RRT during ITU admission have a higher in-hospital length of stay and mortality. For those surviving the ITU period, patients from both groups had similar survival at one year.

P295

Standards of care in acute kidney injury (AKI): a 12-month prospective audit

Dominic Taylor, Joanne Taylor

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Introduction: Our renal unit serves >850,000 people from four referring centres. Patients with AKI are transferred to our unit if renal replacement therapy or specialist input are required. The 2009 NCEPOD report "Adding insult to injury" identified deficiencies in early recognition of AKI, simple appropriate investigations, review and transfer; A series of recommendations were made.

Methods: All patients transferred to our unit with a diagnosis of AKI were included. Data on their admission, risk factors for AKI, management, transfer, and outcomes were audited prospectively from October 2011 to October 2012.

Results: 51 patients (25 male, 26 female) were included. Median Length of stay 17 days (4-60). 51% were referred by medical teams, the remainder by ITU or surgical specialties. 47% had established CKD; 24% had vascular disease. 63% were hypertensive. The aetiology of AKI was predominantly 'renal'. Of pre-renal causes, sepsis was the most common. Electrolytes were checked in 98%. Urinalysis was not performed in 29%; consultant review was after 12 hours in 26%; nephrotoxins were continued in 22% and inadequate fluid resuscitation was given in 20%. 46% underwent imaging of the renal tract in <24 hours. 69% were referred to our service within 24 hours of AKI. Advice or review was within 24 hours in all patients. Transfer to our unit occurred within 48 hours in 85% (excluding those requiring on-going ITU care). Two-thirds received haemodialysis; 10% died in hospital; 20% died within 3 months; 14% needed permanent renal replacement therapy. Baseline eGFR of <60ml/min was associated with significantly increased probability of permanent RRT (χ^2= 0.0004) and of death within 3 months (χ^2= 0.0004).

Discussion: Patients with AKI had recognised risk factors and long length of stay. Initial management of AKI was suboptimal: Early urinalysis, consultant review and timely renal tract imaging were lacking. Timing of advice and transfer was adequate. We have designed a checklist for use by junior staff to improve initial management in these areas. Re-audit is planned once the checklist is in use.

P296

Timing of acute kidney injury- does it matter? A single centre experience

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Introduction: Acute kidney injury (AKI) is a common and poorly identified complication of hospital admission. This study identifies differences in outcomes between patients admitted with AKI, and those who develop post-admission AKI.

Methods: Single-centre, retrospective analysis of 306 patients with AKI who received intermittent haemodialysis. Data was collected for a period of 3 years. Patients were divided into "early" and "late" groups. The early group were admitted with AKI, or developed it within 48 hours. The late group developed AKI after 48 hours. Primary outcomes: patient and renal survival. Secondary outcomes: length of stay, admission to critical care, and length of time on dialysis.

Results: Patients in the early group had a significantly lower mortality rates and shorter lengths of stay. The timing of the AKI did not impact on: admission to critical care, renal dysfunction at discharge, or the amount of time spent on dialysis.

Discussion: Early recognition and intervention reduces patient mortality in AKI. One way of improving outcomes for patients with hospital-acquired AKI could be to assess the impact of care bundles directed at identifying and managing patients at risk.

P297

Urinalysis in acute kidney injury: a survey of acute medical admissions unit staff

Adarsh Babu

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Introduction: Acute kidney injury (AKI) is common and is found in greater than 25% of acute hospital admissions. Urinalysis is important in diagnosing AKI and also in characterising the cause of AKI. I undertook a survey of frontline staff in order to analyse knowledge, attitude and practise with regards to urinalysis in AKI.

Methods: 10 questions were formed based on the renal association guidelines on AKI. The questionnaire were sent out to doctors, nurses and health care assistants working in medical admissions unit.

Results: 33 health care staff responded. 97% of them responded urinalyses is mandatory in all AKI. 75% of them said urinalyses needs to be done immediately after recognising AKI but in practice from their experience only 56% of patients get it in less than 24 hours. Respondents were evenly split at 33% for possible reasons of delay in obtaining urine samples. The reasons were put down to patient factors, unaware of need and unaware of the diagnosis. 59% of the respondents felt that not all members of the team take equal responsibility and most of them feel that it is others' responsibility to obtain urine sample. 49% of the respondents were unaware of the need/significance of protein creatinine ratio although 67 % felt ideal time would be early morning first void sample. Most of them replied that they were unaware of all the investigations that can be done on spot urine sample in the setting of AKI and needed further education/training.

Discussion: This survey highlights the key areas in diagnosing AKI. It demonstrates gaps in knowledge among health care staff including junior doctors with regards to AKI. Better communication and sharing of duties can lead to prompt recognition of cause of AKI. It also highlights the need for better training and education of general medical/nursing staff on AKI.

P298

Acute kidney injury - the chink in the critical care outreach team's armour

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Introduction: Many hospitals now have Critical Care Outreach Teams (CCOT) to provide support in the management of patients who are deteriorating clinically. Theoretically, these acutely unwell inpatients are at high risk of developing Acute Kidney Injury (AKI). The purpose of this study is to investigate the relationship between AKI and CCOT patients.

Methods: Patients at a district general hospital reviewed by the CCOT from 01/01/2012 to 31/03/2012 and not subsequently admitted to Intensive Care Unit were included in this study. Patient health records were studied retrospectively.

Results: 109 patients were included in this study of which 49 patients (45%) developed AKI during their hospital admission. 25 patients had AKI Stage 1, 14 patients AKI Stage 2 and 10 patients AKI Stage 3 as per the Acute Kidney Injury Network staging system. Of the AKI patients, 84% already had developed AKI at the time of CCOT review. The on-site renal team were only involved in 20% of AKI cases. The percentage number of deaths increased with increasing stages of AKI [No AKI 22%; AKI Stage 1 24%; AKI Stage 2 43%; AKI Stage 3 60% (p=0.02)]. Of the patients who survived, the average length of hospital admission in the AKI group was 2.4 days longer than in the non-AKI group. There were also risk factors identified (Table 1).

Risk Factors	RR of Developing AKI	Confidence Interval	P values
Pre-existing CKD	1.96	1.36 to 2.83	0.002
Diabetes	1.83	1.25 to 2.68	0.005
Diuretics	1.72	1.16 to 2.55	0.010
ACE-inhibitor	1.80	1.27 to 2.49	0.026
Metformin	1.43	0.89 to 2.56	0.309
Sepsis	1.34	0.87 to 2.07	0.119
Vancomycin/Gentamicin	1.08	0.66 to 1.76	0.594
ARB	1.04	0.53 to 2.04	0.146
Surgery	0.89	0.57 to 1.39	0.831
NSAIDs	0.89	0.30 to 2.64	0.798
Contrast	0.78	0.50 to 1.23	0.275
Age	15.39* years	8.62 to 22.67 years	0.0001

*Mean age difference between AKI and No AKI groups

Table 1: Risk factors and their accompanying Relative Risks (RR), Confidence Interval and P values for developing AKI

Discussion: This study has for the first time shown that many acutely unwell ward patients reviewed by the CCOT have superimposed AKI. Given the mortality and morbidity associated with AKI, it is important to enlist the help of CCOT to provide opportunistic interventions in the prevention and management of AKI.

P299

Back to basics in acute kidney injury with ABCDE

Caroline Forde, Wendy Marshall, Zoe Foster, Niall Leonard, Jennifer McCaughan

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Acute kidney injury (AKI) is a common, serious and expensive problem. Patients with AKI have longer hospital admissions and increased mortality. Numerous strategies have been implemented in an effort to improve the recognition and management of AKI. In this study, multidisciplinary education sessions and the introduction of a simple 'ABCDE' checklist to aid management were introduced in a district general hospital.

Methods:

1. The incidence of AKI (26µmol/l rise in creatinine) and AKI recognition were measured both hospital-wide and in a pilot general surgical ward.
2. Education sessions on AKI recognition were undertaken involving doctors, nurses, nursing assistants and pharmacists from the pilot ward.
3. The 'ABCDE' checklist (Address drugs, Boost blood pressure, Calculate fluid balance, Dip urine, Exclude obstruction) was introduced.
4. AKI recognition and implementation of the 'ABCDE' checklist were measured.

Results:

- 16% of patients had AKI.
- Initially, AKI was recognised within 24h in 31% of patients. 4 out of 5 'ABCDE' steps were implemented in 20% of patients.
- Following multidisciplinary education, AKI recognition improved to 100% with 4 out of 5 'ABCDE' steps implemented in 67% of cases.
- These results were replicated across the surgical directorate (120 beds) and in the 40-bed medical admission unit.

Discussion: AKI has implications for the patient and the healthcare provider. Early recognition and action may ameliorate the course of AKI and facilitates timely referral to Nephrology. Educating and empowering the multidisciplinary team improves AKI recognition and management and should form a key component of strategies to address AKI.

P300

Aetiology and outcomes for dialysis-dependent acute kidney injury patients on intensive care unit

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Introduction: AKI is a common occurrence in sick hospitalized patients, in particular those admitted to intensive care. Published data suggests that 4–5% of all critically ill patients develop severe AKI and require initiation of renal replacement therapy (RRT). Such patients have high mortality rates often exceeding 60%.

Objectives: We aimed to review the outcomes of patients admitted to ICU and required renal replacement therapy for AKI. We examined whether aetiology of AKI, co-morbidity burden, hospital length of stay and treatment in ICU had any significant association with survival in the study cohort.

Methods: During 2009, 56 patients were identified to have received RRT with AKI who were admitted to the ICU at the Royal Wolverhampton Hospitals NHS Trust. Computerised and paper-based case records were examined for these patients to collect the data. AKIN classification was used to classify the severity of AKI.

Results: Median age at admission was 66 years (27 - 85) with 29 males and 27 females. 31 (55.4%) patients had sepsis and 20 (35.7%) patients had ATN as the main cause of AKI. 32 patients (57%) had three organ failures at the time of commencement of RRT. 46 patients (82.1%) received haemofiltration only. 32 (57%) patients died, with more than 80% of these occurring in ITU. There was no significant difference in survival when compared to duration of haemofiltration, length of stay, number of organs failed and number of co morbidities. However significantly more patients died had AKI due to sepsis ($p=0.003$) or if they received mechanical ventilation ($p=0.48$) or inotropes (0.04). Of the 27 patients who survived till discharge from hospital 18 (66.7%) had normal renal function, 8 (29.6%) had AKIN stage I and only 1 patient required maintenance haemodialysis.

Conclusions: Individuals who develop dialysis-dependent AKI in ICU setting in general terms either die or recover. Sepsis is the most common association with death. The need for mechanical ventilation and inotropic therapy are both associated with increased incidence of death.

P301

Laboratory based electronic AKI (e-AKI) alert to identify the onset and progression of acute kidney injury in hospitalized patients

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Background: Acute Kidney Injury (AKI) is a common complication in hospitalized patients and condition frequently goes undetected, thus worsening outcome for the patient. Guidelines have suggested employing serum creatinine and urine output to detect AKI and, using the former, laboratory information management systems (LIMS) may help with both the diagnosis and management of the condition.

Methods: Utilising Kidney Disease: Improving Global Outcomes (KDIGO) criteria, we have developed and implemented algorithms into our LIMS software (iLab.TP, iSOFT) that stage and alert clinicians to the possible presence of AKI, as a function of current and comparator serum creatinine values. The setting is at Royal Liverpool University Hospital and to ensure optimal clinical sensitivity, we have also used nephrology defined estimated creatinine values when reference value not available.

Results: Following beta implementation, audit data shows that ~10% of serum creatinine results (N=2537) fulfilled KDIGO criteria for AKI and were staged by our LIMS software accordingly (4.5% stage 1, 2.4% stage 2 and 2.7% stage 3 AKI alerts). While some represented multiple samples from one patient, the data shows a significant number of patients' prognosis may be improved by managing their condition appropriately and preventing disease progression. The outcome data analysis in terms of renal recovery of the cases shown a positive trend of renal recovery in all stages of AKI with mean creatinine value.

Conclusion: Implementing algorithms into a LIMS system facilitates detection of AKI in hospitalised patients and may subsequently improve their management and outcome.

AKI Stage	KDIGO criteria (serum creatinine only)	Received AKI alert and stage	No comparator available ("?AKI or CKD" alert)	Total alert
Stage 1	Increase ≥ 26 µmol/L or increase ≥1.5 to 1.9 x reference value	72	44	116 (4.5%)
Stage 2	increase ≥ 2 to 2.9 x reference value	56	6	62 (2.4%)
Stage 3	increase ≥3 x reference value or increase ≥ 354 µmol/l	21	50	71 (2.73%)
			Total	249 (9.6%)

Poster session

Friday 15th March

11:30 - 12:30

CKD Anaemia 1

P302

Associations between darbepoetin use and mortality in an all-cause CKD-population

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Background: Anaemia frequently complicates CKD. Current studies of anaemia management are focused on the role of iron supplementation following a series RCT highlighting potential risks associated with the use of erythropoietin stimulating agents (ESA). In this study we aim to consider any mortality risks associated with ESA use in a real-world CKD cohort.

Methods: Patients were selected from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS). All patients with a history of ESA exposure prior to recruitment were excluded from analysis. 181 patients commenced on darbepoetin subsequent to recruitment were matched for age and eGFR to patients who did not progress to requiring ESA therapy. A second comparator group matched for age, eGFR and CRP was also identified. Multivariate stepwise Cox regression was used to compare risk for all-cause mortality between groups.

Results: When patient groups were matched for age and eGFR, darbepoetin use was associated with an increased risk for death (HR 1.7, $p<0.01$). The significance of this finding was reduced when inflammatory state was included in a multivariate model (HR 1.49, $p=0.14$). When patient groups were matched for age, eGFR and CRP, no increased risk for death was observed in darbepoetin treated patients (HR 0.95, $p=0.8$). A significant inverse correlation between CRP level at time of initiation of darbepoetin therapy and iron saturation was observed (r -0.29, $p<0.001$). Patients in the darbepoetin group treated with intravenous iron had a non-significantly reduced risk for death compared to those who were treated with darbepoetin without iron (HR 0.4, $p=0.08$).

Conclusion: Published RCT only considered patients who were candidates for ESA therapy. This analysis compares groups of CKD patients who are matched for other parameters as well as their need for anaemia management. Our findings suggest that requirement for ESA therapy is a marker of an increased inflammatory state and not a direct cause of increased mortality.

P303

Assessing the iron requirements of a haemodialysis population: the effect of a change in serum ferritin assay

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Introduction: Trends in haemoglobin (Hb) and serum ferritin (sFe) values are a guide to making adjustments to parenteral iron and Erythropoeisis Stimulating Agent (ESA) prescriptions for individual haemodialysis (HD) patients. The local laboratory assay for sFe was recently changed from the 'Beckman Coulter Assay' (BC) to the 'ADVIA Centaur Assay' (AD). The AD assay appeared to give higher values of sFe resulting in parenteral iron dose reductions for many patients.

Methods: We studied patients attending our main (n = 120) and satellite (n = 25) units who received HD treatment for a period extending from 2 months before the assay change to 6 months afterwards. Relevant data (Hb, sFe, ESA dose and parenteral iron dose) were collected on a monthly basis. Changes to ESA and iron prescriptions were made by the regular clinical team in accordance with UK Renal Association guidelines for anaemia management. Data from the beginning and the end of the study period were compared using a two-tailed paired t-test.

Results: There was no significant change in mean Hb or ESA requirements during the study period. For patients attending the main HD unit, parenteral iron requirements were reduced from a mean of 65.6 mg/week to 33.1 mg/week ($p < 0.001$). Despite this, end-of-study sFe values obtained from the AD assay were still higher than pre-study sFe values obtained from BC assay (mean (SD) 541.6 ug/L vs 599.3 ug/L, $p < 0.001$). A similar pattern of results was seen with our satellite dialysis unit patients.

Discussion: This study indicates that the choice of laboratory serum ferritin assay may influence the assessment of iron requirements for individual HD patients, particularly if sFe values are close to the threshold for making dose alterations. It may be helpful to refer to this potential source of variation in national clinical guidelines and also in comparative audit reports. Furthermore, reductions in parenteral iron dose made following the change in serum ferritin assay did not appear to have a significant impact on Hb values and ESA requirements. The latter finding needs to be explored in a larger prospective study.

P304

A multi interventional approach to achieve target haemoglobin levels in haemodialysis patients

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Introduction: Normalisation of haemoglobin in CKD patients lead to excess cardiovascular mortality and morbidity. The risk is pronounced in patients whose haemoglobin is slow to increment and therefore needing higher ESA doses. In the DRIVE study, use of IV iron to increase Ferritin levels to 1200mcg/mL has been demonstrated to lower ESA doses.

Methods: We devised two new protocols to achieve target Hb, to reduce the number of patients exceeding Hb 12g/dL and lower ESA requirements. An IV iron protocol with a serum Ferritin upper limit of 800 mcg/mL rather than 500mcg/mL guided by both TSAT and Ferritin. In parallel we focused on patients with Hb >12g/dL with ESA dose reduction or discontinuation based on haemoglobin levels

Results: There were 137 at start of the protocol and 148 patients 12 months later, dialysing at the unit. There was a significant increase in patients achieving target Hb of 10- 12g/dL from 57% vs. 82% ($P < 0.001$) and the % of patients with a Hb > 12g/dL fell from 26% to 9% at 12 months ($P<0.001$). Mean Ferritin rose from 495 to 612 mcg/mL ($P<0.001$) and TSAT rose from 25.5 to 28.5% ($P=0.04$). There was a significant reduction in darbopoetin requirement, from 0.47 to 0.33 mcg/week/kg post dialysis weight at 12 months ($P<0.001$). This was also true when corrected to haemoglobin (0.043 vs. 0.03 mcg/week/kg/Hb, $P<0.001$). There was no significant difference in CRP at 12 months compared to the commencement of protocol (median CRP 6 vs. 5).

Discussion: The aspirational target for Hb 10-12 g/dL can be achieved in haemodialysis patients with reduced ESA requirements following a multi-interventional approach. This does result in increased ferritin levels with no change in inflammatory markers. The long term effects of iron administration are unclear and currently there are no randomised controlled trials to assess its safety and efficacy and therefore should be used cautiously.

P305

Intravenous iron infusion reduces platelet counts in chronic kidney disease patients

Adil Hazara, Sunil Bhandari

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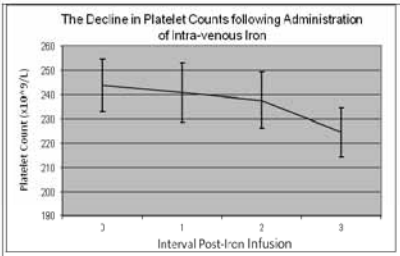
Introduction: Correcting the anaemia of Chronic Kidney Disease (CKD) with Erythropoietin-stimulating agents (ESA) to target haemoglobin levels has demonstrated issues with cardiac safety. IV iron however does not appear to adversely affect cardiac profile. There is anecdotal evidence it may even reduce platelet count. We have examined the effect of IV iron infusion on platelet counts.

Method: Data from a previously published observational study examining the safety and efficacy of accelerated dose Iron Dextran in CKD patients was used to examine the effects of iron on platelet count during a 3 month follow-up period.

Results: 48 patients (Mean age 67), 28 male and 20 females with mean eGFR of 17.7 mil/mil/1.73m^2(range: 4-14) were included. They all received iv Iron Dextran at a median dose of 1000mg over a median time of 2h40mins.



Baseline, 1-Month, 2-Month and 3-Month mean platelet counts were 244.00±10.75, 240.90±12.08, 237.77±11.49 and 224.75±10.11 respectively (all values in x10^9/L).

Over three-months, there was a decline in platelet counts of 15.25 x10^9/L relative to the baseline (p=0.04)

Discussion: Iron Dextran effectively treats iron deficiency and may reduce the potential risk of thrombocytosis by decreasing platelet count. This reduction appears within the first month and becomes more pronounced after three months. This effect may improve the detrimental characteristics that occur in patients with cardio-renal syndrome in association with anaemia of CKD. Prospective data is required to confirm these findings.

P306

Reticulocyte haemoglobin - an alternative marker to guide intravenous iron therapy in dialysis patients

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Introduction: Percentage hypochromic red cell (% hypo) is currently widely used to guide intravenous (iv) iron therapy for haemodialysis (HD) patients. The Renal Association guidelines recognise Reticulocyte haemoglobin (Ret He) as an alternative marker for relative iron deficiency but there are no established targets in dialysis patients. Due to the changes in regional laboratory contracts, new analysers that measured only Ret He but not % hypo were introduced in our centre. We evaluated a protocol to guide iron therapy using Ret He.

Method: Retrospective study of 52 stable HD patients with no evidence of active infection, bleeding, or surgical procedures over a 6 month period was performed. The haemoglobin (Hb) levels, ferritin levels, iv iron (venofer) dose administered and darbepoietin (Dp) dose for 3 months before (using %hypo protocol) and after introduction of Ret He protocol were compared.

Results: The log transformed mean Hb (11.6g/L vs 11.8g/L, p=0.2), Dp dose (35 & 33 micrograms/week, p=0.4), venofer dose (217 & 223 mg/month, p=0.6) remained unchanged in the two periods. Ferritin levels achieved were higher using the Ret He protocol compared to % hypo protocol (571 vs 454 µg/L vs p= 0.002, log transformed mean).

Discussion: Our study shows that the mean Hb attained, the Dp and venofer doses were similar between the % hypo and Ret He protocols, suggesting that Ret He could be used as a reliable and alternative marker for relative iron deficiency. To our knowledge we, for the first time, have developed a protocol for using Ret He to guide iv iron therapy in dialysis patients that could be easily adopted by other centres.

Poster session

Friday 15th March

11:30 - 12:30

CKD Anaemia 2

P307

Haemoglobin at dialysis start - should we re-design our CKD anaemia service or ignore registry performance data?

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The Renal Registry states that "…the Hb at the time of starting dialysis gives the only indication of concordance with the current anaemia management recommendations for the pre-dialysis (CKD stage 5 not yet on dialysis) group." Our unit consistently falls in the lowest quartile of performance for this parameter on Renal Registry Data. Following the 2010 report, we undertook an internal audit to investigate whether this was still the case, and if so, why.

Our audit confirmed the 2010 Registry data in our 2012 cohort - between January and June 2012, our mean Hb in dialysis starters was 9.6, and only 31% of new starters had an Hb>10 at time of dialysis start. Our PD patients were slightly better than our HD starters (39% vs 29%).

Further analysis showed our mean Hb in all CKD stage 5 patients not on dialysis was 11.4 (+/- 1.4)g/dL. All patients with eGFR<18 are managed in a specialised clinic using an anaemia algorithm. However, the prevalent mean Hb fell from 11.9 (+/- 0.7) g/dL in eGFR>15<20 patients, to 11.3 (+/- 1.0) g/dL in eGFR >10<15 patients, to 10.3 (+/- 0.7) g/dL in eGFR<10 patients. The mean rate of fall of Hb was 0.1g/dL per month in eGFR<10 and only 0.02g/dL in eGFR>15, but of those who started dialysis with Hb<10, this translated to a median fall of 1.7g/dL in the last 3 months before HD began. We also identified a narrowing of the Hb range in all our pre-dialysis patients in the service following introduction of a new algorithm, and worsening iron deficiency as eGFR fell.

We feel that although our anaemia management in our CKD 5 (not on dialysis) patients results in a mean Hb of 11.4 (+/- 1.4) g/dL, the Registry measure may not reflect this. We speculate whether we should alter our pre-dialysis anaemia algorithm to aim for a higher "target" Hb in those with eGFR<15. This would increase our mean overall Hb level and improve Registry returns in new dialysis starters. However, higher Hb levels may carry additional costs and risks. Alternatively, we could leave our algorithm unchanged, and argue the Registry measure for CKD 5 (not on dialysis) anaemia management may need refinement.

P308

The introduction of ferinject (Ferric Carboxymaltose) leads to improvement in iron status and reduces erythropoietin stimulating agents (ESAs) requirement in pre-dialysis CKD patients. Optimising iron storage is very cost effective

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Introduction: The benefits of CKD-related anaemia treatment with erythropoietin stimulating agents (ESAs), and parental iron are well recognised. However the arising financial costs are high. A greater risk of CVD is associated with ESAs.

Objective: To evaluate whether our practice in management of pre dialysis CKD related anaemia meets with NICE C G 114(2006), before after the introduction of Ferinject.

Method: We conducted 2 retrospective audits in 2010 and 2012 on non-dialysis patients receiving Aranesp and/or iron infusion therapy. Ferinject was introduced at the end of 2011. Data on patients' demographics, HB, eGFR, T-sat, ferritin and Aranesp dose were retrieved from computerised records.

Results: 86% of non-dialysis CKD patient had HB>10.5 g/dl in 2012 compared to 80% in 2010 (p=0.006). The average ferritin was not statistically different between 2012 and 2010, (411ug/l vs 389ug/l, p=0.3). However, more patients achieved T-sat >20% in 2012 compared to 2010 (86% vs 66%, p<0.0004). Similar proportion of patients achieved HB target >12.5 in both years(21% vs 19.9%,p= 0.54). There was a 14% decrease in the average patient-monthly Aranesp dose in 2012 compared to 2010 (91.9µg vs 78.6µg, p=0.006) which led to significant reduction in the cost of anaemia management in our department (£137k per year, *BNF prices 2012). 8% of the 2012 population were under-treated and iron depleted with both ferritin<200 ug/l and T Sat<20%. However, 80% of them had HB>10.5 g/dl (range 10.8-14.3, mean 12.3g/dl). HB target was achieved using high doses of Aranesp (mean 91µg).

Conclusion: A greater proportion of patients achieved the target HB of 10.5-12.5 g/dl during 2012 compared to 2010, despite a reduction in ESAs during this period. This was associated with the introduction of Ferinject and a greater proportion of patients achieving Tsat > 20%. This potentially reduces the risk of CVD and is very cost effective. More work needs to be done in the future as there is a global consensus to keep HB targets between 10 and 12

P309

Audit of anaemia management in pediatric established renal failure patients through transplantation and beyond in the UK

Shazia Adalat[1], Anna Casula[2], Mairead Convery[3], Manish Sinha[4], Carol Inward[5]

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Introduction: Cross-sectional registry data shows that approximately 40% of children receiving renal replacement therapy (RRT) in the UK have a haemoglobin (Hb) below the target range. A detailed audit was undertaken to (1) document the incidence of anaemia in these children at different time points in the treatment course (2) determine whether management is consistent with the 2006 NICE guideline CG 39.

Methods: A retrospective review of a random sample from of paediatric patients who started RRT1/1/03-31/12/07. Cases (n= 125) from 8 of 13 paediatric nephrology centres were studied from 6 months prior to start of RRT up to 2010. 30 patients received pre-emptive transplantation.17 started dialysis within three months of presentation (late referrals).

Results: Start of RRT; 70% (52/73) of those whose first treatment was dialysis had a Hb below the target range significantly lower than the 30% (9/30) of those transplanted pre-emptively who had Hb levels below the range ($p<0.001$). No difference in anaemia incidence was found between early and late referrals or in ferritin levels between treatment modalities (dialysis and transplantation) or early and late referrals. **At time of transplant**: 31% (35/112) of patients were anaemic with no difference between those transplanted pre-emptively or not ($p<0.4$). 48% (38/79) had low ferritin levels, however levels were significantly higher in the group previously dialysed ($p<0.001$). **At one year post transplant:** 15% (16/106) of patients were anaemic, 80% had low ferritin levels and only 25% were being treated with iron supplements. No correlation was found between anaemia levels and use of immunosuppression. Over time 12-19% of patients received ESAs without receiving supplementary iron.

Discussion: The audit demonstrates significant levels of anaemia in children on RRT, persisting after transplantation in 50%. It also highlights deficiencies in measuring parameters of anaemia control and achieving established naticnal guidelines.

P310

Correction of iron deficiency anaemia in CKD patients with asthma using intravenous CosmoFer

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Background: Intravenous (IV) iron is used for correcting iron deficiency anaemia (IDA) in patients with chronic kidney disease (CKD). There remains a concern for its use in patients with asthma as it may trigger an exacerbation. There is limited clinical data looking into this problem. Patients with bronchial asthma requiring parenteral iron are administered intramuscular iron as per current recommendations.

Methods: In this study we analysed the efficacy and safety of IV CosmoFer (low molecular weight iron dextran) in asthmatic patients. Twenty CKD patients with IDA and a history of asthma were reviewed. Severity of asthma was recorded as per British Thoracic Society Guidelines (BTSG). The level of asthma control was assessed using the Royal collage of physician (RCP) questionnaire. All patients received intravenous hydrocortisone 30 minutes before the test dose of CosmoFer (100mgs in 100mls of 0.9% normal saline over one hour. The remaining total dose infusion was given at the rate of 150mls/hr. Haemoglobin (Hb), serum Ferritin (SF) levels and estimated glomerular filtration rate (eGFR) were measured pre and four weeks post infusion. All patients were followed up for 6 weeks to assess the control of their asthma using the RCP questionnaire.

Results: All 20 patients completed the study. Mean age 62.9yrs (SD 18).Female to male ratio of 1.2:1. Severity of asthma was BTSG step 1, step 2 and step 3 in 30%, 50% and 20% of patients respectively. Mean values pre and post treatment: Hb g/dL 10.0 (SD1.2) vs 11.2 (SD1.4) P= 0.07; SF ng/ml 96.2 (SD60.3) vs 301.5 (SD214.3) P=0.002; eGFR ml/min/1.73m^2 21.05 (10.1) vs 20.5 (9.5) P<0.001. No patients experienced acute reactions to the infusion. At 6 weeks follow-up enquiry, no patient reported worsening of their asthma or other adverse effects.

Conclusions: This study demonstrates that IV CosmoFer may be administered safely in asthmatics by administering a single 50mg pre dose of hydrocortisone. The risk of initiating a potential acute or possibly delayed histamine release response may be negated by hydrocortisone. Caution however should be maintained and further studies are needed to confirm these findings.

P311

Is hepcidin-25 production increased in patients with chronic kidney disease?

Adam Rumjon[1,2], Iain Macdougall[1,2]

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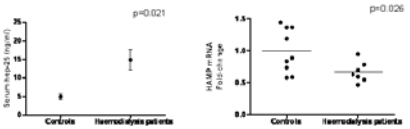
Background: Hepcidin-25 (hep-25) plays a critical role in iron metabolism, and acts principally by blocking the transport of dietary iron through enterocytes, thus reducing the availability of iron for the production of red blood cells. Hep-25 also acts on hepatocytes and macrophages to regulate iron fluxes *in vivo*. Hep-25 levels are elevated in inflammatory conditions, but have also been shown to be elevated in haemodialysis (HD) patients. A combination of reduced filtration and the pro-inflammatory/acidic milieu of CKD is thought to be responsible for this, but the exact contribution of each is unknown. In this exploratory study, we sought to examine the possible pathways that are responsible for the elevated levels of hep-25 in CKD.

Methods: Patients were selected for this study on the basis of the following inclusion criteria; on HD for >3 months, Hb >10 g/dL, CRP <20 mg/L, dialysis via an A-V fistula/PTFE graft, stable IV iron and erythropoietin doses for >1 month, and no hospitalisation/antimicrobials for >1 month. A control group of healthy individuals was selected for comparison. Blood (10ml) was drawn pre-dialysis and separated by Ficoll Hypaque centrifugation. Serum hep-25 levels were measured using liquid chromatography mass spectrometry. Peripheral blood mononuclear cells (PBMCs) were processed immediately (5-6 $x10^6$ cells/mL); total cellular RNA was extracted using RNeasy kits and the extracted RNA (500 ng) was reversed transcribed using a High Capacity RNA-to-cDNA kit. Quantitative RT-PCR was performed using the Applied Biosystems 7900HT Fast Real-Time system. Amplification reactions were performed using Taqman HAMP (encoding hepcidin) and GAPDH (housekeeping) primers. All reactions were performed in triplicate.

Results: To date, 5 males and 2 females have been studied (age 56±20(SD) years, Hb 11.3±0.8 g/dL, CRP 10.4±5.0 mg/L, ferritin 367±90 ng/mL and albumin 39.7±1.8 g/L). The median IV iron dose was 100mg/week, and the median Eprex dose was 46.2 [IQR 18.9-114.6] iu/kg/week. The mean age of the control group was 44±15 years. Serum levels of hep-25 were significantly elevated in the HD population (14.9±2.7 vs 4.9±0.8, p=0.021). Interestingly, however, HAMP mRNA levels were significantly lower than in healthy controls (mean fold-change 0.667±0.06 in HD compared to controls (p=0.026)).

Conclusion: Despite higher circulating levels of hep-25, significantly lower transcription of HAMP mRNA was unexpectedly observed in HD patients. This counter-intuitive result, which has not been described previously, requires confirmation in a larger cohort of patients. Elucidation of this effect is also required; it is possible that negative feedback mechanisms may be in operation in HD patients to reduce hep-25 levels.



Poster session

Wednesday 13th March

18:15 - 19:25

CKD bone disease 1

P312

A survey of the current management of secondary hyperparathyroidism in patients with end-stage renal disease undergoing dialysis in the UK NHS

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Introduction: Secondary hyperparathyroidism (SHPT) impacts on the morbidity and mortality of patients with end-stage renal disease. The UK Renal Registry reports on achievement of targets for single markers of SHPT control but not multiple markers per patient which may be more important. The aim of this study was to so describe achievement of target ranges for serum adjusted calcium (Ca), phosphate (PO4) and parathyroid hormone (PTH).

Methods: Retrospective medical records review was conducted in 8 UK NHS hospital dialysis units. A cross-sectional survey of all adult patients undergoing haemodialysis (HD) or peritoneal dialysis for ≥90 days was performed in June-September 2011. UK Renal Association (RA), National Kidney Federation (KDOQI) & Kidney Disease Improving Global Outcomes (KDIGO) guidelines were used to derive broad 'Study target ranges': Ca 2.1-2.55mmol/L (KDIGO), PO4 1.13-1.78mmol/L (KDOQI) & PTH 150-600ng/L (KDIGO) to allow for different target ranges adopted across centres. Achievement of study target ranges for the most recent clinical results was assessed for each participating patient.

Results: 2361 patients were included; 60% male, median age 67y (range 18-97y), 88% HD, 6% with previous parathyroidectomy. The most recent results were in range for 1207 (56%, n=2158) patients for PO4 (19% low, 25% high), 1753 (81%, n=2159) for Ca (10% low, 9% high) and 810 (54%, n=1510) for PTH (30% low, 17% high). From 1501 patients with a result for all 3 markers 380 (25%) had all 3 in target range at most recent measurement. Of 2063 patients with a result for 2 or more markers, 1285 (62%) had ≥2 markers in range.

Discussion: Even using broad target ranges, the proportion of patients undergoing dialysis who are achieving target range for all 3 biochemical markers of SHPT is very low at 25% of evaluable patients. These data infer we are falling short of what might be considered tight control of these important biochemical parameters and suggest the need for a more rigorous and potentially standardised approach to the management of SHPT in the UK. *This study was sponsored by Amgen.*

P313

Vitamin D status and associated plasma PTH, alkaline phosphatase concentrations, eGFR, and urinary protein in stable renal transplant patients – evidence for functional relevance of vitamin D deficiency

Nathan Gauge, Hugo Penny, Antos O'Rourke-Potocki, Sharon Frame, David Goldsmith

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Background: Vitamin D insufficiency (> 25 < 50 nmol/L) and deficiency (< 25 nmol/L) are common in stable ambulant renal transplant patients (RTx) in the UK (1). This has been associated with adverse skeletal, renal, cardiovascular and cancer outcomes in population studies. However, the health consequences of the lack of vitamin D for individual patients in this population are unclear. We collated all the vitamin D concentration values for RTx in our hospital over a two years period to see if we could determine any clinical sequelae of hypovitaminosis D examining plasma calcium, phosphate, alkaline phosphatase (ALP), eGFR, and urinary protein / creatinine ratios.

Methods: Results from all blood samples drawn from outpatient-attending RTx patients and sent for vitamin D measurements (2010-2012) were retrieved and analysed. Any plasma PTH, calcium, phosphate and alkaline phosphatase values which coincided with the vitamin D estimations were also retrieved. T-test, Spearman correlations.

Results: 856 vitamin D values from 449 patients (age mean 53, median 55, IQR 44-65, range 18-89 years) were located. In addition there were 660 PTH, 801 Calcium, 812 Phosphate, 825 eGFR, 827 ALP, 531 urine creatinine 531, and 408 urine protein values. Vitamin D concentrations were significantly correlated with PTH, eGFR, ALP and urinary protein. There was an inverse correlation with plasma PTH concentration (-0.344 $p = <0.001$), with eGFR (0.095 $p=0.007$), with ALP (-0.159 $p = <0.001$) and with urinary protein (-0.102, $p= 0.043$).

Conclusions: Across a very broad range of vitamin D concentrations in this stable ambulant RTx population there were functionally important and relevant biological correlations : in terms of bone health higher vitamin D concentrations clustered with lower PTH and ALP. In terms of allograft function, higher vitamin D concentrations clustered with higher eGFR and lower urinary protein excretion. These associations help to support the notion that vitamin D status may influence renal allograft and skeletal health in this patient population.

P314

Vitamin D receptor activators for reduction of proteinuria in patients with chronic kidney disease: a systematic review and meta-analysis of randomised controlled trials

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Background: Renin-angiotensin-aldosterone system (RAAS) blockers protect against chronic kidney disease (CKD) progression and cardiovascular complications by reducing proteinuria and blood pressure. However, RAAS blockade is limited by drug side-effects, and residual proteinuria, a key determinant of future renal and cardiovascular complications. Recent small-to-medium-sized randomised clinical trials (RCTs) addressed whether vitamin D receptor activators (VDRAs) reduce residual proteinuria, but results have been inconsistent. Therefore we undertook the first systematic review and meta-analysis of all RCTs examining the effect of VDRA on residual proteinuria in CKD.

Methods: We systematically searched Medline, Embase, and Cochrane Library databases for CKD RCTs featuring VDRA use published between 1950-September 2012, extracting standardised data. We included all studies with any type of VDRA that reported proteinuria or albuminuria as outcome. Primary endpoint was the total reduction is proteinuria from baseline to last follow up, while secondary endpoint was the total number of patients with >15% reduction in proteinuria from baseline to last follow up. We included a sub-analysis of the PRIMO study with only patients that had albuminuria at baseline.

Results: We included eight trials, six with paricalcitol, two with calcitriol, providing data on 732 patients. Most patients (84%) received RAAS blockers throughout. VDRAs reduced residual proteinuria (weighted mean difference from baseline to last measurement -17% [95% confidence interval [CI] -13% to -21%] compared with controls (+2% [95% CI -5% to +8%], p=0.0003) (Figure 1). Proteinuria reduction was achieved more often in VDRA-treated patients (220/416 patients) than in control patients (92/316 patients, OR 2.78 [95% CI 1.74 to 4.46]; p<0.0001). Calcitriol was = paricalcitol, and diabetic = non-diabetic CKD.

Conclusions: VDRAs effectively targets residual proteinuria in CKD patients, in addition to concurrent RAAS-blockade based therapy. The 17% reduction in proteinuria is clinically equivalent to the addition of a further RAAS blocker.

P315

Does strict control of parathyroid hormone levels in severe chronic kidney disease pre-transplantation confer advantages for post-transplant bone health?

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Introduction: Optimal PTH levels are based upon expert opinion. North American practice accepts much higher PTH levels than European. The lack of evidence base in children is made more complex due to growth. European paediatric guidelines suggest normal range PTH levels for as long as possible and as end stage approaches levels up to 2 times the upper limit of normal are acceptable.

Aim: To assess if strict PTH control confers any advantages or disadvantages for post transplantation (Tx) bone health, as evidenced by markers of bone health: growth, PTH levels and use of activated vitamin D.

Methods: We included all transplanted patients from 2010 to March 2011, with sufficient retrievable data. Blood results, anthropometric and medication data were obtained from patient records, starting 12 months pre & post-Tx. Growth data were obtained for months 6 to 18 post-Tx.SPSS was used for analysis.

Results: To date 16 patients (9 males) have been included; mean age at inclusion 9 years. In the year pre-Tx, mean PTH levels were 136 ng/L.The mean Pre-Tx alphacalcidol (1-α)dose was 0.35 μg daily (14 of 16 patients) and calcium (Ca) carbonate 1.5 g (10 of 16).As expected pre-Tx PTH levels associated with ALP ($p=0.001$), and Ca levels negatively associated with Ca carbonate dosage ($p=0.04$).Both pre-and post-Tx calcium levels, were positively, associated with growth rate post-Tx ($p=0.002$ & $p=0.011$ respectively) as was post-Tx phosphate levels ($p<0.05$).Pre-Tx 1-α dosage was negatively associated with post-Tx growth rate. No associations were noted between PTH levels and post-Tx growth.

Discussion: Study demonstrates known associations between ALP, Ca levels & Ca based phosphate binder. Whilst no relationships demonstrated between PTH & bone health, associations between Ca levels & post-Tx growth, between post-Tx phosphate levels & growth and between pre-Tx 1-α and growth were shown; this is not surprising as PTH control is intimately linked to the Ca/Phos/PTH/VitD axis. Further work is needed to unravel the long term skeletal effects of strict PTH control especially as Ca, phosphate & 1-α are implicated in cardiovascular health.

P316

25-hydroxy vitamin D_3 insufficiency in CKD stage 3

Maarten Taal[1,2], Victoria Thurston[1], Natasha McIntyre[2], Nigel Lawson[1], Chris McIntyre[2,1], Richard Fluck[1]

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Introduction and aims: Deficiency or insufficiency of 25-hydroxy Vitamin D ($25OHD_3$) is common in patients with CKD and is associated with increased all-cause and cardiovascular mortality in the general population. Uncertainty remains, however, regarding the optimal strategy for screening or treatment in CKD and most previous studies have been conducted in Secondary Care. We aimed to investigate serum $25OHD_3$ concentration and factors related $25OHD_3$ insufficiency in a large cohort of people with predominantly early CKD stage 3.

Methods: Serum $25OHD_3$ was measured by tandem mass spectometry in 1664 people with previous estimated GFR 59-30ml/min/1.73m^2 recruited from 32 Primary Care practices. Detailed medical history was obtained and each participant underwent clinical assessment as well as urine and serum biochemistry tests. $25OHD_3$ deficiency was defined as <25nmol/L (<10pg/L) and insufficiency as 25-49nmol/L (10-20pg/L).

Results: Median values for key variables were: age 74(IQR 67 to 79)y, eGFR 53(46 to 60)ml/min/1.73m^2, PTH 46(34 to 66)pg/ml, $25OHD_3$ 53(38 to 71)nmol/L. Overall 104 (6.2%) people had $25OHD_3$ deficiency and 648 (38.9%) had insufficiency. $25OHD_3$ deficiency or insufficiency was significantly more common in people of Asian ethnicity, the elderly ≥75y, those with the most social deprivation and those with diabetes, previous cardiovascular events and obesity. Multivariable logistic regression analysis identified Asian ethnicity, social deprivation, BMI, skin autofluorescence, parathyroid hormone, albuminuria, serum albumin and fractional excretion of phosphate as independent risk factors for $25OHD_3$ deficiency or insufficiency.

Conclusion: Whereas $25OHD_3$ deficiency was uncommon, insufficiency was relatively common among people with CKD stage 3 in Primary Care. These data provide support for measuring $25OHD_3$ in all people with CKD stage 3 but further randomised studies are required to evaluate the benefit of $25OHD_3$ replacement.

P317

Effect of long term phosphate loading on endothelial function: a single blind, cross over trial

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University of Glasgow, Glasgow, UK

Background: The effect of sustained short term phosphate loading on endothelial function has not been studied. This study considers the effect of phosphate loading on endothelial function measured by flow mediated dilatation (FMD).

Methods: Healthy volunteers attended for a baseline and 2 subsequent visits. Blood was drawn for measures including bone biochemistry, vitamin D, FGF-23 and klotho. A 24-hour urine collection was performed prior to attendance. FMD was recorded. Volunteers were randomized to take lanthanum carbonate (LC) or Phosphate Sandoz (PS) for 2 weeks prior to the next visit. After a wash out period, volunteers took the other drug and attended for a final visit. One individual, blinded to the order of drug ingestion, performed and analysed each FMD measure.

Results: Of 19 participants, 12 were female. At baseline, mean age was 42±14 years, eGFR 102±10ml/min, serum phosphate 1.05±0.18mmol/L and fractional excretion of phosphate (FeP) 143.4±33.6%. Median FMD was 8.4% (IQR 6.2-11.6%) post cuff inflation. After PS, serum phosphate was unchanged. FGF-23 and FeP rose significantly compared to baseline ($p=0.013$, $p<0.001$). FMD post cuff inflation reduced significantly (3.38% (IQR 2.57-5.26%), $p<0.001$). With LC, serum phosphate was unchanged. FeP fell (114.34±42.5, $p<0.001$). Post cuff inflation FMD was impaired (6.6% (IQR 3.4-10.3%), $p=0.033$). Randomization order had no effect. In a regression model, FeP was an independent predictor of post cuff inflation FMD ($p=0.02$).

Conclusions: Phosphate loading impairs endothelium dependent FMD. Serum phosphate was unchanged. The observed deleterious effect on FMD seen with PS may be explained by elevated total body phosphate with resultant elevated intra-cellular phosphate. FeP is likely a surrogate marker of the state of total body phosphate. This study suggests that sustained phosphate loading is directly detrimental to the vasculature even when serum phosphate is unaltered.

P318

Lanthanum a confounding factor in computed tomography imaging

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Introduction: Lanthanum is a silvery white metal extracted from one of the ore mozanite. Medicinal use is in the form of Fosrenol (Lanthanum carbonate) tablet, commonly prescribed second line phosphate binder for hyperphosphatemia. It is prescribed in patients with chronic kidney disease including those on dialysis. Lanthanum is radiopaque and appearance is similar to other oral contrast agents. This fact has been previously described in the literature but is often forgot prior to any radiological investigation.

Methods: We looked at all our chronic kidney disease patients who were on lanthanum, where a radiological investigation was carried out in the last 5 years and presence of lanthanum in the gut acted as a confounding factor in making diagnosis.

Results: There were 100 patients on Lanthanum carbonate of which 40 of them had undergone Computed Tomography (CT) to find the cause of abdominal pain or intra-abdominal bleeding or renal angiogram. In 8 patients it caused interference with interpretation of results. One patient had undergone CT to look for leaking abdominal aortic aneurysm where presence of lanthanum made it difficult as contrast extravasation could not be studied very well. Another patient had undergone CT virtual colonoscopy to look for occult gastrointestinal bleeding. 6 patients had undergone CT renal angiogram where interpretation was difficult and Lanthanum could have stopped.

Discussion: We once again reiterate the fact that lanthanum acts as a confounding factor in a critical radiological investigations where oral contrast agents should not be given. This fact has to be borne in mind when requesting for elective investigations as it avoids unnecessary exposure to radiation although it cannot be avoided in an emergency. Lanthanum should be omitted prior to investigations for occult gastrointestinal bleeding, angiograms. Also, now the radiology department have included Lanthanum to their checklist of medications that patient is taking prior to any Computed Tomography.

P319

Paricalcitol as treatment of secondary hyperparathyroidism (SHPT) in chronic haemodialysis (HD) patients: the impact of changing target PTH levels

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Introduction: Interventions to control SHPT include modulation of calcium, phosphate and vitamin D metabolism. Our study assessed the long term effectiveness of Paricalcitol in the treatment of SHPT in chronic HD patients. Methods:16 patients (14 males; 2 females) with SHPT, average age 61years, were treated with Paricalcitol (7-30mcg/week) for 3.5 years. Paricalcitol dose was adjusted to achieve the Renal Association Guidelines at the time. PTH, Calcium and phosphate were measured every 3 months. Standard use of phosphate binders and diet control were maintained.

Results: The mean PTH±SD at start of treatment was 616±308pg/ml. By 9 months the mean PTH±SD was significantly reduced to 339±222pg/ml (p=0.011) and by study end 379±193pg/ml (p=0.045). Mean calcium and phosphate levels remained within guidelines. Reversible severe hypercalcaemia (3.3mmol/l) was noted in one patient.

Discussion: Paricalcitol is effective in reducing PTH and maintaining calcium and phosphate balance. New guidelines suggest a less aggressive approach to SHPT is required. The level of evidence to support this is weak (2C). Applying the new guidelines retrospectively only 4 of our study patients would require treatment for SHPT.

P320

Severe hypocalcemia after single dose of denosumab in dialysis patient

Noshaba Naz, Yaser Shah

Arrowe Park Hospital, Wirral, UK

Introduction: Bone Mineral Disorders (BMD) are one of the challenges that nephrologist face in Dialysis patients. Denosuamb has been used for prevention of Osteoporotic fracutres in postmenopausal women. It is being widely used for the metastatic fractures in M.Myeloma, prostatic cancers etc. Charcot's Arthropathy is one of the indications for Denosumab use. Our patient suffered from severe hypocalcemia after single dose of Denosumab for Charcot's arthropathy, questioning it's efficacy/safety in this patient population.

Case: We present a case of 70 years old female, endstage renal disease secondary to diabetic nephropathy and Hypertension. She is currently on thrice weekly hemodialysis via AV fistula. Background of COPD, hypertension, diabetes mellitus, Charcot's arthropathy with recurrent fractures particularly in left 2-5th metatarsals. She was also diagnosed as severe osteoporosis, with T-score of -4 at lumbar spine and -3.2 at cervical spine. Due to Charcot's arthropathy she suffered from recurrent fractures in Charcot's joint, she was on Bisphosphonates but continued to have recurrent fractures, hence decided to start her on Denosumab. 2 weeks post Denosumab, patient was admitted with symptomatic hypocalcemia (peri-oral numbness and paresthesia), adjusted serum calcium was 1.7, and she was commenced on calcium infusion. Her calcium level kept on dipping and required frequent IV calcium for the next couple of days. She was on Paricalcitol for her hyperparathyroidism prior to Denosuamb. She was discharged home with oral calcium supplements with regular monitoring of serum calcium on dialysis.

Discussion: Managing BMD in a dialysis population is an uphill battle. Dialysis patient suffer from variety of renal osteodystrophy e.g. dynamic and adynamic bone disease and osteoporosis. They are at high risk of non-traumatic and traumatic fractures. Denosumab is a fully human monoclonal antibody that has high affinity and specificity for RANK. RANK is vital for osteoclastogenesis and Denosumab neutralizes this effect. It is effective in preventiving vertebral and non-vetebral fractures in post menopausal women. Its role in bony metastatic disease and in multiple myeloma is beyond any doubts. Though it may not be superior to Bisphophonates, as three double-blind randomized trials showed no difference between Denosumab and zolendronic acid in terms of mortality, disease progression, quality of life and pain. More risk of hypocalcemia, though risk of renal failure is less in Denosumab group. One single-dose study monitored the effect of Denosumab in different stages of CKD including dialysis patients; they did find high risk of hypocalcemia. Two patients had to be hospitalized for IV calcium (1). All those patients who suffered from significant hypocalcemia were not on calcium/vit D supplementation. Risk of hypocalcemia is proportional to advancing renal disease. Very clearly evident by very recent publication of severe hypocalcemia after single injection of Denosumab in hemodialysis patient (2), hence questioning it's safety in this particular patient population.

Conclusion: We recommend cauteous use of Denosumab in dialysis patients, with close monitoring of serum calcium after Denosumab and adequate calcium control prior to Denosumab.

References:

1-McCormick BB, Davis J, Burns KD Am J Kidney Dis. 2012 Oct;60(4):626-8.

2-Block GA, Bone HG, Fang L, Lee E, Padhi D. J Bone Miner Res. 2012 Jul;27(7):1471

P321

Prevalence of vitamin D deficiency: a cross sectional observation across CKD stages

Maharajan Raman, Rajkumar Chinnadurai, Eelane Tan, Smeeta Sinha, Rachel Middleton, Grahame Wood

Salford Royal Foundation NHS Trust, Salford, UK

Background: Patients with CKD are at risk of Vitamin D deficiency. Vitamin D metabolism plays an important role in the pathogenesis of secondary hyperparathyroidism in CKD population.

Methods: We performed a retrospective analysis of 197 randomly selected patients who were followed up in our General Nephrology clinic under a named consultant between the years 2008 to 2012. We excluded patients with stages 1 & 2 CKD and patients on calcium or vitamin D supplements. We defined Vitamin D deficiency, as levels <15ng/ml and insufficiency, as levels between 15 to 30ng/ml. We evaluated the relationship between Calcium, Phosphate and PTH levels across CKD stages 3 to 5 against different levels of Vitamin D.

Results: A total of 143 patients were evaluated. Across all three CKD stages only 6% of the patients had Vitamin D levels of >30ng/ml, 57% of them were Vitamin D deficient and 37% had insufficient levels. Among the Diabetic patients with CKD 82% were deficient and 18% of them had insufficient Vitamin D levels. 64% of the female patients were Vitamin D deficient compared to 51% of the male patient. The table illustrates the relationship between Calcium, Phosphate and PTH levels across CKD stages 3 to 5 against different Vitamin D levels.

	D2+D3 Levels	**<15ng/ml**	**>15 to<30ng/ml**	**>30ng/ml**
Mean Calcium (mmol/L)	***Stage 3***	2.27±0.09	2.25±0.72	2.29±0.007
	Stage 4	2.25±0.19	2.25±0.97	2.29±0.14
	Stage 5	2.17±0.09	2.21±0.09	2.49±0
Mean Phosphate (mmol/L)	***Stage 3***	1.09±0.19	0.98±0.19	1.14±0.25
	Stage 4	1.20±0.24	1.24±0.25	1.24±0.21
	Stage 5	1.60±0.41	1.44±0.28	1.41±0
Median PTH (ng/l)	***Stage 3***	63	46	22
	Stage 4	115	114.5	93
	Stage 5	335	210	4

Conclusion: Diabetic patients with CKD had either insufficient or deficient levels of Vitamin D. None of Diabetic patients had levels >30ng/ml. There was an inversely proportional relationship between Vitamin D and PTH levels across all three stages of CKD.

Poster session

Friday 15th March

11:30 - 12:30

CKD other 1

P322

Thromboprophylaxis in patients with severe renal failure - the views and practice patterns of UK nephrologists

Chris Goldsmith

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Reducing venous thromboembolism (VTE) in hospitalised patients is a national priority. Evidence suggests marginal benefit with only Low Molecular Weight Heparins (LMWH) having a statistically significant reduction in deep vein thrombosis but not in pulmonary embolism or mortality. Many of the randomised clinical trials have often omitted patients with severe renal failure with many of the drugs used have limited evidence of efficacy. A short web-based survey was conducted to survey current practice trends and opinions amongst UK Nephrologists regarding the use of anti VTE prophylaxis in medical patients with severe renal impairment (eGFR <30mls/min) in 2012.

Results: 56 responses were received. 29 out 53 respondents used some form of graduated compression stockings. 85% respondents used in patients with acute kidney injury, 93% ill patients with CKD 4 or 5 not on dialysis, 91% on acute ill patients on PD or HD and 67% of patients on daily HD. Prescribing trends were analysed. 8 responders used 5000 units bd unfractionated heparin, 11 used 2500units sc daily dalteparin, 3 used dalteparin 5000 s/c daily, 21 used 20mg enoxaparin, 9 used a variety of tinzaparin doses. 39 respondents used the same LMWH across their institution. Respondents were asked to rate their concerns as; no concerns, negligible, minor or major about four key themes. Recorded minor and major concerns of *efficacy*: 42.6 and 14.8%, *evidence base*: 28.8 and 57.7%, *bleeding risk*: 48.1 and 46.3%, and *monitoring* 64.8 and 18.5% respectively.

Conclusions: The survey showed considerable variety in practice trends of anti VTE prophylaxis. In many the dose used was unlicensed. There were significant concerns of efficacy, evidence base and bleeding risk. A multi centred trial is needed to address the efficacy of LMWH in patients with significant kidney impairment.

P323

Achievement of treatment targets in diabetic kidney disease: an analysis of the national diabetes audit

Christopher Hill[1,2], Christopher Cardwell[2], Christopher Patterson[2], Peter Maxwell[1,2], Glynis Magee[3], Robert Young[4], Beverley Matthews[5], Donal O'Donoghue[6], Damian Fogarty[1,2]

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Introduction: Diabetic kidney disease (DKD) is the most common cause of established renal failure in the UK. Improved blood pressure and blood glucose control can reduce the risk of nephropathy and its progression. We aimed to examine risk factors for poor achievement of treatment targets in DKD.

Methods: Data were available from the National Diabetes Audit 2007-08 cycle. Type 1 and 2 diabetes patients with a valid serum creatinine and urinary albumin:creatinine ratio were included. DKD was defined as the presence of an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2, albuminuria or both. Patients were stratified by eGFR and albuminuria status. Logistic regression was used to examine to examine associations between high systolic blood pressure (SBP ≥140mmHg) or high HbA1c (≥7.5%) and variables including year of birth, year of diagnosis, sex, ethnicity, DKD and Strategic Health Authority (SHA).

Results: 58,791 type 1 and 733,769 type 2 diabetes patients were analysed. Patients with normoalbuminuria were less likely to have high SBP than those with normal renal function. At all levels of eGFR patients with macroalbuminuria were more likely to have high SBP (e.g. odds ratios 1.1 to 1.6 in type 2 patients). In both type 1 and 2 diabetes there was a trend towards lower odds of HbA1c ≥7.5% in those with an eGFR <15 ml/min/1.73m^2. Significant ethnic and regional variations were also present. For example, type 1 and 2 patients of black ethnicity were more likely to have high SBP (OR 1.26 and 1.07 respectively) than those of white ethnicity. Significant regional variations were also present e.g. odds ratios for HbA1c ≥7.5% in type 1 diabetes patients varied from 1.04 in the South East Coast SHA to 1.27 in West Midlands SHA when compared to London.

Conclusions: DKD was associated with worse blood pressure control. Advanced DKD appeared to be associated with improved blood glucose control although this may reflect changes in HbA1c metabolism. This study has highlighted patient groups at higher risk of poor achievement of therapeutic targets as well as the need for innovative approaches to the management of DKD.

P324

The effect of renal artery denervation on ambulatory blood pressure monitoring in patients with resistant hypertension

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Introduction: Percutaneous renal artery denervation (RDN) is a novel technique used to treat patients with resistant hypertension (HTN). It selectively denervates renal sympathetic fibres resulting in a sustained reduction in blood pressure. The aim of this pilot study was to further investigate the 'real world' haemodynamic and physiological effects of RDN in resistant HTN.

Methods: Eligible patients were aged 18-85 years with no secondary cause for HTN and a systolic blood pressure (BP) of ≥160mmHg despite compliance on 3 or more antihypertensive drugs. Baseline measurements included 24-hour ambulatory BP monitoring (ABPM), serum biochemistry and 24-hour urinary protein excretion. Inpatient bilateral RDN was performed. The baseline measurements were repeated 1 day, 1 month and 6 months following RDN.

Results: Eight patients (75% female, n=6) with a median age of 43 years (range 34-63) underwent RDN and completed follow-up between December 2011 and October 2012. All patients had eGFR >60ml/min/1.73m^2. At six-months there was a non significant reduction in mean systolic ABPM (180mmHg±12 to 168mmHg±16), mean diastolic ABPM (107mmHg±13 to 100mmHg±12), and median number of antihypertensives prescribed (5.5 to 4.5). Six patients (75%) responded to RDN as defined by >10mmHg reduction in systolic BP or reduction in pill burden. In this 'responders' group there was a significant reduction in the number of antihypertensives taken ($p<0.05$) and a trend towards a significant reduction in both systolic ($p=0.06$) and diastolic ($p=0.08$) blood pressure. There was no significant change in renal function or urinary protein excretion at the end of follow up.

Discussion: This study shows that RDN is a safe and relatively efficacious treatment in selected patients with resistant HTN. Our results are broadly in keeping with the Symplicity 2 trial, although we focussed on the more robust measure of ABPM rather than office BP. Better phenotyping of patients to identify those more likely to respond to RDN is required.

P325

Exercise anaerobic threshold as a predictor of 5-year survival in patients with advanced chronic kidney disease

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Background: Reduced anaerobic threshold (AT) is an index of exercise intolerance, which carries a poor prognosis among patients with impaired cardiovascular reserve. It is not known whether this measure of sustainable oxygen consumption could identify CKD patients at risk of premature death.

Methods: We performed cardiopulmonary exercise testing in 240 patients (mean age, 50.8±12.4 years; 70% male; median dialysis vintage, 15 (0-48) months) who were waitlisted for kidney transplantation between January 2008 and January 2010. Clinical, echocardiographic, exercise and 5-year mortality data were compared.

Results: On Kaplan-Meier curves, there was a significant difference in survival between patients with AT <11 ml/min/kg and those with AT ≥11 (Fig.1A). Tertiles of AT were associated with an increased risk of death over five-year (Fig.1B). On multivariate Cox regression analysis, patient survival correlated with the AT (HR: 0.6, 95% CI: 0.5-0.8, p <0.001). Prior history of CVD (HR: 1.7, 95% CI: 0.7-3.9, p=0.23) and dialysis vintage >1 year (HR: 2.3, 95% CI, 0.8-6.5 p=0.1) did not correlate with patient survival.

The 24 patients (10%) that died had a significantly lower AT than the survivors (7.9±1.6 vs. 10.7±2.4 ml/min/kg, p <0.001). Non-survivors were more likely to have CVD (38% vs. 13%, p =0.002) and dialysis vintage >1 year (79% vs. 49%, p= 0.005). Age and gender were not significantly different. LV ejection fraction was (55.6 ± 13.1 vs 61.6±10 %, p =0.06) and LVMI (144.6±40.3 vs 124.4±38.1g/m^2, p =0.05) in non-survivors compared to survivors.

Conclusions: Reduced AT is a significant predictor of 5-year all-cause mortality in this population.

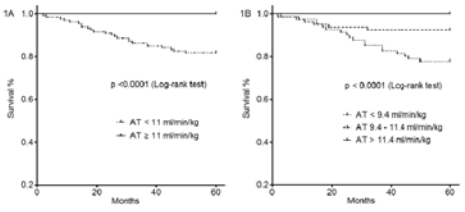

Fig. A. Five-year Kaplan-Meier survival curves of CKD patients according to Anaerobic Threshold (AT).

P326

Renal autotransplantation: excellent outcomes with minimal risk

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Background: Renal autotransplantation is a treatment modality for conditions including loin pain haematuria syndrome (LPHS), renovascular abnormalities (renal artery aneursyms, stenosis, fibromuscular dysplasia), renal tumours, and urethral aberrations. However, the procedure's credibility, especially for pain symptoms, is debated. These concerns focus on symptom relief as well as preservation of renal function. We aimed to establish outcomes in patients undergoing autotransplantation for diverse indications.

Methods: Retrospective analysis was performed of autotransplantations at a single unit (04/2001–02/2012) Patients were assessed regarding outcomes, especially renal function preservation, kidney loss, and surgical complications.

Results: 18 patients were included (14 females, 4 males; mean age 43.7; range 23-71). Indications were LPHS (9 patients), renovascular hypertension (6), renal tumours (2), and bilateral recurrent pyelonepritis (1- bilateral). Renal function was measured as pre-operative and 6 week follow up Creatinine (73 (41-129) and 78µmol/l (45-98) respectively; median (range); p= NS; paired t-test) Mean cold ischaemic time was 159 minutes (range 96-185). One patient who underwent bilateral sequential autotransplantation for recurrent bilateral pyelonephritis required renal replacement therapy and subsequent nephrectomies (transplants performed with renal pelvis flush to bladder) with no other nephrectomies during the follow up period and no mortalities. There were 3 urinary tract infections, 1 pulmonary embolus, and 1 renal bed haematoma requiring surgical intervention.

Conclusion: Fears have traditionally existed regarding autotransplantation's futility but these appear unfounded. Our series demonstrates minimal risk to both kidney and patient. Follow up is limited by the nature of the patients, but appears to offer an effective modality of treatment for patients with intractable symptoms or other disease spectra requiring surgical intervention. Careful case selection, with robust indications, provides excellent outcomes. Systematic comparison with other treatment modalities for these conditions requires further examination.

P327

Tissue content of phosphate in patients with CKD-MBD: is CKD-MBD a state of tissue phosphate depletion?

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Introduction: CKD-MBD is considered a state of phosphate loading. It is postulated that in CKD 3 renal excretion of phosphate is maintained at the expense of a rising serum FGF23 level, which increases the fractional glomerular excretion of phosphate. However, it is not until CKD 4 that elevation of serum phosphate is regularly seen clinically. Unpublished data is now emerging which suggests that CKD may not be a state of positive phosphate balance. We report the results of a pilot study to estimate the phosphate content in skin biopsy samples in 20 dialysis patients, known to have radiological evidence of vascular calcification and 10 control subjects without CKD.

Methods: Dialysis patients with radiological evidence of vascular calcification, and control subjects without CKD, were invited to take part in the study and give written informed consent. Each subject underwent a forearm skin biopsy under local anaesthetic. Samples were acid-digested and incinerated to estimate the tissue content of phosphorous-31. Tissue content of Calcium-43 was also estimated.

Results: In the samples so far analysed (n = 15):

Mean values	Dialysis patients	Controls	P-value (2 sample t-test)
Phosphorous-31	298 mcg/g	364 mcg/g	0.23
Calcium-43	5.5 mcg/g	6.87 mcg/g	0.40

No correlation was seen between tissue content of phosphorous and serum phosphate, or with serum PTH. A positive correlation was seen between the tissue content of phosphorous-31 and calcium-43.

Discussion: Our preliminary data are non-significant, but do not support the supposition that CKD is a state of tissue phosphate loading in skin, with phosphate levels tending to be higher in controls than in dialysis patients. Further sample analysis is on-going and will increase the reliability of these preliminary results.

P328

A randomized controlled trial of remote ischaemic preconditioning in patients with chronic kidney disease for the prevention of myocardial and kidney injury after cardiac surgery

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Introduction: In recent years there has been an increase in the number of patients with chronic kidney disease (CKD) undergoing cardiac surgery. These patients are particularly susceptible to peri-operative complications including myocardial infarction and acute kidney injury. Remote ischemic preconditioning (RIPC) mitigates ischemia–reperfusion injury and may prevent these complications after cardiac surgery, thus providing clinical benefit.

Methods: We studied 86 adult patients with CKD (defined as a pre-operative eGFR < 60mls/min) undergoing coronary surgery with or without concomitant aortic valve replacement with cardiopulmonary bypass in a randomized, single-blind, and controlled pilot trial. Patients were stratified for the type of surgery and diabetes status and then randomized 1:1 to a control group or to receive RIPC, which consisted of 3 cycles of 5 minutes of forearm ischaemia induced with a blood pressure cuff inflated upon the upper arm to 200mmHg with 5-minutes of subsequent reperfusion. The primary end points for this trial were two fold; the primary renal end point was acute kidney injury (AKI) defined in accordance with RIFLE criteria as any post-operative increase in the serum creatinine level of greater than 50% from the preoperative value within 5 days of cardiac surgery. The primary cardiac end point of myocardial injury defined by 72 hour troponin T area under the curve (72 hrs AUC cTnT). In addition, serum (NGAL, IL-18 and cystatin C) and urinary (NGAL, IL-18 and KIM-1) biomarkers of renal injury were also measured.

Results: Baseline demographics, clinical characteristics and operative details were similar between the RIPC and control groups. 16 of 86 patients developed postoperative AKI. The incidence of AKI was not different between the RIPC and the control groups (RIPC 10/43 (23.3%) vs control 6/43 (14.0%); p=0.4065). There was no difference in any of the serum or urinary biomarkers of renal injury between the RIPC and control groups. Furthermore, there was no difference between the RIPC and control groups in terms of the primary cardiac endpoints of 72 hrs AUC cTnT release (RIPC 34686 vs control 31269 ng/L/72hr; p=0.3668)

Conclusions: RIPC using forearm ischaemia confers no meaningful additional myocardial or renal protection beyond current standard anaesthetic and surgical management in patients with CKD undergoing cardiac surgery

P329

Fatigue in patients with chronic kidney disease remains unaddressed

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Introduction: A common complaint of chronic kidney disease (CKD) patients is fatigue[1]. Earlier work[2] has shown that fatigue in CKD is associated with autonomic symptoms and excessive daytime sleepiness. The severity of fatigue experienced is not linked to the level of renal dysfunction. Four year follow up of the original cohort was undertaken to see how levels of fatigue change over time.

Methods: All surviving patients from the original cohort (n=121) were invited to complete a postal survey containing validated questionnaires to document their level of fatigue (using the Fatigue Impact Scale). An assessment was also made of orthostatic symptoms, daytime somnolence and how these symptoms impacted physical and cognitive functioning. These results were correlated with biochemical parameters of renal function and comparisons made to the original study group.

Results: 68/121 surveys were returned (response rate 56%), with a mean follow up of 1544 days (1331-1806). Of those 68, 14 are undergoing renal replacement therapy (including transplantation), 1 has died and 53 continue to have impaired renal function. In this CKD group, there has been stability of renal function (mean loss of eGFR 1.38ml/min/1.73m^2). Fatigue increased marginally over the course of the follow up period (third quartile 58.5 to 65) but this was not significant.

Discussion: Fatigue can significantly impair quality of life and physical functioning for patients. Our study shows that patients with CKD experience no change in their fatigue scores over time and are continuing to face a significant symptom burden. We feel this highlights the need for further exploration of the causes and potential treatments for fatigue in the CKD population.

1. Murtagh FEM, Addington-Hall J and Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. *Adv Chr Kidney Dis.* 2007; 14 (1): 82-99

2. Newton JL, Brown A, Jones DEJ and Sheerin NS. Fatigue in early renal disease. British Journal of Renal Medicine. 2009; 14(2): 10-14

Poster session

Thursday 14th March

12:00 - 13:00

CKD risk and progression 1

P330

Diabetes management in chronic kidney disease patients

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Objective: Management of diabetes in patients with chronic kidney disease (CKD) is challenging. Therapeutic options for patients with type 2 diabetes are limited because a reduced estimated glomerular filtration rate (eGFR) results in the accumulation of drugs and/or their metabolites, therefore insulin injection therapy remains the mainstay of treatment.1 The purpose of this audit was to determine the proportion of diabetic patients with CKD stages 4-5 reaching the glycated haemoglobin (HbA1c) targets in accordance with the National Institute of Clinical Excellence (NICE) guidance, and to make a comparison of glycaemic control with or without insulin therapy.

Methods: A search was performed on a computerised database of all current diabetic patients attending the Ulster Hospital Dundonald with an eGFR <30. We then searched for those on insulin therapy or not, and included the HbA1c level at their most recent hospital attendance, as well as some demographic details. We then analysed the data using an excel spread sheet.

Results: A total of 256 patients were attending with an eGFR <30. Of those 256 patients, there were 45% (116) male, 55% (140) female, 10% (27) type 1 diabetics, 88% (225) type 2 diabetics, and 2% (4) secondary diabetics. Age range was 30-98 with an average age of 72years. Seventy five per cent (193) were on insulin therapy, 25% (48) of which reached the NICE guideline HbA1c target of 6.5-7.5%, 25% (63) were not on insulin therapy, 44% (28) of which reached the target. Of the type 1 diabetic patients on insulin therapy, 15% (4/27) reached the target. Of the type 2 diabetics, 74% (166/225) were on insulin therapy, 27% (44/166) of which reached the target, 26% (59/225) were not on insulin therapy, 46% (27/59) of which reached the target. All of the secondary diabetics were not on insulin therapy, 25% (1/4) of which reached the target.

Conclusions: This data confirms that glycaemic control is difficult in patients with CKD. It also suggests that insulin therapy does not achieve good glycaemic control in this group of patients, and perhaps for type 2 diabetics, switching to insulin therapy may not be beneficial and perhaps they should remain on oral hypoglycaemic agents with appropriate dose adjustment.

References:

1. Abe M. Antidiabetic agents in patients with chronic kidney disease and end-stage renal disease on dialysis: metabolism and clinical practice. Curr Drug Metab, 2011; 12(1): 57-69.

P331

Predicting progression to renal replacement therapy: a single centre study

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Introduction: Progression of chronic kidney disease (CKD) to end-stage renal failure is relatively uncommon compared to the competing risk of cardiovascular death. Risk prediction models may help target individuals at highest risk of requiring renal replacement therapy (RRT). We retrospectively compared the sensitivity and specificity of 3 risk prediction models (Tangri et al [1]) with regard to their ability to predict requirement to RRT over a 5 year period in patients attending a single nephrology centre classified as high risk.

Methods: Analysis was performed on all patients with a diagnosis of CKD and a single eGFR consistent with CKD 3b or 4 in 2008. Data analysis (Age, Gender, eGFR, uACR, Calcium, Phosphate, Bicarbonate, Albumin) was restricted to patients with a complete data set (n= 305), and their clinical status on 1st September 2012 was noted. (3 variable equation: age, gender, eGFR: 4 variable equation includes uACR: 8 variable equation uses all 8 variables collected (n=302).

Results: 43(14%) required RRT: 49(16%) died without commencing RRT

Model	Low Risk	Intermediate Risk	High Risk	Sensitivity	Specificity
3	15	111	179	0.91	0.47
4	164	82	59	0.51	0.86
8	41	96	166	0.91	0.51

Discussion: Our findings suggest that in our population, the highly sensitive 3 and 8 variable equations could be used as screening tools to identify patients at low risk of progression. The highly specific 4 variable equation could be used to target intervention at those at highest risk of requiring RRT. All 3 equations allow for clinically useful quantitative stratification of risk for patients with CKD.

References:

1. Tangri N et al. A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure. JAMA 2011 Apr 20; 305(15):1553-9

P332

Prospective and cross-sectional analyses of renal function in neovascular age-related macular degeneration treated with VEGF inhibition therapy

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Neovascular age-related macular degeneration (nvAMD) shares risk factors and pathological pathways with several diseases affecting the kidney. Previous reports demonstrate association between reduced kidney function and nvAMD and also between VEGF inhibitors and renal dysfunction. VEGF inhibition therapy is currently a standard treatment option for nvAMD. Our primary analysis sought to assess kidney function, measured by estimated glomerular filtration rate (eGFR), in a nvAMD cohort, with a secondary analysis to evaluate whether VEGF inhibitor treatment is associated with decreased renal function (eGFR).

Methods: eGFR was calculated by CKD-EPI equations using IDMS calibrated serum creatinine levels. A pilot study (219 nvAMD cases, 172 no disease controls) was followed by recruitment of 500 prospective nvAMD cases and 1000 no disease controls. Logistic regression analysis estimated effect size of eGFR on AMD risk (adjusted for gender and age). A paired-samples t test was used to analyse eGFR before and after VEGF inhibition therapy in the nvAMD patients.

Results: Preliminary analysis of pilot data indicated that moderate CKD (defined as eGFR<60mL/min/1.73m^2) was associated with a non-significant increased risk for nvAMD (OR=1.27, CI: 0.69-2.34; P=0.45) in a minimally adjusted model (age, gender, smoking status). nvAMD was associated with a non-significant increased risk for moderate CKD (OR=1.18, CI: 0.64-2.17; P=0.60) in a minimally adjusted model. Potential associations between VEGF inhibition therapy and reduced kidney function will be tested in the prospective nvAMD study.

Discussion: Independent studies have demonstrated an increased risk of AMD associated with impaired renal function. Although not significant, the direction of effect in our pilot data is consistent with this association. VEGF inhibition therapy for ophthalmic conditions may influence long term kidney function.

P333

Hypervitaminosis A is prevalent in children with CKD and contributes to hypercalcaemia

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Introduction: Vitamin A accumulates in renal failure, but the prevalence of hypervitaminosis A in children with chronic kidney disease (CKD) is not known. Current guidelines for vitamin A intake in CKD children allow twice the Reference Nutrient Intake (RNI), are not evidence based and may drive elevated serum levels of vitamin A. Hypervitaminosis A has also been linked with hypercalcaemia. We studied the relationship between dietary vitamin A intake, serum levels of vitamin A and associated retinols and serum calcium levels.

Methods: Serum retinol and its metabolite retinoic acid (all trans [ATRA] and 13-cis) were measured in 106 children with CKD stage 2-5, dialysis and post-transplant. Dietary vitamin A intake was assessed through a detailed food diary.

Results: 25 children were in CKD 2-3, 36 in CKD 4-5, 23 on dialysis and 22 post-transplant. 53% had vitamin A intake above the RNI. Children receiving nutritional supplements compared to diet alone had both higher median intake (relative to RNI) and higher serum retinol concentration relative to upper limit of normal ($p=0.018$ and $p<0.001$ respectively). Serum retinol levels were elevated in 86% of children in CKD 2-5 and dialysis. There was an independent and graded association between eGFR and retinol levels: for every 10ml/min/1.73 m^2 fall in eGFR there was a 13% increase in retinol ($p<0.001$). Similarly, ATRA also showed an inverse association with eGFR ($p=0.001$). In a multivariate linear regression only serum ATRA and vitamin A intake by weight were significant predictors of serum calcium (adjusted R^2 0.58; $p<0.001$). Intake of calcium and vitamin D and eGFR did not show multivariate associations.

Conclusions: Hypervitaminosis A is seen in early CKD and increases with eGFR decline. Serum ATRA and vitamin A intake account for over half of the variation in corrected calcium concentration. Revision of RNI for vitamin A in CKD may be indicated to reduce the risk of hypervitaminosis A and associated hypercalcaemia.

P334

Blood pressure control in patients with CKD stage 3 in primary care

Simon Fraser[1], Paul Roderick[1], Natasha McIntyre[2], Scott Harris[1], Christopher McIntyre[2], Richard Fluck[2], Maarten Taal[2]

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Introduction: Chronic kidney disease (CKD) stage 3 is principally managed in primary care in the UK, including blood pressure (BP) management and albuminuria testing. Controlling BP is the key intervention for improving outcomes in CKD. This study aimed to identify BP control and its associations in individuals with CKD 3.

Methods: 1,741 patients with CKD stage 3, recruited from 32 GP practices, underwent medical history, clinical assessment, and biochemistry testing (including three urine samples for albumin creatinine ratio (ACR)). Optimal BP control was defined according National Institute for Health and Clinical Excellence (NICE) CKD guidelines (<140/90 or <130/80 in people with diabetes or ACR>70mg/mmol, which are similar to the recently published Kidney Disease: Improving Global Outcomes (KDIGO) guidelines except for people with diabetes but no albuminuria), and National Kidney Foundation Kidney Disease Outcome Quality Initiative (KDOQI) (BP target <130/80). Univariate and multivariate logistic regression was used to identify independent associations with BP control.

Results: Prevalence of hypertension was 88% and of albuminuria 16%. Among people on antihypertensive medication, the NICE BP target was achieved in 829/1426 (58.1%), and the KDOQI target in 512/1426 (35.9%). 1123/1426 (78.8%) of people on antihypertensive medication were taking renin-angiotensin aldosterone system inhibitors, but 615/1426 (43.1%) were only taking one antihypertensive agent. Optimal BP control was less likely in older patients (Odds ratio (OR) 0.25 (95% confidence interval (CI) 0.14,0.43) for >80y compared to <60y), diabetes (OR 0.35(95%CI 0.27,0.47)), and any albuminuria ((OR 0.25(95%CI 0.14,0.43)).

Conclusion: Suboptimal control of hypertension was common and greatest in those most at risk of adverse outcomes. This study suggests there is scope for improving BP control by the use of more antihypertensive agents in combination while considering issues of adherence and potential side effects.

P335

Fibroblast growth factor 23, parathyroid hormone and phosphate excretion in CKD stage 3

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Introduction and aims: Fibroblast growth factor (FGF)23 has been identified as an important regulator of phosphaturia that becomes elevated early in CKD to increase urinary fractional excretion of phosphate (FePhos) and maintain phosphate balance but its importance relative to PTH requires further elucidation. We aimed to investigate FGF23 and PTH levels in relation to GFR as well as the relative impact of each on FePhos in people with CKD stage 3.

Methods: Serum intact FGF23 (Kainos ELISA) and PTH (Roche E170) were measured in 1667 people with previous estimated GFR 59-30ml/min/1.73m^2 recruited from 32 Primary Care Practices. Detailed medical history and clinical assessment were performed as well as urine and serum biochemistry tests.

Results: Median values for key variables were: age 74(IQR 67 to 79)y, eGFR 53(46 to 60)ml/min/1.73m^2, PTH 46(34 to 66)pg/ml, FGF23 42(33 to 53)pg/ml, FePhos 23(19 to 29)%. PTH and FGF23 were elevated in similar proportions of participants at all levels of GFR. Multivariable analysis identified GFR, serum calcium, phosphate, logPTH, uric acid concentrations as well as log urine PCR and BMI as independent determinants of serum FGF23 concentration (adjusted R^2=0.22). Median FePhos was 22.0% if PTH and FGF23 were normal; 24.3% if FGF23 alone was elevated, 24.5% if PTH alone was elevated and 29.8% if FGF23 and PTH were elevated (P<0.001). Both log serum PTH and FGF23 concentration were independent determinants of FePhos, as well as age, gender, diabetes, current smoking status, BMI, eGFR, Hb, HDL cholesterol and log hsCRP (adjusted R^2=0.33).

Conclusion: FGF23 and PTH become elevated in CKD stage 3 and together mediate an increase in FePhos. Multiple factors in addition to GFR and serum phosphate are independent determinants of FGF23 in CKD stage 3. Further research is required to identify factors that provoke a rise in FGF23 as well the relative importance of FGF23 and PTH in increasing FePhos.

P336

Measurement and associations of albuminuria in people with chronic kidney disease stage 3 in primary care

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Introduction: Albuminuria is an independent risk factor for adverse outcomes in people with CKD. CKD 3 is principally managed in primary care in the UK, including albuminuria testing. This study aimed to identify associations of albuminuria in individuals with CKD 3 in primary care, and the degree of agreement between a single measure of ACR, used to derive risk in most cohort studies, and 'two of three' measures (reflecting clinical practice).

Methods: 1,741 patients with CKD stage 3, recruited from 32 GP practices, underwent medical history, clinical assessment, and biochemistry testing (including three consecutive early morning urine samples for albumin creatinine ratio (ACR)). Albuminuria was defined as ACR ≥2.5mg/mmol (men), ≥3.5 mg/mmol (women). The Bland Altman method was used to examine the degree of agreement between single ACR and two of three ACRs. Considering albuminuria in 2 of 3 specimens as the reference test, sensitivity, specificity, and positive predictive value of single ACR measure were also calculated. Multivariable logistic regression was used to identify independent associations of albuminuria.

Results: 296/1741 (17.0%) had microalbuminuria on single ACR measure, and 280 (16.1%) on two of three ACR measures. Comparing one vs. two of three measures of ACR, the mean difference was 0.0064 mg/mmol (SD 4.69, % limits of agreement -9.19 to +9.199). The sensitivity of single ACR was 94.6%, specificity 97.9%, and positive predictive value 89.8%.After adjustment for age, sex, diabetes, hypertension, smoking, and eGFR, albuminuria was associated with men (OR 3.83 (2.85,5.14),lower eGFR (OR 4.98 (1.69,14.63) for <30 compared to 45-59), diabetes (OR 2.50 (1.83,3.42)), hypertension (OR 2.32 (1.28,4.22)), and current smoking (OR 2.28 (1.26,4.11), compared to never smokers).

Conclusion: Defining albuminuria by single ACR misclassified some individuals but the sensitivity, specificity and positive predictive value of single ACR remained high. Identifying albuminuria in CKD in primary care is central to defining risk of adverse outcomes and targeting interventions at those at highest risk.

P337

Improving ascertainment of chronic kidney disease with laboratory-based case-finding

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Introduction: Since the introduction of GP CKD registers as part of the Quality and Outcomes Framework (QOF), there has been a substantial rise in identification of CKD. There is marked variation in prevalence between practices, with rates of 1.3-9.0% in our population. We hypothesised that this variation was not due to genuine differences in population CKD prevalence.

Methods: Our population is mostly served by a single laboratory. We identified all adults with any eGFR <60 mL/min/1.73m^2 in 2009-2012 (n=44,445) and extracted all their serum creatinine results over that period. We excluded those without results >90 days apart (n=3,087). For patients with eGFRs straddling 60 mL/min/1.73m^2, those with >50% of time <60 mL/min/1.73m^2 were classified as CKD, as a mimic of 'real world' decision-making. Patients were grouped by practice to derive laboratory CKD prevalence (LabP) for each practice, and analysed against reported QOF prevalence (QOFP) for the same period.

Results: QOFP and LabP are strongly correlated ($r=0.74$, $p<0.01$), but there is a higher variance in QOFP. In 2011, LabP was higher than QOFP by 0.42% (95% CI 0.16, 0.69). In 2012, QOFP rose and the difference was reversed to -0.14% (95% CI -0.40, 0.12). Relative difference ((QOFP-LabP)/QOFP) was negatively correlated to QOFP ($r=-0.54$, $p<0.01$) but not to deprivation, list size or rurality, suggesting practices reporting high prevalence rates tend to overestimate and *vice versa*. LabP was moderately associated with rurality (rho=0.46, $p<0.01$) and rurality was negatively associated with list size (rho=-0.50, $p<0.01$).

Discussion: CKD 3-5 is predominantly a laboratory diagnosis. In 2011, there were ~1600 CKD patients not on the register. In 2012, QOFP is similar to LabP, but with significant variation across practices. Additionally, some individuals are erroneously labelled with CKD, and may be subject to unnecessary monitoring. Our study reveals a weakness in the QOF registers which can be improved through centralised laboratory reporting. Our report does not account for demographic differences to explain variation, and work on that is underway.

P338

KIM-1 and MCP-1 do not predict CKD progression

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Background: Kidney Injury Molecule -1 (KIM-1) is a type 1 transmembrane protein with immunoglobulin and mucin domains. KIM-1 is expressed in the apical membrane of proximal tubules. It is up-regulated in Acute Kidney Injury (AKI) and in various human primary and secondary kidney diseases (e.g. focal glomerulosclerosis, IgA nephropathy, or membranoproliferative glomerulonephritis). KIM-1 is a good marker of AKI, but recently it has been suggested that it may also have value in the predicting the rate of Chronic Kidney Disease (CKD)progression. Monocyte Chemoattractant Protein-1 (MCP-1), also known as CC-chemokine ligand 2, is the most potent chemokine for recruiting monocyte /macrophages and is a marker of acute inflammation. As inflammation is integral to the development of fibrosis, its level may reflect the rate of kidney damage. Therefore we tested the hypothesis that the urine levels of KIM-1 and MCP-1 may predict the activity of the fibrotic program and thus the rate of CKD progression.

Methods: Urine samples were collected from 277 patients with various types of CKD and rate of progression, 33 healthy individuals and 17 diabetic patients with no evidence of CKD. These were analysed for KIM-1 and MCP-1 using the ELISA Duoset system from the R and D systems. Patients were categorised into none progressive, progressive or rapidly progressive based on loss of eGFR per year (<2, 2-5 or >5ml/min/yr respectively). Values were corrected for volume by correction to creatinine.

Results: There was no increase in KIM-1 in any type of chronic disease or disease stage compared to healthy individuals (17-519 pg/ml). However, when patients were grouped by the rate of progression over the 3 years post sample collection, there was a significant increase in patients with rapidly progressive CKD compared to both healthy individuals and those with non-progressive CKD by both concentration and as a creatinine ratio ($p<0.05$). KIM-1 levels were subsequently divided into normoalbuminuria, microalbuminuria and macroalbuminuria groups. There was a significant ($p<0.05$) increase in KIM-1 in macroalbuminuria compared to normal, but no significant difference between normoalbuminuria, microalbuminuria and macroalbuminuria CKD groups. There was no correlation between eGFR decline and KIM-1 levels. Receiver Operating Characteristics (ROC) curve analysis was performed to determine the potential of urine KIM-1 in predicting the progression of CKD. This produced an area under the curve value (AUC) of 55% accuracy for urine KIM-1 in predicting CKD progression compared to 56.4% for the albumin-creatine ratio (ACR) in the same patients. There was no increase in urinary MCP-1 in any type of CKD compared to the normal range (98.8-556.4 pg/ml). MCP-1 levels did not change by stage of CKD, rate of CKD progression or level of albuminuria. Calculation of the AUC by ROC analysis showed a prediction accuracy in predicting rate of CKD progression of only 49.4%.

Conclusion: KIM-1 and MCP-1 can both be measured in urine, but levels are not related to CKD stage and have no value in predicting the progression of CKD. KIM-1 and MCP-1areboth inferior to the currently used ACR in predicting CKD progression.

P339

Prevalence and associations of chronic kidney disease (CKD) in patients with psychotic disorders

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Background: We aimed to assess the prevalence of chronic kidney disease (CKD) in a cohort of community based patients with established psychotic illnesses.

Method: We conducted a cross sectional survey to ascertain estimated glomerular filtration rate (eGFR) measurements and prevalence of CKD in patients with psychotic disorders registered with community mental health teams. CKD was staged 1-5 according to KDOQI using their eGFR. We looked for associations between eGFR and metabolic parameters.

Results: There were 313 patients (184 male, 129 female) whose mean age was 43.27 +/- 10.45 years). Mean eGFR was 81.58 +/-10.51 mL/min. Females had a significantly lower eGFR (79.62+/-10.20 mL/min) compared with males (82.94 +/- 10.53 mL/min) (t=2.787, df=311, p=0.006). The prevalence of CKD with an eGFR < 60 mL/min in this cohort was 2.9% (n=9). By stage, 146 patients (46.6%) had stage 1 CKD, 158 (50.5%) had stage 2, and 9 (2.9%) had stage 3 with no one suffering from either stages 4 or 5 CKD. There were no significant differences in age (stage 1 & 2 CKD, 43.28 yrs; stage 3, 43.01yrs) and no increased rate of lithium use in those with CKD 3 (data not shown). Interestingly there were no significant differences in HbA1c, TG or HDL-C levels in those with stage 3 compared with stages 1 & 2 CKD.

Discussion: This study demonstrates an association between established psychotic disorders and stage 3 CKD. The rate of stage 3 CKD was higher than the normal population. This is not surprising given the known high prevalence of metabolic syndrome in these patients and its association as a predictive variable in the development of CKD. It is likely that entire our population is at increased risk of developing higher rates of CKD in the future given their young age, the increased prevalence of metabolic syndrome as well as a more inconsistent and fragmented approach to their physical health care. Therefore, these patients should be carefully monitored in the long-term.

Poster session

Wednesday 13th March

18:15 - 19:25

CKD risk and progression 2

P340

No associations between rs2030712 and rs7456421 single nucleotide polymorphisms of HIPK2 gene and the incidence of chronic kidney disease; results of the family-based study

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In the light of the promissing literature data from March 2012 concerning homeodomain-interacting protein kinase 2 (HIPK2) upregulation in damaged kidneys animal model and increased levels of this protein in patients with various kidney diseases, we performed this research to analyse the influence of rs7456421 and rs2030712 single nucleotide polimorphisms (SNPs) of HIPK2 gene on CKD incidence and progression.

The study group consisted of 109 children with CKD and their parents creating 109 family "trios". Among CKD patients (48 females and 61 males in mean age 15.5 ±6.45 years) 72.5% suffered from interstitial nephritis (CIN) with- or without concomitant urinary tract defect (UTD) and 27.5% from chronic glomerulonephritis (CGN).

Based on TDT results, we did not demonstrated the influence of rs7456421 and rs 2030712 SNPs of HIPK2 gene on prevalence of CKD. In the multiple stepwise regression, history of CGN (OR=17.3, p=0.000027) or CIN without UTD (OR=4.4, p=0.019) and CT genotype of rs 2030712 (OR=2.6, p=0.05) were determinants of more rapid CKD progression.

P341

RCP/GP renal referral criteria correctly determines need for nephrology review

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Background: Guidelines such as those of the RCP/GP Joint Specialist Committee for Chronic Kidney Disease (CKD) provide useful decision aids as to who requires specialist nephrology care. However too rigid adherence may exclude some requiring review and potentially miss opportunities for intervention. Here we review the outcomes of referrals assessed for appropriateness using these guidelines.

Aims: To assess the nephrology outcomes of patients referred to a large Renal Unit and whether the RCP/GP guidelines are a suitable method of identifying those needing specialist review.

Methods: Patient socio-demographic and clinical data provided were prospectively collected on new referrals to one large renal unit during 2006. The decision on whether the patient required review in the renal clinic or alternatively return to GP was made using the recommendations of the RCP/GP Renal Joint Specialist Committee. Outcomes 6 years after initial referral were obtained from hospital records for those still under renal unit care and for those referrals returned to Primary Care, the information was collected from their General Practitioners

Results: In total 503 patients were referred. 377(75%) were seen in the clinic, and 126(25%) were returned with advice. Those seen were significantly younger (60[17] vs 66[19], p=0.012) and had worse kidney function (eGFR 49[24] vs 57[22], p<0.001). Following an average of 6.1 years follow-up, 9(7%) of the 126 patients returned were later seen in the nephrology clinic and 15(12%) had died. The remaining 102(81%) continued with Primary Care monitoring with an average GFR of 51(23). In the 377 seen in clinic, 34(9%) died, 27(7%) started RRT, 9(2%) commenced a conservative care pathway, 17(5%) were being prepared for RRT, and 98(26%) were later discharged to their GP.

Discussion: In this analysis, deciding on specialist review according to RCP/GP guidelines appears safe, with very few patients not originally seen subsequently requiring nephrology care. It could be argued the guidelines are not particularly specific as 26% were later returned to their GP, though the extra workload is likely to be minimal and this is a safer option. These guidelines are both an appropriate way of screening referrals and a useful resource for non-nephrologists to gauge the need for specialist review.

P342

Obesity associates with kidney disease in type 1 and 2 diabetes: analysis of the national diabetes audit

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Introduction: Obesity is increasingly prevalent in many countries. Obesity is a major risk factor for type 2 diabetes but its association with diabetic kidney disease (DKD) is less clear. Additionally, some studies suggest the metabolic syndrome (including obesity) may be a risk factor for the development of DKD in type 1 diabetes. We investigated the association between obesity and DKD.

Methods: National Diabetes Audit data were available for the 2007-08 cycle. Type 1 and 2 diabetes patients with a valid serum creatinine and urinary albumin:creatinine ratio were included. Obesity was defined as a body mass index ≥30 kg/m^2. Diabetic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2, albuminuria or both. Patients were stratified according to eGFR and degree of albuminuria. Logistic regression was used to analyse the association of obesity and other variables including year of birth, year of diagnosis, ethnicity, Strategic Health Authority (SHA) and stage of kidney disease.

Results: 58,791 type 1 and 733,769 type 2 diabetes patients were included in the analysis. After adjustment, type 1 DKD patients were up to 2 times more likely to be obese than those with normal renal function. Type 2 DKD patients were also more likely to be obese than those with normal renal function. However, type 1 patients on renal replacement therapy (RRT) had a lower odds ratio (95% confidence interval) for obesity – OR 0.67 (0.46-0.97). There was no significant difference in type 2 patients on RRT. Ethnicity also affected risk of obesity e.g. both type 1 and type 2 patients of Asian ethnicity had lower odds ratios for obesity than those of white ethnicity; OR (95%CI) 0.77 (0.69-0.85) in type 1 and 0.28 (0.27-0.28) in type 2 patients.

Conclusions: This study has confirmed the association between obesity and DKD in type 2 diabetes. It has also highlighted a strong association between obesity and DKD in type 1 patients. If causal in nature this could predict a future rise in DKD among type 1 patients as obesity rates rise in the population.

P343

Physical activity levels in the UK chronic kidney disease population

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Background: Chronic kidney disease (CKD) results in greater risk of cardiovascular disease, muscle atrophy associated with functional decline and mortality, depression and reduced quality of life. Physical activity and exercise interventions have the potential to positively impact on these areas and exercise is recommended in the NICE guidelines. However, incorporation into routine care is lacking and little is known about the activity levels of the UK CKD population and its association with disease severity.

Aim: To explore activity levels of general nephrology (CKD1-3) and pre-dialysis (CKD 4-5) patients in Leicestershire. Also to assess the relationship between activity levels and biochemical markers relating to disease severity in CKD.

Methods: 265 patients (133 male; median age: 62 years; age range: 21-93 years; mean eGFR 36.3+/-1.73mL/min/1.73m^2) completed 3 validated questionnaires to assess physical activity levels: the Duke Activity Status Index (DASI) which calculates habitual activity in Metabolic Equivalent of Tasks (METS), Leisure Time Exercise Questionnaire (LTEQ) and GP Physical Activity Questionnaire (GPPAQ). eGFR, haemoglobin, and serum cholesterol, albumin and bicarbonate were extracted from the medical records.

Results: 52.5% were classified as 'inactive' and 10.6% as 'moderately inactive' as defined by the GPPAQ. 80.4% were classified as 'insufficiently active' by the LTEQ. DASI was positively correlated with eGFR ($p<0.001$), haemoglobin ($p<0.001$) and albumin ($p=0.003$). There were no correlations between DASI and cholesterol or bicarbonate levels.

Conclusions: The UK CKD population lead sedentary lifestyles; 72% of the sample was eligible for entry into the 'Physical Activity Care Pathway' as defined by the GPPAQ. The positive correlations demonstrate the link between physical activity capacity and habits with CKD stage, renal anaemia and nutritional status. This highlights the need for CKD-specific physical activity interventions and strategies for incorporation of exercise into the routine care of the renal population.

P344

Improving diagnosis and care for people with kidney disease. A Plymouth collaborative project with NHS Kidney Care and Health Intelligence Ltd

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The NICE guideline on chronic kidney disease (CKD) was published in 2008, yet on average 30% of people are still referred late to nephrology services either with acute renal failure or advanced CKD. Strategies aimed at earlier identification and prevention of progression to established renal failure is therefore needed. We report the findings of the Health Intelligence Ltd. CKD Dashboard which analysed primary care patient data from 11 Plymouth GP practices covering a population of 84,894.

We found a large variation in the Quality and Outcomes Framework (QOF) prevalence rates of CKD in the 11 GP practices (range 0.1-6.1%). The Dashboard identified an additional 613 patients who have CKD but who were not recorded on the practice register as having CKD. Patients were identified as having CKD if they have one or more of the followings: abnormal urinary albumin/creatinine ratio of >30mg/mmol with or without a structural abnormality, 2 or more eGFR readings of <60ml/min in the preceding 3 months or have undergone a kidney related procedure. There were also 417 patients with CKD stages 4 or 5 noted within the practice but who were not known to secondary care. 1543 patients had rapid decline in renal function, with no recorded referral to nephrology service (291 patients with eGFR fall of >5 ml/min and 119 patients with eGFR fall of >10ml/min in the last 12 months plus 1133 patients with eGFR fall of >10ml/min in the last 5 years). There were a further 8030 patients who have not had an eGFR recorded in the last 15 months but who were on nephrotoxic drugs requiring monitoring of renal function.

In summary, there is wide variability in the QOF CKD prevalence rates between practices which cannot be explained by differences in thresholds for CKD testing and deprivation alone. Altogether there were 1960 patients with either CKD 4/5 or have rapidly declining renal function who should have been referred to nephrology in accordance with the NICE CKD guideline. Whilst CKD Dashboard can facilitate patient identification, continual education of CKD referral criteria is still required.

P345

Testing a care bundle for managing chronic kidney in primary care: the results of the ENABLE project

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Introduction: Chronic kidney disease (CKD) is a common condition usually managed in primary care but current care is variable. Care bundles have been successfully employed in secondary care to reduce variation but experience in primary care is very limited.

Aim: The aim of the ENABLE project was to improve quality and reduce the variability in care of people with CKD in primary care using a care bundle approach.

Methods: A care bundle was developed and piloted. There were four bundle elements: three were closely based on NICE guidance for CKD; the fourth involved asking if the patient wished to participate in a programme of collaborative self-management. The self-management component was designed and led by our patient and service user advisory group. Ethical approval was obtained and the project registered with the Comprehensive Local Research Network. The setting for bundle application within practices (ad-hoc, dedicated CKD clinic, long-term conditions clinic) was not prescribed. The following anomymised data were collected: care bundle reliability data; baseline and monthly practice-level CKD outcome data (using in-house MIQUEST queries); and qualitative post-intervention data from focus group held with patients and practitioners.

Results: Twenty-nine practices were initially recruited; nineteen completed the project. The care bundle was applied to 1,310 patients of whom 69.3% agreed to the self-management component. The bundle was applied to ≥20% of the registered CKD population in 14 practices, ≥30% in 10 and ≥50% in 5. The recorded mean prevalence of CKD in the 19 practices who completed the project was 4.1% (±1.5%) at the start and 4.8% (±1.6%) at the end, equivalent to an additional 826 patients identified during the programme. The mean reliability for practices returning > 6 months data was 76%, 87%, 98%, 98% and 100% at months one, three, six, nine and twelve respectively. Overall NICE blood pressure targets were achieved in 47% of those with registered CKD and diabetes at the start of the project and 52.2% at the end; for people with CKD but no diabetes these figures were 70.9% and 76.7% respectively. The self-management intervention was well received by both patients and practitioners.

Conclusions: Application of a care bundle for managing CKD in primary care is feasible and can result in improvements of care at practice level. People with CKD welcome opportunities to self-manage their condition. Further studies are required to formally assess the impact of the self-management intervention on measures of patient activation and outcome.

P346

The relationship between estimated renal function and rural-to-urban migration in an Indian population: cross-sectional data from the Hyderabad arm of the Indian migration study

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Urban migration, both within and between countries, is associated with an increased risk of hypertension, obesity and diabetes. This is true for South Asian migrants. This study assessed the relationship between internal migration and renal function amongst South Asians from the Hyderabad arm of the Indian Migration Study.

We assessed 841 subjects who were either urban non-migrants (n=158, 19%), urban migrants (n=424, 50%) or rural non-migrants (n=259, 31%). Renal function was estimated using the 4-variable MDRD formula and muscle mass was ascertained from DXA scanning. For further analysis we excluded urban non-migrants and derived urban life years for urban migrants and rural non-migrants. Multivariable linear regression was used to examine the association between tertiles of urban life years and eGFR.

Mean eGFR was lower in urban non-migrants and urban migrants compared to rural non-migrants. As the number of urban life years increased, eGFR declined though there was no obvious dose response effect (eGFR for tertiles 2 and 3 compared to baseline; -4.72, -4.67 ml/min/1.73m^2; p value for trend 0.008). After adjustment for muscle mass, the associations were attenuated and the trend was consistent with chance (p=0.08). Further adjustment for HOMA-IR, diabetes, smoking, cholesterol and BMI weakened the association to a small degree (p=0.11). Results were similar for men and women.

Urbanization appears to be associated with reduced MDRD –derived renal function. This association appears mostly to be due to higher muscle mass with a small contribution from adverse cardiovascular risk factors. Further work is required to confirm if this effect is seen with *measured* renal function.

P347

Prevalence of Tuberculosis in chronic kidney disease - results from a socio-economic diverse renal unit in the United Kingdom

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Introduction: Patients with chronic kidney disease (CKD) are at increased risk of tuberculosis (TB). There is limited information on the magnitude of the problem within the Birmingham area, an area with the highest incidence of TB in the UK, outside London.

Method: We identified 54 patients with TB within a single renal centre serving a diverse socio-economic area in the West Midlands. Data collected included patient demographics, TB site, stage of CKD, type of renal replacement therapy and clinical outcome. Prevalence of TB at different stages of CKD was also calculated.

Results: Of the 54 patients identified as having TB, 32 were male and 22 female. Mean age was 59.8 years (range 26 – 87 years). 41 (76%) of patients were from the Indian subcontinent, 9 were of European origin and 4 were of African origin. 24 patients had pulmonary TB, 22 had extrapulmonary TB and 8 had a combination. Extrapulmonary sites included mediastinum lymph node, pericardium, peritoneum, soft tissue and spine. 30/54 (55%) patients were pre-dialysis (3 patients had CKD2, 17 CKD3, 7 CKD4 and 2 CKD 5). 19/54 (35%) were on haemodialysis, 1/54 (1.8%) was on peritoneal dialysis and 3/54 (5%) were transplant patients. One patient presented acutely. Prevalence of TB was 2.2% in haemodialysis patients, 7.9% in transplant patients, 0.4% in pre-dialysis patients and 0.6% in peritoneal dialysis patients.

Conclusion: Tuberculosis has a high prevalence within the CKD population, particularly transplant recipients. A high index of suspicion is required in our patient population across all stages of CKD. Further studies are required to assess whether screening for latent TB infection of certain CKD subpopulations would be of benefit.

P348

What actually happens to patients with advanced CKD after they make a choice about their preferred future management?

Rebecca Sherlock[2], Kieron Donovan[1], Stephen Riley[2], Gareth Roberts[3], Jean Jenkins[1], Justine Aggett[1], Julia Pugh[1], Alison Pritchard[1], Anwen Goodland[1]

[1]University Hospital Wales Nephrology and Transplant Directorate, Cardiff, Wales, UK, [2]Cardiff University, Cardiff, Wales, UK, [3]Anuerin Bevan Health Board, Pontypool, Wales, UK

Introduction: 'People with CKD should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals.' - *NICE clinical guideline 73, 2008.* Patients with advanced CKD referred to our Pre-dialysis Service are counselled about their management options through home visits, telephone contact, and Specialist Nurse-led clinics. We investigated whether patients actually received their preferred management option.

Methods: Data from all new patients (n=1834) seen by the service between 2005 and 2012 was censored at 31st July 2012, and analysed retrospectively.

Results: 1668 patients (90.9% of those seen) had an event – either starting RRT or Death. Median time from choice to first event was 1.25 years (±1.24).

		% Actual Starting mode				
Choice	**N**	**PD**	**HD**	**T'plant**	**Cons**	**Died**
PD	424	43.6	27.1	7.1	0.2	10.8
HD	856	0.5	57.6	1.2	0.1	20.3
Transplant	58	19.0	25.9	32.8	0.0	1.7
Home HD	34	0.0	91.2	5.9	0.0	2.9
Cons	296	0.0	3.0	0.0	97.0	-

At the study end point 47%, 28%, 16% and 8% who chose Transplant, PD, Home HD and HD respectively had received successful transplants.

Discussion: Patients opting for HD were more likely to start on their preferred treatment than those opting for PD. Reviewing what happens to patients after they have made treatment choices is important. It may help identify areas for improvement in providing patients with their preferred renal replacement treatment.

P349

Should all elderly (≥ 80 years) patients with advanced CKD be referred for formal education and counselling about the options for RRT?

Rebecca Sherlock[2], Kieron Donovan[1], Stephen Riley[2], Gareth Roberts[3], Jean Jenkins[1], Justine Aggett[1], Julia Pugh[1], Alison Pritchard[1], Anwen Goodland[1]

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Introduction: It is difficult to quantify survival and quality-of-life benefits of dialysis for elderly patients in whom the balance of potential benefits versus hazards of treatment is more precarious. Within the cohort of advanced CKD patients there are sub groups with non-progressive and progressive CKD. What are the outcomes of intervention in these sub groups and how might the rate of decline in a patient's eGFR influence our management approach?

Methods: All new patients referred to our Senior Nursing team between 2005 and 2012 were analysed. Survival of non-progressors (↓ eGFR < 2.5 ml/min/yr) was compared to that of progressors. The impact of conservative management (Cons) vs renal replacement therapy (RRT) was also assessed in both groups.

Results: 1834 patients were seen, of which 338 were ≥80 years and known for >3months. This data (n=338) was analysed by Kaplan Meier survival and Log Rank tests.

Group tested	Comparison	Median Survival (yrs)	p value
All CKD	Prog v Non prog	1.9 v 2.9	< 0.001
Progressive CKD	RRT v Cons	3.2 v 1.5	< 0.001
Non progressive CKD	RRT v Cons	2.6 v 3.0	= 0.559

45.3% of referred patients ≥80 had progressive CKD; this group had poorer survival. Dialysis was associated with improved survival in progressive CKD but not in non-progressive CKD. Survival in non-progressive CKD was similar to that of dialysed patients with progressive CKD.

Discussion: Our data suggests that the elderly with non-progressive CKD need not be subjected to the anxiety and stress of formal referral for consideration of RRT. The use of ↓ eGFR helps identify those with non-progressive CKD to inform this process.

Poster session

Friday 15th March

11:30 - 12:30

Clinical nephrology 5

P350

A review of percutaneous renal biopsy activity in north-central London

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Introduction: The Royal Free Hospital manages renal services in north-central London. We undertook an analysis of the indications, results, and complications of all percutaneous renal biopsies performed in a two-year period.

Methods: We retrospectively analysed all percutaneous renal biopsies performed in a two year period 2010-2012 (n=653; 49% native, 51% graft). Data was collated from discharge summaries, clinic letters, and pathology databases.

Results: Acute kidney injury was the most common indication in native biopsies (47%), followed by proteinuria (36%). A rising creatinine was the most common indication in graft biopsies (44%), followed by protocol biopsies (33%), and delayed graft function (7%). 41% of all biopsies utilised a fast-track results service giving same-day initial results, of which 51% were for a rising creatinine or DGF in a transplant patient. Complications were observed in 2.9% of patients, more frequently in day-case biopsies (4.8%) than ward biopsies (1.6%) ($p=0.01$). The eGFR in day-case patients (median eGFR=50.5) was higher than in admitted patients (median eGFR=16) ($p=0.02$). Bleeding (including haematuria) was the most common complication (58% of complications). The majority (72%) were managed conservatively, but 28% required intervention including embolisation. All complications requiring intervention were initially day-case procedures. Other complications included: pain prolonging admission (5%), and hypertension (11%) requiring intervention or observation. There were no fatalities.

Conclusions: Renal biopsies are most frequently performed for a raised creatinine in both native and graft biopsies. Renal biopsies have a low complication rate (<3%), with <0.5% requiring subsequent intervention due to complications. Complications are more frequent in biopsies performed as a day-case, but the reason for this is uncertain.

P351

An inpatient renal consultation service for patients not on renal replacement therapy

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Introduction: We set out to evaluate our inpatient renal consultation service with the aim of improving service provision. The hospital is a large teaching hospital and a tertiary referral centre for a range of specialties including liver and transplantation, cardiac services and nephrology.

Methods: A retrospective analysis of all inpatient referrals between August 2008 and December 2011 was performed. Referral data was extracted from the renal unit database and further information was manually collected this database and the hospital electronic patient notes.

Results: 1,210 referrals (for 1,097 patients) were received, 854 of which were for patients not under active renal follow-up. Medical specialties accounted for the largest proportion of referrals (36%), followed by cardiac services (17%) and the liver unit (13%). The renal team took over the care of 154 referrals (13%) at some stage during the admission. Acute renal replacement therapy (RRT) was delivered to 157 (13%) referrals and 21 (9%) underwent renal biopsy. The majority receiving RRT (73%) had not been attending a renal clinic prior to admission. Average length of stay for all referrals was 27 days. 14% of all referrals died as an inpatient and 21% of referrals had died within 90 days of discharge. Mortality was highest for the referrals previously unknown to nephrology and lowest amongst those known to a low clearance clinic. 626 of the referrals not previously known to nephrology were still alive at 6 months, but only 154 (25%) were followed-up in the same time period. This included 47 who had received acute RRT.

Discussion: This data highlights the importance of a nephrology service within an acute hospital setting. It is an underestimate of the consultation service because it does not include referrals from other hospitals, phone advice or referrals not entered on the database. The data has highlighted a significant mortality rate amongst those referrals requiring renal consultation. Further investigation is required to look into the apparently low follow-up rate amongst those patients not previously under nephrology.

P352

An inpatient renal consultation service for patients on renal replacement therapy (RRT) in a tertiary referral centre

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Renal Unit, King's College Hospital, London, UK

Introduction: Our renal unit cares for 427 haemodialysis (HD) patients, 94 peritoneal dialysis (PD) patients and 316 transplant (Tx) patients on an outpatient basis. These patients, as well as those known to other renal units, are frequently admitted to non renal wards under the care of other teams. We investigated the consultation service we provide, with the aim of improving future service provision.

Methods: A retrospective analysis of all inpatient requests for consultation between Aug 2008 and Dec 2011 was performed. Referral data was extracted from the renal unit database and all patient on RRT were identified. This was supplemented by manually collected data from the database and the hospital electronic patient notes.

Results: 474 consultations (313 patients) were provided over 167 weeks. Of these, 358 were for HD patients, 27 for PD patients and 89 for Tx patients. 108 (23%) referrals were for patients primarily under the care of other renal units. Medical specialties accounted for the largest proportion of referrals (32%), followed by cardiac services, hepatology and general surgery (11% each). The renal team took over the care of 71 referrals (15%) at some stage during admission. Average length of stay was 16 days. Of the 474 patients referred, 157 (33%) are known to have died by the time of publication. 7% of all referrals died as an inpatient. 14% of referrals had died within 90 days of discharge from hospital, rising to 27% after one year. Mortality was higher for dialysis patients compared to Tx patients. Death during admission or within 90 days of discharge was associated with older age, white ethnicity and increased length of stay.

Discussion: This data demonstrates the value of a renal consultation service in a tertiary referral centre. Patients receiving RRT present to a wide variety of specialties and often require specialist renal input. Of note in this study was the relatively low percentage of referrals that were transferred to the care of the renal team. This may be partly attributable due to bed availability.

P353

Day case renal biopsy: single centre experience

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Lancashire Teaching Hospitals NHS Trust, Preston, UK

Aims: There has been an increase in number of renal biopsies being performed on day case basis in recent years. Day case renal biopsy offers advantage of patients being discharged home same day. We aim to look at our practice in the last 3 years at Royal Preston Hospital, specifically looking at minor and major complications, biopsies with adequate tissue yield, patients discharged home same day and mean length of stay if admission was required.

Method: We retrospectively analysed 312 renal biopsies done between 2010-2012.Data was gathered using Quadramed system and histopathology database. Minor complications included macroscopic haematuria or perinephric hematoma. Need for transfusion or intervention was regarded as major complication. Serious complications included death, loss of kidney or life-threatening haemorrhage. If complication occurred after discharge, it was regarded as a delayed complication.

Results: Number of biopsies has increased with each consecutive year. In more than 93% of biopsies, adequate tissue yield was obtained. While minor complications increased as biopsies increased, major complications remained few. Only 3 patients required intervention in the form of CT angiography in 3 years; only 1 out of these 3 needed embolisation. Most patients just stayed overnight if they could not be discharged from day case unit.

Conclusions: If patients suitable for day case renal biopsy are selected using set criteria, they are more likely to be safely discharged from day case unit. If haematuria warrants inpatient admission, overnight stay is sufficient for majority of patients. With ultrasound guided technique using automated biopsy gun, number of complications is small. Therefore day case renal biopsy remains a safe procedure in majority of patients.

P354

Do we need to stop antiplatelet therapy or use vasopressin analogues to reduce bleeding complications after renal biopsy?

Rebecca Herbert, James Bushnell, Udaya Udayaraj

The Richard Bright Renal Unit, Southmead Hospital, Bristol, UK

Introduction: There is wide variation in clinical practice regarding cessation of antiplatelet therapy and use of (including indications for) vasopressin analogues (VP) prior to renal biopsy.

Objectives: To evaluate the rate of complications post renal biopsy, risk factors associated with it including continuation of antiplatelet therapy pre-biopsy.

Methods: A single centre retrospective study of all renal biopsies (n=132, 75 native, 57 transplant) was performed (May 2011 – October 2011). Antiplatelet therapy was discontinued for 5 days if possible prior to non urgent biopsies and VP was not used in our centre.

Results: Antiplatelet therapy was ongoing in 14.4% patients at time of procedure (Aspirin (n=18) dipyridamole n=1). The complication rate was similar to published literature and there was no association with age (18 – 87), blood pressure (within range 90-177 / 54-106) or use of antiplatelet therapy.

		NBT renal unit		
	Corapi et al meta-analysis rates 2012	Total rates	Native rates	Transplant rates
Macroscopic haematuria	3.5%	3.8%	4%	3.5%
Embolisation	0.6%	0.76%	1.3%	0%
Blood transfusion	0.9%	0.76%	1.3%	0%

Discussion: Without routine use of vasopressin analogues or cessation of antiplatelet therapy in emergency situations, our biopsy complication rates were similar to published rates (Corapi et al, Am J Kidney Dis. 2012 Jul;60(1):62-73) suggesting these interventions may not be necessary or cost effective. We have not identified any patient characteristic that was associated with increased bleeding risk in our population. There was no increased risk of bleeding identified up to a maximum blood pressure of 177/99.

P355

Cumulative savings from green nephrology innovations

Frances Mortimer[1], Ian Stott[2], Andrew Connor[3]

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Introduction: Green Nephrology (GN) case studies document local innovations with environmental benefits.

Aim: to review cumulative environmental and financial benefits from GN innovations and estimate potential savings from widespread replication.

Methods: Innovations were categorised as "infrastructure" (requiring capital investment), "process" or "model-of-care"(MoC). Greenhouse gas (GHG) emissions calculations were updated using the latest DEFRA conversion factors. Duplicate initiatives were classed as a single innovation, and their costs/benefits averaged. Total annual savings in GHG, water and financial cost were calculated for each category. Potential savings from scaling up across the UK were estimated by multiplying savings for each innovation by (total UK HD population)/(no. HD patients in original unit) x (0.3 or 0.6)* (*representing an uptake of infrastructure innovations in 30% units and process innovations in 60% units). MoC innovations were excluded due to poor data quality; one process innovation was excluded as non-transferable.

Results: Six infrastructure innovations included water reuse, use of baling machines for waste recycling, and central delivery of acid for haemodialysis. Total capital investment amounted to £121,000, with annual savings at £57,000, 84 tonnes CO_2e and 12 million litres of water. Eleven process innovations ranged from paperless laboratory reporting to waste reductions in food, linen and dialysis consumables to improved waste segregation. Annual savings were £186,000 & 183 tonnes CO_2e. Three MoC innovations demonstrated the improved use of tele-communications in patient management. Financial savings were difficult to quantify due to the uncertainty of commissioning arrangements. Total carbon savings for the three MoC innovations were 6 tonnes CO_2e. Potential savings from widespread replication of GN case studies in UK renal units were estimated at £7 million, 11,000 tonnes CO_2e and 470 million litres water per year.

Conclusions: Although not every innovation will be applicable everywhere, the systematic implementation of GN innovations across UK renal units offers significant financial and environmental rewards.

P356

Single centre review of pregnant patients reviewed in a joint renal/obstrectis clinic

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Salford Royal NHS Foundation Trust, Salford, UK

Introduction: Patient with chronic kidney disease have less ability to cope with renal changes needed for a healthy pregnancy. Pregnancy in a CKD patient carries a risk to both mother and foetal.

Method: We retrospectively reviewed data patients from Joint Renal/obstrectics clinic. A total of 30 patients were reviewed between the period of 2005 till 2011. We excluded patients on dialysis and transplant patients.

Results: Mean age of pregnant patients were 28.1 years. At the time conception, there were 5 patients on ACE inhibitor and these were stopped immediately. There were no reported foetal abnormalities. Only eight patients had protienuria at the time booking. Mean creatinine was 79 $\pm$ 42. Three patients had creatinine over 130 making them in the medium risk group. Average PCR in the first trimester was 149.8, 2nd trimester was 151 and 3rd trimester was 238 gms. Only nine patients were some form of anti-hypertensive.There was a loss creatinine and increase of protienuria of 20 % in all medium risk group with one patient suffered miscarriage. 26 patients had successful delivery with 4 had miscarriage during the pregnancy. Average gestational birth weight was 2635.4 gms. Complication during pregnancy included pre-elampsia (2 patients), placenta previa, corioamnionitis and increase of proteinuria. Mean creatinine and PCR at 3 months post preganancy was 88.88 and 139.73913 gms.

Conclusions: In our group of patients there appears to be good maternal and foetal outcome. This is a result from a multidisciplinary team involving comprising nephrologists, obstetricians, midwives, dietician in the joint clinic.The baseline creatinine and proteinuria is associated with worsening in renal function post pregnancy in our cohort of patients as reported in the literature.

P357

Atheroma within fibromuscular dysplasia double trouble

Allyson Egan, Wady Gedroyc, Adam McLean

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Fibromuscular dysplasia is an idiopathic, segmental, non-atherosclerotic disease of the walls of the musculature of the small and medium-sized arteries that predominantly affects women in their third or fourth decade and is associated with renovascular hypertension. Atherosclerotic disease is a more common cause of renal artery stenosis usually affecting older patients and is associated with renal parenchymal disease. We report a case of co-existing atheromatous disease in a patient with fibromuscular dysplasia and the outcome of percutaneous renal transluminal angioplasty (PTRA).

A sixty year old lady was referred with hypertension BP 225/120 which was first documented in her thirties and also recorded in several family members. Medication included Candesartan, sotalol, diltiazem and Indapamide. Atrial fibrillation was observed on examination and her serology indicated eGFR 74ml/min, Cr 82 umol/L, and cholesterol of 6.8. CT angiography demonstrated extensive bilateral fibromuscular dysplasia with string-of-bead appearance caused by multiple dilations and strictures with severe tortuosity and co-existing atheromatous disease. At PTRA a pressure gradient of 25mmHg was measured bilaterally and a series of overlapping successive balloon angioplasties along the length of left renal artery and cannulation with dilatation along 4cm of the right renal artery resulted in widening and smoothing of the contours of the arteries. Post bilateral balloon angioplasties medical therapy was reduced from quadruple to dual agent therapy with reduced dosages of medication required. BP recordings at home were BP 120/75 (clinic BP142/82 with serum Cr 8 umol/L 1, eGFR 85ml/min. Statin therapy was also commenced.

In the presence of dual FMD and atherosclerotic disease long standing high blood pressure control was improved with PTCA to bilateral renal arteries and continues to be controlled three months post procedure.

Poster session

Thursday 14th March

12:00 - 13:00

Clinical nephrology 1 : ANCA and GN

P358

Evaluation of the EUVAS histopathological classification of antineutrophil cytoplasm antibody associated vasculitis (AAV) in 104 patients at a single centre

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Introduction: The first histological classification for AAV, was proposed by *Berden et al* in 2010. Four subgroups were described based on histological features on light microscopy: focal, crescentic, mixed and sclerotic. Our aim was to evaluate the prognostic value of this classification in our patient population.

Methods: Patients were identified with AAV according to the Chapel Hill criteria, at least 10 glomeruli on biopsy and a minimum of 1 year follow up. Clinical data for patient and renal survival as well as relapses, were obtained retrospectively.

Results: 23 of the 104 patients were classified as focal, 26 crescentic, 48 mixed and 7 sclerotic. Renal survival according to class is illustrated in figure 1. There was no significant difference by class in relapse rate or patient survival. Renal survival also correlated with percentage normal glomeruli, degree of tubular atrophy, and starting renal function.

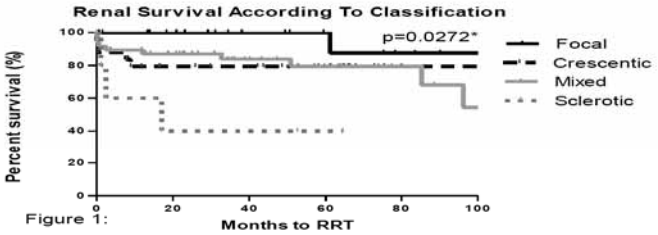

Figure 1:

Discussion: This large study provides validation of the EUVAS classification. Prognostic value was also shown for percentage normal glomeruli and tubular atrophy and we propose possible incorporation of these histological parameters. This classification has important implications for guided therapy in AAV.

P359

Outcomes of elderly patients with anca-associated vasculitis treated with immunosuppressive therapy

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Introduction: ANCA-associated vasculitis (AAV) is a common cause of acute kidney injury (AKI) in the elderly. Treatment requires immunosuppression (IS), which can have significant toxic effects. The aim of this study was to assess morbidity and mortality associated with immunosuppression in elderly patients with AAV.

Methods: A retrospective review of all patients presenting with AAV to a tertiary renal unit between 1990 and 2011 was conducted using the units' information database. 264 patients were reviewed and 32 who did not receive standard IS were excluded. 232 patients given induction therapy with prednisolone and cyclophosphamide (P&C) were studied

Results: There were 146 (63%) males and 86 females (37%). 122 patients were PR3 positive and 110 were MPO positive. Mean creatinine at presentation was 528 µmol/L. Median duration of follow-up was 59 months. 76 patients had pulmonary involvement (18 severe). Older patients (aged >65) were significantly more likely to require dialysis at presentation (RR 1.66 [1.13-2.5]) and longer-term and were treated with lower total cyclophosphamide dose (mean 6.5g) than those <55 years (mean 10.5 g). Older patients were more likely to develop leukopaenia (RR 2.3 [1.7-3.3]) and infections in the first year (RR 2.4 [1.5-3.9]). After multivariable adjustment, age and dialysis at presentation were significant predictors of death (HR 1.07 [1.03-1.11, p=<0.001] and HR 2.2 [1.10-4.38, p=0.03] respectively).

Discussion: Among patients treated with P&C, older age and dialysis-dependency were associated with worse survival. Older patients were also more likely to develop treatment-related complications despite lower cumulative doses. Morbidity and mortality associated with treatment must therefore be carefully balanced against that associated with the disease process itself.

P360

Vasculitis patients receiving immune suppressants are at risk of active cytomegalovirus (CMV) infection with end organ damage: a case for active CMV surveillance

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Introduction: CMV in renal transplant patients is a well known entity and usually a program of active surveillance or prophylactic valgancyclovir is instituted. However CMV disease in immune compromised patients due to vasculitis is not well described.

Methods: We report 4 cases of CMV infection with end organ damage. They presented to our unit within 2 – 28 weeks after diagnosis of vasculitis.

Case 1: 68 year old lady had PR bleeding, on prednisolone and mycophenolate 7 months after diagnosis of cANCA vasculitis. She had CMV cclitis and viraemia of 29,169 copies.

Case 2: 83 year old lady with HSP vasculitis had small bowel resection and CMV viraemia of >100,000 copies within 2 weeks of prednisolone and azathioprine,

Case 3: 73 year old man with cANCA vasculitis became pancytopenic 4months after diagnosis whilst on azathioprine. He had deranged liver functions, diarrhoea and CMV PCR of 18,479 copies.

Case 4: 57 year old lady with pANCA vasculitis received methyl prednisolone for predominantly neurological symptoms. Her bowel resection showed CMV inclusions and PCR of 24,764 copies.

Results: All above cases were treated with valgancyclovir and reduction of immune suppression. However Case 4 became anuric required intravenous cyclophosphamide, plasma exchange and dialysis. Case 2 & 4 underwent small bowel resection. Case 3 did not respond to treatment and died.

Conclusions: Infection is the leading cause of death in patients with vasculitis within one year of diagnosis. Unless specifically tested CMV disease remains largely undetected as a cause of death. We recommend a policy of CMV surveillance for one year in all CMV positive patients with vasculitis.

P361

Severe fatigue and psychological morbidity in ANCA-associated vasculitis

Andrew McClean[1], Neil Basu[2], David Jones[3], Matthew Morgan[1], Jos Bosch[4,1], Lorraine Harper[1]

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Introduction: Patients with ANCA-associated vasculitis (AAV) report fatigue as a main debilitating symptom, but little systematic research has been done to assess its impact. We aimed to characterize the severity of this fatigue, and its influence on patients' well-being and psychological morbidity.

Methods: We recruited 151 patients with AAV in remission for at least 6 months, 68 CKD disease controls, and 81 healthy controls to this cross-sectional observational study. Participants completed a questionnaire comprising the Multi-dimensional Fatigue Index (MFI-20), and a number of other symptom rating scales including the Hospital Anxiety and Depression Scale (HADS).

Results: The AAV group reported more severe 'General Fatigue' than the CKD group (mean score (with SE) 14.27 (0.355) vs 12.87 (0.542), p=0.021), and similar scores across the other dimensions of fatigue. Both disease groups reported more severe fatigue than the healthy group (7.71 (0.481) for 'General Fatigue', p<.001 multivariate across all dimensions of fatigue). The mean scores of the AAV group are comparable to the norm levels in chronic fatigue syndrome (CFS), Sjögren's Syndrome, and cancer. Both disease groups also reported that fatigue is a major impairment to professional, family, and social life (p<.001 for all, compared to healthy controls). Moreover, 27% of AAV patients had clinically significant anxiety and/or depression (scores of >10 for anxiety or depression subscales of the HADS); this was comparable to the values found in the CKD group, and three-fold higher than in the healthy group (p<.001). Stepwise regression analysis showed that individual differences in fatigue explained differences in anxiety and depression, but not vice-versa, possibly suggesting a causal association.

Conclusions: Fatigue in AAV is comparable to the levels seen in CKD, CFS, Sjögren's Syndrome and cancer, and is associated with major role impairments. High levels of anxiety and depression are also seen in this group, possibly secondary to fatigue. This indicates the need for further research into the determinants and treatment of severe fatigue in AAV.

P362

Rituximab monotherapy (without cyclophosphamide) in ANCA associated vasculitis in patients with serum creatinine above and below 500 µmol/l

Noshaba Naz, Hiremath Jay, Neville Nicholas, Anindya Banerjee, Yaser Shah

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Introduction: There is limited data on using rituximab (without cyclophosphamide combination) as the primary immunosuppressive agent in ANCA associated vasculitis with serum creatinine > 354 µmol/l. RAVE excluded such patients; in RITUXIVAS patients received at least 2 doses of intravenous cyclophosphamide along with rituximab. We used rituximab as the main immunosuppressive agent (without cyclophosphamide combination) as induction therapy in 32 ANCA associated vasculitis patients including 13 patients with serum creatinine > 354µmol/l. We grouped our patients into a presenting creatinine of higher or less than 500µmol/l. Our aim was to investigate the renal outcome in these two groups in the first year of presentation and to identify rates of infection, relapse, malignancy and mortality between these groups.

Methods: We retrospectively assessed new ANCA associated vasculitis with acute renal failure. Patients were grouped into two based on their presenting serum creatinine. Group A with serum creatinine < 500µmol/l and Group B with serum creatinine >500µmol/l. Serum creatinine at 3, 6 and 12 months of presentation was compared with baseline serum creatinine. Incidence of infection, mortality, malignancy and relapse rate was also compared in these 2 groups at their first 12 months of treatment.

Results: All patients received IV methyl prednisolone followed by oral prednisolone with rituximab 375 mg m² weekly for 4 weeks. 11 (7 with serum creatinine >500 µmol/l) also received plasma exchange. Table 1 show a significant improvement in serum creatinine in both groups at 3, 6 and 12 months of presentation. Serum creatinine plateaued at 3 months in Group A but took more than 3 months in Group B suggesting severe ischemia and acute tubular necrosis in group B.

TABLE 1: Group A (Serum creatinine <500µmol/l), number=19						
Baseline creat µmol/l (iqr)	**Creat at 3 months (iqr)**	**Significance compared to baseline**	**Creat at 6 months (iqr)**	**Significance compared to baseline**	**Creat at 12 months (iqr)**	**Significance compared to baseline**
209(190)	**154(66)**	**0.09**	**15(189)**	**0.79**	**146(145)**	**0.94**
Group B (serum creatinine >500 µmol/l), number 13						
649(454)	**352(66)**	**0.002**	**294(180)**	**0.003**	**349(186)**	**0.006**

We also found no statistically significance difference in infection, relapse, mortality and malignancy rate in the 2 groups at their first year of rituximab therapy.

Conclusion: We concluded that rituximab was a very effective and well tolerated induction agent without cyclophosphamide combination in ANCA associated vasculitis irrespective of the level of renal failure.

P363

Use of rituximab (without cyclophosphamide) in pulmonary-renal syndrome secondary to anti-neutrophil cytoplasmic antibody-associated (ANCA) vasculitis

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Arrowe Park Hospital, Wirral, UK

Since the advent of the use of cyclophosphamide and corticosteroids in patients with ANCA-associated vasculitis the outlook for patients has dramatically improved. Pulmonary vasculitis is a rare but potentially lethal complication of ANCA associatedvasculitis but the response rate is 70-95% with steroid and cyclophosphamide based regime. Novel agents like rituximab showed similar renal outcome compared to cyclophosphamidein RAVE and RITUXIVAS but its role in patients with pulmonary vasculitisis less clear. There is also limited data of the use of rituximab without cyclophosphamide combination in ANCA vasculitis affecting lungs. Wehave used rituximab as a monotherapy (without cyclophosphamide) in six pulmonary-renal syndrome secondary to ANCA associated vasculitis. All of them also received 4 grams of intravenous methylprednislone followed by oral prednsilone for at least one year along with 5- 7 sessions of plasma exchange. None of them required any ventilator support. Mean age 51.6 (21-71) years. Five of them were PR3 positive. One died and the rest had excellent pulmonary and renal outcome. We highly recommend the use of rituximab without cyclophosphamide in pulmonray – renal syndrome secondary to ANCA associated vasculitis.

P364

Evidence of altered perception and reduced cardiovascular fitness causing severe fatigue in ANCA-associated vasculitis

Andrew McClean[1], Neil Basu[2], David Jones[3], Matthew Morgan[1], Jos Bosch[4,1], Lorraine Harper[1]

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Introduction: Up to 70% of people with ANCA-associated vasculitis (AAV) report severe fatigue, the main cause of reduced quality of life in this group. However, the underlying mechanisms are not understood.

Methods: We recruited 48 patients with AAV in remission and 41 matched healthy controls. Fatigue was measured using the Multidimensional Fatigue Index (MFI-20). The AAV group was divided into 'severely fatigued' and mildly fatigued' groups according to the 95th centile 'General Fatigue' score of the healthy group. Participants underwent a submaximal exercise test; cardiovascular fitness was assessed by estimated VO2max, and perception of exertion was assessed using the Borg scale. A DEXA scan was performed to assess muscle mass. Quadriceps muscle strength and voluntary muscle activation were measured by repeated maximal voluntary contractions (MVC) with super-imposed stimulation. Stamina was assessed with a sustained 50% MVC; super-imposed stimulations allowed assessment of muscular reserve at the point of subjective exhaustion.

Results: Median scores are given, with IQR. Fatigue scores were 17.5 [3] for the 'severely fatigued' group, 10 [6] for the 'mildly fatigued' group and 6 [4] for controls ($p<.001$). Comparing the 'severely fatigued' group to the healthy group revealed important differences in perception of exertion, as evidenced by Borg ratings during cardiovascular exercise (0.152 [0.181] vs 0.114 [0.0651], p=.032), reduced voluntary muscular activation (64.83% [29.19] vs 76.16% [19.51], p=.011), and early cessation of the endurance test (65.17s [51.65] vs 91.18 [51.43], p=.012) with greater muscular reserve at point of cessation (77.09% [27.43] vs 59.34 [22.98], p=.002). There was also a reduction in VO2max (23.918 [11.7] vs 32.115 [12.1], p=.017). There was no difference in muscle mass or strength. No significant differences were seen between the 'mildly fatigued' and healthy groups.

Conclusions: This evidence suggests that severe fatigue in AAV is dependent on altered perception of exertion as well as reduced cardiovascular capacity. Future strategies to improve fatigue should address both these mechanisms.

P365

Subclinical retinal vasculitis identified in patients with systemic small vessel vasculitis

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Introduction: This study aimed to assess whether wide-field fluorescein angiography is useful in patients with primary small vessel vasculitis to determine disease activity.

Methods: Between September 2010 and January 2012, consecutive patients under investigation for systemic vasculitis were assessed using slit lamp examination followed by fluorescein angiography with a Staurenghi lens to gain peripheral views of the retina for evidence of retinal vasculitis.

Results: Forty-six patients were assessed; when categorised by anti-neutrophil cytoplasmic antibody (ANCA) type, 5 of 12 patients positive for c-ANCA PR3 and 2 of 8 patients with p-ANCA-MPO had evidence of retinal vasculitis on retinal angiography. These changes were also seen in 2 of 5 patients with atypical p-ANCA and 3 of 17 ANCA negative patients. When categorised by diagnosis, 10 of 22 patients with a diagnosis of Wegener's granulomatosis and three of 15 patients who were under investigation for vasculitis but no confirmed diagnosis had features suggestive of retinal vasculitis on angiography. None of 4 patients with Churg Strass syndrome and none of 3 patients with rheumatoid arthritis associated vasculitis had evidence of retinal vasculitis. Only one patient had a diagnosis of microscopic polyangiitis and they had evidence of retinal vasculitis on angiography.

Discussion: These results show that 45% of our patients with Wegener's granulomatosis have evidence of subclinical retinal vasculitis. C-ANCA PR3 positivity was also associated with retinal vasculitis on angiography (42%). Fluorescein angiography is a minimally invasive test which allows us to directly visualise the retinal circulation. We believe that wide-field fluorescein angiography should be used as a tool in the diagnosis and management of small vessel vasculitis.

P366

ADAPTIV: A Delphi study to assess morbidity prevention and treatment in vasculitis

Nina Brown[1], David Tooth[2], Angela Summers[1], Michael Venning[1]

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Background: Vasculitis is a complex multi-system disorder that may be cared for in a variety of clinical settings. Increasing numbers of vasculitis patients are surviving the acute initial disease episode with adverse effects from disease damage and therapy creating challenges for the long- term management of this patient group.

Aim: The objective of this Delphi study was to create guidelines for the holistic management of the vasculitis patient, incorporating the areas of: disease monitoring, cardiovascular disease, bone health, infection, malignancy and fertility.

Methods: On behalf of the UK Vasculitis Rare Disease Working Group, a 3 round Delphi study was carried out using the 7comms Delphi software. The panel was comprised of experts from the field of vasculitis but also from the relevant areas outlined above. Panel members were invited to answer up to 27 questions covering the above areas of patient management. Responses created 275 statements to which participants were asked to rank their agreement/disagreement on a Likert scale. Statements reaching consensus (defined as 80% agreement) were considered for future guidelines.

Results: Seventy- one statements achieved consensus in Round 2 and will be considered for inclusion in the Vasculitis RDWG guidelines, incorporating areas such as: the role of primary/ secondary/patient-led care in vasculitis management, cardiovascular risk assessment and infection prophylaxis. The remainder of the statements will be discussed to achieve consensus in the final round of the Delphi, a round table discussion between the expert panel members.

Conclusions: Until clinical studies provide evidence for all aspects of vasculitis patient care, use of expert opinion is an acceptable alternative. Using Delphi methodology we have achieved consensus where previously there was considerable variability in practice. We anticipate publication of these guidelines in summer 2013, routine use of which should assist in improvement of quality of care of the vasculitis patient and subsequent reduction in morbidity and mortality.

Poster session

Wednesday 13th March

18:15 - 19:25

Clinical nephrology 2 : ANCA and GN

P367

Respiratory manifestations of anca-associated vasculitis

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Background: The prevalence of pulmonary manifestations of ANCA-associated vasculitis (AAV) is not well understood. This study assesses the prevalence of respiratory complications of AAV in patients presenting to a tertiary renal centre with primarily renal disease, not initially requiring dialysis; evaluates whether such complications are recognised and investigated appropriately, and examines the relationship between pulmonary vasculitis and mortality.

Methods: 58 patients with AAV were identified from the Chronic Renal Insufficiency Standards Implementation Study database, which is a prospective epidemiological study of patients with CKD stages 3-5, not requiring dialysis. Patients were identified as having AAV between 2000 and 2012. Presentation data was only available for 38 patients.

Results: A chest x-ray on presentation was available for 36 out of 38 patients, of which 16 (44.4%) had changes that could be associated with vasculitis. Only 31.3% of these were followed up with pulmonary function tests, a CT scan or respiratory review. 14 patients from the entire cohort of 58 had had a CT thorax during the course of their disease: 100% of these showed abnormalities, the most common being fibrosis (71.4%) and bronchiectasis (64.3%). 15 of 58 patients (25.9%) had confirmed pulmonary vasculitis, either as documented after respiratory review or as demonstrated by changes associated with vasculitis on a CT scan. There was no evidence of a link between pre-existing respiratory disease and this diagnosis (Fisher's Exact Test: $p=0.103$). The relationship between survival and pulmonary vasculitis was analysed using Cox-regression (correcting for age, smoking status, pre-existing respiratory disease and diabetes) and was not found to be statistically significant ($p=0.077$), although there was a trend towards increased mortality in those with pulmonary vasculitis.

Conclusions: Pulmonary manifestations of ANCA-associated vasculitis occurred in a significant proportion of patients. Only a small proportion of patients had had thorough respiratory investigations, even after an abnormal chest x-ray, suggesting that the pulmonary manifestations of AAV may be under-diagnosed.

P368

A survey of induction therapy for ANCA vasculitis in the UK

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Introduction: Recent trials have suggested that pulsed cyclophosphamide and Rituximab are alternatives to oral cyclophosphamide for induction therapy in ANCA vasculitis. Between December 2011 and June 2012 a survey on preferred induction therapy for a first presentation of ANCA vasculitis was sent to all 74 main UK renal units. A follow up second survey was sent to determine what therapy was used for male and female patients of childbearing potential.

Results: Responses were received from 57 units (77%). 25 units used daily oral cyclophosphamide, 5 used pulsed cyclophosphamide for 3 months, 4 used pulsed cyclophosphamide for 6 months (dosed according to the CYCLOPs trial). 9 units used cyclophosphamide but the dosing schedule varied depending on individual patient features, and a further 5 depended on individual consultant preference. 7 units gave Rituximab or cyclophosphamide depending on individual patient features. 2 replied as 'other'. In response to the second survey, replies were received from 41 units, and results are given in the following sequence in each case: (1) male patients of childbearing potential, (2) female patients of childbearing potential and (3) patients in whom fertility is not an issue. The results showed that 18;14;20 would use 3 months of daily oral cyclophosphamide, 7;6;8 would use 3 months of pulsed cyclophosphamide therapy, 2;1;3 would use 6 months of pulsed therapy, 2;2;4 would use a cyclophosphamide schedule but this varied according to patient features. 4;4;4 would use a cyclophosphamide schedule but this varied according to consultant choice. 1;3;0 would use Rituximab, and 4;7;1 would use cyclophosphamide or Rituximab depending on patient characteristics, and 3;4;1 units replied as 'other'.

Conclusion: 3 months of daily oral cyclophosphamide remains the overall preferred treatment for all patient groups in the UK. There is a tendency to limit cyclophosphamide use in female patients of childbearing age. These results highlight is a wide variation in practice amongst UK renal units which reflects the uncertainty regarding the best treatment for ANCA vasculitis.

P369

Induction treatment of ANCA associated vasculitis with a single dose of Rituximab

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Introduction: Rituximab is effective in inducing remission in ANCA-associated vasculitis (AAV), with randomised evidence to support its use as 4 infusions of 375mg/m^2 (the conventional lymphoma dosing schedule). We questioned the need for repeat dosing (as B-cell depletion (BCD) occurs rapidly after the first dose) and adopted a standard single-dose protocol of 375mg/m^2 to treat active AAV.

Methods: All consecutive cases with newly diagnosed or relapsing AAV for whom conventional immunosuppression was contraindicated/ineffective were enrolled. All were Rituximab naïve and 7 (37%) were on additional immunosuppression at the time of Rituximab treatment. Circulating CD19 B-cells and clinical and serological markers of disease activity were recorded at regular intervals. Complete remission (CR) was defined as absence of clinical features of AAV with prednisolone dose <10mg/day.

Results: Nineteen patients were included, 17(89%) with generalised disease and 2(11%) with severe disease (creatinine level >500μM). All but 1(5.3%) patient achieved satisfactory BCD (<0.005 cells/uL) after a median of 13 days. 3-month BCD probability was 92%. Median time to CR following a single dose of Rituximab was 38 days and the three-month probability of CR was 80% Median time to B-cell repopulation was 9.5 months, and to disease relapse/re-dose was 27 months. Use of this single-dose protocol saved an estimated £4534/ patient compared to a 4x375mg/m^2 dosing schedule.

Discussion: Our single centre experience suggests that a single dose of Rituximab of 375mg/m^2 is a reasonable, and more cost effective, therapy for inducing remission in patients with AAV who have non-organ threatening disease.

P370

A cohort study of mycophenolate mofetil for induction and maintenance treatment of lupus nephritis with long term follow up

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Introduction: Recent EULAR and ACR guidelines endorse MMF as an alternative to cyclophosphamide (CYP) for treatment of lupus nephritis (LN) class 3-5. Several studies have compared MMF to CYP, primarily examining shorter term outcomes. Clinical experience with longer term outcomes remains more extensive with cyclophosphamide. This retrospective cohort study examined the efficacy of MMF in LN patients at a single centre over an extended period. *Methods* Inclusion criteria were 1) first episode of biopsy proven LN (ISN/RPS class 3-5), diagnosed after 1993; 2) clinical data available; 3) No prior MMF or CYP treatment <1 year before diagnostic biopsy; 4) No biologic therapy. Cohorts were defined as MMF or non-MMF (combinations of CYP, steroid, azathioprine and ciclosporin) regimes. Primary outcome: reduction of proteinuria (<0.5g/24hr or ACR<30) with stable creatinine (normal or <110% baseline) without treatment failure. Secondary measures: serological improvement, steroid dose and outcomes irrespective of treatment failure between groups (intention to treat). *Results* 92 patients enrolled, 46 MMF, 46 non-MMF. Median follow-up was 5 years. Ethnicity and biopsy class were comparable between groups. Primary outcome was achieved by 74% and 49% for MMF and non-MMF groups respectively (p=0.0259). Statistically different results were not seen for serology variables (dsDNA, C3, C4). Achievement of prednisolone dose ≤10mg was 82% and 43% in MMF and non-MMF cohorts respectively (p=0.0003). A greater proportion of MMF patients achieved and maintained the primary outcome over 5 years. MMF patients required consistently lower prednisolone doses. *Discussion* MMF was more effective at inducing and maintaining remission up to 5 years after LN diagnosis. Prednisolone doses were lower in MMF group.

P371

Capillary dilatation and congestion: a novel finding on renal biopsy in HIV patients

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Introduction: Existing guidelines use low GFR and heavy proteinuria as criteria to indicate when a renal biopsy might be performed in HIV patients. Tenofovir associated renal impairment has prompted more referrals of HIV patients with good renal function but persistent microscopic haematuria for evaluation. Renal biopsies were performed in these patients to help HIV clinicians evaluate the potential risks and benefits of tenofovir use.

Methods: Between June 2011 and November 2012 13 HIV patients with persistent microscopic haematuria underwent renal biopsy. Renal tissue was put into formaldehyde immediately and fixed for 24 hours before routine processing for H+E staining and immunohistochemistry on paraffin sections. CT and/or MR renogram was performed in all patients subsequently.

Results: At the time of renal biopsy HIV virus was undetectable in 9 patients, CD4 count was normal in 9 patients and 2 patients had not started antiretroviral therapy. The average GFR was 76 ml/min (range 48 - >90 ml/min). Histopathological examination showed mild to severe glomerular and peritubular capillary dilatation and congestion in all cases. Nine patients showed additional tubular changes (ATN) and 2 patients interstitial change (oedema, chronic inflammation or fibrosis). One patient with GFR <60 ml/min also had features of HIVAN. CT and MR renogram did not show any abnormality to account for these changes.

Discussion: Capillary dilatation and congestion is a consistent finding in patients with HIV and microscopic haematuria. This appears specific for HIV infection as 2 patients were pre-treatment. Hepatitis B and and Hepatitis C renal biopsies processed in the same way do not show these features. It is not clear whether capillary congestion is a risk factor for renal impairment with tenofovir use or a predictor of high cardiovascular risk and merits further investigation. Nephrologists should consider a screening HIV test for patients with persistent microscopic haematuria when a renal biopsy is not considered necessary.

P372

Intravenous cyclophosphamide is an effective therapy for nephrotic idiopathic membranous nephropathy

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Introduction: Idiopathic membranous nephropathy (IMN) is the commonest cause of nephrotic syndrome amongst UK adults. Data on the use of intravenous (IV) cyclophosphmide is limited and conflicting, with some authors reporting no benefit. For the past few years, our centre has used an IV cyclophosphamide and oral prednisolone regimen for IMN, here we report the outcomes.

Methods: We performed a retrospective analysis of all patients diagnosed with IMN from Jan 2006 to Jan 2011. Patients with significant nephrotic syndrome (albumin <30, volume overload and 24h urinary protein >4g) were identified. Within this cohort 18 were treated with standard medical care (ACE-inhibitor /ARB/diuretic/BP control),17 were treated with 3 weekly pulse IV cyclophosphamide and prednisolone (total 6 months therapy). At baseline, there was no difference between groups in terms of serum albumin (p=0.71), proteinuria (p=0.28), age (p=0.76) and gender (p=0.3). There was a significant difference in eGFR at the time of diagnosis in untreated and treated groups (mean eGFR 79.8ml/min vs. 43.5ml/min, respectively, P=0.0004). Median time from biopsy to treatment was 5.39 months. Use of Diuretics/ACE inhibitors/ARBs were similar in both groups. The follow up period was 18 months.

Results: At 18 months, the mean increase in eGFR was 33% in the treated group, whilst in the untreated group eGFR decreased with a mean decrease of 28% over the same time period. By 18 months, serum albumin returned to normal in 86% of the treated group (accompanied by a fall in proteinuria), whilst only 18% of the untreated group had albumin in the normal range by 18 months. In terms of side effects, 3 patients suffered leucopenia necessitating dose reduction, 2 patients were diagnosed with pneumonia which responded to antibiotics, and 1 patient developed herpes zoster.

Conclusion: Our study has demonstrated that in the short to medium term, IV cyclophosphamide combined with regular steroids for 6 months is an effective treatment strategy for treating nephrotic syndrome due to IMN.

P373

Focal necrotizing (FNGN) and crescentic glomerulonephritis (CGN) in patients presenting with normal serum creatinine

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Background: FNGN and CGN usually present as rapidly progressive glomerulonephritis and have poor prognosis if left untreated. We aimed to establish the frequency and outcomes of patients presenting with FNGN/CGN and normal serum creatinine at our centre. **Methods:** We conducted a retrospective review (1995-2011) of all adult patients who presented with native renal biopsy proven FNGN/CGN and normal serum creatinine (<120micromol/l). **Results:** A total of 38 patients were identified, median age 57 years (range 17-78), 29% male, median 14 glomeruli per biopsy (4-33), with 32% (4-100%) of glomeruli affected by necrosis/crescents. All patients received immunosuppression in accordance with local protocols at time of biopsy. Median duration of follow-up was 45 months (2-184). Clinical features and outcomes summarised in table below. 2 patients progressed to ESRF (both secondary to lupus nephritis, at 21 & 29 months) and 4 patients died during follow-up (at 2, 12, 96 & 122 months). **Conclusions:** FNGN/CGN may occasionally present in patients with normal serum creatinine. Low threshold of clinical suspicion, with prompt biopsy and early initiation of treatment may prevent irreversible kidney damage and improve long-term outcomes in these patients.

Diagnosis	**Number of cases (%)**		**% affected glomeruli**
Pauci-immune GN	28 (74%)		32% (4-100%)
Lupus Nephritis	7 (18%)		17% (4-50%)
Anti-GBM disease	2 (5%)		36% (26-47%)
IgA Nephropathy	1 (3%)		50%
Biochemistry	**At Biopsy**	**At 1 year***	**At Last Follow-up***
Creatinine (umol/l)	84.00 (52-115)	82 (58-145)	77.0 (57-107)
Albumin (g/dl)	29.0 (10-40)	38 (30-46)	37.0 (22-45)
uPCR (mg/mmol)	71.2 (0-681)	23 (0-272)	15.0 (0-238)

Results expressed as median (range). *Censored for ESRF/Death.

P374

Tacrolimus is an effective steroid sparing treatment for lupus nephritis in pregnancy

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Background: Flares of lupus nephritis (LN) in pregnancy increase morbidity and mortality for mother and baby. Treatment is challenging as several drug options are teratogenic. Steroids alone are unlikely to control disease activity and are associated with increased pre-term delivery, sepsis and gestational diabetes. Safety and efficacy of tacrolimus (Tac) in pregnancy has been established in renal transplant patients but data on treating LN is limited. We report the largest case series to date where Tac was used to either treat LN flare or maintain stable disease in pregnancy.

Methods: 9 women entered pregnancy on Tac or had Tac added for LN flare. Tac dosed to trough levels of 5-8ng/ml. Remission- Complete (CR): urine PCR <50mg/mmol; Partial (PR): PCR non-nephrotic + >50% fall.

Results:

	Class LN	Gestation at Flare (weeks)	Gestation Tac started (weeks)	Peak Urine PCR at Flare & Time to Remission	Gestation at Delivery (weeks)	Birth Weight (g)
1	IV-G (A/C)	18	18	PCR – 1514, PR 32/40, CR 5/12 post-partum	37	2476
2	IV-G (C)	8	30	PCR – 384, PR 1/12 post-partum, CR 8/12 post-partum	37	2988
3	V	No Flare	Pre-conception	Mean PCR <20	39	3460
4	IV-G (A/C)	No flare	Pre-conception	Mean PCR 86	36	2512
5	IV	8	8	PCR – 602, CR 3/12 post-partum	30	1130
6	V	10	10	PCR – 769, PR 19/40, CR 30/40	38	3320
7	IV-G (C)	8	20	PCR – 570, PR 1/12 post-partum	35	2912
8	IV-G (A/C)	No flare	Pre-conception	Mean PCR 196, CR 12/12 post-partum	39	2786
9	V	12	21	PCR– 1116, PR 6/12 post-partum, CR 12/12 post-partum	33	1400

Renal outcomes: 3 patients on Tac prior to conception remained stable through pregnancy with no flare. All 6 patients who had LN flare in pregnancy achieved partial or complete remission after starting tacrolimus regardless of their stage of CKD entering pregnancy. Serum creatinine remained stable in pregnancy or returned to pre-pregnancy baseline within 6 months post-partum in all patients.

Obstetric outcomes: 4 spontaneous vaginal deliveries, 2 elective and 3 emergency caesarean sections. 9 live births.

Conclusions: Tac was well tolerated and allowed avoidance of either initiating or increasing steroids. Proteinuria remained stable or reduced in all cases. We propose Tac as either adjuvant or alternative therapy to steroids in treating LN flare or maintaining stable disease.

P375

Short synacthen test: outcome in patients with glomerulonephritis on long term steroids

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Background: Although potency, dose and duration of steroid use are important predictors of presence of hypothalamic-pituitary axis suppression, the preferred method to assess adrenocortical function is the response to synthetic ACTH. Short synacthen test is widely used for assessing adrenal function prior to weaning off long term steroids.

Aim: In our regional renal vasculitis clinic, we see a large population of renal patients with glomerulonephritides requiring long term immunosuppression. We specifically looked at our practice of performing short synacthen test before completely stopping steroids in this population.

Method: We retrospectively analysed data obtained from biochemistry database at Wythenshawe Hospital along with patients' case notes. We gathered data on 50 patients who had one or subsequent short synacthen test between 1993 and 2007. These patients were in remission and had been maintained at 5 mg daily or less of Prednisolone for some weeks or months. We divided them into those that had been successfully weaned, those that are still on steroids and those that were back on steroids after complete withdrawal.

Results: Time taken to completely come off steroids ranges from 3 months to 30 months. Three different regimes are being used for tapering the dose-1) Reduction by 1 mg every month 2) Missing dose a day and subsequently longer in a week 3) Alternate day dosing and reduction. Relapse or presence of active disease has been the main reason for prolonged continuation of steroids. There was no documented evidence of major complication in the form of addisonian crisis when steroids were weaned after adequate cortisol response to synacthen. Most patients have required 60 min test to confirm adequate response.

Poster session

Thursday 14th March

12:00 - 13:00

Clinical nephrology 3

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Initial steroid sensitivity is a high risk predictor for focal segmental glomerulosclerosis recurrence post-transplant

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Introduction: Recurrence of FSGS post-transplant is high in the paediatric population with rates of up to 50%. A putative circulating factor is thought to be a major player in FSGS recurrence. Current evidence shows that genetic mutations decrease the risk of post-transplant recurrence, while Caucasian race, progression to ESRF within 3 years and history of recurrence with previous transplants indicate a greater risk. Several other risk factors have been studied but with no definitive results as to their role in predicting recurrence.

Methods: We reviewed the clinical characteristics of consecutively transplanted FSGS patients with and without recurrence and compared: age at diagnosis, initial steroid sensitivity (at presentation), time to end stage renal failure, age at transplant, early versus late recurrence, genetic results, family history, presence/absence of native kidneys and other phenotypic features.

Results: 24 children with FSGS were transplanted in a 15 year period, of which 11 children suffered from recurrence. Treatment with intensive plasma exchange and methylprednisolone resulted in 5 patients achieving full remission. 6 patients were relatively resistant to plasma exchange and required long term plasma exchange. Recurrence risk was significantly higher and occurred in all patients who showed initial steroid sensitivity ($n = 6$, $p=0.0046$, $OR = 29.6$). Those with initial steroid sensitivity did not have any genetic or extra-renal abnormalities or family history. Analysis of risk factors between those who went into remission versus those with long term recurrence did not reveal any differences in age at diagnosis, age at transplant or time to ESRF.

Discussion: Initial steroid sensitivity has not been previously studied as a predictive factor for recurrence, and may signify the presence of an immunologically derived circulating factor. We conclude that initial steroid sensitivity is a marker for high recurrence risk, with the added implication that this is an early indicator of non-genetic forms of FSGS.

P377

Fibrillary glomerulonephritis: a clinico-pathologic series with glomerular proteomics

Eoin Dinneen[1,2], Janet Gilbertson[2], Nigel Rendell[2], Graham Taylor[2], Aine Burns[3], Paul Bass[1], Helen Lachmann[2]

[1]Department of Histopathology, Royal Free Hospital London, London, UK, [2]National Amyloidosis Centre, UCL Medical School, Royal Free Campus, London, UK, [3]Department of Nephroloogy, Royal Free Hospital London, London, UK

Fribrillary Glomerulonephritis (FGN) is a rare primary glomerular disease characterized by EM features of straight, non-branching, randomly arranged fibrils (ranging from 10 – 30nm in diameter) deposited diffusely in the glomerular basement membrane and the mesangium. Here we report the first UK based case series. The characteristics of 13 patients with FGN referred to a single institution are reviewed. The most common light microscopy pattern was mesangial proliferative/sclerosing followed by membranoproliferative glomerulonephritis. At the time of biopsy, mean age was 48 years (range 27-75 years). Mean proteinuria at biopsy was 5.91g/24 h (range 0.5 – 11g). Mean serum creatinine at biopsy was 174 µmol/l (range 49 – 426 µmol/l), and 62% of patients had renal insufficiency. Mean follow-up period was 45.4 months. Four patients progressed to end stage renal failure, another 4 have chronic kidney disease stage 4, 3 patients have progressive renal disease and 2 patients had partial remission of disease. Five patients' renal biopsy tissue was obtained for laser microdissection (LMD) and tandem mass spectrometry (MS). Glomerular proteomics demonstrated universal complement deposition, presence of immunoglobulins in 4 of 5 cases, and proteins associated with renal amyloidosis in 2 patients. Glomerular proteomics using LMD and MS has not previously been reported in the literature. In conclusion, the clinico-pathologic series demonstrates findings, which whilst entirely consistent with previous studies on FGN, emphasise the high degree of heterogeneity in the presentation, the histological features, the co-morbid profile and the prognosis of patients with FGN. Now, for the first time, there is evidence to suggest a heterogeneous glomerular proteomic profile also. Taken together, this suggests that the histological features FGN results from a spectrum of different pathological pathways which all result in protein fibrillogenesis within the glomerulus.

P378

The role of renal biopsy in diabetic adults with renal disease

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Introduction: The diagnosis of diabetic nephropathy is generally made on clinical grounds. A renal biopsy with histological confirmation of renal involvement is sometimes needed to rule out a non-diabetic etiology where there is doubt.

Objectives: We investigated the spectrum of non-diabetic renal disease in diabetic adults, as revealed by renal biopsies.

Methods: We retrospectively evaluated all diabetic patients who underwent renal biopsies over a 10 year period in our centre (n=65). Indications for biopsy included nephrotic range proteinuria, significant microscopic hematuria, or rapidly declining renal function.

Results: Thirty-nine of 65 (60%) biopsies were diagnostic of non-diabetic renal disease: 9 interstitial nephritis, 5 rapidly progressive (crescentic) glomerulonephritis, 5 membranous nephopathy, 3 focal segmental glomerulosclerosis, 3 IgA nephropathy, 3 acute tubular necrosis, 2 minimal change nephropathy, 2 ischaemic changes, 1 mesangiocapillary glomerulonephritis type I, 1 amyloidosis, 1 oxalate nephropathy, 1 myeloma cast nephropathy, 1 fibrillary glomerulonephritis, 1 collagenofibrotic glomerulopathy, and 1 hemolytic uremic syndrome. Twenty-four (36.9%) biopsies revealed isolated diabetic nephropathy. The remaining 2 (3.1%) patients had normal findings. The patients histologically diagnosed with concurrent non-diabetic nephropathy were older than those with isolated diabetic nephropathy [62 ± 12.4 years vs. 53 ± 14.9 years; P=0.015] and required alterations in therapeutic management based on biopsy findings. There was no statistical difference in the number of patients that eventually required renal replacement therapy between the two groups.

Conclusion: We found significant non-diabetic renal disease in patients with diabetes mellitus undergoing renal biopsy. The findings suggest that early and accurate detection of concurrent non-diabetic renal disease is important for diabetic patients with unusual clinical presentation since prognosis and treatment may vary according to the underlying cause.

P379

Medical ionising radiation exposure in patients on renal replacement therapy – a prospective multicentre study

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Introduction: The aim of this multi-centre prosepctive study was to quantify the ionising radiation exposure in a large cohort of prevalent and incident patients on renal replacement therapy (RRT) in all of the renal centres in the West of Scotland and translate this in to an estimated excess cancer risk using existing reference data.

Method: For each patient on RRT during the period 01/07/2010 - 02/03/2012 the number of days of exposure to RRT and the number and type of radiological procedure during that period of exposure were calculated. The radiation dose in mSv for each procedure was calculated from published reference tables.

Results: 2833 patients with median follow up of 610 days (IQR 610-610) had median of 4 radiological procedures (IQR 1-9) with median ionising radiation exposure of 0.6mSv per patient per year (IQR 0-6.3) translating in to a median of 0.03 excess future fatal cancers per 1000 patients per year of radiation exposure [IQR 0.0 – 0.03]. The largest contributors to radiation exposure were CT scans and haemodialysis access related procedures comprising 43% and 28% of the radiation exposure respectively. There was wide variation in exposure: patients on haemodialysis (n=1394) and peritoneal dialysis (n=188) had significantly more exposure than patients with a transplant (n=1251) (median 4.1 v 1.6 v 0.0 mSv/patient/year respectively; $p<0.0001$). By multivariate analysis RRT modality, increasing age, male sex, new RRT patients and shorter duration of RRT were all independent predictors of the highest quartile of ionising radiation exposure. Haemodialysis patients>65 years starting renal replacement therapy (n= 170) had median ionising radiation exposure of 6.6mSv/patient/year (IQR 2.5 -12.57) translating to 0.3 excess future cancers per 1000 patients.

Discussion: Patients on RRT are subjected to large numbers of radiological studies. The ionising radiation exposure for most appears modest but nephrologists should be aware that a small number of patients have very high exposure.

P380

A rare cause of infant hypertension

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We report the case of a 10 week old baby who presented with vomiting and was found to be hypertensive on examination. Investigations revealed an alkalosis and hyponatraemia. Imaging demonstrated a mass adjacent to the right renal hilum. The blood pressure was controlled with anti-hypertensives and the mass was removed surgically. Histology revealed the mass to be aneurysmal vascular tissue which was not in continuity with any vessel. Given the location however it was felt that this tissue had arisen from the renal vessels. Although hypertension secondary to compromise of the renal vessels, either from external compression, for example by a tumour, or from an aneurysm of the renal vessel itself, has been well reported we believe that this scenario of external compression from aneurysmal vascular tissue has not been previously described.

In addition this case highlights the difficulties in measuring blood pressure in infants and serves of a reminder of the fact that a common paediatric presentation can have a rare underlying cause.

P381

Renal biopsy training and sample adequacy – results of audit and re-audit at a uk teaching hospital

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Introduction: Renal biopsy is an essential competency of UK nephrology specialty training curriculum. Sample adequacy is well recognised to be dependent on the operator undertaking this procedure. In our unit more biopsies are performed by radiologists. A series of inadequate biopsies triggered a retrospective audit in 2011 which recommended an increase in renal biopsy training nephrologists, a minimum of 2 cores and a re-audit in 2012.

Methods and data: Renal histopathology report is taken as audit standard for sample adequacy. Histopathology provided data of all renal biopsies between January to June 2012(as previously, November 2010 to April 2011). Local results (IT) system used to identify operator, number of cores and sample adequacy. Biopsies done for renal tumours and by surgeons were excluded. Only US guided renal biopsies included and divided into 2 operator groups-Radiologist (Rad) and Nephrologist(Nep).Number of cores grouped as 1 core or ≥2 cores. Adequacy compared for each sample as inadequate, marginal or adequate.

Results: 84 US guided biopsies were performed, 45 native and 39 transplant (2011; 90=47:43). More biopsies were performed by nephrologists in 2012, (25% v 18%) as recommended (Fig.1).Overall combined ≥2 cores rate was higher at 77.4 %(60%) (Fig 2). Inadequacy rate improved to 9.5 %(14%) but with operator split 5 %(Rad) and 24%(Nep) (Fig 3).Compared to 1 core, adequacy was higher when ≥2 cores obtained at 93.4%Vs 88%(Rad) and 77.7% Vs 66.6 (Nep)(Fig 4).

Discussion: Despite more biopsies with ≥2 cores 85.7%(74.6%),nephrologists adequacy rate was lower than the radiologist 76% Vs 95%.This emphasizes poor technique and an on-going gap in the renal biopsy training of the nephrologists. This could be due to far less and infrequent number of procedures performed. Formal education and training in the use of available ultrasound machine along with 'nephrologist first' policy for most renal biopsies may help improve renal biopsy training and sample adequacy if renal biopsy is to remain an essential competency for renal trainees.

P382

Nephrotic syndrome in transition

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Nephrotic syndrome (NS) affects both the adult and paediatric population with significant morbidity and mortality.The majority of children affected outgrow their disease before adulthood but in 5% of cases, the disease persists and follows a relapsing-remitting course. We have created a specialised transition clinic for young people and their families with NS,to our knowledge unique in the UK, to improve the care of this challenging group of patients as they transfer from the paediatric environment to an adult kidney centre. The clinic numbers 46 young adults referred principally form Great Ormond Street Hospital for Children. Treatment options for this group of patients are non-specifically immunosuppressive with often prolonged use of steroids. Rituximab (RTX) a monoclonal anti-CD20 lymphocyte antibody, has been used to induce remission in children and young adults with NS with variable results. We selected a cohort of 5 males (age range 20-33) with biopsy-proven minimal change disease, to investigate the hypothesis that RTX can prolong steroid-free remission. All patients had at least one relapse/year and over the last 5 years the number of relapses/patient ranged between 3 to 7.All had received cyclophosphamide, mycophenolate mofetil and/or levimasole. Prednisolone exposure ranged between 8-30mg/day and the steroid-free period over the last 5 years ranged between 3-10monthsl. All were currently on a calcineurin inhibitor (CNI) with an average CNI exposure of 15yrs. Average EDTA GFR was 64ml/min (range 57-78), SBP 148mmHg (126-185) and DBP 77mmHg (60-92). 4 out of 5 patients were on an ACE inhibitor and 3 out of 5 required a second agent to control their blood pressure.To date, 3 out of the 5 patients have received 2 doses of RTX. Steroids have been withdrawn in all patients. They all remain in remission, 12, 4 and 3 months later respectively. Our findings demonstrate the significant morbidity associated with frequently relapsing, steroid-dependent nephrotic syndrome and the potential for Rituximab to be used as a therapeutic agent to maintain this group of patients in a steroid-free remission.

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Retrospective audit of 10 years investigation of familial vesico-ureteric reflux in infants

Rachel Hubbard[2,1], Nick Collins[2,3], Dave Matthew[2,3], Laura Baines[1], Heather Lambert[2,1]

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Vesico-ureteric reflux (VUR) is known to be a familial inherited condition, but screening asymptomatic individuals is controversial. In Newcastle, families with an index case with proven VUR or evidence of reflux nephropathy on imaging are counselled about the inherited nature and the increased risk of urinary tract infection and association with scarring and reflux nephropathy. Contrast micturating cystourethrogram (MCUG) is offered for newborns and infants. In addition, carers are informed about the generalised and non-specific nature of symptoms of UTI in young babies and advised to seek early detection & treatment. The aim of this audit was to look at the outcome of screening infants by contrast MCUG.

Reports on MCUGs done in infants in one hospital in the past ten years were examined and additional clinical information was inspected where necessary. Of the 1738 MCUGs performed, 207 were requested for the indication of family history of VUR or reflux nephropathy. Two further MCUGs were requested but not actually performed. 42 cases with VUR were found: 2 (5%) with grade 1, 27 (64%) with grade 2, 8 (19%) with grade 3 and 5 (12%) with grade 4.

The initial findings of this audit illustrate that 21% of asymptomatic infants screened for VUR of a family history in a first degree relative themselves have VUR. There is evidence from animal work and clinical case series that delayed treatment of UTI in the presence of VUR is associated with an increased risk of acquired renal damage (scarring). Thus the purpose of detecting VUR is to enable resources and attention to be focussed on these high-risk infants for rapid diagnosis and urgent treatment of UTIs with the aim of preventing acquired scarring. This involves education and awareness, open access to phase contrast microscopy service on the children's assessment unit and use of prophylactic antibiotics. The next phase is to analyse long-term outcome data.

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Use of an electronic alert system for identification of diabetic patients with nephropathy and declining renal function

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Introduction: Approximately 40% of patients with diabetes mellitus develop nephropathy. Early identification of patients with an estimated glomerular filtration rate (eGFR) below a specified value would have significant benefits in early recognition and subsequent management in the form of medication changes and plans for renal replacement therapy (RRT). North Middlesex Hospital has 21 consultant and nurse-led diabetes clinics per week. We found there were patients with declining renal function who were not being identified to the Renal team.

Methods: We set up an electronic alert system whereby clinic patients with an eGFR < 50 not known to Nephrology were identified by the biochemistry lab and notified to, and discussed at, a monthly Renal/Diabetes multidisciplinary team meeting. We concentrated on those patients with an eGFR < 30 or with rapidly declining function. This is a retrospective study of 145 patients discussed between November 2010 and November 2011.

Results: 1. Demographics: [R – retinopathy, N – neuropathy IHD – ischaemic heart disease]

eGFR	Number	Male (%)	Female (%)	R (%)	N (%)	IHD (%)
< 15	3	33	67	67	67	33
15- 30	106	54	45	90	79	22
>30	36	64	34	89	83	50

2. Outcomes: [LCC – low clearance clinic, MCM – maximum conservative management]

eGFR	Referred to LCC (%)	Referred for RRT (%)	Decided for MCM (%)	Medication changed (%)
< 15	0	100	0	33
15- 30	45	6	7	36
>30	8	3	8	53

Discussion: This electronic alert system has enabled us to identify diabetic patients with declining renal function at an earlier point where intervention may delay progression of disease or allow plans for RRT to be made. We feel that this is a useful model which could be expanded further.

Poster session

Friday 15th March

11:30 - 12:30

Clinical nephrology 4

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Benefits of resistance exercise training in CKD: A randomised controlled trial

Emma Watson[1], Neil Greening[2], Jaspreet Aulakh[1], Hannah Young[2], Maurice Dungey[3], James Burton[2], Jonathan Barratt[1], Alice Smith[2,1]

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CKD patients suffer from muscle wasting due to uraemia, acidosis and chronic inflammation. This can limit their ability to take aerobic exercise which has proven cardiovascular benefits in this very high risk population. Progressive resistance exercise (PRE) is an effective way to increase muscle mass in the general population, but its ability to overcome the catabolic influences associated with pre-dialysis CKD has not been properly studied. The aim of this randomised controlled trial was to investigate the effect of 8 weeks PRE in CKD stage 3b-4.

18 patients completed the PRT programme, consisting of 3 sets of 10-12 leg extensions at 70% 1 repetition maximum, 3 times a week for 8 weeks. 15 controls continued with usual physical activity. Assessments of Rectus Femoris Anatomical Cross-Sectional Area (ACSA) by ultrasonography, isokinetic muscle strength by dynamometry, exercise capacity by endurance shuttle walk test (ESWT) and perception of uraemic symptoms using the Leicester Uraemic Symptom Score were made before and after the 8 week period.

No changes were seen in the controls for any outcome measure, except for a decrease in ESWT performance (P=0.03). 8 weeks PRE resulted in significant increases in ACSA (6.03±2.1 vs 6.6±2.2cm^2 P=0.002), knee extensor strength (95.6±8.2 vs 108.9±8.5nM, p<0.001), and ESWT performance (9.7±7.7 vs 12.4±8.0min P=0.03). The patient-reported impact of uraemic symptoms was also reduced after the exercise programme (P=0.001)

In conclusion, PRE provided significant gains in skeletal muscle ACSA and strength, showing that appropriate exercise effectively overcomes the catabolic influences associated with CKD. Although aerobic training was not undertaken, walking performance also significantly improved, indicating that muscle wasting and weakness are an important limiting factor in the physical capacity of CKD patients. Together with the improved uraemic symptom scores, this highlights the necessity of including resistance training as part of a rehabilitation programme to manage cardiovascular risk and maintain quality of life in CKD.

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Prediction and assessment of response to renal artery revascularization with dynamic contrast-enhanced MRI: a pilot study

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Revascularization in atherosclerotic renal artery disease is not broadly supported, due to the associated risks and the fact that only 20-30% of patients derive net benefit. There is a need for identifying the patients that are likely to benefit, but current prognostic indices are limited by failure to detect recoverable intra-renal parenchymal injury distal to the stenosis. We aimed to assess the potential of dynamic contrast-enhanced MRI (DCE-MRI) measurements of renal function and perfusion to predict and evaluate functional outcome after renal artery revascularization in humans.

Methods: 16 patients with renal artery stenosis underwent DCE-MRI and radioisotope measurement of single-kidney glomerular filtration rate (SK-GFR) at baseline, and 4 months after revascularization. Quantitative analysis of DCE-MRI also produced a measurement of SK-GFR, and additional measures of perfusion (blood flow, blood volume) and function (extraction fraction, tubular MTT, functional volume). SK-GFR values of DCE-MRI and radioisotopes (n=64) of all kidneys (n=32) were compared by Bland-Altman analysis. Stented kidneys (n=23) were divided into three response groups on the basis of changes in isotope SK-GFR: improved (n=5), stable (n=14), deteriorated (n=4). Statistical significance was defined at $p<0.05$.

Table 1. Pre-procedure	Deteriorate	Stable	Improve
Blood Flow(ml/min/100ml)	219 ± 62	208 ± 97	209 ± 122
Blood Volume (ml/100ml)	35 ± 4.2	40 ± 10	44 ± 8.8
Extraction Fraction (%)	9.5 ± 4.3	9.5 ± 3.3*	6.1 ± 2.7
Tubular MTT (min)	2.3 ± 0.8	2.8 ± 0.6	3.9 ± 1.5
Functional Volume (ml)	174 + 51	196 + 96	143 + 57
(DCE-MRI) SK-GFR (ml/min)	22 ± 15	21 ± 15	11 ± 8.3
(Isotope) SK-GFR (ml/min)	24 ± 17	24 ± 15*	12 ± 8.9

Results: There was no significant difference between SK-GFR values obtained from DCE-MRI or radioisotopes, and both showed the same trends in all groups. Kidneys that improved renal function had lower extraction fraction; higher blood volume and lower SK-GFR at baseline, but these trends were not significant. Post procedure blood flow and -volume were increased, but only the latter showed significance. Improved kidneys had increased functional volume whereas deteriorated kidneys had reduced functional volume and extraction fraction.

Discussion: DCE-MRI has the potential to replace radioisotope SK-GFR for planning and follow-up of renal artery revascularisation, and may improve patient selection through the additional information on vascularity. Specifically, this pilot study suggests that well-vascularised kidneys with low extraction fractions are most likely to benefit. The result agrees with preclinical studies showing that a preserved microvasculature is associated with better outcome. Future studies should aim at increasing statistical power by including more kidneys that show strong changes under therapy.

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AA amyloidosis changing epidemiology – a 20 year case series

Jennifer Pinney[1,2], Julian Gillmore[1,2], Ashutosh Wechalekar[1], Simon Gibbs[1], Dorota Rowczenio[1], Thirusha Lane[1], Sanjay Banypersad[1], Janet Gilbertson[1], Dorothea Gopaul[1], David Hutt[1], Mark Pepys[1], Philip Hawkins[1], Helen Lachmann[1,2]

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Background: AA amyloidosis is the most feared complication of chronic inflammatory conditions. Presentation is usually a consequence of renal involvement and progression to end stage renal involvement is common. It is thought that the disease is becoming less common in the developed world; however few systematic data exist. In the UK we hold systematic data on the largest cohort of patients with AA amyloidosis in the world

Objective and methods: To analyze the experience of AA amyloidosis over the past 20 years at a single national centre.

Results: 516 patients with confirmed AA amyloidosis were assessed between January 1993 and December 2012. Referral rates of new AA patients have been stable during the past decade at ~30 per year, in contrast with a three-fold increase among other types of amyloidosis. The commonest underlying diseases are: rheumatoid arthritis (RA) 27%, chronic sepsis 19% and seronegative arthritis 10%, but in 18% the underlying inflammatory disease was uncharacterized at diagnosis. Comparing the cohort referred from1993 to1997 with the most recent 5 years, there has been a reduction in patients with RA from 36% to 20% (p 0.007), and juvenile idiopathic arthritis from 23% to 2% ($p<0.001$), but a rise in AA amyloidosis of unknown aetiology from 6% to 25% ($p <0.001$). Age at referral has risen from a median of 49 to 60 years ($p < 0.001$), and the proportion referred with established end-stage renal failure (ESRF) has remained stable between 21-28%. In the earlier cohort median survival from ESRF was 70 months and survival from diagnosis 86 months. Median survival was undefined in the recent cohort from diagnosis and ESRF. Age at death has increased from a median of 60 years in the earliest cohort to 66 in the most recent cohort ($p < 0.01$).

Discussion: In contrast to a threefold increase in referrals to the NAC of AL and other types of amyloidosis during the past decade, referral rates for AA have not changed. Ages at both diagnosis and death have increased significantly over the last 20 years. The incidence amongst patients with inflammatory arthritis appears to have decreased which may be due to the use of novel agents. A greater proportion of recent AA patients have uncharacterized underlying inflammatory disorders, posing challenges for clinical management.

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Intramuscular amino acid profile in response to resistance training in chronic kidney disease (CKD)

Nichakarn Ruttanaporn[1], Emma Watson[1], Neil Greening[2], Hannah Young[2], Maurice Dungey[3], James Burton[2], Jonathan Barratt[1], Alan Bevington[1], Alice Smith[2]

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Patients with CKD experience muscle wasting resulting from uraemia, acidosis and chronic inflammation and this is associated with increased morbidity and mortality. An early step in this process is depletion of free amino acids from skeletal muscle cells, which has been described both in vitro and in vivo, and may trigger the wasting illnesses. In a previous study(1), we found walking exercise worsened this depletion of intramuscular free amino acids in pre-dialysis patients, which could ultimately prevent them from building muscle in response to an exercise programme. The aim of the current work was to determine if resistance training, which classically stimulates muscle hypertrophy, could overcome intramuscular amino acid depletion and reduce muscle wasting in pre-dialysis CKD.

19 patients CKD stage 3b-4 were recruited and consented to give muscle biopsies. 12 patients (60.5 [45-72] years, eGFR 26.5 ± 7.1ml/min/1.73^2) were randomised to an 8 week PRE programme exercise performed 3 X weeks consisting of 10-12 repetitions of leg extension exercises at 70% 1 repetition maximum. 7 patients (73 [46-77] years, eGFR 20.3 ± 6.4ml/min/1.73^2) were randomised to control and continued with normal physical activity. Anatomical Cross-Sectional Area (ACSA) of the vastus lateralis was measured, and fasted blood and skeletal muscle biopsies obtained before and after the 8 week period. Muscle and plasma were analysed by High Performance Liquid Chromatography (HPLC) for 18 individual amino acids, and group analysis of branched chain amino acids (BCAA: Leucine, Isoleucine, Valine) was analysed further for their known anabolic effect in muscle.

8 weeks of PRE resulted in a significant increase in vastus lateralis ACSA (6.30 ± 2.1 to 6.6±2.2 cm^2, p=0.002) with no changes observed in the controls (5.06±1.2 to 5.07±1.1cm^2 P=0.902). No changes were seen in either intramuscular or plasma profiles of individual amino acids (P>0.05 in all cases) or BCAA (P=0.96) in either group, which is in contrast to the depletion we previously described with walking exercise.

These results suggest that PRE can overcome the amino acid depletion that is induced by walking exercise, and is a powerful tool to help increase muscle mass in this cachectic population. Muscle wasting is associated with mortality, morbidity, high cardiovascular risk, compromised physical functioning and reduced quality of life. This study highlights the importance of including resistance exercise in CKD rehabilitation programmes to improve or maintain muscle mass, manage comorbidities, and promote general wellbeing.

(1) Clapp, EL. et al. (2010) Presented at the conference on Renal Nutrition and Metabolism.

P389

The utility of serum and urine paraprotein screening in new patients referred from primary care with CKD

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Introduction: Screening for occult serum and urine paraproteins is commonly undertaken in the work up of patients presenting with chronic kidney disease (CKD) to exclude multiple myeloma and amyloidosis. However, there is a lack of consensus regarding the utility of screening and no clear guidelines are available.

Methods: We reviewed the records of all patients with CKD referred to the Sheffield Kidney Institute (SKI) by their GP between 01/10/2009 and 30/09/2011 and correlated this with information from the Immunology Department on all serum and urine assays performed within the same period. Data sets were then compared to identify patients with newly presenting CKD referred by their GP who had undergone screening. Exclusion criteria involved referrals from secondary care, patients with known light chain disease and those with acute kidney injury.

Results: Over the 2 year period, a total of 1859 patients were referred by their GP to SKI for investigation of CKD. Of these, 776 (41.7%) had testing on either serum or urine samples or both. Samples initially had electrophoresis performed and underwent immunofixation if any abnormality was detected. 556 patients (29.9%) had only serum samples tested, 22 patients (1.2%) had only urine samples tested, while 198 patients (10.7%) had both urine and serum samples tested. Of these, 59 patients (7.6%) tested positive for paraproteins on presentation. There were more males (38) than females (21) (M:F ratio 1.8) and their mean age was 79.8 (SD 9.6) There were 6 new diagnoses of Multiple Myeloma, 12 new diagnoses of Monoclonal Gammopathy of Unknown Significance (MGUS), 1new and 1 probable diagnosis of Amyloidosis. All patients newly diagnosed with multiple myeloma had hypertension and a mean CKD staging of 3.2 SD (0.91) but no other common demographics were found.

Conclusion: The detection rate of clinically significant paraproteinemias is low (1% of those tested) in newly referred patients with CKD from primary care. Patients with positive tests tended to be older and male. The utility of paraprotein screening in the investigation of CKD should be evaluated in a larger cohort.

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Retrospective study of granulomatous interstitial nephritis in a UK renal centre

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King's College Hospital, London, UK

Introduction: This retrospective study reports on all patients presenting with a histological diagnosis of granulomatous interstitial nephritis (GIN) between 2000 and 2012 at our unit.

Methods: Data on 21 patients were collected at baseline, at 1 year and at last follow-up.

Results: 38% of patients were of Black ethnicity, 57% were male and the mean age was 59 years. 8 cases were associated with sarcoidosis with evidence of extra-renal disease and 5 with renal-limited sarcoid. 5 patients had tuberculosis (TB) infection, 1 case was related to drugs and 2 were idiopathic. The mean duration of follow-up was 46 months. Those with sarcoidosis presented with a mean eGFR of 23mls/min, minimal proteinuria (0.4g/24h) and serum angiotensin-converting-enzyme (ACE) of 106 IU/L (8-52 IU/L). All received prednisolone. At 1 year, renal function had improved to 43mls/min with a reduction in serum ACE to 32 IU/L. At final clinic visit, renal function remained stable (mean eGFR 43mls/min). In multivariate logistic regression analysis, ethnicity, age, sex, eGFR, serum ACE and calcium at presentation, proteinuria and fibrosis score on biopsy did not predict response to treatment. In those with TB infection, mean eGFR was 27mls/min and proteinuria was 0.7g/24h at presentation. Treatment was delayed by a mean of 29 months in 3 patients as the biopsy findings did not conclusively demonstrate TB infection. Development of extra-renal TB infection led to the initiation of treatment. Two patients with extra-renal TB had a presenting eGFR<20mls/min and developed ESRD. The remaining 3 patients had a mean eGFR of 24mls/min at 1 year and 30mls/min at the end of follow-up. The idiopathic and drug related cases, presented with a mean eGFR of 46mls/min and all started steroids. The mean eGFR at last follow-up was 34mls/min.

Conclusion: To our knowledge, this study represents the largest cohort of patients with GIN in the UK and supports previous findings that patients with sarcoid have a favourable outcome with steroid treatment. Those with TB, particularly with manifestations of extra-renal infection and eGFR<20mls/min, have an inferior prognosis which may be related to delayed diagnosis. Efforts to expedite diagnosis along with a consideration of a trial of anti-TB therapy should be considered.

P391

Reduced eGFR in systemic sclerosis associated pulmonary arterial hypertension is a marker of severity

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Introduction: The prognosis of Systemic Sclerosis associated Pulmonary Arterial Hypertension (SSc-PAH) is determined by the severity of pulmonary arterial hypertension (PAH) and other organ involvement. The prevalence of renal impairment in SSc-PAH is unclear. We have examined the prevalence of reduced eGFR in SSc-PAH and its association with clinical demographics, pulmonary function tests and haemodynamics.

Patients and methods: We included 865 SSc patients followed by the National Pulmonary Hypertension Unit in the Centre for Rheumatology at the Royal Free Hospital in London between 1996-2010. In 580 patients who underwent a right heart catherisation (RHC) and eGFR prior to RHC, 290 patients had PAH (mean pulmonary arterial pressure ≥25mmHg and pulmonary capillary wedge pressure <15 mmHg). 209 patients had limited cutaneous SSc (lcSSc) and 81 patients had diffuse cutaneous SSc (dcSSc). eGFR was calculated using the 4-variable Modified Diet in Renal Disease (MDRD) equation. Patients were divided into two groups: "reduced GFR" (<60 ml/min/1.73m^2) or "normal eGFR" (≥ 60 ml/min/1.73m^2). Demographic, clinical and haemodynamic parameters were compared between groups using Student's t-test, Mann-Whitney U test or Chi-Squared analyses where appropriate.

Results: 77/290 (27%) patients had a reduced eGFR. There were more females (92% vs 77%, p<0.01) in the reduced eGFR group who were older (63.5 vs 56.8 years, p<0.01), more likely to have lcSSc (91% vs 65%, p<0.01) than dcSSc and a lower WHO functional class (86% vs 79%, p=0.085) compared to those with normal eGFR. DLCO was significantly lower (42% vs 38%, p<0.05) in the reduced eGFR group but there was no significant difference in forced vital capacity (FVC) (87% vs 73%, p=0.37). The mean pulmonary artery pressure (mPAP) (42 vs 36mmHg, p<0.01) and pulmonary vascular resistance (PVR) (730 vs 524dyn.s.cm^{-5}, p<0.01) were significantly higher in the reduced eGFR compared to the normal eGFR group.

Conclusion: Reduced eGFR in SSc-PAH is more frequent in limited cutaneous SSc, female and older patients and is associated with a reduced DLCO and preserved FVC. A higher mPAP and PVR reflects more severe pulmonary vascular disease.

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Performance of estimated glomerular filtration rate (GFR) equations for prescription of carboplatin chemotherapy- comparison with isotopic measured GFR

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Background: Calculation of renal function is crucial for prescription of carboplatin-based chemotherapy. Oncological practice uses isotopic GFR to calculate dosing. Estimated GFR (eGFR) formulae have improved assessment of renal function. We assessed potential impact of GFR estimating formulae on carboplatin dosing.

Methods: 115 male subjects (mean age 40.3, std dev. 10.1) were identified who had received single agent adjuvant carboplatin for stage 1 seminoma. All patients underwent 51Cr-EDTA measurement of GFR and carboplatin dose was calculated using the Calvert formula, based on GFR uncorrected for body surface area (BSA). Theoretical carboplatin doses were calculated using eGFR values using the CKD-EPI and MDRD4 formula; with additional calculation to uncorrect for BSA. Creatinine clearance was calculated by Cockcroft-Gault (CG) formula.

Results: Mean measured GFR was 96.9ml/min and 116.4ml/min/1.73 m^2 of BSA. Bias was similar among the three equations, with a median difference between eGFR and isotopic GFR of -3.8 and 7.6ml/min/1.73 m^2 with MDRD4 and CKD-EPI and 5.0ml/min for CKD-EPI uncorrected for BSA. CKD-EPI had greatest precision based on interquartile range of the difference between eGFR and measured GFR. Compared to 'gold' standard of carboplatin dose calculated by the Calvert method using isotopic GFR, 57.4% patients would have received within 10% of the correct dose using eGFR calculated using the CKD-EPI formula compared to 44.3% with CKD-EPI formula uncorrected for BSA, 42.6% with CG corrected for ideal body weight, 39.1% for CG and 23.5% for MDRD4. Based on CKD-EPI eGFR, patients predicted to receive an inadequately low carboplatin dose had a larger BSA ($p<0.01$) and body mass index ($p=0.01$), whilst there were no obvious predictors of the 18.4% who would have received too great a dose.

Conclusions: eGFR formulae appropriate to level of renal function may permit appropriate carboplatin dose calculation in selected patients. Alternative methods for calculation of renal function may reduce the need for isotope studies, minimising exposure to radiation, cost and delays in therapy.

P393

Selective renal artery embolization for post renal biopsy bleeding. A single centre experience

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Background: Renal artery embolization (RAA) is the gold standard treatment for life threatening post biopsy bleeding (PBB), however it is not easily available in all centres. We decided to audit our use of RAA in the management of PBB.

Methods: All RAAs performed for PBB between 2000 and 2010 at the University Hospital of Wales (UHW) were identified. Demographic, clinical, radiological and histological details were obtained from a review of the pts clinical notes and hospital information systems. Data regarding timing of biopsy, technique, time to onset and nature of symptoms and time to embolization was also recorded.

Results: 9 cases of post biopsy bleeding treated with renal embolization were identified. Nearly all patients (8) developed symptoms on the day of biopsy, the most common being pain and hypotension with or without haematuria. 5 patients required RAA the same day all developing pain and evidence of shock unresponsive to fluid therapy. Average time to development of symptoms was 3hrs (range 1 min to 6hrs). Average time to embolization from symptoms was 2hrs 35mins (range 1hr 38 min to 3hr 21min). 4 patients had super selective RAA with 1 patient requiring embolization of the whole kidney due to inability to cannulate the bleeding artery. This patient subsequently died after a prolonged inpatient stay. Of the remaining 4 pts in whom embolization was not performed on the day of biopsy 3 of them had symptoms on the day of biopsy (pain and haematuria) that settled, with persistent haematuria being the indication for embolization. 1 pts developed bleeding 2 days post biopsy complicated by the need for intravenous heparin. There were no adverse events associated with embolization. Super selective RAA was not associated with deteriorations in renal function.

Discussion: Life threatening PBB is an uncommon complication of renal biopsy, given its superiority over nephrectomy we believe that all centres performing renal biopsies should have easy access to RAA. When present life threatening PBB presents in clinically obvious ways however its presentation can be delayed by several hrs underlining the importance of performing biopsies as early as possible.

Poster session

Wednesday 13th March

18:15 - 19:25

CKD: cardiovascular disease 1

P394

How common is aortic vascular calcification (VC) in recurrent renal stone formers (RSF) – any evidence for an underlying calcification tendency?

Daniel Leckstroem, Christopher Pereira, Thakshyanee Bhuvanakrishna, Matthew Bultitude, Andrew McGrath, David Goldsmith

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

Background: VC is common, and is both a marker and a cause of increased cardiovascular (CV) morbidity and mortality. Nephrolithiasis is also a common condition with a lifetime risk exceeding 6.3% in men and 4.1% in women in the United States, and is known to be associated with osteoporosis, fractures and CV disease. We wanted to see if these two "ectopic calcification syndromes" had any overlap. To do this, we studied the severity of abdominal aortic calcification (AAC) in two populations, one with stones, and one with a negligible stone burden.

Methods: 93 RSF subjects who had undergone percutaneous nephrolithotomy (PCNL) in 2011 were compared with 93 living kidney donors (LKD) of similar age and eGFR also studied in 2011. AAC was assessed non-blinded examining abdominal CT imaging : CT KUBs (RSF) and CT aortograms (LKD) - using a manual scoring to calculate total aortic calcium load (AAC severity score). The prevalence, severity and associations of AAC between these two populations were then compared ($p<0.05$).

Results: 51/93 stone formers and 50/93 donors were male (p=NS), and the respective mean ages were 51.1±3.2 years vs. 45.9±1.8 years ($p<0.05$ both). RSFs had an average eGFR of 80.28±6.13 ml/min/1.73m^2, compared to 88.73±2.97 ml/min/1.73m^2 for the LKDs (p=0.017). The RSFs had more of their abdominal aorta calcified compared to the LKDs (19.22±5.73% vs. 7.14±3.07%, $p<0.001$), and showed a significantly higher AAC severity score (4.19±1.83 vs. 0.98±0.56, $p<0.001$). In RSFs > 50 years of age there was significantly more AAC than in those < 50 (8.09±3.40 vs. 0.53±0.60, $p<0.001$). A similar but milder pattern was seen with the LKDs (2.47±1.56 vs. 0.31±0.29, $p<0.001$).

Conclusions: AAC was present in both groups, but it was significantly more intense in RSFs than in LKDs. This has not been reported previously. There was also a steeper age-relationship with increasing AAC severity in RSFs than in LKDs. It seems that RSFs may have a propensity for simultaneous blood and urine-based ectopic calcification, perhaps indicating a loss of natural VC inhibitors.

P395

Traditional risk factors do not predict early mortality in dialysis patients undergoing cardiac surgery

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Introduction: The high cardiovascular mortality among people with endstage renal disease (ESRD) is well recognised but there is little consensus on how to assess the risk-benefit ratio of cardiac surgery in the context of this increased risk. We investigated preoperative risk factors and outcomes among a cohort of dialysis patients having cardiac surgery to improve our understanding of which patients are likely to benefit from such operations.

Methods: We identified 44 dialysis patients referred from two tertiary renal units to a single cardiac centre, who underwent cardiac surgery between 2005 and 2011. 25 patients had coronary artery bypass graft (CABG) surgery alone. 21 patients had other cardiac surgeries, with or without CABG. We compared risk factors for cardiovascular mortality (gender, age, diabetes, hypertension, hyperlipidaemia, family or personal history of ischaemic heart disease and smoking) as well as preoperative angina status, dyspnoea status, ejection fraction and dialysis modality between survivors and non-survivors.

Results: Overall mortality was 23% at 30 days and 36% at one year. Dyspnoea status correlated with poor outcome: relative risk for mortality at 30 days was 3.7 for those with New York Heart Association (NYHA) Class III or above, but this was not statistically significant (95% CI 0.87-15.29, p=0.07). No other preoperative variable was associated with mortality outcome at 30 days or one year. 17 patients had been referred to cardiac services in relation to workup for possible renal transplantation. 1-year mortality among these patients was 29% compared to 44% for those who were not being currently considered for transplant (p=0.52).

Discussion: Early mortality was high in this cohort of dialysis patients undergoing cardiac surgery, even among patients having cardiac surgery to render them fit for renal transplant. The risk factors traditionally used to predict cardiovascular mortality in a general population were not predictive of postoperative mortality in this group. Further research is needed if we are to improve our identification of dialysis patients likely to benefit from cardiac surgery.

P396

Pulse wave velocity in children: comparison between vicorder and sphygmocor

Louise Watt[1], Laura Milne[1], Karen McNeill[1], Phil Chowienczyk[1], Manish Sinha[2]

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Introduction: Pulse wave velocity (PWV), a marker of arterial stiffness, can be measured using ECG-referenced carotid and femoral tonometry, or by using simultaneous volumetric recordings from sensors in pressure cuffs. These can be applied to the carotid and femoral arteries or the brachial and femoral arteries. This simplified technique may be more suitable for use in children.

The purpose of this study was to compare PWV measured over the carotid-femoral path (PWVcf) with that over the brachial-femoral path (PWVbf) using a volumetric system (Vicorder) and to compare values of PWVcf obtained by the volumetric and a tonometric method (SphygmoCor) in children.

Methods: PWVcf and PWVbf (Vicorder) were measured in 137 children with chronic kidney disease and/or hypertension (81 males, aged 3-18years), PWVcf (SphygmoCor) was also measured in a sub-sample of 106 children. Measurements were done in triplicate on each device to allow assessment of repeatability.

Results: Vicorder PWVbf and PWVcf were closely correlated ($R= 0.75$, $P <0.0001$ with mean difference 1.87±1.25m/s). However, Vicorder PWVcf was only moderately correlated with SphygmoCor PWVcf ($R=0.51$, $P <0.0001$, mean difference 0.40±0.90m/s). Within subject coefficients of variation for repeated measures were 6.6%, 8.3%, and 8.6% for PWVbf (Vicorder), PWVcf (Vicorder) and PWVcf (SphygmoCor) respectively.

Discussion: These results suggest that PWVbf measured using brachial and femoral cuffs may be slightly more reproducible than other measures of PWV and may be a reasonable surrogate for PWVcf. The technology and choice of path length appears particularly suitable for use in children. However, the volumetric and tonometric methodologies for measuring PWVcf do not appear interchangeable.

P397

Arterial stiffness in children relates to age and blood pressure but not the presence or absence of CKD

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Introduction: The aim of this study was to investigate the relationship of PWVcf with blood pressure and renal function in children with pre-dialysis chronic kidney disease (CKD).

Methods: One hundred and fifty children (94 boys), aged 3–18 years, were recruited from paediatric nephrology and hypertension clinics. CKD was present in 112 (75%) with mean (SD) eGFR 59 (34) ml/min/1.73m^2; hypertension but with no CKD in 21 (14%); and 17 (11%) controls. PWVcf was measured using the Vicorder system.

Results: The mean (SD) PWVcf was 5.2 (0.85) m/s with no significant gender difference (P=0.81). Children with CKD had lower body mass index (BMI) and pulse pressure (PP) (P=0.046, P=0.02, respectively) but similar age, SBP, DBP, mean arterial pressure (MAP) and PWVcf (P=0.21, 0.25, 0.83 and 0.50 respectively) compared to those without CKD. Across CKD stages 1-5 there was a significant difference in height (P=0.02) and antihypertensive use (P=0.006) but no difference in age, SBP, DBP, MAP, PP, BMI or PWVcf. On univariate analysis PWVcf was positively correlated with age (r=0.48, P<0.001), BMI (r=0.28, P<0.001), height (r=0.47, P<0.001), SBP (r=0.41, P<0.001), DBP (r=0.23, P=0.004), MAP (r=0.34, P<0.0001), PP (r=0.23, P=0.004). On multivariable analysis, incorporating age, gender, GFR, use of antihypertensives, and BP variables (SBP, DBP, PP and MAP individually), PWVcf was independently correlated only with age (β = 0.37, P <0.001), SBP (β=0.22, P =0.01) and MAP (β = 0.16, P =0.46).

Discussion: These results suggest that, in our cohort, age and blood pressure are the most important determinants of arterial stiffness independent of the degree of renal dysfunction.

P398

Stroke incidence and risk factors in peritoneal dialysis

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Introduction: Stroke is the leading cause of disability in the UK with markedly higher rates in dialysis cohorts. There are very few studies examining stroke in peritoneal dialysis [PD] despite increasing numbers of patients on this modality. Of concern these suggested greater stroke mortality in PD compared to haemodialysis [HD] in analyses of cohorts over 10yrs old. We aimed to describe stroke epidemiology in contemporary PD cohorts.

Methods: This multicentre retrospective study [Jan 2002-Mar 2012] examined patients incident to PD. Stroke was defined as an acute neurological event >24hrs duration with compatible findings on neuroimaging. Subdural haematoma was excluded. Factors associated with stroke risk were examined with multivariate Cox models and a competing-risks approach. The effect of stroke on survival assessed using Weibull models.

Results: 1511 patients were studied [mean age 54.7±16.5yrs, 35% diabetic, 7% with pre-existing cerebrovascular disease] over 3672 total patient years follow-up. 36 strokes occurred [overall incidence 9.8/1000 pt years] of which 31/36 [86%] were ischaemic, 14% haemorrhagic. Stroke occurred in older patients [mean age 60.5±12.5 vs 54.2±16.6yrs, p=0.01] after a median of 11 months on PD. After age-adjustment, established cerebrovascular disease was the only factor independently associated with a greater stroke risk [HR 4.2, p<0.001] whereas gender, ethnicity, diabetes, atrial fibrillation were not. 1-year mortality after stroke was 19% with no significant difference by subtype. On multivariate analysis acute stroke was independently associated with worse patient survival [HR 4.6, p<0.001].

Conclusion: Stroke incidence is ten-fold greater in PD compared to the general population. In the largest study of its kind to date we found incidence rates lower in PD cohorts compared to HD [15-30/1000 patient years]. The relatively fewer haemorrhagic events seen may relate to casemix, anticoagulation exposure, residual renal function and volaemic control.

P399

Aggressive management of CKD patients following stroke leads to good short and medium term outcome

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Introduction: Patients with chronic kidney disease are at high risk of stroke due to underlying medical conditions. There is limited data about the short and medium term functional outcome in this cohort following aggressive initial treatment. We aimed to analyse this further.

Methods: We retrospectively analysed hospital database to obtain patient data and followed up for 1 year after discharge.

Results: We screened 2151 patients admitted to Acute Stroke Unit from Jan 2009 to Aug 2011 with diagnosis of Stroke and found 149 patients to have chronic kidney disease. Of these, 98 were males and 51 were females with mean age of 76.4 years. Mean creatinine prior to admission was 133.4. 50 patients had DM and 4 patients had Pre-Diabetes. 39 patients had both Diabetes Mellitus and hypertension. 110 patients were discharged home (73.8%), 6 were discharged to Intermediate care (4%) for further rehab, 3 patients to sheltered accommodation (2%), 23 patients were discharged to residential or nursing homes (15.4%) and 7 patients died in hospital (4.6%). Stroke admissions during the same period showed that 59.2% were discharged home, 7.2% to care home, 13% to intermediate care and 15% death in overall population.

Conclusion: Our cohort of CKD patients had better functional outcomes after stroke compared with overall stroke admissions during the same period. It is likely that the improved outcome is due to the pre-optimisation of risk factors in this cohort. CKD patients are likely to have good short and medium term outcome if managed aggressively following stroke.

P400

Renal sympathetic denervation for resistant hypertension: a real world experience

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Introduction: Hypertension affects more than 25% of the adult population and contributes to 62% of strokes, 49% heart disease and 7.1 million deaths a year worldwide. Resistant hypertension, raised BP >140/90 mmHg despite treatment with 3 or more antihypertensive agents at optimal doses, has a prevalence of 10-20% in hypertensive population. Recently, renal sympathetic hypertension (RSD) has been shown to significantly lower clinic BP, average 32/12 mmHg, in resistant hypertensives at 6 months (Simplicity HTN 1 & 2 studies). Here we describe our single centre experience of RSD in resistant hypertensives.

Method: This is a retrospective analysis of efficacy of RSD in 9 resistant hypertensives that completed 6 months of follow-up. RSD was done by experienced intervention cardiologist and radiologists. All patients had clinic and 24 hour ambulatory BP (ABP) before and 6 months after RSD.

Results: The median age of patients was 52 (40-66) years, 6 males, 3 were diabetic and 2 had stage 4 CKD. The mean duration of hypertension was 10.8 years. Mean clinic BP pre-RSD was 195/109 mmHg (±20/16), mean daytime ABP was 171/95 mmHg (±15/10), and the mean number of antihypertensive agents was 5.2 (4-6). All patients had secondary hypertension and non-adherence excluded. At 6 months, the mean clinic BP was 167/98 (±27/19) and mean daytime ABP was 159/90 (±20/17), giving a mean reduction in clinic BP of 28/11 and day ABP of 12/5 (p=ns). Three (1/3) patients had no improvement in BP after 6 months, 1 had improvement at 3 months but BP rose to pre-RSD level at 6 months. One of the 2 patients with stage 4 CKD responded but there was no significant improvement in eGFR or proteinuria. Apart from groin haematoma in 1 patient, there was no early or late complication.

Conclusion: In this single centre experience, whilst RSD was found to be safe, the improvement in BP at 6 months was less satisfactory than the trial experience especially when assessed by ambulatory BP; 1/3 of patients had no reduction in BP at all. In the trials, not many patients had ABPM. A long term follow up of a larger number of patients with ABPM will help ascertain the usefulness of RSD in treating resistant hypertension in clinical practice.

P401

Intradialytic profiles of spatial QRS/T angle for arrhythmic risk stratification

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Introduction: Spatial QRS/T angle derived from a single digital surface ECG has prognostic value for arrhythmic death in dialysis patients. Dynamic changes of the QRS/T angle from exercise ECG add prognostic information in patients with ischaemic heart disease. The aim of the study was to investigate the dynamic profiles of spatial QRS/T angle expressed as Total Cosine R to T (TCRT).

Methods: In 49 stable maintenance haemodialysis patients (33.9% diabetics, age 58.2±14) with no recent ACS, continuous 5-hour Holter recordings were obtained during dialysis and repeated five times at 2-weeks intervals. TCRT was calculated every 5 seconds in overlapping 10-second ECG segments. Recordings with fewer than total 1000 analysable segments or fewer than 100 segments during the first or the last hour of the recording were excluded.

Results: 187 intradialytic recordings were included in the final analysis containing on average 2699±592 ECG segments. Mean intradialytic TCRT was 0.28±0.58. Comparison between averaged values during the first and after the third hour of each recording showed statistically significant differences in TCRT in 179 (95.7%) recordings ((independent sample t test $p<0.05$). Intradialytic change was expressed as (last hour value-first hour value)/first hour value and denoted as TCRTD and was -0.46±2.25. Repeated measures ANOVA showed intrasubject stability of TCRT and TCRTD (F 1.656, P 0.182 and F 2.083, p 0.148 respectively) for the five consecutive recordings. More than 10% intradialytic increase was noted in 16 (28.6%) subjects while more than 10% decrease in 14 (25%) subjects. Two patients who sustained cardiac arrest during 10±2 months follow up had extremely low mean TCRT values (-0.67±0.17) and low intradialytic change (-0.02±0.11)

Conclusion: TCRT exhibits differential subject specific dynamic profiles in response to fluid and electrolyte changes on dialysis. Low TCRT values and low intradialytic changes may be associated with increased risk. Analysis of repolarization dynamics from intradialytic continuous electrocardiogram can be a useful tool for risk stratification.

Poster session

Thursday 14th March

12:00 - 13:00

Developmental biology and genetic renal disease 1

P402

The role of cyclic AMP in pathogenesis of ADPKD

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Rationale and hypothesis: ADPKD is the most common genetic cause of ESRD. By understanding of the molecular pathogenesis of the disease, we may be identifying a novel treatment for the disease by creating agents targeting the process responsible for the development of the cysts. PGE2 increase the level of cAMP which induces cell proliferation, and fluid secretion into the cyst. The level of PGE2 and its receptor (PTGER2) are increased in renal cyst epithelia leading to increases in cAMP levels in these cells.

Objectives: To establish a 3D cell culture model system using cells derived from patients with ADPKD. Test the effect of PGE2 on cyst growth, the effect of PTGER2 receptor antagonists.

Methodology: A total of 8 cell lines were used in 3D cyst assay cultures. Cells were tested for their ability to form cysts or tubules in culture using different kinds of the supporting matrix. Three different concentration of PGE2 was added to 3 cystic lines. Cyst expansion measured over 7 – 10 days. qPCR and western blotting used to determine the expression of PTGER2 in normal and cystic cell lines. Immunohischemical study to demonstrate the expression of PGER2 on both normal and cystic kidney tissue.

Findings: qPCR and microarray showed an increase in PTGER2 in cystic as a compared with normal cells. Western blotting has detected PTGER2 protein in cystic human cells. Two of the cystic cell lines formed cysts inside the matrigel, increased in size over a period of 7 – 10 days. The effect of PGE2 on cyst growth was inconclusive. There is increase in PTGER2 expression in cystic kidney tissue by immunohistochemistry.

Conclusion: We established the conditions for a cell culture 3D cyst assay in which ADPKD cells form cysts and normal cells form tubules. Work is ongoing to determine the levels of PTGER2 in these cells.

P403

How prevalent is the aHUS associated factor H mutation c.3643C>G, pArg1215Gly in Devon?

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Introduction: The county of Devon in the United Kingdom is home to the largest worldwide pedigree with an atypical haemolytic uraemic syndrome (aHUS) associated complement factor H mutation, with 24 affected individuals and 18 carriers. In 2009 a 65 year old male was diagnosed with aHUS after losing a renal transplant to a thrombotic microangiopathy. Subsequent mutation screening revealed the same *CFH* mutation (c.3643C>G, pArg1215Gly) without him being knowingly related to the local kindred. We designed a study to investigate the prevalence of this mutation in the local area. In addition, we examined the diagnoses of pre-existing haemodialysis patients to determine whether other patients might be at risk of carrying the same *CFH* mutation.

Methods: The Exeter Ten Thousand [1] (EXTEND) is a research database aiming to recruit 10,000 volunteers over the age of 18 living within 25 miles of Exeter. We genotyped 4000 EXTEND samples for *CFH* c.3643C>G, pArg1215Gly. We reviewed the diagnoses of 294 haemodialysis patients in the Devon area and genotyped 7 patients with end stage renal disease of unknown aetiology, malignant hypertension or renovascular disease.

Results: *CFH* c.3643C>G, pArg1215Gly was not detected in any of the 7 haemodialysis patients or the 4000 individuals within the EXTEND study.

Discussion: We conclude that *CFH* c.3643C>G, pArg1215Gly is not endemic in Devon. This reinforces our existing practice of genotyping only patients with renal failure and evidence of a thrombotic microangiopathy for this mutation.

References:

[1] www.exeter10000.org

P404

HNF1B renal disease – how many patients are we missing?

Rhian Clissold[1], Richard Oram[1], UNITED team[2], Barbara Fraser[3], Sian Ellard[1], Andrew Hattersley[1], Coralie Bingham[1]

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Introduction: *HNF1B* gene mutations/deletions are the commonest known genetic aetiology of renal developmental disorders. They also cause maturity onset diabetes of the young (MODY). As the *HNF1B* phenotype is very variable, we suspect that many cases go undetected. MODY is commonly misdiagnosed as type 1 diabetes (T1D) but the two conditions can be distinguished by endogenous insulin production and autoantibody status. Our aim was to look for undiagnosed *HNF1B* renal disease in a large cohort of individuals in South West England with presumed T1D.

Methods: Urine C peptide/creatinine ratio (UCPCR) was used to assess endogenous insulin production in 943 patients with diabetes. If this confirmed significant endogenous insulin production, antibody testing (GAD/IA2) was performed. If antibody positive, the diagnosis of T1D was confirmed; otherwise MLPA dosage analysis was performed to identify *HNF1B* gene deletions along with genetic analysis of other MODY genes.

Results: 88/943 patients had endogenous insulin production and were autoantibody negative so underwent genetic testing. In 2/88 patients, a spontaneous whole gene deletion of *HNF1B* was found:

-Patient 1 was diagnosed with presumed T1D aged 29 years. Post-study, multiple cysts on his left kidney and pancreatic insufficiency have been detected.

-Patient 2 was diagnosed with presumed T1D aged 11 years. Post-study, severe pancreatic insufficiency requiring enzyme replacement therapy has been detected. Renal imaging showed loss of corticomedullary differentiation in both kidneys.

Discussion: We found 2 missed cases of *HNF1B* disease in 943 diabetic individuals from the South West, an area with a high level of local expertise in MODY. We would predict an additional 2 missed cases as *HNF1B* gene mutations are seen at a similar frequency to deletions but were not looked for in this study. This highlights the need for a better method of selecting patients for genetic testing so the condition can be recognised and managed appropriately.

P405

A natural Chinese herb to treat polycystic kidney disease?

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic renal disease and can cause of end-stage renal failure, with currently no effective medical treatment. Triptolide is a compound derived from the Chinese herb *Tripterygium Wilfordii Hook F*. The aim of this project was to investigate the mechanism of action of triptolide on PC2 and to study its effects on *in vitro* models of cyst formation.

Methods: Ratiometric Ca^{2+} imaging in transient and stably transfected cells; 3D gel cultures; apoptosis assays (cleaved caspase-3 staining); NFκB activity assays.

Results: Triptolide suppressed TNFa activation of an NFκB luciferase reporter but did not induce intracellular Ca^{2+} release in transient or stably transfected PC2 expressing cells. In 3D gel assays, triptolide significantly stimulated apoptosis in murine wild-type and Pkd1 cells at higher doses (500-1000nM) but had no effect on cyst growth in human cystic or MDCK cells at the same concentrations.

Discussion: The major effect of triptolide in this study was pro-apoptotic. Murine cells were more sensitive to triptolide than human or canine cells. An anti-inflammatory effect of triptolide was confirmed. No significant effects on cell proliferation or Ca^{2+} release were found. These results suggest that species differences between murine and human cells may reduce the effectiveness of triptolide in treating human ADPKD.

P406

Functional study of genetic variants is important in patients with membranoproliferative glomerulonephritis and C3 glomerulopathies

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Introduction: Membranoproliferative glomerulonephritis (MPGN) and C3 glomerulopathy (C3GN) are forms of glomerular disease associated with hypocomplementaemia which result in progressive renal failure. MPGN and C3GN have shared risk factors that result in dysregulation of the alternative pathway (AP) of complement. This is often due to the presence of an autoantibody which stabilises the C3 convertase of AP. These autoantibodies are generically called C3 nephritic factors. Genetic variants of complement factor H, an important regulator of AP have been described in both diseases. We examine the functional significance of novel variants identified in patients with MPGN and C3GN.

Methods: Genetic variants in factor H have been identified in patients with MPGN or C3GN. Structural modelling was used to predict functional significance. Recombinant wild type and mutant sequence variants were generated in *Pichia pastoris* in the setting of the N-terminal region of complement factor H (CFH). We determined binding of CFH to C3b using surface plasmon resonance. We then investigated decay-accelerating activity (DAA) and co-factor activity (CA) using surface plasmon resonance and fluid phase assays.

Results: Structural modelling showed that the variants were not localised to a specific region at the interface between CFH/C3b. We demonstrate variants in CFH which impair binding to C3b, resulting in loss of CA and DAA. Other mutations bind C3b with normal affinity but result in loss of CA or DAA suggesting impaired factor I or factor B binding respectively. In other sequence variants we fail to demonstrate any functional perturbation.

Discussion: This study demonstrates that genetic variants found in MPGN and C3GN result in a range of functional consequences ultimately resulting of loss of complement regulation and over-activation the alternative pathway of complement. The presence of functionally preserved variants also highlights the need for caution in interpreting genetic variants in the absence of functional data.

P407

CFHR5 nephropathy in a family without Cypriot ancestry

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C3 glomerulopathy (C3G) describes glomerular pathology associated with predominant deposition of complement C3 and associated with genetic and acquired factors that result in abnormal complement regulation. Distinct entities include dense deposit disease and C3 glomerulonephritis. We have previously described familial C3 glomerulonephritis in association with two heterozygous genomic rearrangements within the complement factor H-related (CFHR) locus, implicating CFHR dysfunction in the pathogenesis of C3G. In one family, the condition segregated with a hybrid *CFHR3-1* gene. In another study we described families from Cyprus in which the disease segregated with an internal duplication within the *CFHR5* gene ('CFHR5 nephropathy'). This mutation resulted in an abnormal CFHR5 protein which contained a duplication of the first two short consensus repeat domains. Here we demonstrate that an identical abnormal CHFR5 protein, arising from a mutation distinct from that which we reported in affected individuals with Cypriot ancestry, is associated with familial C3 glomerulonephritis in a family without Cypriot ancestry. The phenotype in the two geographically distinct cohorts is remarkably similar. The demonstration of an association between familial C3G and an abnormal CFHR5 protein generated through different mutations strongly suggests that the change is causative. We recommend that CFHR analysis is performed in all cases of C3G.

P408

Whole exome sequencing in familial kidney disease

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Introduction: In many patients the cause of kidney failure is unknown. In a proportion of these cases monogenic disorders are responsible, especially where there is a family history. We used unbiased whole exome sequencing in patients with known or likely Mendelian kidney disease to identify the molecular basis.

Methods: Exomes from 48 unrelated patients with unexplained likely monogenic kidney disease were enriched and sequenced using an Illumina Genome Analyzer IIx. Alignment, mapping, variant calling and annotation was done using standard techniques and variants were filtered if non-coding, synonymous or present in >0.5% of the 1000 genomes database. This yielded between 400 and 1200 rare coding/splice site variants per person. Literature and database searches were used to identify likely disease-causing variants.

Results: 10 families were found to harbour pathogenic mutations in genes known to be associated with monogenic kidney disease. 8 families harboured a novel variant in a plausible candidate gene not previously associated with similar human disease. These are currently under study. In the remaining 30, no single likely causative mutation was identified. This is presumed to result from one of: causative variants missed or filtered by the exome sequencing strategy used; mutations in novel, unsuspected genes; or non-monogenic disease. Comparison of variants across different families and within families (ie linkage) is underway.

Discussion: Index case exome sequencing can be a useful first step in investigating Mendelian kidney disease. Here we identified the likely causative variant in 20% of cases and in the remainder excluded coding mutations in known genes in a single step, obviating the need for individual candidate gene sequencing. This approach will become more valuable as more genes responsible for kidney disease are identified, and observing separate mutations in the same gene among unrelated families with similar clinical features will likely prove to be a powerful way of identifying new disease genes, provided collaborations can be established to do this.

P409

Renal and liver function tests as potential biomarkers for discriminating *HNF1B* disease from other forms of MODY

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Introduction: *HNF1B* gene mutations/deletions are the commonest known genetic aetiology of renal developmental disorders. They also cause maturity onset diabetes of the young (MODY) and are associated with hyperuricaemia and deranged liver function tests (LFTs). *HNF1B* gene deletions have recently been identified by screening individuals with young-onset diabetes in the absence of known renal disease. Our aim was to test the role of simple biochemical tests, such as renal function, uric acid and LFTs, as biomarkers to help distinguish *HNF1B* disease from other types of MODY.

Methods: Plasma from diabetic individuals with *HNF1B* mutations/deletions (n=33) and MODY due to mutations in the *HNF1A* and *HNF4A* genes (n=66) was analysed for urea, creatinine, uric acid and LFTs (including bilirubin, ALT, AST, GGTP and albumin). Results were analysed using non-parametric statistical tests.

Results: There was evidence of renal structural abnormality in 79.2% of the *HNF1B* group (vs. 0 in the *HNF1A/HNF4A* group, $p<0.0001$). The percentage of patients with 2 or more abnormal LFTs was higher in the *HNF1B* group (34.8% vs. 7.7%, $p=0.02$). Looking at LFTs individually, GGTP was also higher in the *HNF1B* group (median 56 vs. 12 U/L, $p<0.001$; AST 35 vs. 27 U/L, $p=0.07$; AST 24 vs. 15 U/L, $p=0.15$). Renal function was worse in the *HNF1B* group (median creatinine 133 vs. 83.5 μmol/L, $p<0.001$). This group had higher uric acid levels (median 293 vs. 192.5 μmol/L, $p<0.001$) but this may be explained by the significantly worse renal function and a greater percentage of males (54.2% vs. 25.9 %, $p=0.03$).

Discussion: Our results suggest renal function and LFTs may be useful as biomarkers to help discriminate *HNF1B* disease from other forms of MODY. Biomarkers and clinical features could be combined in a single model to define the probability of a patient having an *HNF1B* mutation/deletion. This would lead to improvements in disease recognition and aid selection of subjects for genetic testing. A genetic diagnosis is important as it raises the possibility of sub-clinical renal disease and the 50% risk of affected offspring.

P410

Karyomegalic interstitial nephritis: an unusual cause of progressive renal impairment

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Introduction: Karyomegalic Interstitial Nephritis (KIN) was first described in 1974 and since then only 12 families with KIN have been reported. Mutations in *FAN1*, an effector of the Fanconi anaemia pathway, were recently implicated (1). We describe a case of KIN which, to our knowledge, is the first report in the UK.

Case report: A 40 year old woman, of Pakistani origin, was referred to the renal clinic with progressive chronic kidney disease (CKD). She had symptoms of occasional nocturia and mild fatigue. There was no family history of note except for a distant cousin with Fanconi anaemia. Previously, she was noted to have CKD of unknown cause, with a blood pressure of 102/66 mmHg together with negative urinalysis, negative serology and no other symptoms. She was advised to be at low risk of progression and that a renal biopsy was not indicated. At the time of referral her eGFR had fallen from 42 to 35 over the preceding 8 months. Renal ultrasound demonstrated slightly small kidneys. Following extensive discussion of potential risks and benefits, she underwent a renal biopsy which showed typical changes of KIN. Following informed consent, we undertook a molecular genetic analysis of the *FAN1* gene and identified a novel missense mutation, affecting a highly conserved residue and predicted to be pathogenic.

Discussion: This patient developed progressive renal dysfunction in the absence of the usual risk factors such as hypertension or proteinuria, thus a possible interstitial nephritis was suspected. She was aware that with small kidneys, the chances of the histological diagnosis affecting management and outcome were remote. A histological and molecular genetic diagnosis now allows some insights into her disease pathogenesis and other family members can be screened. We speculate that other cases, labelled as slowly progressive CKD, may be due to underlying genetic abnormalities which contribute to fibrosis.

References: 1. *FAN1* mutations cause karyomegalic interstitial nephritis, linking chronic kidney failure to defective DNA damage repair. Zhou et al, Nat Gen 44: (8)910-917(2012)

P411

A review of the renal genetics service, Queen Elizabeth Hospital, Birmingham

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Recent advances in molecular genetics mean that more accurate and more predictive testing is available into well known and less well known inherited conditions. The utilisation of these methods offers increased diagnostic certainty, reduces the need for more invasive investigations such as renal biopsies, allows early intervention thereby altering the disease progress and importantly allows genetic counselling for affected families. This audit is a review of the renal genetics service provided at the Queen Elizabeth Hospital, looking at genetic testing offered and their outcomes.

Method: A review of renal genetic testing over the 5 year period -Jan 2007 – Dec 2011 was undertaken. A database was compiled of all genetic tests performed by the renal genetics service for renal associated conditions during this period. The notes of families were reviewed to obtain details surrounding testing along with test results.

Results: Genetic testing was performed for the following conditions and their associated genes: Alports syndrome associated with COL4A5 and autosomal COL4A3 and COL4A4; polycystic kidney disease analysing PKD1, PKD2 and PKHD1; renal cyst and diabetes syndromes analysing HNF1b and HNF1a, mitochondrial disorders such as mitochondrial encephalopathy lactic acidosis and stroke like syndrome and uromodulin associated nephropathies. The most requested genetic tests were for genes associated with Alports syndrome. Tests included diagnostic tests (54%) and familial mutation analyses (46%), where individuals were tested for mutations formerly identified in their families. Mutations were identified in 65% of tests performed. Mutations were identified in 71% of familial mutation analyses but only in 54% of diagnostic tests.

Conclusion: Genetic testing is useful in the diagnosis of renal inherited disorders. It is helpful to families in which a mutation has already been identified, by allowing active monitoring, early intervention and genetic counselling for affected individuals.

Poster session

Friday 15th March

11:30 - 12:30

Endothelial and vascular pathology, experimental hypertension 1

P412

Calcimimetic R-568 inhibits vascular smooth muscle cell calcium deposition

Guerman Molostvov[1], Simon Fletcher[0,2], Rosemary Bland[1], Daniel Zehnder[1,2]

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We have previously demonstrated expression of a functional calcium-sensing receptor (CaSR) in human artery, aortic smooth muscle cells (HAoSMC), and a correlation between CaSR expression and calcification. Here we investigate the effects of calcimimetics allosteric modulators of CaSR on HAoSMC CaSR expression and calcification.

HAoSMC were cultured under static or cyclic biaxial strain (7% stretch, 30 cycles/min) for up to 7 days in the presence of 5mM β-glycerophosphate. Cells were treated with 2 or 5mM Ca^{2+} with or without the calcimimetic R-568 (10nM, 100nM, 1μM) or 1μM S-568 (inactive enantiomer). CaSR expression was analysed by Western blot, while calcification was assessed with alizarin red staining. Data were analysed by ANOVA and Tukey's multiple comparison tests.

CaSR expression was dramatically down-regulated (by 70%, $p<0.01$) after treatment with 5mM Ca^{2+} in static cultures. Addition of 10nM R-568 significantly attenuated the observed decrease of CaSR expression ($p<0.05$), however, treatment with higher doses of R-568 (100nM, 1μM) did not restore CaSR expression. Incubation with S-568 did not produce any significant changes. HAoSMC culture under a cyclic strain resulted in a marked up-regulation of CaSR (by 31%, $p<0.05$), both in cells treated with 2 and 5mM Ca^{2+}. Addition of 10nM R-568 to strained cultures produced a moderate further increase in CaSR level, which was not significant. Alizarin red staining revealed a dramatic increase in calcium deposition in 5mM Ca^{2+} static cell cultures. Importantly, it was dramatically reduced in the presence of 10nM R-568 (by 32%, $p<0.01$) and even further in 100nM and 1μM R-568 cultures (by 48%, $p<0.01$). The reduced calcium deposition with R-568 under static cell culture condition was comparable to effects observed with strain conditions.

These data indicate that (1) culture of HAoSMC under mechanical strain partially restored CaSR level inhibited by treatment with high (5mM) Ca^{2+}; (2) reduced CaSR expression was associated with increased calcification in vascular SMC; (3) R-568 significantly inhibited calcium deposition in HAoSMC, suggesting an important role for calcimimetics in regulating vascular calcification in patients with CKD.

P413

Vitamin D deficiency and excess similarly accelerate atherosclerotic calcification in apolioprotein E deficient mice

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Background: Observational data link lower levels of 25-hydroxy vitamin D (25OH-D) to cardiovascular morbidity and mortality in populations with/without kidney disease, but interventional data demonstrating cardiovascular benefits of supplementation are lacking.

Aims: To investigate the cardiovascular patholcgy induced by dietary 25OH-D deficiency on an atherogenic background.

Methods: Atherosclerosis-prone apolipoprotein E-deficient mice were fed high fat diets deficient or replete in 25OH-D and coadministered paricalcitol/ vehicle by intraperitoneal injection (giving 4 groups n=7-8 per group). Blood pressure was monitored over a 20 week intervention period then atheroma burden and character were assessed in sections through the aortic root, with von Kossa staining of calcification. Left ventricular morphology was analysed histologically and by echocardiography; bone changes were assessed by microCT.

Results: Vitamin D deficient diet induced significantly lower levels of plasma 25OH-D (56nM vs. 13nM $p<0.001$) and trabecular bone density (16% vs. 12% $p<0.01$) within 12 weeks of the intervention, with a small non-significant increase in parathyroid hormone (PTH). Administration of paricalcitol suppressed PTH and significantly increased plasma calcium-phosphate product (7.3 vs. 4.9μM^2 $p<0.05$), but did not reverse the trabecular bone changes accompanying 25OH-D deficiency. Plasma lipid profile and blood pressure were not changed by interventions. Left ventricular function and morphology were also not affected by intervention group, nor were atherosclerosis burden, cellularity or lipid content. However, the 25OH-D deficient group had a significant increase in the number of atherosclerotic calcifications (4.6 vs. 2.0 $x10^{-4}/\mu m^2$ $p<0.01$) almost equal to the group administered paricalcitol (4.9 $x10^{-4}/\mu m^2$) at a dose inducing hypercalcemia.

Conclusion: Dietary 25OH-D deficiency induced atherosclerotic calcification before other cardiovascular pathologies were evident and to a degree similar to that of an established model of vascular calcification.

P414

Inhibition of Ca2+ influx through the Na+/Ca2+-exchanger (NCX) preserves endothelial barrier function in response to thrombin: evidence from in vitro and in vivo models

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[1]*Barts and the London School of Medicine, London, UK,* [2]*The Institute of Cancer Research, London, UK*

Patients with chronic kidney disease (CKD) exhibit higher levels of plasma thrombin activity. We believe that high thrombin levels could have a direct effect on the vascular endothelium, through its main receptor protease activated receptor -1 (PAR-1), leading to loss of barrier function; thus, contributing to the pulmonary and peripheral oedema that are hallmarks of CKD and are believed to exacerbate the severity of this multifaceted disease. Additionally, CKD patients have also higher cytosolic myocardial Ca2+ levels. However, the effect of Ca2+ influx on cell signalling in the endothelium remains largely unknown.

We have recently reported that in primary human umbilical vein endothelial cells (HUVECs), Ca2+ influx through reverse-mode NCX is critical for extracellular regulated kinase 1/2 (ERK1/2) activation and angiogenesis in response to vascular endothelial growth factor (VEGF). In the present study, we investigated whether Ca2+ influx through NCX plays also a role in ERK1/2 activation and endothelial barrier dysfunction in response to thrombin.

In HUVECs, ERK1/2 activation in response to thrombin required an influx of extracellular Ca2+ and this was suppressed by the specific reverse-mode NCX inhibitors SN-6 and SEA0400 in a dose- and time-dependant manner. Furthermore, SN-6 or SEA0400 attenuated thrombin-induced Ca2+-transients. Knocking down NCX1 (the primary NCX isoform in HUVECs) with siRNA suppressed thrombin-induced ERK1/2 phosphorylation. Conversely, loading HUVECs with Na+ by inhibiting the Na+-K+-ATPase with ouabain, thus promoting reverse-mode NCX, accelerated ERK1/2 activation. Reverse-mode NCX inhibitors also suppressed ERK1/2 activation in response to a specific peptide agonist of the protease activated receptor 1 (PAR-1), indicating that NCX could act downstream of PAR-1. Importantly, inhibiting reverse-mode NCX with SN-6 and SEA0400 or the ERK1/2 pathway with PD98059 had a functional effect and preserved endothelial barrier function in response to thrombin in vitro. Finally, SEA0400 suppressed Evans Blue-Albumin extravasation to the lung and kidneys of C57bl/6 mice and attenuated oedema formation, in response to exogenously applied thrombin.

Taken together, our in vivo and in vitro work indicates that Ca2+ influx through reverse-mode NCX is a novel determinant of vascular permeability in response to thrombin and drugs targeting reverse-mode NCX could be beneficial in treating conditions where endothelial barrier function is impaired, such as CKD or sepsis.

P415

Angiopoietin-2 is a marker and mediator of cardiovascular disease in children with severe chronic kidney disease

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Introduction: Children with chronic kidney disease (CKD) develop early onset cardiovascular disease (CVD). One of the earliest signs of CVD in individuals with CKD is endothelial damage and dysfunction; therefore we hypothesised that an alteration in angiopoietin (Ang)-1 and -2, growth factors which regulate endothelial and vascular function could be involved.

Methods: We measured circulating levels of Ang-1 and Ang-2 in a cohort of paediatric patients with chronic kidney disease, both pre-dialysis (n=20) and dialysis (n=30) and correlated this with markers of vascular disease. Patients were compared with healthy age- and gender- matched children. In addition, to explore the possibility that Ang-2 may directly contribute to CVD, we examined its effect on calcification through *ex-vivo* organ culture using whole arterial rings obtained from CKD patients.

Results: The endothelial survival factor, Ang-1 was low in children with pre-dialysis CKD whereas the pro-inflammatory Ang-2 was elevated in children on dialysis. In dialysis patients, Ang-2 positively correlated with time on dialysis, systolic blood pressure, and carotid artery intima media thickness. Elevated Ang-2 levels in dialysis versus pre-dialysis CKD patients were also associated with an anti-angiogenic (high soluble VEGFR-1 and low VEGF-A) and pro-inflammatory (high urate, E-selectin, P-selectin and VCAM-1) milieu. Ang-2 was immunodetected in arterial biopsy samples whilst the expression of VEGF-A was significantly downregulated in dialysis patients. Serum urate correlated with Ang-2 levels in dialysis patients and addition of uric acid was able to induce rapid release of Ang-2 from cultured endothelial cells. Arterial rings obtained from CKD patients exhibited an elevated calcium load when stimulated with Ang-2 in a high calcium-phosphate media, compared with rings grown in calcium and phosphate without Ang-2.

Conclusion: Ang-2 may not only be a marker for CVD in children but also directly drive this process; this may hold considerable relevance to the adul CKD population given that increasing circulating Ang-2 levels have been shown to be predictive of mortality. Therapies targeting angiopoietins may be of clinical benefit for both paediatric and adult patients in the future.

P416

Is galectin-3 responsible for microvascular dysfunction in chronic experimental uremia?

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Introduction: Microvascular dysfunction is universal in uraemia and contributes to cardiovascular mortality. The aetiology of chronic uremic microvascular dysfunction remains elusive. We investigated microvascular dysfunction in experimental chronic uraemia by intravital microscopy (IVM) of leucocyte endothelial interactions in cremasteric postcapillary venules used routinely in such studies. We aimed to establish if the pro-adherent leucocyte cell surface protein Galectin-3 – (which is elevated in uremic leucocytes) would augment the interaction.

Methods: Wild Type (WT) C57Bl mice subject to 4 weeks 0.25%Adenine diet (AD n=8) or Sham Diet (SD n=6) underwent cremasteric IVM. Leucocyte rolling velocity, adhesion and transmigration were assessed. Galectin-3 Knockout (G3KO) mice were then subjected to 4 weeks AD (n=5) vs 4 weeks SD (n=3) and had Cremasteric IVM performed.

Results: WT AD fed mice had significantly more cell adhesion vs WT SD ($p=0.008$), Cell rolling velocity and emigration were not significantly altered. In Galectin-3 KO on AD the cell adhesion was normalised. Interestingly the G3KO on AD had a milder uraemic phenotype than WT on AD with significantly higher body weights and lower creatinine. A reduction in the uremic phenotype is likely to be due to a reduction in macrophage infiltration as Galectin-3 is a chemoattractant for monocytes and activates macrophages towards a pro-fibrogenic M2 phenotype.

Conclusion: Leucocyte adhesion on post capillary venules is increased in experimental uremia which is either directly or indirectly regulated by Galectin-3 interactions.

P417

The vascular vitamin d hormonal system is blunted in arteries from patients with CKD when comparing to arteries from healthy individuals

Guerman Molostvov[1], Maria A. Lubczanska[1], FT Lam[0,2], Rosemary Bland[1], Daniel Zehnder[1,2]

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Background: Patients with failing kidneys have increased vascular complications and premature death. Vitamin D and its active compounds have been associated with a beneficial therapeutic effect on this deleterious vascular process. We aimed to characterize artery vitamin D receptor (VDR), key vitamin D activating (CYP27B1, 25-hydroxyvitamin D 1α-hydroxylase) and inactivating enzyme (CYP24A1, 24-hydroxylase) expression in human arteries.

Method: Artery from CKD patients undergoing a renal transplant (n=10) and healthy donors (n=13) were used to characterise VDR, CYP27B1, CYP24A1 mRNA and protein. Alizarin red staining for vascular calcium and Cbfa1/RUNX-2 for cell phenotype characterisation was used. Artery explants were incubated for 14 days with 100nM calcitriol or 300nM paricalcitol in normal or calcification medium containing 5mM Ca^{2+} and 5mM β-glycerophosphate. Expression of target gene mRNA was quantified by real-time PCR.

Results: VDR protein expression was found throughout the smooth muscle cell layer of the artery wall. Expression levels varied in healthy and CKD groups. Increased expression was observed in healthy artery after calcitriol and high calcium treatment. CKD artery had a blunted response, without an increase of VDR expression. CYP27B1 expression, the enzyme that activates vitamin D locally, was suppressed in CKD ($P<0.05$). Calcitriol, paricalcitol or Ca^{2+} treatment had no effect on its expression. High mRNA levels in CKD were suppressed by calcitriol or paricalcitol. CYP24A1 protein, the enzyme that catabolises vitamin D, was present in human artery. Exposure to high dose calcitriol (>100x, $p<0.001$) or paricalcitol (>900x, $p<0.001$) for 14 days, resulted in a dramatic CYP24A1 mRNA increase. This increase was also observed with concomitant high Ca^{2+} treatment. No CYP27B1 response was observed for high Ca^{2+} treatment alone. Smooth muscle cell phenotype transformation (RUNX-2, osteocalcin), vascular remodelling (MMP2, MMP9) and vascular wall inflammation was increased with CKD. Only paricalcitol was able to suppress Runx-2 in artery from CKD.

Conclusion: The vitamin D hormonal target receptor and the vitamin D activating and catabolising enzymes are expressed in artery from healthy and CKD groups. Prolonged treatment with active vitamin D compounds result in activation of the catabolic vitamin D enzyme, potentially causing direct vascular therapeutic resistance.

P418

Klotho regulats vascular smooth muscle aging in CKD

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Background: Premature vascular aging occurs in patients with CKD with the consequence of arterial stiffening and cardiac strain. Klotho is a 130kDa transmembrane protein that is expressed in arterial smooth muscle cells. We previously showed that arterial Klotho deficiency and pro-calcific environments in CKD result in accelerated calcification. We postulate that Klotho is central to regulating vascular smooth muscle cell aging and its deficiency results in accelerated age-related changes.

Methods: Human aortic smooth muscle cells (HA-SMCs) were subjected to replicative senescence or high calcium (2.7mM) and high phosphate (2mM), circulating stress factors found in CKD. HA-SMC aging was determined by accumulation of the aging markers, pre-lamin A, senescence associated β-galactosidase (SAβG) and phenotypic adaptation.

Results: Our results show that senescent, old HA-SMCs ((passage) P14-P17) compared to young (P4-P7) cells exhibited marked suppression of endogenous Klotho. This was associated with accumulation of aging prelamin A, SAβG and age-related changes, including suppression of smooth muscle cell markers Smoothelin, Serum Response Factor (SRF) and Calponin together with upregulation of the ostegenic marker, Cbfa1. We next showed that suppression of Klotho by high calcium and high phosphate was resulted in accumulation of aging markers, suppression of smooth muscle cell markers and upregulation of Cbfa1. Functional studies demonstrated that senescent, old HA-SMCs exhibiting Klotho suppression were prone to develop accelerated calcification when compared to young HA-SMCs. Finally, suppression of Klotho by Klotho siRNA exhibited accumulation of pre-lamin A and SAβG, together with loss of smooth muscle cell phenotype and osteogenic transformation.

Conclusions: We show here for the first time that loss of endogenous Klotho expression in HA-SMCs under both replicative senescence and in the presence circulating mineral stressors found in CKD results in age-related changes with an increased propensity to calcify. Transfection studies showed that Klotho deficiency directly causes age-related changes in HA-SMCs. Our results point to a central role of vascular Klotho in the regulation of vascular health.

Poster session

Wednesday 13th March

18:15 - 19:25

Fibrosis 1

P419

Chronic renal allograft failure: the differing roles of heparan sulphate interactions and transglutamination in latent TGF-β binding to renal epithelia

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TGF-β is an initiator of renal fibrosis in the context of chronic renal allograft failure. Upon secretion as a pro-peptide bound, latent cytokine complex, TGF-β is sequestered on the surface of renal epithelial cells. This 'pool' of latent TGF-β then has the potential to be activated, leading to fibrosis. This study investigated the mechanisms by which latent TGF-β is sequestered within transplanted kidneys.

A biotinylated probe based on the N-terminal region of latent TGF-β binding protein-1 (LTBP-1) – a component of the latent TGF-β complex responsible for sequestration – was synthesised in a bacterial expression system. The probe, referred to here as LTBP-1-biotin, was found to bind heparin and heparan sulphate (HS) *in vitro* in a solid-phase binding assay. Applying soluble heparin to heparin-bound LTBP-1-biotin resulted in significant ($P<0.0002$) removal of bound probe, and a similar finding was observed with soluble heparins that were *N*- and 6-*O*-sulphated only ($P<0.002$). Heparins that were lacking *N*- or 6-*O* sulphation were unable to remove bound LTBP-1-biotin from heparin, whereas de-2-*O*-sulphated heparin was able to do so ($P<0.05$). These data demonstrate the importance of *N*- and 6-*O* sulphation of heparin-like glycosaminoglycans (GAGs) for LTBP-1 binding.

Immunofluorescent staining experiments assessed the relative roles of HS interactions and isopeptide bond formation in LTBP-1 sequestration by cultured human dermal fibroblasts (HDFs). Both soluble heparin ($P=0.005$) and the transglutaminase inhibitor cystamine dihydrochloride ($P<0.05$) significantly reduced LTBP-1 binding to HDFs when added at the initiation of HDF cultures. However, soluble heparin was unable to remove sequestered LTBP-1 when added at the end of 14 day cultures, suggesting that although HS is important for initial binding, LTBP-1 is 'locked' in place by transglutamination over time.

This study demonstrates the initial importance of *N*- and 6-*O*-sulphated HS, and the subsequent requirement of transglutaminase activity for LTBP-1 deposition.

P420

Antisense oligonucleotides targeting Kirsten RAS reduces interstitial fibrosis and protects kidney function in the chronic folic acid nephropathy model

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Introduction: Previously we have demonstrated the importance of Kirsten Ras (Kras) in the pathogenesis of renal fibrosis secondary to urinary obstruction. In this study we have characterised a novel mouse model of chronic folic acid nephropathy (CFAN) and have used antisense oligonucleotides (ASO) to silence Kras expression within this model. Here we report the effects of these ASOs on interstitial fibrosis and renal function.

Methods: CFAN model: Male CD1 mice were given Folic acid (FA) 125mg/kg IV in $NaHCO_3$ on day 0 (d0) and d21. Shams received $NaHC0_3$ alone. Animals were sacrificed at d35, d56 and d85 for model characterisation. Therapeutic study: CFAN groups received saline (vehicle) or ASO (20mg/kg) SC 3X per week from d35 reducing to 2X per week from d49 and were sacrificed at d85.

Results: CFAN model: Induction of fibrosis was seen at d56 and d85 with a 3.4 fold mean increase in collagen staining and a 2 fold increase in collagen I mRNA by D85 associated with a doubling of Kras mRNA ($p= 0.0016$, $n=11$). An induction of α-SMA expression was seen at d56 and d85 of 1.2 and 0.6 fold respectively ($n=3$); IHC showed diffuse α-SMA expression in fibrotic areas, co-localising with collagen deposition. Therapeutic study: ASO resulted in a knockdown of Kras of 43% compared to the placebo-treated group ($p= 0.0185$, $n=7$). IHC for ASO showed marked accumulation of the ASO in the proximal tubules and interstitium. Total area of fibrosis, as measured by collagen deposition, was reduced by 37% in PMT staining and 27% in PSR staining in ASO-treated groups compared to placebo mice ($n=7$). ASO-treatment was associated with a 70% reduction in serum creatinine at d85 compared with placebo ($p=0.053$, $n=7$).

Discussion: In this study we have demonstrated that Kras inhibition can inhibit renal fibrosis in new model of CFAN. Encouragingly, we have also shown that this is associated with a marked improvement in renal function. We conclude that targeting Kras may prove to be a useful therapeutic tool for treating human chronic kidney disease.

P421

Hyaluronan (HA) assembly and its role in BMP-7 driven antagonism of renal fibrosis

Lucy Duggal[1], Adam Midgley[1,2], Robert Steadman[2], Aled Phillips[1,2], Soma Meran[2]

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Fibrosis leading to organ failure is a leading cause of morbidity and mortality and is mediated through myofibroblasts activity. In renal disease, a mediator of fibrosis that is up-regulated and correlates strongly with disease severity is the glycosaminoglycan hyaluronan-(HA). Transforming-Growth-Factor-β1-(TGFβ1), a known promoter of fibrosis, drives myofibroblast differentiation in a process dependent on HA synthesis and accumulation. In contrast, Bone-Morphogenetic-Protein-7-(BMP7) is down-regulated in renal disease and both prevents and reverses TGFβ1-driven renal fibrosis in animal models. Previous work has shown that HA can have anti-fibrotic as well as pro-fibrotic properties and can both modulate and mediate BMP7 responses. This project aims to investigate whether BMP7 antagonises TGFβ1 responses through alterations in HA matrix. Methods: Fibroblasts were used to test two models of BMP7-driven antagonism of differentiation - a reversal model, where cells were exposed to TGFβ1 followed by BMP7, and a prevention model where cells were exposed first to BMP7, then TGFβ1. RT-QPCR & Immunohistochemistry were used to assess expression of HA Synthase, Hyaluronidase enzymes, HA matrix structure and myofibroblast differentiation. Results: BMP7 both reversed and prevented TGFβ1-driven myofibroblast differentiation in a dose-dependent manner. This was associated with a marked alteration in the associated myofibroblast HA matrix. Pericellular HA coats were lost, there was increased intercellular HA and presence of intercellular HA strands. These changes in HA matrix were associated with specific changes in HA Synthase and Hyaluronidase expression. Namely there was increased HAS2 & HAS3 expression, and reduced HYAL2 expression compared to Myofibroblasts. Conclusions: BMP-7 alters TGF-β1-driven HA matrix in a manner likely to lead to prevention/reversal of myofibroblast phenotype. Further work will delineate these changes further investigating a causal link between the changes and cell phenotype, a fuller understanding of which may aid development of future therapeutic strategies. This work was sponsored by KRUK.

P422

IFN-γ alters mesothelial cell response to TGF-β1, promoting peritoneal fibrosis

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Problem: Peritonitis infections are a serious complication for patients receiving peritoneal dialysis (PD) leading to progressive fibrosis of the peritoneal membrane, one of the major reasons for treatment failure in PD patients.

Purpose: To investigate how pro-inflammatory signalling alters Transforming Growth Factor-Beta (TGF-β1) responses. TGF-β1 is a key regulator of tissue repair and the fibrotic process and the interaction between TGF-β1 and pro-inflammatory signalling may affect how cells respond to this cytokine either by repair and resolution, or by fibrosis and disease.

Design: *In vivo* and *in vitro* systems have been used to characterise the interplay between TGF-β1 signalling and Signal Transducer and Activator of Transcription (STAT) activation by Interleukin 6 (IL6) and Interferon gamma (IFN-γ). The *in vivo* system consists of a murine model of inflammation driven fibrosis, where mice are injected with repeated inflammatory stimulation resulting in scarring of the peritoneum. The *in vitro* system comprises culture of primary human peritoneal mesothelial cells (HPMC) in the presence of TGF-β1 +/- IFN-γ.

Findings: Stimulation of HPMC with TGF-β1 results in induction of matrix metalloproteinase 3 (MMP3) at the mRNA and protein level, which is specifically inhibited in the presence of IFN-γ. IFN-γ did not alter other TGF-β1 responses. Increased matrix production has been shown in the *in vivo* system thus supporting the *in vitro* findings. Chemical inhibition of mitogen activated kinase pathway (MAPK) through blockade of ERK 1/2 and p38 signalling prevented the TGF-β1 dependent induction of MMP3. This induction was also blocked via inhibition of SMAD 3 phosphorylation, thus suggesting that MMP3 induction via TGF-β1 requires both SMAD dependent and SMAD independent signalling pathways.

Conclusion: Within HPMC, IFN-γ appears to promote fibrosis by favouring matrix accumulation over remodelling through specific inhibition of MMP3. Current investigations are directed at the mechanism by which IFN-γ regulates MMP3 expression.

P423

Association of transglutaminase-2 and syndecan-4 in the 5/6th subtotal nephrectomy (SNx) rat model of progressive renal scarring

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The role of Transglutaminase-2 (TG2) in the pathogenesis of kidney fibrosis is well established. TG2 extracellular trafficking and post translational modification of extracellular matrix (ECM) shifts ECM homeostasis towards ECM accumulation, while its recruitment of large latent TGF- 1 elevates active TGF- 1 in kidney. Since we showed that the cell surface trafficking and transamidase activity of TG2 are linked to the cell surface receptor Syndecan-4, we quantified the expression of Syndecan genes (Sdc) relative to that of TG2 in a disease model *in vivo*. Gene expression profiles of Syndecan family members in the rat 5/6th subtotal nephrectomy (SNx) model of progressive renal scarring revealed that Sdc1, Sdc2 and Sdc4 transcripts were present in kidney but only the expression of Sdc4 doubled 90 days post SNx, thus following the progression of renal scarring and the loss of renal function. TG2 expression correlated with Sdc4 expression during fibrosis progression, with the two proteins found to be partly co-associated on the tubular cell basolateral membrane and/or the tubular basement membrane in kidneys post SNx. The interaction pattern was in keeping with prior findings of TG2 association with the heparan sulphate chains of Syndecan-4 *in vitro* and their potential cooperative role in fibrosis. Our findings provide evidence of an association between TG2 and Syndecan-4 for the first time *in vivo*, in experimental fibrosis. As TG2 is the most highly expressed Transglutaminase member in diseased kidneys, controlling the Syndecan-4-TG2 interaction could represent a novel approach to the treatment of kidney scarring.

P424

Autosomal dominant polycystic kidney disease (ADPKD) fibroblasts show abnormalities polycystin-1 (PC-1), ciliary, and focal adhesion (FA) associated with fibrotic changes

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UCL Centre for Nephrology, London, UK

Background: ADPKD is a common, monogenic disease in which aberrant PC-1 function leads to end-stage renal disease with a highly variable age of onset. As ADPKD cyst expansion is associated with pericystic fibrosis, we hypothesize that alterations in ADPKD fibroblast function play an important role in renal functional decline. Although ADPKD abnormalities have been studied in detail in cystic epithelia where PC-1 is localized in primary cilia, cell-cell adherens junctions and cell-matrix FAs, little is known in ADPKD fibroblasts. Previously we identified a hyperproliferation defect in ADPKD fibroblasts analogous to that seen in cystic epithelia. The aim of this study was to further analyse the differences between the normal human kidney (NHK), early (E-ADPKD) and endstage (ES) ADPKD fibroblasts.

Methods: Western blot and immunolocalization (IHC) techniques were used to compare PC-1, fibrotic, ciliary and FA proteins together with *in vitro* functional assays on primary cell cultures.

Results: *In vivo* IHC showed that PC-1, integrin-linked linked kinase (ILK), pILK and fibrotic markers of collagen deposition, stress fibre-associated alpha smooth muscle actin (α-SMA) and TGF-β increased with disease-stage. PC-1 was detected in all fibroblasts but ADPKD cells showed loss of full-length (~460kD) protein. Down-regulation of the putative C-terminal (~30kD) fragment was associated with reduced nuclear localization of PC-1 in ADPKD cells. Cilia were detected in all fibroblasts, but decreased in length with ADPKD stage (NHK=5.8$\pm$1.5μm; E-ADPKD =4.3$\pm$0.6μm; ES-ADPKD=3.8$\pm$0.3μm). Comparison of NHK, E- and ES-ADPKD fibroblasts showed disease stage-related increases in expression of FA kinase (FAK), paxillin and ILK and altered phosphorylation of FA proteins (pFAK (Y397), pILK (Ser 246), pPaxillin (Y31)); similar to changes seen *in vivo* while functional assays revealed increased matrix-adhesion and cell spreading in ADPKD cells as well as differences in migration and contraction.

Discussion: These data suggest that altered processing, cellular distribution and function of PC-1 in ADPKD fibroblasts is associated with ciliary, FA and functional changes relevant to fibrosis.

P425

Combined transcriptomic and proteomic analysis of extracellular matrix in glomerular disease

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Background: There is a plethora of evidence in the literature that both gender and racial background influence the development of a range of nephropathies. Many of these disorders are characterised by expansion of glomerular extracellular matrix (ECM). However, susceptibility genes have not been consistently identified and the reasons for this susceptibility remain poorly understood. In this investigation we employed a combined transcriptomic and proteomic approach to determine whether genetic background and gender influence the composition of glomerular ECM.

Methods: Four cohorts of mice were used for this study; males and females from nephropathy resistant (C57), or susceptible (FVB) genetic backgrounds. Mouse glomeruli were isolated by Dynabeads perfusion followed by magnetic particle concentration. We developed a fractionation method to isolate glomerular ECM and confirmed ECM enrichment by Western blotting. The four-way comparison was analysed using LC-MS/MS of enriched glomerular ECM and with whole glomerular expression microarray. Hierarchical clustering, network and pathway analyses were employed to provide an unbiased analysis of the datasets. In parallel, the glomerular ultrastructure was analysed using 3-view transmission electron microscopy.

Results: Preliminary proteomic data correspond with Western blot analysis and confirm ECM enrichment. Initial analysis of microarray data suggests that 840 matrisome genes are differentially regulated in a strain and gender dependent manner. Of these genes 29 % are core collagens, proteoglycans and glycoproteins and 71 % are secreted growth factors, matrix remodelling and matrix-associated proteins.

Conclusion: We have developed a methodology to isolate and interrogate glomerular ECM components in a global and unbiased manner. Integration of the proteome and transcriptome datasets will now be used to generate hypotheses for the mechanisms of ECM regulation in disease states.

Poster session

Thursday 14th March

12:00 - 13:00

Haemodialysis 1

P426

Association of HbA1c and mortality risk in diabetic haemodialysis patients: an individual patient data meta-analysis

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Introduction: Diabetes is the most common cause of established renal failure in many countries. In patients with normal renal function improved blood glucose control reduces the risk of complications and improves survival. However, glycosylated haemoglobin (HbA1c) metabolism changes in established renal failure. To date, studies investigating the association between HbA1c and mortality have shown conflicting results.

Methods: We searched Medline, Medline In Process, Embase, Cochrane and Web of Science for studies published before April 2012 glycaemic control and mortality in diabetic haemodialysis (HD) patients. Authors were asked to provide either anonymised individual patient data or re-analysed results. Where available we adjusted for age, sex, haemoglobin, diabetes type and dialysis vintage. Meta-analysis techniques were used to pool estimates across studies.

Results: Anonymised data (n=4), requested results (n=3) or extracted results (n=1) were available for 8 studies including 78,226 HD patients. After adjustment, compared with a baseline (single measurement at study entry) HbA1c of 6.5-7.4% very low baseline HbA1c (≤5.4%) wasn't associated with increased mortality (HR=1.09, 95%CI 0.79-1.51) but very high levels (≥8.5%) were associated with a slight increase (HR=1.14, 95%CI 1.09-1.19). After adjustment, compared with a mean (over course of study) HbA1c of 6.5-7.4% very low mean HbA1c values (≤5.4%) were associated with an increased mortality (HR=1.23, 95%CI 1.19-1.27) as were high (≥8.5%) mean HbA1c values (HR=1.3, 95% CI 1.24-1.36). Sensitivity analysis of incident (time on HD <90 days) and prevalent (time on HD ≥90 days) patients showed a similar distribution of hazard ratios.

Conclusions: Despite concerns over the use of HbA1c in HD patients this study has shown that mean levels at the extremes of the distribution are associated with an increased mortality risk. In the absence of any prospective clinical trials, this suggests that increasingly tight glycaemic control has no mortality benefit in HD patients whose HbA1c is less than 8.5% and may actually cause harm.

P427

Striving for sustainability in an innovative quality improvement programme in renal replacement therapies

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Introduction: The Salford Renal Network started work on a quality improvement (QI) project to improve the delivery of renal care to patient within the network. In year 1, four teams were given a different clinical indicator to work on. Salford Haemodialysis Unit aim was to have 60% of their haemodialysis patients achieve a pre – dialysis blood pressure below 140/90 by end of April 2011. This target was met successfully

Objective: To achieve sustainability in the successful improvement made by Salford Haemodialysis unit regarding blood pressure management.

Methods: Monthly tracker measures prompted a 'big push' to maintain sustainability. We re-enforced the importance of weekly QI BP meeting to focus on work in the unit and patients on blood pressure protocol adopted by unit. We used PDSA (Plan – Do –Study –Act) to facilitate staff education from a range of sources on topics including the use of blood volume sensors, fluid assessment and the importance of blood pressure control. Visual aids such as posters in the department and information / 'cue' cards for patient and dialysis unit staff were used to engage staff and patient alike.

Results: Fluid related events

	Pre intervention	Year 1	Year 2
Number of episodes	12	6	8
Total bed days	155	47	79
Transfer to > level 3 care	2	0	1
Death	2	0	1

Conclusion: It is not unusual after successfully implementing changes to struggle with sustaining these changes due to a variety of reasons. However, small concerted efforts have helped to maintain these on-going improvements as we enter year 3 of this programme to transform the network's renal services.

P428

Significant neurological disturbance due to an extreme hypochloraemic metabolic alkalosis in a haemodialysis patient

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A 33 year old accountant with a history of bulimia nervosa developed ESRD secondary to hypokalaemic nephropathy following recurrent episodes of self-induced vomiting. Three months after starting haemodialysis she presented with a generalized seizure after her 3 day interdialytic interval. This was followed by marked global disorientation and confusion. Neurological examination revealed no localising signs. No other abnormalities were noted on examination other than dehydration. Initial serum values (in mmol/L) on admission showed: Sodium 136, potassium 6.2, chloride <50 and bicarbonate 57. White cell count and CRP levels were normal. Soon after admission the patient was noted to have a temperature of 39.5°Celsius, and was therefore commenced on empirical antibiotics and aciclovir.

The patient attended her regular haemodialysis session, and was dialysed using her standard prescription against a bicarbonate concentration of 32mmol/L. Investigations, including lumbar puncture, CT brain, MRI brain and peripheral and central line blood cultures were normal and excluded an infective cause. Thus antibiotics and aciclovir were discontinued. Her symptoms were felt to be due to extreme metabolic alkalosis.

The patient required a total of 3 daily dialysis sessions to resolve her hypochloraemic alkalosis. After her third dialysis session her cognitive state had returned to baseline.

Since this admission she has suffered 3 further episodes of confusion and generalized seizures associated with bicarbonate levels greater than 50 mmol/L secondary to vomiting. It has been noted that the confusion precedes the seizures.

This case highlights the fact that extreme metabolic alkalosis in dialysis patients can occur due to persistent purging. It can have profound neurological consequences and can be mistaken for encephalopathy or central nervous system infection. The treatment is daily haemodialysis using a standard bicarbonate concentration.

P429

The relationship between symptoms and blood pressure during maintenance haemodialysis

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Background: Intradialytic hypotension (IDH) is recognised as a detrimental complication of maintenance haemodialysis, but how it is defined and reported varies widely in the literature. European Best Practice Guidelines require symptoms and a mitigating intervention to fulfil the diagnosis, but morbidity and mortality outcomes are largely based on blood pressure alone. Furthermore, little is known about the incidence of Asymptomatic Hypotension – a potential cause of sub-clinical hypoperfusion injury.

Methods: Seventy seven patients were studied over 456 dialysis sessions. Blood pressure was measured at 15 minute intervals for the entire session and compared with post-dialysis symptom questionnaire results using mixed modelling to adjust for repeated measures in the same patient. The frequency of Asymptomatic Hypotension was estimated by logistic regression using a variety of commonly cited blood pressure metrics that describe IDH.

Results: In 113 sessions (25%), symptoms were not reported to dialysis staff. When symptoms were reported, an intervention invariably followed. Dizziness and Cramp is strongly associated with changes in systolic (SBP) but not diastolic blood pressure (DBP). Nausea occurs more frequently in younger patients and is not associated with blood pressure. The threshold which maximised the probability of an intervention rather than a session remaining asymptomatic was SBP <100mmHg or a 20% reduction in SBP from baseline. The probability of an asymptomatic session experiencing a SBP <100mmHg was 0.23.

Conclusion: Intradialytic symptoms are underreported, suggesting that IDH is more problematic than reflected by current guideline definitions. Asymptomatic hypotension appears to be a significant burden and is potentially detrimental but requires continuous blood pressure monitoring to unmask its true incidence.

P430

Pleural effusion in haemodialysis patients – diagnostic investigations and clinical outcome

Richard Corbett, Damien Ashby

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Pleural effusion is common in dialysis patients – although usually transudative, exudative effusions are also frequent. Dialysis treatment often alters the clinical presentation, and the optimum diagnostic investigations are unknown. In this retrospective study, all haemodialysis patients undergoing diagnostic aspiration during an 18 month period were identified from electronic records. Diagnostic data were collected and examined in the light of the final clinical diagnosis.

Twenty-two pleural aspirations were identified in 19 patients (aged 30–83, mean 64.6) of which 9 were ultimately diagnosed as transudates. Amongst the remaining 13 cases there were 4 empyemas, and other effusions were parapneumonic (5) or due to malignancy (1), eosinophlia (1), tuberculosis (1) and blunt trauma (1).

Individual components of Light's criteria were poor indicators of effusion type, and in combination had sensitivity and specificity for non-transudative effusion of 92% and 44% respectively. Compared to transudates, exudates did have higher fluid protein levels (44.0 vs 30.2mg/L, p=0.018) and in ROC analysis, fluid protein was reasonably useful as a discriminator, with area under curve 0.782 (p=0.030). CT imaging was available in all but 2 cases, and proved the most useful test, providing diagnostic accuracy beyond effusion type (for which it was 83% sensitive and 88% specific), but no single test was fully reliable and clinical judgement remained essential. Over a mean follow-up period of 271 days, median survival was 249 days, with no significant difference between effusion types (p=0.196).

Pleural fluid biochemistry is of limited diagnostic value in dialysis patients, in whom CT imaging provides the most useful information. In this group of patients mortality is high, and clinical judgement remains paramount.

P431

Single centre experience on the serological response to hepatitis B vaccination among haemodialysis patients. Single nurse-led approach using four doses protocol

Khaled Abdulnabi, Hsu Pheen Chong, Asad Ullah, Hasnain Raza, Rema Saxena, Pearl Pai, John Sexton, Gordon Bell, Tilly Leach, Vicky Ashworth, Mathew Howse, Atif Khalil

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Introduction: Primary prevention of HBV infection through vaccination is a first choice to reduce the morbidity from HBV. In 2005, we identified that just less than 50% of our dialysis patients had sufficient immunity to HBV post vaccination.

Objective: To evaluate the serological response to hepatitis B virus (HBV) vaccination before and after the adoption of a new protocol and vaccination based on the Renal Association guidelines, 2009**(Guidelines BBV 5.1–5.8)**

Method: We conducted two retrospective audits on the serological response to hepatitis B virus (HBV) vaccination in 2005 and 2011. Data was collected on 90 patients in 2005 (received dose of HBvaxPRO40 in Deltoid muscle at 1,2 and 6 months) and 84 patients in 2011 (received simultaneous 2 doses of Engerix 20mcg in Deltoid and the contra-lateral Vastus Lateralis muscles at 1,2,3 and 6 months). HBsAb titre was checked 2 months after the last injection. Patients with HBsAb titre> 10 IU/ml were labelled as responders and scheduled to receive a booster dose in a year, while those with a titre< 10 IU/ml received a booster dose.
A single dialysis Nurse was in charge of the vaccination programme in 2011.

Results: The serological response rate to HBV vaccination was 76% in 2011 compared to only 46% in 2005 (P=0.001). In the 2011 cohort, responders had higher mean albumin level than non-responders (36 g/l vs 25 g/l, p=0.001) and a lower mean CRP level (18mg/l vs 34mg/l, p=0.001). Likewise, they had a higher arteriovenous fistula (AVF) rate (95% vs 76%, p=0.002). Age, gender, anaemia duration on dialysis and diabetes mellitus were not statistically different between both groups. A higher AVF rate was achieved in 2011 compared to 2005, (90% vs 66%, P=0.001).There was no statistical difference between 2011 and 2005 in terms of age, gender, duration on dialysis, diabetes mellitus and anaemia.

Conclusion: A single nurse led vaccination approach in implementing the above protocol has led to an increased seroconversion for HBsAb rate. On univariant analysis, presence of an AVF, higher albumin or lower CRP was associated with seroconversion. Although seroconversion rates have improved they remain sub-optimal at 76% emphasising the importance of pre-ESRD vaccination.

P432

Home haemodialysis- an audit on practice

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Introduction: National Institute for Health and Clinical Excellence recommends that all patients suitable for home haemodialysis (HD) should be offered the choice of having HD at home or in a renal unit. The aim of our audit was to determine if patients suitable for home HD had been offered the option in our dialysis unit.

Methods: A questionnaire survey of the dialysis patients was undertaken in January 2012. The following patient details were collected including ability and motivation to carry on HD, stability on HD, presence of complications and concomitant disease that would render home HD unsuitable or unsafe, good functioning vascular access, patient's carers involved in decision making when involved in assisting with home HD, suitable space and facilities within the home. It was determined if patients meeting the essential criteria had been offered the option of home HD.

Results: There were a total number of 84 patients on HD of which only 18 patients were suitable for home HD. 75 patients showed commitment to HD treatment, 68 stable on dialysis, 60 able to manage haemodialysis individually and 34 free of complications and significant co-morbidities. There were ongoing discussions among 6 of the 18 patients fit for home HD. 5 patients were not offered the option, 2 patients opted for another modality, 2 patients refused and the carers refused home HD in another 2 patients. One of the 5 patients not offered the option of home haemodialysis was a recent transfer from another dialysis unit.

Discussion: Although home HD is associated with better patient survival and less expensive than hospital or satellite based HD a significant number of patients were not offered the option. There is a need to actively identify these patients and to improve this process we have a dedicated home HD nurse at our unit.

P433

Timing of pre-dialysis education in patients over 65 years of age- when is the right time to educate on choices for renal replacement therapy?

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Background: Educating patients at the pre-dialysis stage ensures they understand the need for renal replacement therapy (RRT) and that they choose a modality in a timely and informed fashion. Most patients are referred for pre-dialysis education (PDE) at our centre when, on the basis of declining renal function (glomerular filtration rate (GFR) ≤25 mls/min), the need for RRT becomes evident. However the rate of renal decline is difficult to predict and means that some patients receive education many months before they need to start RRT. For the elderly patient, early education does not always equate to the patient choosing a modality early on and often means the patient has to be re-educated when the GFR drops later on. Currently no specific guidelines exist as to when to deliver PDE to patients who are approaching the need for RRT or on the optimal GFR for imparting education.

Aims: To establish whether we are delivering PDE to patients over the age of 65 appropriately and in a timely fashion at our centre.

Methods: We looked at age and GFR at time of PDE, age and GFR at start of dialysis, time to start of dialysis, modality of RRT chosen by patient, outcome at 18 months following PDE and cause of CKD.

Results: 320 patients over the age of 65 received pre-dialysis education from 2007 to 2009 (58% male, 42% female). 83% (266) were European, 14% (44) were from the Indian subcontinent and 3% (10) were Afro-Carribean. 34% of the cohort (108) who received PDE started dialysis in the 18 month follow up period. 95 (88%) patients chose haemodialysis. In this cohort the mean age at education was 74.88. The mean age at dialysis was 75.42. The mean GFR at education was 13.80 and the mean GFR at dialysis was 9.15. The mean time from education to dialysis was 0.6 years. 13 (22%) patients chose peritoneal dialysis. In this group the mean age at education was 70.72. The mean age at dialysis was 71.46. The mean GFR at education was 12.90 and at dialysis 8.87. The mean time from education to dialysis was 0.74 years. In the non-dialysed cohort (212 patients) the mean education age was 77.5. The mean education GFR was 17.4. 104 patients died in the 18 month follow up period (33% of the total cohort). The remaining 108 (34%) did not progress to dialysis in the follow up period. The most common causes of CKD in our cohort were diabetic glomerulosclerosis (103), uncertain aetiology (90), a combination of other conditions (72) and renovascular disease (55).

Conclusions: Patients over 65 years were educated at GFRs between 10 and 20, which is timely. A third of the patients who had PDE progressed to dialysis, a third did not and a third of the patients died within 18 months of starting PDE. Our data suggests that over half of the over 65 cohort who receive PDE at our centre do not start dialysis or die within 18 months of commencing dialysis.

P434

A single center experience of pregnancy in women receiving dialysis

Arvind Ponnuswamy, Maharajan Raman, Hayley. L. Mcmanus, Daniel. J. Hall, Philip. A. Kalra, David. I. New, Teresa Kelly

Salford Royal NHS Foundation Trust, Salford, UK

Introduction: Patients with end stage renal disease rarely conceive due to anovulatory menstrual cycle.

Method: We undertook a retrospective review of pregnancy in women on renal replacement therapy from 2007 to 2011. All patients are cared in a multidisciplinary team involving comprising nephrologists, obstetricians, midwives, dietician and dialysis nurses from the antenatal period to delivery and beyond.

Results: There were 4 pregnancies during this period all of which resulted in a live newborn giving an incidence rate of 2 per 1000 dialysis patients/year. They were no reported case unsuccessful pregnancy. However, one of the cases was a twin pregnancy whereby one of twins died. The mean age was 34 years (range 29-42). Three patients were Asian and 1 was Caucasian. All patients were on aspirin and some form of anti-hypertensive medication. All pts were on daily dialysis – or at least 6 times/week with a mean frequency was 5.5 times/week. Our patients tolerated daily dialysis. Average urea levels were less than 17 mmol/L. Mean UF during the dialysis was 1.4 $\pm$ 1 litres. Average gestational age at delivery was 32.3 $\pm$ 3.3 weeks. The average birth weight was 1827 $\pm$ 750 g. Table below shows the laboratory features of these patients during pregnancy.

	1st trimester	2nd trimester	3rd trimester
Hb	104+ 11	99 + 14	93.2 + 19
Uric Acid	0.27 $\pm$ 0.1	0.31 $\pm$ 0.1	0.31 $\pm$ 0.02
Systolic BP	127	122	128

Conclusion: Evidence on pregnancy in dialysis patients is scattered and heterogeneous.

Our cohort of patients had good maternal and foetal outcome. This is due to combination of daily dialysis, optimum BP control, dietary input for PO4/fluid gains/essential vitamins, aspirin as pre eclampsia prophylaxis and careful monitoring foetus.

Poster session

Friday 15th March

11:30 - 12:30

Haemodialysis 2

P435

Cognitive impairment in elderly renal inpatients: an under-identified phenomenon

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Cognitive impairment is a common but under-recognised problem in patients with chronic kidney disease (CKD), and is likely to become more significant as this patient population ages.

This cross-sectional study focussed on inpatients aged ≥65 years at a tertiary renal unit, and consisted of two parts. Part 1 considered whether cognitively impaired inpatients were being identified, and if so, whether they were being appropriately investigated and referred to memory services. In Part 2 cognitive function tests (CFT) were attempted using two different methods (MMSE, 6CIT).

Our findings showed that, in Part 1 (29 patients), CFT was attempted in only 3 patients at admission, and 2 patients subsequently. No patients were referred to memory services. In Part 2 (105 patients, age 65-89 years, 82 on haemodialysis), CFT was not performed in 11 patients who were discharged prior to testing, and in 12 patients mostly (8) because of language problems. In the 82 patients who had CFT, MMSE was abnormal (score <27) in 78.5% (score 21-26: 28.9%, 15-20: 28.9%, 10-14: 13.3%, <10, 8.4%). 6CIT was abnormal (score ≥8) in 61.4%. There was a close correlation between MMSE and 6CIT ($r=0.735$). Only 7.2% (6 patients) of those assessed had a documented cognitive deficit prior to admission.

This is the first study looking at cognition in elderly inpatients with CKD. There appears to be a much higher rate of cognitive impairment than expected and this is largely unidentified. The findings could be due to delirium as well as underlying cognitive deficits. These deficits are likely to have a major impact on both inpatient and outpatient management, as well as on issues surrounding capacity for future health-related decisions.

P436

Systolic blood pressure variability predicts mortality in incident haemodialysis patients

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Introduction: Visit-to-visit systolic blood pressure variability (SBPV) is an independent risk factor for mortality and cardiovascular (CV) events in the general population. We investigated the effects of SBPV on all-cause mortality in incident haemodialysis (HD) patients.

Values: mean±SD or n (%)	VIM below median n= 100	VIM above median n=103
Age (yrs)	65±17	68±13
Male	68 (68)	65 (63)
Diabetes	20 (20)	41 (40)
Prior CV disease	28 (28)	39 (38)
Mean SBP (mmHg)	145±16	144±17
Mean DBP (mmHg)	75±11	74±9

Methods: We performed a longitudinal observational study of 203 patients commencing HD between 2005 and 2011 in our region. We excluded patients with CV events within 6 months of starting HD. SBPV was assessed by variation independent of the mean (VIM) using short-gap, pre-dialysis SBP readings over a consecutive 3 month period between 3 and 6 months after commencing HD.

Results: 37 (18.2 %) patients died during a mean follow-up of 2 years. Those with VIM of SBP above the median were 2.4 (95% CI 1.18-4.87) times more likely to die during follow-up than those below the median after adjustment for diabetes, prior CV disease, gender, age, mean SBP and DBP.

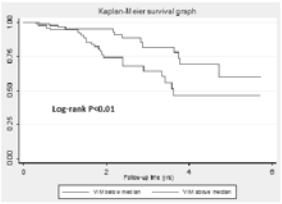

Table 1: Baseline demographic characteristics

Discussion: Our study shows that variability of systolic BP is a strong and independent predictor of all-cause mortality in incident HD patients. Further research is needed to understand the mechanism as this may form a therapeutic target or focus for management.

P437

Haemodialysis away from base in countries with a high prevalence of blood borne viruses: does supplying consumables prevention transmission of infection?

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Several reports have emphasised the risk of seroconversion when patients dialyse away from base (DAFB) in countries with a high prevalence of blood borne viruses (BBV). We previously reported on 5 cases (out if 21 visits) of seroconversion for hepatitis C following DAFB in SE Asia and highlighted the costs to the NHS of treatment with anti-viral therapy. In early 2010, we started to supply consumables to patients travelling to countries rated by WHO criteria as having a high or moderate prevalence of BBV infection in haemodialysis patients. The aim of this audit was to review the take up and cost effectiveness of this practice.

Patients who had DAFB from 1st Jan 2010 to Oct 2012 were identified and data on destination of travel, length of stay, whether consumables were taken and post visit BBV serology results were collated.

A total of 40 visits were made to high/moderate risk counties. 37 patients were offered consumables (1 could not be ascertained). 7 patients declined the offer all of whom were travelling to Africa or Saudi Arabia. There was only one episode of seroconversion in a patient who became Hep BsAg/ Hep B DNA PCR positive following DAFB in India. This patient had not been offered consumables. The total potential number of weeks for which consumables were supplied in this period was 212 at an estimated total cost of £3969 (based on needles and dialysers only). This compares to an estimated average cost of >£6000 for treatment per case of hepatitis C.

These data provided strong circumstantial evidence that provision of dialysis consumables reduces the risk of contracting BBV when patients have DAFB in high risk countries. This policy was based on anecdotal evidence from visiting nephrologists that reuse of consumables is common in these countries. There is a strong argument based on financial calculations alone to provide consumables for patients travelling to 'unsafe' areas in an attempt to reduce the risk of transmission of BBV infection.

Providing consumables may not be feasible for some patients who spend long periods of time away nor practicable for those who cannot transport or store the equipment. However, providing this service may also enable those who have hesitated about DAFB to travel abroad with greater confidence.

P438

Quality improvement program of modifiable risk factors in hospital haemodialysis

Vishal Dey, Robert MacTier, Kath Kearny, Dalene Thomson, Val Jeffrey, Morag Ryan, Kath McCreadie, Graeme Crawford, Maria Smith, Morag Gorrie, Stuart Rodger, Siobhan McManus, Keith Simpson

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Introduction: Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) have documented a higher relative risk of death in haemodialysis (HD) patients who fail to achieve URR > 65% (RR 1.13, p = 0.0023), haemoglobin (Hb) >10g/dl (RR 1.21, p <0.0001), pre-dialysis serum phosphate <1.8mmol/l (RR 1.11, p=0.001) and facility central venous catheter use <10% (RR 1.20, p < 0.0001). The target URR should be 70% or higher when aiming to achieve URR >65% every month and the target Hb concentration should be 10.5g/dl or higher when aiming to achieve Hb concentrations above 10g/dl on a consistent basis.

Methods: As part of a quality improvement program (QIP) we performed a prospective, nurse led audit of these 4 modifiable clinical risk factors in all of the patients in the Stobhill HD unit every month for 2 years from August 2009 (maximum number of patients = 111). A QIP score of 1 or 0 was awarded according to whether each of the following surrogate dialysis related variables were achieved or not each month: URR = 70% or higher; Hb 10.5 or higher; pre-dialysis serum phosphate below 1.8; fistula used as the current form of vascular access. When combined into a global score each patient may have a QIP score ranging between 0-4.

Results: Mean ± 1SD for each variable are shown in the Table.

6 monthly audit period	Aug 2009 -Jan 2010	Feb 2010 -Jul 2010	Aug 2010 -Jan 2011	Feb 2011 -Jul 2011	P value
Mean % URR> 70	76.0± 6.93	77.6± 7.47	80.1 ±3.87	90.0* ±3.18	*0.0155
Mean % Hb > 10.5 g/dl	76.8± 2.94	72.7*±4.20	75.8 ±1.93	80.6 ±6.15	*0.0237
Mean % PO_4^{2-} < 1.8	61.3± 2.64	62.3 ±4.58	63.8 ±3.65	63.7 ±5.09	-
Mean % fistula use	71.0± 2.27	71.0 ±4.43	80.4** ±1.57	80.6* ±1.44	*0.001 **0.0001
Mean global score	2.93 ± 0.09	2.84 ±0.08	3.0 ±0.09	3.16* ±0.10	*0.0232

Each audit period was compared to the baseline and previous 6-month periods. All significant results (p< 0.05) are shown. There was a significant improvement in the global score for all patients in the final 6 months of the audit when compared with the first six months' data; p = 0.0232). This was due to serial improvements in the % of patients achieving monthly URR > 70% and higher use of fistulas.

Conclusion: In the second year of a QIP audit a significantly higher % of HD patients achieved a 6-monthly average URR >70 % and fewer patients used central venous catheters for vascular access. There was only a small rise in the % of patients achieving target Hb and phosphate levels. Monthly multidisciplinary nurse led audit of modifiable risk factors in HD patients promotes patient and staff awareness of quality improvement targets and this can increase the % of HD patients who consistently achieve audit measures that are associated with improved patient outcomes.

P439

A very low prevalence of occult hepatitis B virus infection in a large multi-ethnic patient cohort on haemodialysis in a London NHS Hospital Trust

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Introduction: Haemodialysis patients in the UK are regularly screened for hepatitis B virus (HBV) surface antigen so that measures can be taken to prevent nosocomial transmission. This retrospective study was undertaken to determine the prevalence of occult HBV infection, which denotes the presence of HBV core antibody (anti-HBc Ab) and HBV DNA in blood without any detectable HBV surface antigen (HBsAg).

Methods: A total of 796 patients were identified undergoing haemodialysis at Royal Free Hospital and its satellite units in 2009-2010. Information regarding their HBV test results was retrieved. Stored serum samples from anti-HBcAb positive, HBsAg negative patients were anonymised and tested for HBV DNA by a real time quantitative PCR assay.

Results: Fifteen (1.8%) out of 796 patients were HBsAg positive and anti-HBc Ab positive indicating chronic HBV infection. A total of 158 (20%) of the remaining 781 patients were anti-HBc Ab positive but HBsAg negative. Of these 158 patients, 136 also had anti-HB surface antibody (anti-HBs Ab). Sera were available for DNA testing from138 anti-HBc Ab positive, HBsAg negative patients. Three (2.17%) of 138 anti-HBc Ab positive patients had very low level HBV DNA detected (3, 5 and 9 IU/ml); one patient was from anti-HBc Ab positive/anti-HBs Ab positive cohort and 2 were from anti-HBc Ab alone cohort. Liver function tests were normal in these patients.

Conclusions: The prevalence of occult HBV infection is very low in a large cohort of haemodialysis patients in a London centre. The very low levels of HBV DNA are unlikely to pose a nosocomial transmission risk, particularly if a robust HBV vaccination programme is implemented in dialysis units.

P440

Blood volume monitoring in combination with haemodiafiltration is associated with a reduction in interdialytic pre-syncopal symptoms: results from a single-centre crossover study

Chee Kay Cheung[1], Andrew J. Scally[0,2], Tracey Harrison[1], Annie Wong[1], John Stoves[1]

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Introduction: The clinical utility of haemodiafiltration (HDF) and biofeedback systems such as relative blood volume monitoring (BVM) and thermoregulation (BTM) remains unclear. We assessed whether use of a combination of these systems could improve haemodynamic stability and reduce intradialytic and interdialytic symptoms in haemodialysis (HD) patients.

Methods: HD patients prone to intradialytic hypotension (IDH) were identified and offered inclusion in the study if there was no improvement following a review of 'dry weight' and antihypertensive medications (AHM). Patients were monitored on HD and then received HDF, HDF+BVM, HDF+BTM and HDF+BVM+BTM in a randomised monthly sequence with interval washout periods. Primary outcomes were frequency of IDH and patient recall of symptoms after each dialysis session and at the end of each treatment month. Secondary outcomes included changes in intradialytic systolic blood pressure (SBP), biochemical parameters and AHM.

Results: 42 patients participated in the study. There was no difference between modalities in the frequency of stopping ultrafiltration or administering fluids for IDH, however summative questionnaire-based patient recall indicated a reduction in severity of intradialytic symptoms with HDF-based treatments compared to HD ($p = 0.022$) with no additional advantage for BVM or BTM. Intradialytic SBP reduction was not influenced by treatment modality, but higher intradialytic SBP nadirs were recorded with increasing duration of HDF-based treatments ($p=0.013$). There was a lower frequency of reported interdialytic symptoms of dizziness ($p<0.001$) and pre-syncope ($p = 0.029$) with HDF + BVM (+/- BTM). All patients elected not to revert to HD after the study. There were no significant changes in biochemical parameters, AHM or ESA dose requirements between the start and the end of the study.

Discussion: There was no additional advantage of BVM +/- BTM over HDF alone in reducing IDH, but HDF + BVM in combination reduced interdialytic dizziness and pre-syncope. This needs to be validated with a larger prospective study.

P441

A randomised control trial of taurolidine-heparin-citrate line locks in prevention of recurrence of catheter related bacteraemia in haemodialysis patients

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Imperial College Renal and Transplant Centre, London, UK

Introduction: Catheter related bacteraemia (CRB) is a cause of significant morbidity in patients maintained on long-term tunnelled haemodialysis catheters for vascular access. Catheter salvage (antibiotic treatment without removal of the catheter) is advocated for individuals without signs of systemic sepsis, who have a favourable initial response to antibiotics. The study was designed to assess the hypothesis that taurolidine-heparin-citrate (THC) line locks are superior to heparin in preventing recurrence of CRB.

Methods: An open-label parallel-group randomised controlled trial was designed comparing THC (containing heparin 500units/ml) against heparin (5000units/ml) line locks. All patients on established haemodialysis within our in-centre and satellite dialysis units, with evidence of a CRB and who had commenced treatment for catheter salvage were considered eligible. Patients were randomised within two weeks of a bacteraemia to either THC or heparin line locks following each dialysis for 6 months, in addition to standard antibiotic therapy. The pre-specified primary outcome measure was bacteraemia free catheter survival.

Result: 26 patients were recruited to the study with 13 patients in each group. A significant difference in the primary outcome measure was seen with improved catheter survival in individuals receiving THC ($p=0.009$). No recurrence of CRB occurred in the THC group, while 5 catheters were removed in the heparin group during the six month trial period. The trial size was too small to meaningfully interpret pre-defined secondary outcome measures, though there was an increased thrombolytic use in the THC arm.

Discussion: Despite the small study size, THC line locks appear to be beneficial in the prevention of recurrence of CRB. It is uncertain whether this is at the expense of catheter dysfunction at a later point. THC line locks should be used as an adjunctive therapy in the setting of catheter salvage, while their role as a standard line lock remains unclear. (Clinical Trial No: NCT01243710).

P442

The introduction of online haemodiafiltration is associated with an improvement in patient reported symptoms

Ben Caplin[1,2], Ruth Yang[2], Andrew Davenport[1,2], Jenny Cross[2]

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Introduction: Haemodiafiltration (HDF) has been reported to be a superior modality for the delivery of outpatient chronic renal replacement therapy. As part of service improvement we regularly undertake surveys of patient reported symptoms (PRS) in outpatient dialysis clinics. We investigated whether PRS changed following the introduction of HDF.

Methods: PRS (scored 1-5; multiple dimensions; Figure) as well as self-reported time to recover from treatment were collected using questionnaires filled in at a single satellite dialysis unit 3-6 months prior to commencing, and a similar period following, the introduction of HDF. Contemporaneous laboratory data were also collected. Differences in PRS were analysed using a Wilcoxon signed-rank test.

Results: 123 patients completed both questionnaires. Significant reductions in the symptoms of cramps, headache, sickness, abdominal pain, backache, itching, dizziness, tiredness, coldness, hypotension and breathlessness were reported following the introduction of HDF (Figure). No differences in the time to recover were observed and no differences in haemoglobin, phosphate, c-reactive protein, albumin or dialysis adequacy accompanied the introduction of HDF.

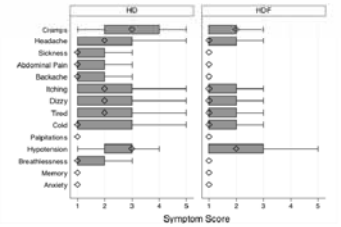

Figure: Box-and-Whisker Plot of PRS before and after the introduction of HDF. Box: $25^{th}/75^{th}$; Whiskers: $5^{th}/95^{th}$ centiles. Diamond: median. Outside values excluded.

Conclusions: In a single centre introduction of HDF was associated with a short-term improvement in PRS. Whether these improvements relate specifically to dialysis modality and/or are sustained over time requires further investigation.

Poster session

Thursday 14th March

12:00 - 13:00

Immunopathological renal disease 1

P443

Macrophage depletion protects against interstitial fibrosis and tubular atrophy in a chronic renal allograft rejection model

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Aims: Chronic renal allograft damage, histologically characterised by interstitial fibrosis and tubular atrophy (IFTA), presents a challenging and therapeutically stubborn problem; it is responsible for a 5% loss of renal transplants each year. Macrophages (MΦ) are known to contribute to fibrosis in a number of different organ systems, however their role in renal post-transplant IFTA remains unclear. We hypothesised that MΦ have a key role in alloimmune injury and that depletion of these MΦ in the transplant recipient by liposomal clodronate (LC) would be protective against the development of IFTA.

Methods: Our murine model of chronic allograft injury, characterised by a single class II mismatch between BM12 (H-2^{bm12}) donor and C57Bl/6 (H-2^{b}) recipient is known to develop progressive IFTA when compared to syngeneic (C57Bl/6) control transplants. LC was given on days 4, 7 and 10 and mice culled at either day 13 or day 28. Controls received Liposomal PBS (LP). IFTA was quantified by analysis of immunohistochemical staining. Additionally, the effects of MΦ (F4/80) depletion upon surrounding B cells (B220) and T cells (CD3) were investigated.

Results: Allografts developed marked MΦ (F4/80) infiltration and IFTA vs. isografts $p<0.01$. LC successfully depleted allograft MΦ and relative MΦ depletion persisted to day 28 vs. LP allografts $p<0.0001$. MΦ depletion was associated with a reduction in tubular necrosis $p<0.05$ and fibrosis (picrosirus red staining) $p<0.01$ at both day 13 and day 28. There was no significant difference in the number of infiltrating CD3+ and B220+ cells in the MΦ depleted allografts.

Discussion and conclusions: Early depletion of MΦ in the murine chronic allograft damage model is associated with significant protection of tubular integrity and a reduction in interstitial fibrosis. Further work is required to characterise this dynamic population of macrophages in the allograft and to establish the direct and indirect immunological mechanisms through which they contribute to the challenging clinical problem of chronic renal allograft failure.

P444

Genetic susceptibility in experimental autoimmune vasculitis (EAV)

John McDaid[1], Anisha Tanna[1], Gurjeet Bhangal[1], Jacques Behmoaras[1], Mark Little[2], Terence Cook[1], Frederick Tam[1], Alan Salama[3], Charles Pusey[1]

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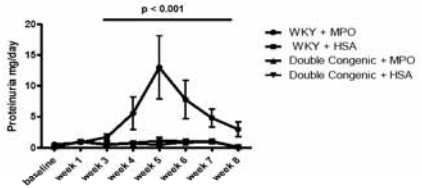
Introduction: The genetic susceptibility to anti-neutrophil cytoplasm antibody (ANCA) associated vasculitis is incompletely understood. We have recently discovered that the Wistar Kyoto (WKY) rat is susceptible to experimental ANCA associated vasculitis (EAV), but Lewis (LEW) rats are resistant. We have generated congenic rat strains to dissect out the role of selective quantitative trait loci (QTL) in EAV.

Methods: Rats were immunised with human myeloperoxidase (MPO) in adjuvant to induce disease. Control rats were immunised with human serum albumin (HSA) in adjuvant. Disease progression was assessed by measuring proteinuria, haematuria, serum ANCA titre and by histology. Double congenic WKY rats with introgression of QTL from LEW chromosomes 13 and 16 were used.



Results: WKY rats developed proteinuria (Figure), haematuria and glomerular abnormalities. Double congenic WKY rats, introgressed with loci from the Lewis strain, did not develop proteinuria or haematuria and were protected from glomerular injury. Both WKY and double congenic strains developed equivalent ANCA titres.

Conclusion: This is the first study demonstrating that genes located on chromosomes 13 and 16 are important in the pathogenesis of EAV.

P445

Synergistic effect of GCSF and LPS in ANCA vasculitis

Reena J Popat, Simon J Freeley, Michael G Robson

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Introduction: Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis is a systemic disease causing fibrinoid necrosis in glomeruli and alveoli. Granulocyte colony stimulating factor (GCSF) is a cytokine that is important in mobilizing neutrophils from the bone marrow but also has a range of pro-inflammatory effects. We have previously shown that circulating GCSF is raised in patients with active vasculitis, and exacerbates disease in an established murine model (Annals Rheum Dis 2012). LPS was given to all mice in that previous study, though we had not shown if this was required with GCSF.

Objectives: To investigate the relative roles of GCSF and LPS in this murine model.

Methods: Purified murine MPO was used to immunise MPO knockout mice to generate anti-MPO antibody. Four groups of wild type C57BL/6 mice were used (n=5-6 per group). They were given GCSF or control subcutaneously starting 3 days before the induction of disease with anti-MPO (day 0). LPS or control was administered by intraperitoneal injection on day 0 and 3. Serum, urine and histology were assessed on day 7.

Results: The group which received both LPS and GCSF had significantly higher serum creatinine levels at day 7 compared to mice with administration of neither LPS nor GCSF, administration of LPS alone or GCSF alone (12.3 ± 0.8 umol/L compared to 9.0 ± 0.5 umol/L, 8.3 ± 0.6 umol/L, 9.5 ± 0.4 umol/L respectively. $p= 0.001$). At day 7 the group given both LPS and GCSF had significantly higher glomerular crescents (31.6 ± 5.2 compared to 0 ± 0, 0.3 ± 0.3, 0.2 ± 0.2 per 100 glomeruli respectively, $p<0.0001$) and glomerular macrophage numbers (15.3 ± 1.3 compared to 0.5 ± 0.1, 2.2 ± 0.3, 4.1 ± 0.8 cells per glomerular cross section respectively, $p<0.0001$).

Conclusion: This study shows that both LPS and GCSF are required to obtain robust disease in this model, and this also has implications for pathogenesis.

P446

Bioinformatic analysis of human endogenous retrovirus HRES-1 indicates a potential viral trigger for systemic lupus erythematosus (SLE)

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[1]Departments of Nephrology and Rheumatology, Royal Wolverhampton NHS Trust, Wolverhampton, UK, [2]Immunology Research Group, School of Applied Science, University of Wolverhampton, Wolverhampton, UK

Introduction: The aetiology of SLE may involve a viral agent together with a genetic predisposition. Recently Human Endogenous RetroViruses (HERVs) incorporated within DNA, including HRES-1 and ERV-3, have been suggested as possible triggers. We have assessed the potential for molecular mimicry between HRES-1 virus and 19 SLE autoantigens using bioinformatics computer programmes.

Methods: HRES-1 and autoantigen amino acid sequences were extracted from the NCBI/Genbank database and *in silico* analysis performed for antibody epitopes using online software programmes (http://expasy.ch) for predicting antigenic regions. Protein sequences were scanned for similarity using LALIGN software (http://www.ch.embnet.org). Molecular models were developed using PyMOL (http://pymol.org). The possibility of epitope spreading between autoantigens that may occur following an immune response to viruses was investigated.

Results: HRES-1 exhibited similarities to 9 autoantigens associated with SLE.

SmD1	**EAGAGRVR**	Ribosome P1	**PAAAAQP**	Ribosome P0	**PAAAAQP**
HRES-1	**EAVAGRGR**	HRES-1	**PAAGAAP**	HRES-1	**PAAAAAP**
SmN	**RPPRP**	SnRNP BB'	**RPPRP**	Ro/SSA-60	**ALR**W**A**
HRES-1	**RPPRP**	HRES-1	**RPPRP**	HRES-1	**ALR** K **A**
La/SSB	**AAQP**D**S**	anti-U1 RNP	**PGPSTL**	Histone H2B	**APAP**R
HRES-1	**AAQP**G**S**	HRES-1	**PGPS**P**L**	HRES-1	**APAP**K

Furthermore amino acid sequence alignment between autoantigens were observed:
SnRNP BB' **TP**M**GMPPPGMRPPPPG**M**RGPPPPGMRPPRP**

SmN **TP** I **GMPPPGMRPPPPG** I**RGPPPPGMRPPRP**

Discussion: Homology between HRES-1 and 9 SLE autoantigens suggests that molecular mimicry could mediate an undesired immune response to host proteins during an immune reaction to HERVs, and might also occur where amino acid substitutions do not affect protein configuration. The autoimmune response might spread to other autoantigens through epitope spreading. From this work, synthetic peptide mimics will be assessed as potential diagnostic and therapeutic agents.

P447

Genetic susceptibility to experimental autoimmune glomerulonephritis

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Imperial College London, London, UK

Background: The WKY rat strain is susceptible to experimental glomerulonephritides, including nephrotoxic nephritis (NTN) and experimental autoimmune glomerulonephritis (EAG), whereas the LEW strain is resistant. In previous studies by our group, genome-wide screening identified a QTL on Ch13 (designated *crgn1*) linked to disease severity in both models. A QTL on Ch16 (*crgn2*) was additionally linked to disease severity in NTN alone. We have previously shown that introgression of LEW.*crgn1* onto a WKY background conferred protection from disease in EAG. We sought to examine the additional effect of introgressing LEW.*crgn2* onto a WKY background in this model.

Methods: Reciprocal double congenic (DC) rats were generated (WKY.LEW*crgn1,2* and LEW.WKY*crgn1,2*), immunized with recombinant rat α3(IV)NC1, and assessed for EAG development.

Results: Shown in table below.

Conclusions: Additional introgression of LEW.*crgn2* onto a WKY background confers greater protection from EAG than seen with LEW.*crgn1* alone. These results confirm our previous observations in NTN, and highlight the importance of macrophage activation (regulated by *crgn2*) in these models, and as a potential therapeutic target. Despite making high levels of anti-GBM antibodies, LEW.WKY*crgn1,2* did not develop disease, suggesting that additional genetic factors contribute to disease resistance in the LEW strain.

	WKY	LEW	WKY.DC	LEW.DC
Proteinuria (mg/day)*	90	0	8	0
% Crescents*	39	0	6	0
Macrophages/glom*	14	1	4	0
Anti-GBM antibody (au)§	195	144	312	143

Results expressed as median/group. Statistical analysis by 1-way ANOVA.
*$p<0.0005$. § not significant.

P448

Seasonal variability in presentation of ANCA-associated small vessel vasculitis

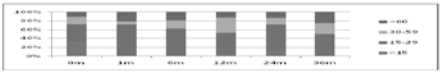
Vinod Dibbur, Rajiva Ibakkanavar, Rhodri Pyatt, Beverly Ely, Sian Griffin

University Hospital Of Wales, Cardiff, UK

Background: The cause of ANCA-associated Small Vessel Vasculitis (SVV) is unknown, but an infectious trigger in a genetically susceptible individual has been postulated.

Methods: We performed a retrospective analysis of all patients presenting with SVV to a tertiary renal unit since 1/1/2008.

Results: Forty seven patients were diagnosed with pauciimmune SVV, corresponding to an incidence of 6.5 per million population per year. Twenty six (55.3%) were male. Forty four (94%) were ANCA positive, with 23 having specificity for PR3 (age 65.1±11.9 years), and 19 having specificity for MPO (age 69.1±11.8 years). No specific antigen was detected in two patients. Patients were significantly more likely to be diagnosed between the winter months of October-March (29) than the summer months of April-September (18), (p=0.01), student's t test). At presentation, 20 (42.5%) patients required dialysis. All of these patients received plasma exchange, with 11 (55%) recovering independent renal function. The mean eGFR at presentation for those who did not require dialysis was 25.3±18.5ml/min. 40/46 patients completed a course of 6 – 10 pulses of iv cyclophosphamide. Mild transient neutropenia (ANC<1.5X10^9/L) occurred in 9 of these patients. One patient received Rituximab. There were 10 episodes of infection (21%), two of life threatening severity (peritonitis and CMV pneumonitis). Thirty four patients (72%) achieved initial remission, with four subsequent relapses. There were 8 deaths occurring between 12 and 409 days after presentation; none were due to active vasculitis. For those patients who were dialysis independent at presentation, or recovered independent renal function, there was a continued improvement in renal function over the subsequent three years, with the proportion of patients in each eGFR range shown below:



Conclusions: The incidence of SVV in this study was lower than previously reported, but with a predominance of severe renal disease, suggesting milder cases may have presented to other specialties. The patient characteristics were otherwise similar to other reports. The increased frequency of presentation in the winter months supports a possible infectious trigger.

Poster session

Friday 15th March

11:30 - 12:30

Inflammation 1

P449

What determines peritoneal dialysate cytokine levels?

Catriona Goodlad[1], Frederick Tam[1], Sohail Ahmad[1], Gurjeet Bhangal[1], Bernard North[0,2], Edwina Brown[1]

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Introduction: Cytokines are readily detected in spent dialysate using ELISA. Dialysate cytokine levels might reflect intraperitoneal production and ongoing peritoneal inflammation, or could depend on cytokine transfer from the circulation, correlating with the serum cytokine level and membrane permeability. Knowing what determines dialysate cytokine levels is important, as they are potential biomarkers of changes in the peritoneal membrane.

Methods: We analysed paired serum and dialysate cytokine levels (IL-6, MCP-1, CCL18, CCL15 and angiogenin) from 150 PD patients. The serum/dialysate ratio of known molecular weight (MW) proteins not produced in the peritoneum was used to assess intra-peritoneal cytokine production. Primary mesothelial cells isolated from patients' spent dialysate were cultured and production of cytokines assessed. The significance of clinical variables (such as glucose exposure and duration of PD) as predictors of dialysate cytokine levels was assessed by multivariate analysis including D/P creatinine and serum cytokine levels.

Results: Dialysate levels of CCL15 and angiogenin approximate those expected for their MW; dialysate levels of CCL18 are lower than predicted. On multivariate analysis (all p values < 0.05) the best predictors of these three cytokines were D/P creatinine and the serum level. Dialysate levels of IL-6 and MCP-1 can exceed serum levels and are higher than expected for MW. Significant predictors of these cytokines were D/P creatinine, glucose exposure and PD duration (IL-6). Non-stimulated cultured mesothelial cells produced IL-6 and MCP-1 as expected, but also (in smaller amounts) angiogenin and CCL18. Angiogenesis and fibrosis, features of peritoneal membrane damage seen with long term PD, might be mediated by these cytokines. No CCL15 production was seen; this may reach the dialysate from the circulation.

Conclusions: Dialysate levels of CCL18, angiogenin and CCL15 are determined by simple transfer from the circulation but this is not so for IL-6 and MCP-1. These cytokines may be involved in membrane pathologies determining D/P creatinine.

P450

TGFβ1-mediated signalling in human podocytes and regulation of alternative splicing

Tarunkumar Madne, Mysore Phanish, Mark Dockrell

South West Thames Institute for Renal Research, London, UK

Introduction: Growth factors such as TGF**β** and CTGF play an important role in glomerular response to injury; initially in a putative repair response but also as pro-fibrotic stimuli. The induction of fibronectin (Fn) can potentially be part of repair but the alternative splicing of the pre-mRNA to produce EDA+ Fn is strongly associated with fibrogenesis. We previously described TGF**β**1-induced EDA+Fn expression in human podocytes. In this study we investigate possible signalling pathways involved.

Objective: We aim to identify the intracellular signalling pathways activated by TGF**β**1 in human podocytes in culture and investigate which pathway(s) may underlie the alternative pre-mRNA splicing of Fn.

Methods: Experiments were conducted on conditionally immortalised human podocytes incubated with TGF**β** (2.5ng/ml). Western blotting analysis was performed to detect EDA+Fn expression as well as intracellular signalling proteins. Chemical inhibitors were used to selectively block p38MAP kinase, SB202190, and PI3K/Akt signalling, LY294002. On discovery of novel Smad1/5/8 signalling CCN3 (360ng/ml) was employed to investigate CTGF involvement.

Results: TGF**β**1 induced canonical Smad signalling as well as non-canonical kinase signalling. Suprisingly, TGFβ1 also induced Smas1/5/8 signalling. To investigate role of CTGF in this signalling we co-incubated the cells with the endogenous CTGF antagonist CCN3 and observed a selective down regulation of phosphoSmas1/5/8. This did not alter EDA+Fn expression. Co-incubation with the PI3kinase inhibitor LY294002 did attenuate EDA+Fn expression.

Conclusion: TGFβ induced EDA+Fn expression in a PI3kinase dependent manner in podocytes suggesting a role for PI3k in pathological alternative splicing in glomerular disease. It would also appear that endogenous CTGF is expressed by podocytes that can mediate the activation of Smad1/5/8 in these cells as evinced by the inhibitory actions of CCN3. The latter was not involved in EDA+Fn expression, further studies are required to investigate its role.

P451

Role of CCN3 on TGFβ1-induced pro-fibrotic pathways in human proximal tubule cells

Simon Winn[1], Bruce Riser[0,2], Mysore Phanish[1], Mark Dockrell[1]

[1]*South West Thames Institute for Renal Research, London, UK,* [2]*Rosalin Franklin Univeristy, Chicago, USA*

Introduction: CCN proteins are context specific modulators of growth, differentiation and extracellular matrix homeostasis. CTGF (CCN2) potentiates the pro-fibrotic actions of TGFβ1 through extracellular interactions as well as direct actions on target cells. Recent data has indicated that CCN3, another member of the CCN family is able to counteract some of the pro-fibrotic effects of TGF β1–induced CTGF. Using a transformed human proximal tubule epithelial cell (PTEC) line, HKC-8 which expresses CTGF both under basal conditions and in response to TGF β1, we investigated the effect of CCN3 on signalling, fibrosis and phenotype.

Methods: Cells were incubated in the presence of TGFβ1 (1.25ng/ml) alone & recombinant human CCN3 (360ng/ml) +/- TGFβ1. Incubation was for 60 min for signalling and 24 h to investigate mRNA expression. Activation of signalling molecules was assessed by Western Blotting. Q PCR was used to investigate the expression of, CTGF, TGFβ1, E-cadherin, fibronectin, Collagen I, and αSMA.

Results: CCN3 inhibited all TGFβ-induced signalling, reducing phospho Smad2 and 3 by approximately 40%, with a more marked affect on SMAD1/5/8 and p38. There was no modulation of TGFβ1-induced mRNA expression. Interestingly, there was a significant increase in "basal" E-cadherin mRNA expression.

Conclusion: CCN3 appears to regulate TGFβ1-induced signalling in human PTEC. It has been reported that TGFβ1-induced Smad1 is regulated by CTGF; our data supports this. Interestingly, CCN3 inhibited p38 MAP kinase signalling, a signalling cascade activated by CTGF. CCN3 also caused a significant elevation in E-cadherin expression in the absence of TGFβ1. Taken together these last two results indicate that CCN3 has either unmasked an affect of "basal" endogenous CTGF directly regulating human PTEC in culture.

P452

Elevated soluble and galectin-3 expressing monocyte levels in experimental uraemia is reversed by anti advanced glycaemic end products (AGE) therapy

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Barts and the London School of Medicine and Dentistry, London, UK

Introduction: Galectin-3 expressing monocytes and macrophages are implicated in the pathogenesis of chronic inflammatory and fibrotic diseases. Moreover, in human studies elevated soluble plasma Galectin-3 levels are associated with Advanced Glycaemic End product (AGE) and determine poor cardiovascular outcomes.

Methods: A murine model of progressive tubulointerstitial nephritis - the Adenine Diet (AD) - was used to define Galectin-3 levels in circulating murine leucocytes and tissue resident macrophages (by FACS analysis and Real Time Quantitative PCR) subject to progressive uraemia. Plasma AGE was quantified by ELISA in AD compared to sham diet (SD) at 0 and 2 weeks. Mice were then given the anti-AGE compound Pyridoxamine in drinking water (400mg/kg) or standard drinking water for 2 weeks of 0.25% Adenine diet and leucocyte Galectin-3 expression was re-evaluated.

Results: Plasma Galectin-3 is significantly raised at 7 days to 28 days in AD fed mice(n=33) vs SD (n=30). Circulating monocytes and granulocytes in AD fed mice(n=5) demonstrate significantly higher Galectin-3 Median Fluorescence Intensity(MFI) on FACS analysis at 14-28 days vs SD(n=5) (p=0.0317 AD vs SD at 28 days). At 28 days resting peritoneal macrophages and cardiac homogenate failed to show increased expression in Galectin-3 MFI and Galectin-3mRNA levels respectively. Plasma AGE is significantly raised at 2 weeks 0.25% Adenine Diet and significantly reduced by supplementation with 400mg/kg of pyridoxamine in drinking water(n-5) vs standard drinking water(n=5)(p=0.0079). Pyridoxamine supplementation also significantly reduced adenine diet induced Galectin-3 expression of circulating monocytes at 14 days.

Discussion: In experimental uraemia only Circulating Galectin-3 monocyte levels are increased with accumulation of AGE's. Targeting elevated Galectin-3 levels by anti-AGE strategies may be important given Galectin-3's pathogenic role in inflammatory cardiovascular disease.

P453

Calprotectin (MRP8/14) amplifies the pro-inflammatory response

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Introduction: Calprotectin, an endogenous TLR4 agonist, present in neutrophils, monocytes and infiltrating macrophages, promotes endothelial cell activation and transcription of pro-inflammatory cytokines. We've previously shown patients with ANCA associated vasculitis have elevated cell surface expression and serum levels, and relapsing non-renal patients have higher early serum levels than non-relapsers. Calprotectin (+) macrophages are found in crescentic but not sclerotic glomerular lesions, and calprotectin deficient mice (cal-/-) are protected from disease in nephrotoxic nephritis (NTN). We investigate the proinflammatory effects of calprotectin on bone marrow derived macrophages (BMDMs), endothelial cells (EC) and mesangial cells (MC). We investigate whether creating bone marrow chimeric mice can transfer disease protection in NTN.

Methods: EC isolated from wild-type (WT) mice, BMDMs from WT, TLR4-/- and cal-/- mice, and MC from WT and TLR4-/- mice were stimulated with calprotectin. WT EC were co-cultured with WT BMDMs or cal-/- BMDMs. Cytokines were measured in supernatants by ELISA. The phagocytosis ability of WT and Cal-/- BMDMs were compared using opsonised beads. Bone marrow transplants (BMT): WT→WT, Cal-/-→WT, WT→cal-/- were performed and NTN induced.

Results: The calprotectin induced increase in IL-8, TNF-α, MCP-1 in BMDMs was abrogated in TLR4-/- BMDM ($p<0.001$), but no differences seen in MC. Cal-/- vs WT BMDM stimulated with exogenous calprotectin demonstrate little pro-inflammatory activity and less TNF-α, IL-6, IL-8 ($p<0.005$). The increase in IL-6, IL-8 and MCP-1 following co-culture of EC and WT BMDM was absent with cal-/- BMDM. Cal-/- BMDMs demonstrate decreased phagocytosis ($p<0.005$). NTN resulted in disease in all the BMT groups.

Conclusion: Calprotectin has inflammatory effects mediated by TLR4 on BMDMs and a TLR4 independent effect on MC. Cal-/- BMDMs lack a pro-inflammatory effect, suggesting a role for calprotectin in amplifying inflammation. BMT results suggest total deficiency of calprotectin is required for disease protection.

P454

Increased urinary angiogenin (ribonuclease 5) in patients with active lupus nephritis

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Objective: Angiogenin (Ang), also known as Ribonuclease 5, is a 123 amino acid protein, involved in stimulating RNA transcription after localisation into the nucleus, leading to angiogenesis and growth stimulation. The presence of Ang in glomerular disease is not known. This is the first description in relation to activity of lupus nephritis (LN).

Methods: Ang was measured by ELISA on 342 urine samples from 34 patients collected over a 4 year period. During that time all patients had at least 1 episode of biopsy proven ISN/RPS class III/IV/V LN, for which they received the steroid sparing "Rituxilup" regimen. Median age at time of biopsy 44 yrs (IQR 27 years). Urine Ang (uAng) levels were normalised for urinary creatinine (creat) level. The relationship between uAng/creat ratios and serum creat and urine protein/creat ratio (uPCR) in the samples taken within +/- 5 weeks of biopsy were investigated. Effect of immunotherapy on uANG/creat ratios +/- 5 weeks of achieving partial remission (PR=uPCR <300mg/mmol with a >50% reduction from baseline with <15% rise in serum creat) and complete remission (CR=uPCR<50mg/mmol with <15% rise in serum creat) were evaluated.

Results: 33, 28 and 30 samples analysed at biopsy, PR and CR respectively. There is a significant correlation between uAng/creat and serum creat at time of active biopsy ($p=0.011$, Spearman's correlation $R=0.45$), but not with uPCR. uAng/creat is significantly reduced in PR and CR by 51% ($p<0.05$) and 84% ($p<0.001$) respectively.

Conclusion: uAng is associated with the severity of renal impairment at time of biopsy of active lupus nephritis, and showed significant reduction in patients with remission following immunotherapy. The lack of correlation of uAng with uPCR at presentation suggested that uAng is not a simple consequence of proteinuria. The potential role of Ang in the development of LN will need further investigation.

P455

The role of mannose receptor in ischaemia - and folate-induced acute kidney injuries

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Introduction: Ischaemia-reperfusion (IR) and folic acid (FA) administration both induce acute tubular injury which is associated with heavy macrophage (Mo) infiltration. We have previously demonstrated deficiency of mannose receptor (MR) protects mice from glomerulonephritis via altered cytokine production and FcR mediated signalling, and we have now evaluated the role of MR deficiency in the IR and FA mediated acute kidney injuries.

Methods: MR-/- mice and control WT C57BL6 mice were used at 8−12 weeks age. In IR model, left renal pedicle was temporary clamped for 30min (ischaemia) followed by adequate reperfusion. In FA model, 240mg/kg FA was injected intraperitoneally with 0.2ml sodium bicarbonate as vehicle. Mice were sacrificed at different time point and we assessed renal function, histological damage using an acute tubular injury (ATI) score and immunohisto-chemistry staining. Real-time quantitative polymerase chain reaction (qPCR) was used to evaluate gene regulations.

Results: At acute stage following injury, serum urea and creatinine were similar between WT and MR-/- mice; however, the ATI score was higher in WT mice than MR-/- mice (IR: 72.00±5.67 vs 27.80±6.04 and FA: 60.20±16.56 vs 10.67±1.78 respectively) with decreased CD68 staining in MR-/- mice. Using qPCR, we found the M1 gene iNos was down-regulated while M2 gene Arg1 was up-regulated in MR-/- mice at early acute stage. The trends changed to iNos up- and Arg1 down-regulation at late acute stage and may suggest a Mo phenotypic change.

Discussion: Mannose receptor deficient mice are protected from acute Mo mediated kidney damage, with evidence of reduced infiltration and attenuated alternative Mo activation. MR antagonism may be a novel therapeutic strategy for various forms of acute kidney injury mediating an important effect on Mo activation.

Poster session

Wednesday 13th March

18:15 - 19:25

Pathophysiology 1

P456

Female DBA/2 mice have relative resistance to folic acid induced acute kidney injury

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Introduction: DBA/2 mice are commonly used for clinical research, including experimental studies in nephrology. Administration of folic acid (FA) to induce acute kidney injury (AKI) is becoming a popular experimental model, but minimal information is available about its use in this particular strain. We sought to determine the dose of FA required to induce AKI in female DBA/2 mice.

Methods: We administered either FA in 0.3M sodium bicarbonate, or sodium bicarbonate alone, intraperitoneally (ip), to adult female DBA/2 mice (Harlan, UK). A starting dose of 240ug/g was used as this concentration or less is reported to induce AKI in other strains. Response was monitored by analysis of serum biochemistry and weight.

Results: 240ug/g FA did not result in any difference in weight or serum biochemistry compared to controls (see table 1). Following this lack of effect the dose was increased. 480ug/g resulted in profound clinical deterioration and weight loss after 3 days. Elevation of serum urea was apparent, along with histological evidence of acute tubular injury. Similar results were obtained with 360ug/g.

FA dose (ug/g)	Day 0 urea	3 day urea	2 wk urea	5 wk urea
Control (n=4)	8.3	NM	7.5	8.3
240 (n=6)	8.3	6.1 (n=2)	8.8 (n=4)	6.7 (n=4)
360 (n=2)	8.1	189 (n=1)	NA	NA
480 (n=2)	5.3	92	NA	NA

Table 1: Mean serum urea (mmol/l) measurements over time for each FA dose.

Conclusion: Our results suggest that to consistently induce acute tubular injury in female DBA/2 mice, higher doses of ip FA are required compared to those reported for other common strains. Moreover, this study emphasizes the strain dependency on required FA dose to induce AKI and thereby highlights the importance of pilot dose finding experiments when using this model.

P457

An investigation of the effects of fetuin-A on paraquat-induced oxidative injury in renal proximal tubular epithelial cells

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Introduction: Fetuin-A is a hepatically synthesised protein. It is a potent inhibitor of vascular calcification. Low levels of serum fetuin-A are found in patients with chronic kidney disease (CKD) and is associated with consequent vascular calcification. Patients with CKD also have a pro-oxidant milieu which contributes to associated morbidity and mortality. Our aim was to investigate the effects of fetuin-A at a range of concentrations on oxidant injury caused to renal epithelial cells by the oxidant paraquat (PQ).

Methods: Cultures of NRK-52E cells, a rat proximal tubular cell-line, were incubated with increasing concentrations of PQ (0-5 mM) in Dulbecco's Modified Eagle's Medium (DMEM) for 24 hours. Cultures were also incubated with fetuin-A (0.01, 0.1 and 1.0 mg/mL) for either 24 hours prior to (pre-incubations) or at the same time as PQ (co-incubations). Cell viability was assessed via spectrophotometric measurement of the mitochondrial-dependent conversion of MTT into formazan. Data are presented as mean % cell viability±S.D., analysed using one-way ANOVA and Bonferroni's post-testing.

Results: PQ produced a significant reduction in the viability of NRK-52E cells at a concentration of 3 mM (untreated cells: 100.0±3.5% *vs.* PQ only: 15.9±7.7%, $p<0.05$, n=6). Co-incubation with fetuin-A at a physiological concentration (1 mg/mL) and PQ (3 mM) produced a significant reduction in PQ toxicity (PQ only: 15.9±7.7% *vs.* PQ+fetuin-A: 33.8±6.2%, $p<0.05$, n=6). Pre-incubation with fetuin-A (1 mg/mL) for 24 hours produced a greater reduction in PQ toxicity compared to co-incubation (PQ only: 15.9±7.7% *vs.* fetuin-A then PQ: 67.5±7.1%, $p<0.05$, n=6). A sub-physiological concentration of fetuin-A (0.1 mg/mL) also protected against PQ toxicity following pre-incubation (PQ only: 15.9±7.7% *vs.* fetuin-A then PQ: 46.44±.7%, $p<0.05$, n=6).

Conclusions: These data suggest that physiological and sub-physiological concentrations of fetuin-A provide significant protection against oxidant injury. Our results demonstrate that pre-incubation is significantly more protective than co-incubation. The cellular mechanisms underlying this protection warrant further investigation.

P458

The role of heme oxygenase in the development of diabetic nephropathy

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Introduction: Hyperglycaemia induced oxidative stress is involved in the pathogenesis of diabetic nephropathy. Heme oxygenase (HO) is a potent antioxidant and exists as two isoforms: heme oxygenase-1 (HO-1), the inducible isoform, and heme oxygenase-2 (HO-2), the constitutive isoform. It is important to understand the role of both isoforms in the protection against oxidative stress and therefore in the development of diabetic nephropathy.

Methods: Analysis of HO-1 and HO-2 protein expression by Western blot in mesangial cells and podocytes under normal and high glucose and following hydrogen peroxide treatment. Assess cell death by trypan blue and MTS assay in mesangial cells treated with a specific HO-1 inhibitor or inducer then exposed to normal, high glucose and hydrogen peroxide; assess cell death following high glucose and hydrogen peroxide treatments after silencing *ho-2* by siRNA.

Results: In mesangial cells and podocytes high glucose and hydrogen peroxide induced the overexpression of HO-1 and HO-2. High glucose and hydrogen peroxide generally caused cell death but the presence of the inhibitor doubled the number of dead cells under high glucose and hydrogen peroxide compared to the cells not treated with the inhibitor. There was a significant decrease in cell death under high glucose and following hydrogen peroxide when the cells were treated with the inducer compared to the untreated ones. There was a significant increase in the number of dead cells when *ho-2* was silenced and cells were exposed to normal or high glucose and hydrogen peroxide compared to the control samples.

Conclusions: High glucose and H_2O_2 have some effect on the expression of HO-1 and HO-2 suggesting that both isoforms might be involved in the development of diabetic nephropathy. Both enzymes look equally important to avoid an excessive production of reactive oxygen species and to protect the cells against oxidative stress. If one of the two proteins is not active there is an increase in cell death suggesting that they act through different mechanisms to reduce the stress and if one of them is not active it is not compensated by the other isoenzyme.

P459

Tumor necrosis factor-α and interleukin-6 disrupt insulin-stimulated glucose uptake in mouse podocytes

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Introduction: We have previously demonstrated that human podocytes are insulin responsive *in vitro* at the level of glucose uptake and that podocyte insulin sensitivity is critical for normal glomerular function *in vivo*. Tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are inflammatory cytokines associated with insulin resistance. Here, the effects of TNF-α and IL-6 on podocyte insulin responses were investigated.

Methods: Conditionally immortalised wild-type mouse podocytes were grown in the presence of TNF-α and IL-6, individually and in combination, at concentrations of 0.1ng/ml and 1ng/ml. Cells were serum-starved for 4-6 hours, before stimulation with 100nM insulin for 15 minutes. The effects on glucose uptake were determined via a 2-deoxyglucose (2-DOG) uptake assay. Western Blotting was performed to assess the activation of insulin-stimulated phosphorylation cascades.

Results: Insulin results in a 77.42 ± 7.49% increase in glucose uptake in mouse podocytes. Incubation of podocytes with TNF-α for 10 days reduces insulin-stimulated glucose uptake (0.1ng/ml = 51.69 ± 5.44%, 1ng/ml = 53.14 ± 11.86%). TNF-α and IL-6 in combination further reduces the insulin-stimulated response (0.1ng/ml = 48.84 ± 5.98%, 1ng/ml = 74.08 ± 9.22%). Shorter incubations with these cytokines do not appear to effect insulin-stimulated glucose uptake in mouse podocytes. Western Blotting of matched samples demonstrates the phosphorylation of Akt at Ser473 remains unchanged following cytokine incubation. Preliminary data also suggests insulin-stimulated ERK phosphorylation decreases at cytokine doses of 1ng/ml.

Discussion: Wild-type mouse podocytes respond to insulin at the level glucose uptake and via activation of PI3K/Akt and ERK pathways. Exposure of podocytes to TNF-α and IL-6 in cell culture suppresses insulin-induced glucose uptake. Understanding the effects of these cytokines on podocyte insulin sensitivity will enhance our understanding of podocyte insulin responses in glomerular disease associated with insulin resistance.

P460

Paradoxical outcomes of pre-conditioning strategies in ischaemia-reperfusion injury

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Ischemia reperfusion injury (IRI) is a major cause of acute renal failure and delayed graft function. Heme-oxygenase-1 (HO-1) has important roles in limiting IRI. We examined the effects of chemical induction and inhibition of HO-1 in both murine renal IRI and rat myocutaneous IRI.

Methods: Renal IRI was induced in 8 week old male FVB mice by occlusion of the left renal pedicle for 25 minutes with a contralateral nephrectomy. Renal injury was assessed up to day 7. IRI was induced in male Lewis rats (10 weeks old) in an abdominal myocutaneous flap by occluding the superior epigastric vessels for 30 minutes. Skin blood flow and necrosis was assessed up to 48 hours. HO-1 was induced before IRI with heme arginate (HA, 30 mg/kg) and inhibited with tin mesoporphyrin (SnMP, 20 mg/kg).

Results: HA significantly induced systemic HO-1 protein and bioactivity, whilst SnMP inhibited HO-1 bioactivity. Following renal IRI HA did not improve renal function. By contrast, SnMP resulted in lower serum creatinine on days 1, 4 and 7 following injury. (Mean ± SEM, n= 12 per group, *p<0.01)

serum creatinine (μmol/l)	Day 1	Day 4	Day 7
Control	96 ± 9	75 ± 16	23 ± 4
HA	99 ± 10	66 ± 18	34 ± 6
SnMP	55 ± 9*	24 ± 3	16 ± 2

ATN scores were similar; however SnMP treatment reduced macrophage and neutrophil infiltration. Following myocutaneous IRI, HA resulted in more extensive skin necrosis (% area) compared to either control or SnMP treated animals (HA 35±10 vs Contol 5±3 vs SnMP 6±5, n=10 p=0.006). Furthermore, HA treatment reduced skin perfusion measured by laser Doppler imaging.

Conclusions: This study shows firstly, that up-regulation of HO-1 using HA in young adult mice was not protective of renal IRI and exacerbated myocutaneous IRI in adult rats. Secondly, SnMP protected from renal IRI mostly likely related to HO-1 independent effects on blood flow and inflammatory response.

P461

Alteration of the gut microbiome by vancomycin: impact on renal ischemia tolerance

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Background: The importance of the intestinal microbiome in the pathogenesis of human disease is becoming increasingly recognised. Alteration of intestinal microbiota is associated with multiple disease states including obesity, diabetes and cardiovascular disease. A recent study[1] in rats demonstrated that alteration of gut microbiota using oral vancomycin, increased myocardial ischemia tolerance, which was shown to be mediated by a reduction in serum leptin. The role of leptin in ischemia reperfusion injury is controversial: leptin has been shown by different groups to both increase and reduce myocardial ischemia tolerance. The effects of vancomycin induced alteration in gut microbiota on renal ischemia reperfusion injury is unknown.

Methods: 24 male Wistar Rats were split into 2 groups. Group 1 were treated with Vancomycin 0.5mg/ml added to their drinking water for 7 days, Group 2 were given water with no additive. After 7 days both groups underwent a right nephrectomy followed by 45 minutes of left renal artery occlusion. The rats were then left to recover for 48 hours before being sacrificed with blood taken for markers of renal dysfunction and serum leptin.

Results:

	Control (n=12)	Vancomycin (n=12)	p
Creatinine (µmol/l)	327 (203)	395 (200)	NS
Urea (mmol/l)	48 (28)	55 (21)	NS
Potassium (mmol/l)	4.7 (2.3)	4.7 (1.3)	NS
Sodium (mmol/l)	142 (6)	145 (5)	NS
Phosphate (mmol/l)	4.4 (1.9)	5.1 (2.1)	NS
AST (I/U)	82 (32)	67 (19)	NS
Leptin (ng/ml)	6.7 (3.6)	3.9 (1.2)	0.02

Conclusions: In this study we have confirmed that treatment with vancomycin leads to a 42% reduction in serum leptin levels however, unlike the myocardium this does not appear to lead to an alteration in renal ischemia tolerance.

1. Lam V et al. Intestinal microbiota determine severity of myocardial infarction in rats. *FASEB J.* 2012;26:1727-1735

Poster session

Wednesday 13th March

18:15 - 19:25

Peritoneal dialysis 1

P462

Microbiological profile of patients undergoing encapsulating peritoneal sclerosis surgery: a service evaluation

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Objective: Two UK centres are commissioned to provide a national service for Encapsulating Peritoneal Sclerosis (EPS) surgery. There are no guidelines on antimicrobial management. In this service evaluation we assess the current antimicrobial prophylaxis regimen of meropenem, vancomycin and fluconazole and the incidence of multidrug resistant organisms in one centre.

Methods: Laboratory records were examined for patients who underwent EPS surgery from 01 April 2009 to 01 August 2012. We focussed on rates of resistance in pre-, intra-, and post-operative isolates including vancomycin resistant enterococci (VRE), meropenem resistant Gram-negative bacilli (MRGNB) methicillin resistant *Staphylococcus aureus* (MRSA) and *Candida* species.

Results: 40 patients underwent 49 operations. Among 40 first operations, resistant organisms were recovered more often post-operatively than pre-or intra-operatively. MRGNB were recovered from 1 (2.5%), 3 (7.5%) and 5 (12.5%) patients; and VRE were isolated from 0 (0%), 2 (5%) and 6 (15%) patients pre-, intra- and post-operatively respectively. Patients with, rather than without, bowel perforation were more likely to have intra-operative samples with either MRGNB (3 of 4 (75%) patients vs 0 (0%) of 36 patients respectively, $P < 0.0005$*), or VRE (1 of 4 (25%) vs 1 of 36 (3%) respectively $P = 0.19$*). No pre-operative clinical samples were available for patients with bowel perforation. The remaining MRGNB were *Pseudomonas* sp. isolated from sputum. *Candida* species were isolated from 4 patients intra- and 3 patients post-operatively and none were fluconazole-resistant. No MRSA was isolated.

Conclusions and recommendations: Significant meropenem resistance was identified amongst inter hospital transfers with bowel perforation. VRE was more commonly isolated post-operatively. No MRSA was isolated. Following this evaluation vancomycin was removed from the EPS surgery antibiotic prophylaxis regimen and all EPS surgery patients will be screened on admission for VRE and meropenem resistant organisms. * Fisher's Exact Test (Two-Tailed).

P 463

Establishing preferences for different modes of dialysis, and different characteristics of dialysis provision, using labelled choice discrete choice experiment (DCE) questionnaires

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Introduction: Although patients have several options for dialysis including home based peritoneal dialysis, unit haemodialysis and home based haemodialysis, little is known about the preferences of UK renal patients for these options.

Methods: Respondents selected one of the 3 labelled choice DCE dialysis options. Preferences of renal patients, renal healthcare professionals, and carers for home based peritoneal dialysis (PD), dialysis unit haemodialysis (HD), or home based HD, were assessed as characteristics of dialysis provision changed (i.e. frequency of dialysis; quality of dialysis; level of care [self care, shared care, or professional care]; timing of dialysis; and the costs to the NHS of dialysis). Results were evaluated using econometric analysis.

Results: There were 636 respondents in the patient sample. Relative to dialysis unit HD (the base case), on average home PD was valued positively, but home HD was valued negatively. Increasing the frequency of dialysis was valued negatively, but may have been valued positively if it was necessary to ensure higher quality dialysis (valued positively). Increased choice with respect to dialysis timing is valued positively, and costs of dialysis to the NHS was statistically significant, but not highly valued.

Discussion: This is first UK application of DCEs to assess preferences for renal dialysis. It demonstrates that on average patients seemed to prefer home based PD.

P464

Should PD patients be kept 'wet' to preserve residual renal function?

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Background: Preservation of residual renal function (RRF) is a cornerstone in the management of PD patients, with loss of RRF associated with technique failure, LVH and death.

Objective: To clarify whether long-term alterations in volume status measured using bioimpedance are associated with preservation of RRF.

Methods: Patients undergoing peritoneal dialysis between March 2003 and January 2011 at 2 tertiary university hospitals, who had a set of paired bioimpedance measurements and dialysis adequacy measurements 12 months apart were considered. Amputates, patients with cardiac pacemakers or those who were anuric at baseline were excluded. 427 pairs of data from 237 patients were included for analysis. RRF as measured by urine Kt/V (uKt/V), was correlated with baseline demographic, biochemical and physiological parameters. Additionally to investigate whether a relative change in hydration status affected RRF, the cohort was divided into tertiles both by baseline ECW/TBW and 12-month follow up ECW/TBW. We examined whether a change from baseline hydration tertile to follow up hydration status tertile was associated with alterations in loss of RRF over the 12 month follow-up.

Results: Loss in RRF as measured by change in uKt/V at 1 year compared to baseline was not correlated with dialysis vintage, PD modality (CAPD v APD), ethnicity, sex, BMI, presence of diabetes, HbA1c, PTH, albumin, CRP, number of antihypertensive medications, hemoglobin, serum sodium or change in hydration status as measured by change in ECW/TBW between baseline and year 1. However there was a correlation between loss of RRF and baseline mean arterial pressure ($r=0.13$, $p<0.02$), a younger age($r=0.15$, $p<0.0005$), greater daily UF volume ($r=0.12$, $p=0.03$) and a higher baseline RRF as measured by daily UO ($r=0.4$, $p<0.0001$). In addition changes in volume status (overhydrated v neutral v underhydrated) over a 12-month follow up did not alter loss in RRF (1-way ANOVA $p=0.21$: Dunn's multiple comparison test no demonstrated significant difference between any group).

Conclusions: Both relative and absolute changes in volume status over a 12-month period do not appear to significantly alter loss in RRF. Clinicians should not 'chase' hydration status to ensure preservation of RRF.

P465

Bioimpedance spectroscopy can predict survival in peritoneal dialysis patients

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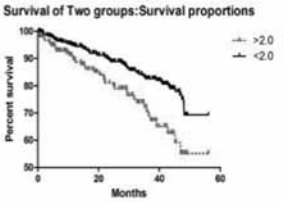
Accurate assessment of hydration status is critical to care of a dialysis patient but difficult to assess. We wished to validate bioimpedance technology (Body Composition Monitor, BCM) in PD. In a retrospective analysis of prospectively collected data in a single PD centre we hypothesised that:

1. BCM overhydration readings should correlate Cardiac Troponin T (cTnT), an independent predictor of long-term mortality & cardiovascular death and events.
2. Severe BCM defined overhydration should be an independent predictor of mortality.
3. Baseline BCM may correlate with changes in cTnT over time.

Results:
529 PD patients had data collected during the study period (see table)

	BCM >2 n=169	BCM <2 n=360	p value
Age in yrs (SEM)	57.57 (1.2)	55.49 (0.81)	0.150
Male	134 (79.3%)	195 (54.2%)	0.000
Diabetic	78 (46.2%)	95 (26.4%)	0.000
IHD	22 (13.0%)	31 (8.6%)	0.120
Dialysis vintage in months	27.01 (4.54)	30.14 (2.85)	0.550
Na mmol/L (SEM)	139.74 (0.27)	139.56 (0.18)	0.550
Alb g/L (SEM)	38.45 (0.47)	39.77 (0.32)	0.020



BCM remained an independent predictor in multivariate analysis (OR 0.411, 95% CI 0.25 - 0.69, p=0.01). Interestingly, residual renal function as measured by 24 hour urinary volume or CrCl did not predict survival.

In a subgroup of 93 patients that had corresponding BCM and troponin readings, we found that BCM correlated with concurrent troponin (r^2=0.057, p=<0.01) but BCM did not correlate with changes of troponin over 6 months (p=ns).

Conclusion: BCM can predict survival and does correlate with troponin. Further studies need to be performed to see if treatment, guided by BCM can improve survival. The patients that had a baseline BCM>2L had a significantly shorter patient survival (Figure X). Hazard Odds Ratio was _____ (p<??).....Using unadjusted data, we also showed that prior diagnosis of ischaemic heart disease predicted patient survival (Figure Ya) as was Diabetes (Figure Yb). We also found that age predicted survival (Odds ratio____). Interestingly, residual renal function as measured by 24 hour urinary volume or CrCl did not predict survival. Multivariate analysis confirmed that BCM over hydration status remains a statistically significant independent predictor of surivival (Table B). However, after adjusting for age, diabetes was no longer predictive. Find some other papers that look at predictors of survival and let's review what other stats/information they report (ie different models etc).

P466

Peritoneal protein clearance as a predictor of survival in peritoneal dialysis patients

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Background: Historical studies reported that fast peritoneal transport status, through small pores was associated with increased morbidity and mortality in peritoneal dialysis (PD) patients. Recent studies have shown that there is little evidence to suggest that this may be the case, whilst peritoneal protein clearance, through large pores may be a predictor of survival.

Design: The aim of this study was to evaluate the factors associated with PD protein loss and the cardiovascular outcomes and death. All patients who were undergoing peritoneal dialysis in our hospital who have had a peritoneal equilibrium test (PET) and a peritoneal dialysis adequacy were included in this study. We collected data on demography, co morbidities and biochemical data and the echocardiogram findings of all patients prospectively. Follow up was until death or end of study period.

Results:A total of 290 patients were included. Mean age of the study population was 55.3 years. Mean peritoneal dialysis loss was 89 mmol/l and patients with greater protein losses had lower serum albumin 39.0 mmol/l (SD 4.79) vs. 37.5mmol/l (SD 4.23) compared to the low protein loss groups ($p<0.05$). In this cohort age ($p = 0.018$, HR 1.037, CI 1.006-1.068), serum albumin ($p= 0.033$ HR 0.884, CI 0.789-0.990), BNP ($p=0.020$, HR 2.014,CI 1.118-3.627) peritoneal protein clearance ($p= 0.058$, HR 0.022, CI 0.000-1.130) , peritoneal protein loss ($p= 0.026$, HR 1.008, CI 1.001-1.015), BMI ($p =0.056$, HR 0.920, CI 0.845-1.002) and presence of diabetes mellitus ($p= 0.006$, HR 0.336, CI 0.155-0.730) were predictors of mortality, whereas dialysis adequacy, Davies co morbidity score, CRP and gender did not predict survival.

Conclusions: Loss of protein through the peritoneal membrane is associated with hypoalbuminaemia, vascular inflammation and accelerated atherosclerosis. This study shows that increased large pore protein loss is associated with increased mortality in PD patients, supporting peritoneal protein loss as a risk factor.

P467

Transplant waiting list status predicts outcome following surgery for peritoneal dialysis-related encapsulating peritoneal sclerosis

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Introduction: Encapsulating peritoneal sclerosis (EPS) is an uncommon complication of peritoneal dialysis (PD) and is associated with recurrent episodes of peritonitis and prolonged duration of PD.

Methods: We sought to compare the outcomes of patients following EPS surgery using transplant waiting list status as a surrogate for general fitness, comparing those with a kidney transplant, those on or recently suspended from the TWL, and those deemed unfit and permanently removed from the TWL. The notes of all patients presenting with EPS secondary to PD and undergoing surgery since 1st April 2009 were reviewed. Perioperative (≤30days) and one-year survival was recorded. Only the first presentation with EPS was considered.

Results: 44 patients proceeded to surgery with an overall one-year survival of 74%. 16/44 patients had been permanently removed from the transplant list by the referring centre. All four perioperative deaths were in this group of patients (i.e. 25% mortality for those not fit enough to be on the TWL). The one-year survival of this group was **64%**, still better than that reported in the Pan-Thames Audit where medical management predominated (Balasubramaniam et al. NDT2009; 24; 3209). Patients (n=19) suspended from the TWL had a **77%** one-year survival, while patients with a functioning transplant (n=9) had an **86%** one-year survival. Four patients were admitted with bowel perforation, requiring immediate surgery and stoma formation; half survived. In the same period seven patients underwent surgery for recurrence on one (n=5) or two (n=2) occasions; one died as a result from an enterocutaneous fistula. Other factors associated with poor outcome following EPS surgery were high C-reactive protein and low serum albumin at the time of surgery

Conclusion: Surgical treatment for EPS is worthwhile, even in high risk patients. As might be expected, transplant waiting list status appears to be a surrogate for outcome following EPS surgery.

P468

Growth in infants and children commencing dialysis under two years of age in the UK

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Objectives: The aim of this analysis, a BKPA funded project, was to describe anthropometric changes during dialysis in this cohort.

Methods: A retrospective case-note review of growth in all children under two years of age commenced on chronic dialysis, over a 5-year period. All data presented as median z-scores calculated for age and gender.

Results: Birth weight (wt) and start of dialysis wt were available for 82 of the 102 patients identified, mean birth wt 2.95kg, z-score -1.24. 38% infants were born preterm at a median gestation 35 weeks. At dialysis start: The median age was 6-months with wt -1.58 and height (ht) -2.17. The change in median weight z-score from birth to start of dialysis was -0.42. On dialysis: During the first year, little change was observed for wt (n=67) -1.55 to -1.48 and ht (n=43) -2.16 to -2.17. Infants starting dialysis at less than 1 month of age (<1/12) had deterioration in both wt (n= 18) -1.55 to -2.51 and ht (n=9) -1.19 to -1.96. Improvement was seen in those with a gastrostomy at start of dialysis, with significant change in weight [p<0.005] and an increase in height (n=11) -2.51 to -1.83. Infants with the greatest growth deficit at start (z score <-1.88), had significant improvements in both height and weight [p<0.005]. For the 32 children on dialysis for 2-years, weight remained unchanged but height deteriorated (-2.52). At transplantation (n=44): Median age 2.45 years following a median dialysis duration of 1.9 years, had z-scores: ht -2.26 and wt -0.98. Children starting dialysis at <1/12 of age (n=7) had the greater deficits, ht -2.51, wt -1.22 and those with a gastrostomy at start (n=10) better growth, ht -1.32 and wt -0.39.

Conclusion: Children starting dialysis at <2 years of age weigh less at birth than the general population and the further decline in their growth in the interval before dialysis commences needs addressing. To maximise growth early consideration should be given to gastrostomy tube placement.

P469

Continuous ambulatory peritoneal dialysis (CAPD) – a forgotten modality in children?

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Objectives and study: Despite being the first effective chronic peritoneal dialysis (PD) treatment for children, CAPD is only used in 10% of UK paediatric patients. We, therefore, tried to ascertain whether CAPD remains an effective treatment.

Methods: A retrospective study was undertaken reviewing all paediatric patients commencing PD, both automated (APD) and CAPD for established renal failure (ERF) from September 2002 to August 2010. Demographic data, duration and reason for cessation along with complications were studied. Comparisons of dialysis adequacy between modalities were made.

Results: 69 treatment episodes of PD were studied in 62 patients. 29 patients received CAPD and 33 APD. 6 patients changed from CAPD to APD. One had 2 APD episodes. 40 patients were male and 22 female. CAPD patients were older than APD patients with a median age of 12.2 years (range 5.1-16.6 years) compared to 7.5years (range 0.2-19 years) for APD patients ($p = 0.004$). Median duration of treatment was 16.1 months for CAPD and 18.8 months for APD (p= ns). Peritonitis was slightly more common in CAPD patients at a rate of 1 in 35.4 patient months for CAPD and 1 in 16.4 patient months for APD. 17 patients from each group had peritonitis ($p = 0.16$). Full dialysis adequacy was available in 48 treatment episodes (26 APD, 22 CAPD). There was no difference in total kT/V between the groups whilst creatinine clearance (CrCl) was better in the CAPD group ($p = 0.024$). Looking just at dialysis adequacy both CrCl and kT/V were slightly higher in the APD group but these differences were not significant.

Conclusion: CAPD is an effective treatment for ERF in children. Good clearance can be attained as can acceptable peritonitis rates. It is cheaper than APD and ought to be considered – particularly where resources are limited.

P470

Can changes in the matrix metalloproteinase (MMP) system predict peritoneal membrane damage or EPS in peritoneal dialysis (PD)?

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Background: Peritoneal dialysis (PD) is an important option for renal replacement therapy. Peritoneal sclerosis (PS) limits PD duration due to loss of ultrafiltration (UF) capacity, while about 3% of PD patients experience a condition termed Encapsulating Peritoneal Sclerosis (EPS). In many fibrotic diseases reduced Extracellular-matrix breakdown due to lowered MMP activity occurs, often from over-expression of Tissue inhibitors of MMP (TIMPs).

Hypothesis: changes in the MMP system in the peritoneum underlie PS &/or the switch to EPS, such that levels in PD fluid have value as non-invasive biomarkers of these conditions.

Methods: Three patient cohorts have been studied: 2 Sheffield cohorts plus 209 samples from the Global Fluid Study (GFS) including 12 EPS & 42 matched controls. MMP activity was assessed using the ENZchek assay system. TIMPs, MMPs, Albumin, I 2 microglobulin, transferrin & IgG were quantified by ELISA.

Results: Minimal MMP activity was found in PD fluid. MMP-1, 9, & 13 were almost undetectable. MMP-2 & 3 were present averaging 46 & 2.1 ng/ml respectively. In contrast TIMP-1, & 2 and to lesser extent TIMP-3 had significant levels in peritoneal fluid from commencing PD (109, 17, and 0.29 ng/ml respectively). TIMP-1, & 2, plus MMP-2 negatively correlated with UF ($r = -0.7, -0.7, -0.6$, respectively, all $p<0.001$). Importantly there was a rapid >7 fold increase in TIMP-1 within 100 days of EPS diagnosis, which when normalised to TIMP-2 levels was 100% accurate in predicting EPS. Predicting filtration rates by reference to the molecular weight of filtered only proteins suggests that TIMPs 1 & 2 as well as MMP-2 have significant peritoneal production.

Conclusions: Negligible MMP activity in PD fluid results from high TIMP levels which could underlie the development of PS. TIMP-1, 2, & MMP-2 are useful predictors for peritoneal membrane damage. Elevated TIMP-1 in fluid may have value as a diagnostic tool or late biomarker of EPS.

P471

Can omentin (intelectin-1), dermatopontin, and collagen (□1) I predict peritoneal membrane damage in peritoneal dialysis (PD)?

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Background: Peritoneal dialysis (PD) is an important option for renal replacement therapy in patients with end-stage kidney failure. Peritoneal sclerosis (PS) limits PD duration due to loss of ultrafiltration (UF) capacity. The development of PS and UF loss can be difficult to frequently monitor. Recent application of 2D gel proteomics on PD fluid has identified several proteins that are elevated in patients with membrane damage. Here, we have hypothesised that PD fluid levels of 3 of these, Omentin, Dermatopontin and collagen (I 1) I, may allow prediction of UF capacity from spot measurements.

Methods: 50 Sheffield PD patients had fluid and plasma samples taken during a routine PET test. Omentin, Dermatopontin and collagen (I I1) I were quantified by commercial ELISA in PD fluid, with levels then correlated to clinical parameters of membrane function and damage. Analysis was performed using Microsoft Excel 2007 software and GraphPad Prism (Prism 5.01 for windows). $p < 0.05$ was considered statistically significant.

Results: Omentin (1.5 ng/ml), Dermatopontin (1.5 ng/ml) and collagen(I 1) I (6.3ng/ml) were all detectable in PD fluid by ELISA. All significantly positively correlate with D/Pcr at 2hr ($r=0.5$, $p=0.006$ / $r=0.44$, $p=0.03$ / $r=0.53$, $p=0.005$ respectively) and negatively correlated with the loss of UF ($r=-0.6$, $p=0.0009$ / $r=-0.52$, $p=0.008$ / $r=-0.5$, $p=0.01$ respectively).

Conclusions: Omentin (Intelectin-1), Dermatopontin, and collagen(□1) I are significantly correlated with risk factors of peritoneal membrane damage, Spot measurements of these may have value in estimating UF capacity.

Poster session

Thursday 14th March

12:00 - 13:00

Peritoneal dialysis 2

P472

Safety and long term outcomes of percutaneous peritoneal dialysis catheter insertion by nephrologists

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Introduction: Peritoneal dialysis catheter (PDC) insertion by nephrologists may improve access to the modality. The safety and long term outcomes of this technique are uncertain.

Methods: We reviewed outcomes of 324 Percutaneous catheters (PC) inserted using the Seldinger technique under local anaesthesia and 219 catheters inserted under general anaesthesia by mini-laparotomy. Initial procedure failures were not included in analysis of long term outcomes. Patients who died, were transplanted or transferred were excluded from the analysis period.

Results: 78% of PC catheters were first catheters compared to 45% of surgical. Median Hb at insertion was lower at insertion for PC catheters compared to surgical. (10.5 vs 11g/dl p=0.001). Initial procedure failure was higher for PC catheters than surgical (10%vs 4% p=.013). Patients undergoing insertion by PC technique were significantly less likely to require dialysis through a central venous catheters (CVC) than patients with surgical insertions (19% vs 37% P<0.001) Peritonitis and exit site infection within 30 days of insertion were not significantly different between groups. Catheter patency was not significantly different between techniques at 30 days (87% vs 85%), 6 months (56%vs 61%) and 12 months (43% vs 45%) for first catheter insertions. For second and subsequent insertions the surgical approach was superior. Median hospital stays were shorter for patients undergoing PC insertion (0 vs 4 days p=<0.001)

Conclusions: Percutaneous catheter insertion was associated with reduced requirement of pre-procedure haemodialysis through CVCs, a shorter hospital stay and was performed at a lower Hb than surgical insertion. Infectious and patency outcomes were not significantly different between approaches for first catheters, for second and subsequent insertions surgical insertion was superior.

P473

Laparoscopic peritoneal dialysis catheter (PDC) insertion: does it really make a difference?

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Introduction: Permanent peritoneal dialysis (PD) access was first described and introduced in clinical practice more than 40 years ago. It is still undergoing modification and adaptation to various insertion techniques. Catheter placement is thought to be the key to a successful PD programme and the economic advantages are lost if a patient switches to HD during the 1st year due to failure of PD.

Aims and methods: The objective of this document was to conduct an evidence-based assessment of a minimally invasive approach to PD catheter insertion, with particular regard to failure rates secondary to catheter dysfunction.

Results: Table 1

TABLE 1: Outcomes after laparoscopic versus open PDC insertion

Study	N (L/O)	Catheter flow obstruction	Peri-catheter leak rates	Follow interval (month)	Catheter survival
LU 2003, CS	148	31%	0	42	53% [a]
Wang 2005, CS	20	10%	5%	1	90%
Haggerty 2007, CS	31	6.5%	0	14	93%
Maio 2008, CS	100	6%	5%	22.35±16.5	91%
Crabtree 2009, CS	428	3.7%	2.6%	21.6	87%
Daschner 2002, PPNR	42 (25/23)	8% (L) 8.6% (O)	8% (L) 21.7% (O)	1	88%
Mattioli 2007, PPNR	30 (15/15)	0 (L) 20% (O)	6.1% (L) 17.5% (O)	14	100%
Gajjar 2007, PNR	75 (45/30)	2.5% (L) 14.28% (O)	11% (L) 13.4% (O)	6	97.8%[b] 80%[b]
Gadaliah 1999, RCT (P)	148 (78/72)	7.9% (L) 11.1%(O)	1.3% (L) 11.1 (O)[b]	36	51.3%(L)[a,b] 36%(O)
Wright 1999, RCT	50[c] (21/24)	0 (L) 0 (O)	8% (L) 0 (O)	18.5	57% (L)[a] 54%(O)
Tsimoyiannis (40) 2000, RCT	50 (25/25)	0 (L) 12.5% (O)	0 (L) 32% (O)	21±11	96% (L) [a,b] 76% (O)
Jwo 2010, RCT	77 (37/40)	2.7% (L) 0 (O)	15% (L) 18.9% (O)	31	67.5% (L)[a] 77% (O)

a = Uncensored Catheter survival, b= p≤0.05, c= 5 exclusions, PNR= Prospective non randomised, PPNR= Paediatric prospective non randomised, CS= Case series, RCT= randomised controlled trial, L=Laparoscopic (P=Peritoneoscopic), O=open surgery

Conclusion: Laparoscopic placement of peritoneal dialysis catheters is safe, and useful for insertion of PD catheters in a complex cohort of patients having undergone previous abdominal surgery. However, good grade I evidence is lacking and open surgery may be quicker, though results from on-going trial are awaited with interest.

P474

Which technique for peritoneal dialysis catheter placement?

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Objectives: Renal replacement therapy by Peritoneal Dialysis (PD) retains independence and reduces the restrictions on daily life of approximately 34,000 patients in the UK. Catheters can be placed in a variety of ways: laparoscopically, via open surgery or percutaneously. We compared patency rates between these techniques in 148 patients treated in 2 hospitals between March 2009 and July 2011. The aim was to identify if any one method conveyed superior patency.

Methods: Patients were identified from theatre records. Outcome data up to October 2012 were collected from prospectively compiled databases in 2 hospitals. Patients were grouped depending on the method of PD catheter placement i.e. laparoscopic with pre-peritoneal tunnel (n=58); open surgery (n=42) and percutaneous placement (n=48).

Results: Six month patency for the laparoscopic group was 68% compared with 84% (open surgery) and 76% (percutaneous). Kaplan-Meier analysis revealed estimated median patencies of 748 days for the laparoscopic group, 515 days for open surgery and 686 days for the percutaneous group. There were no significant differences in the rate of complications, infection or membrane failure between the groups. Although there were more cases of catheter obstruction in the laparoscopic group compared with the open surgery group this did not reach significance (n=5 vs n=0, P=0.07). Overall there was no significant difference between the patency of the PD catheters in the three groups (P=0.994).

Conclusion: No previous studies have compared percutaneous placement of PD catheters with advanced laparoscopic and open techniques. Although no method appeared to convey any advantage, percutaneously placed catheters avoid the need for general anaesthetic and are a relative low cost procedure. A reasonable approach would therefore be to use percutaneous PD catheter placement as a first choice in suitable patients.

P475

Nutritional status of patients presenting to a national centre for surgery for encapsulating peritoneal sclerosis (EPS)

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Patients with Encapsulating Peritoneal Sclerosis (EPS) are often catabolic and can be severely malnourished since they present with features of bowel obstruction and consequent inability to utilise nutrition enterally. Chronic Kidney Disease (CKD) patients may also have additional factors that contribute to poor nutritional intake.

We report on the nutritional status of patients who have progressed to surgical intervention for EPS within our Nationally Commissioned Centre. These patients are at varying stages of post surgical intervention, from present to over 3 years.

Since our service gained National Commissioning status in April 2009, 44 CKD patients have undergone surgery. Patients presenting to the service whilst receiving dialysis (n=35; 23 male) were compared to those presenting with a functioning renal transplant (n=9; 6 male). Anthropometric markers of nutritional status monitored for EPS patients include changes in body weight and hand grip strength (HGS), as well as mid arm muscle circumference and triceps skinfold thickness. Data for weight loss leading up to original surgery and handgrip strength at presentation to the service are presented here:

	% weight loss		% HGS (for age / sex)	
	Dialysis (n=33)	**Transplant (n=9)**	**Dialysis (n=30)**	**Transplant (n=9)**
Mean ± SD	15 ± 12	15 ± 5	60 ± 22	67 ± 26
Median	14	15	62	67
Range	0 - 56	8 - 22	23.8 - 110	30.5 - 106

Patients presenting for EPS surgery show a significant percentage loss of body weight and evidence of malnutrition (assessed by HGS) whether on dialysis or with a functioning transplant. Early diagnosis and referral to a specialist EPS Centre is beneficial to optimise nutritional status pre surgery. A Dietitian is an essential component of the MDT for the management of these complex patients; equally important is the provision of a Dietitian in their locality for continued nutritional management.

P476

Encapsulating peritoneal sclerosis: prediction and outcomes of recurrent disease

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Introduction: Encapsulating Peritoneal Sclerosis (EPS) is a rare but devastating complication of Peritoneal Dialysis (PD). Thickening of the peritoneal membrane with bowel encapsulation results in intractable intestinal dysfunction. Surgical enterolysis provides the only definitive treatment strategy for primary disease. There are anecdotal reports that Tamoxifen may be beneficial. As a specialised international referral centre we have observed recurrence of EPS requiring repeat surgical intervention. We aimed to establish predisposing factors, incidence and outcomes of recurrent EPS within our patient cohort.

Methods: A retrospective analysis of EPS cases over a 12 year period was performed (186 referrals, 143 operated; Feb 2000-May 2012) Patients with recurrent disease were assessed focusing on outcomes, type of surgery and adjuvant therapy usage. Potential predictive factors for recurrence were assessed including treatment with Tamoxifen, time to recurrence, transplant status and duration of PD exposure.

Results: 9 (6.3%) developed recurrent disease (1 – 2 recurrences). All had previously had definitive peritonectomy and enterolysis. Mortality was not significantly different in the recurrent group compared to overall mortality. 5 patients had functioning transplant at the time of reoccurrence. 4/9 patients received Tamoxifen after the initial procedure (0 mortalities) whilst 5/9 did not (3 mortalities; p=0.16,). Recurrence occurred earlier in those patients receiving Tamoxifen (7 (4-32) vs. 13.5 (9-17) months; p= 0.81,). PD duration was not associated with reoccurrence.

Conclusion: Recurrent EPS appears to be a rare entity with similar outcomes to primary disease. There is a predilection to early recurrence and although not significant, there is a tendency for a lower mortality when patients are treated with Tamoxifen although recurrence was earlier in this group. There appear to be no overt predictive factors in previous disease course or patient factors to predict incidence or outcome

P477

Encapsulating peritoneal sclerosis in a contemporary incident peritoneal dialysis cohort in Scotland: an analysis of risk and outcomes after prolonged follow-up

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Background and aim: Encapsulating peritoneal sclerosis (EPS) is a devastating complication of peritoneal dialysis (PD), but there is disagreement in the literature regarding the incidence and outcome of EPS. We sought to quantify the risk and outcome of EPS in a contemporary PD cohort.

Methods: The cohort of incident adult patients who started PD between 1st January 2000 and 31st December 2007 in Scotland (n=1238) was identified from the Scottish Renal Registry (SRR). The 10 adult renal units in Scotland identified potential EPS cases among this incident cohort, and medical records were examined to ensure cases met the International Society for Peritoneal Dialysis (2000) diagnostic criteria.

Results: The first data analysis in 2008 incorporated 19 EPS cases diagnosed in the incident cohort giving an incidence of 1.5%. Further follow-up to 30th June 2011 identified a further 16 EPS cases (35 total) giving an incidence of 2.8%. The incidence rises exponentially with increased PD exposure with an incidence of 7.6% for patients with >4-5 years, 12.8% for patients with >5-6 and 15.4% for those with >7 years of PD exposure. Outcomes for EPS patients are poor with a 46.5% mortality at one year. If patients survive to 2 years they appear to have good chance of ongoing survival. The median survival for EPS cases and the remainder of the cohort are comparable but Kaplan Meier survival analysis shows that the EPS cases were experiencing better survival until the EPS diagnosis when their survival plummets. EPS cases who were subsequently transplanted demonstrate impressive survival compared to those who did not receive a transplant, although survivor bias is potentially contributing. Patients presenting less acute or severe presentations suffer comparable survival to patients who present with overt bowel obstruction.

Conclusion: With prolonged follow-up we have accurately quantified the risk of EPS in Scotland, and confirmed its poor prognosis. The outcome for patients surviving 2 years and/or receiving a renal transplant are encouraging. The comparable outcomes for patients with and without acute bowel obstruction serve as a counter argument to altering the diagnostic criteria for EPS.

P478

Risk factors for peritoneal dialysis-associated peritonitis in a contemporary national incident cohort

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Background and aim: Peritoneal dialysis (PD) associated peritonitis is a major cause of morbidity and the leading cause of technique failure in the UK. Numerous potential risk factors have been identified but differences in study population, methodology and clinical practice across the world contribute to the inconsistency in published literature. We sought to identify potentially modifiable risk factors in a national PD cohort.

Methods: All 10 adult renal units prospectively collect details of all peritonitis episodes, PD treatment failure, PD adequacy and other clinical parameters for all Scottish PD patients and report it to the Scottish Renal Registry (SRR) 6-monthly. Details of dialysis history, demographic data and relevant blood results downloaded from the SRR database along with complete audit data from all **incident** patients for all units between 01/01/2000-31/12/2007 (n=1324) were analysed (using the Kaplan Meier method and the Log Rank Test for time to first peritonitis and thereafter Cox Proportional Hazards analysis of potential predictors of peritonitis). Sub-analysis examining risk factors for specific organism or outcome was also performed.

Results: 668 of 1324 incident patients (50.4%) experienced 1318 episodes of peritonitis. There were clear differences between units in proportion of patients experiencing peritonitis, recurrence rates, specific organisms and outcome according to antibiotic protocol. On multivariate analysis the predictors of peritonitis were being on CAPD versus APD (HR 1.40 (1.29-1.52) p=0.000) and serum albumin immediately prior to start of PD (HR 0.98 for every 1g/l increase (0.96-0.99), p=0.005). Patients with diabetes mellitus (DM) had a significantly higher risk of staphylococcus aureus peritonitis (HR 1.84 (1.2-2.9), p=0.01) and of recurrent peritonitis (HR 2.1 (1.3-3.3) p=0.003).

Conclusion: The differences between renal units suggest potentially modifiable clinical practice which could reduce the peritonitis risk. CAPD is associated with increased risk, but this may reflect an era effect whereby more patients are on CAPD earlier in the study period. Hypoalbuminaemia and DM are not immediately modifiable, but may identify patients to target with preventative strategies such as exit site prophylaxis.

P479

How long can a patient expect to continue peritoneal dialysis (PD) in Scotland; can we predict PD longevity and should we limit PD to certain groups or for a defined duration?

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Background and aim: Even if patients escape early access problems, avoid severe peritonitis, continue to achieve dialysis adequacy targets, and their peritoneal membrane continues to provide sufficient ultrafiltration (UF), continuing PD longterm may now be considered undesirable because the risk of encapsulating peritoneal sclerosis (EPS). The aim of this study was to examine patient outcome data to identify any predictors for poor outcome on PD and to determine whether this should prompt changes to local clinical practice.

Methods: Data from all incident PD patients (n=1324) starting PD 01/01/2000-31/12/2007 were analysed to identify potential predictors of poor outcome by the study end 30/06/2011. Outcomes were death, transplantation or technique failure (transfer haemodialysis). Technique failure was subdivided into recognised causes. Potential predictors of each outcome were analysed using Kaplan Meier Survival analysis, and if significant were incorporated into multivariate analysis using Cox regression analysis.

Results: The 1324 patients had combined 6446.3 years of patient follow-up (between 3.5-11.5 years since start of PD). Median survival to death from start of PD was 6.8 years (95% confidence interval 6.2-7.4 years). Predictors of survival were transplantation, age, diabetes mellitus (DM), serum albumin, residual renal function (RRF) and primary renal disease. The main reasons for stopping PD were death (23.3%), transplantation (22.5%) and technique failure (47.3%): peritonitis (42.9%) and inadequate dialysis (22.1%) were the main causes of technique failure. Predictors of technique failure are DM, RRF, and earlier PD era. Only 25.2% of patients are still alive on PD by 3 years, but only 17.2% of diabetics, 17.2% of those >70 years, and 21.5% of those with serum albumin <30g/l at the start of PD.

Conclusion: Certain patient groups experience poorer patient and technique survival but without comparative outcome data to state they would fare better on HD we cannot use our data to justify limiting PD to specific groups. Similarly, the reality that only 13.5% of patients make it to 4 years of PD means few are at major risk of EPS, but those that experience technique survival beyond this point are arguably the ones with the most to lose (renal limited disease, younger). Limiting duration of PD must be decided on a case by case basis, and informing patients about the EPS risk with prolonged PD is important.

P480

Embedded peritoneal dialysis catheter; 4 years experience

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Aims: In stage 4 chronic kidney disease (CKD) there is no linear pattern in the decline of estimated glomerular filtration rate (eGFR) to accurately predict the start of dialysis. Embedded peritoneal dialysis (PD) catheters evolved as a means of having an easily accessible PD catheter without the maintenance needs and infection risks of an *in situ* PD catheter. Also, eliminate the need for emergency surgery or temporary dialysis access. We evaluated the 4 year experience and outcome relating to this technique in one of the UK transplant centers.

Methods: A retrospective analysis of prospectively collected data including renal function, date of insertion, externalisation and the time PD was commenced was performed. Patients were divided into 3 groups: A: non-externalised PD (NEPD), B: externalised PD (EPD) and C: removed before externalisation (RBEPD)

Results: 54 patients, mean age (range) 63 years (23-87) underwent embedded PD catheter between December 2008 -November 2012 via open (7 cases) or laparoscopic (47 cases).

A) NEPD group (n=23): Median (range) eGFR at time of insertion 17ml/min (16-23). The median time (1^{st} quartile, 3^{rd} quartile: interquartile range) that catheter was embedded was 236 days (146, 594:448).1 patient developed a wound haematoma & 2 were lost to follow-up.

B) EPD group; (n= 26) The median time that the catheter was embedded was 241 days; (120, 413: 293). Median eGFR at time insertion was 17 (16- 24). Median eGFR at time of externalisation 13 (10-14). Before externalisation no complications were recorded. After externalisation 4 PD catheters did not immediately function (15%) of which 2 required exchange. 2 developed late exit site infections post-externalisation and 4 (15%) developed PD peritonitis 3, 7, 8 &12 months of which 2 required removal. Furthermore 2 required exchange due to poor drainage several months after externalisation.

C) RBEPD group (n=5); All were transplanted before externalisation of the PD catheter. Median eGFR 18 (17-19). Median time of catheter stay 124 days, (56, 292: 235) No complications were recorded in this group of patients.

Conclusions: We feel that the use of embedded PD catheter is justified because of the significant variability in the pattern of renal function decline and negligible complications before externalisation. Embedded PD catheters provide an effective solution in patients with stage 4 CKD when PD is suitable but a start date cannot be predicted.

P481

Hospitalisation for peritonitis in peritoneal dialysis patients starting renal replacement therapy in England between 2002 and 2006

James Fotheringham[2,1], Meguid El Nahas[2], Michael Campbell[1], Martin Wilkie[2]

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Introduction: Guidance exists on peritoneal dialysis (PD) peritonitis rates, but no national or centre-specific rates of PD peritonitis have been reported.

Methods: UK Renal Registry data from 46 centres linked to Hospital Episode Statistics data were used to identify PD catheter insertions in the 12 months before start of PD, hospitalisation for PD related infections, modality changes and death in patients starting renal replacement therapy between 2002 and 2006 in English centres with more than 20 PD patients per centre. International Society of PD guidelines were used to determine centre-specific rates of peritonitis. Standardisation across centres was performed using zero-inflated negative binomial regression, adjusting for demography, comorbidity and late presentation.

Results: 6,256 patients experienced 4,894 peritonitis admissions over 12,718 patient years (0.4 events/year). Peritonitis complicated 21% of admissions in PD patients, with 49% of patients experienced one or more peritonitis admission. 86% of patients were coded as having a PD catheter inserted; a mean of 31 days before first PD treatment (centre-specific mean 8 – 73 days). Late presentation and time from catheter insertion to start of PD had no influence on peritonitis rates. Modality at 30 days post-discharge from first peritonitis admission were as follows: 66% PD, 26% haemodialysis (HD), 1% transplant, 1% therapy withdrawn, 6% dead (centre proportion dead or on HD at 30 days 12% - 59%). Mean length of stay was 18 days in those changing modality vs 6 days in those staying on PD ($P<0.001$). Centre specific peritonitis rates ranged from 0.15 – 0.79 per year and following adjustment for age, socioeconomic status and comorbidity the number of centres with higher than expected peritonitis rates reduced from 7 to 5.

Conclusions: Linked data allows the first national and centre-specific reporting of peritonitis, with hospitalisation a marker of greater severity. Variation in catheter timing and modality switches following first hospitalised peritonitis episode were identified. Despite adjustment variation in hospitalised peritonitis infection rates persisted. Coding practices and admission thresholds need further exploration.

Poster session

Thursday 14th March

12:00 - 13:00

Podocyte biology, mechanisms of proteinuria 1

P482

Glomerular involvement in the arthrogryposis, renal dysfunction and cholestasis (ARC) syndrome

Amelia Holme[1,2], Jennifer Hurcombe[3], Anna Straatman-Iwanowska[4], Carol Inward[2], Paul Gissen[4,5], Richard Coward[2,3]

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Background: Arthrogryposis, Renal dysfunction and Cholestasis (ARC) syndrome is a multisystem autosomal recessive disorder caused by defects in two genes (VPS33B and VIPAR), involved in localisation of apical membrane proteins. Affected children usually die by one year of age, often secondary to infective complications. The classic renal manifestation previously described in ARC syndrome is proximal-tubular dysfunction. The aim of this study is to gain further insight into the renal manifestations of this syndrome.

Methods: Clinical review of three-cases of ARC syndrome presenting to a tertiary centre. Together with measurement of VPS33B and VIPAR protein expression in the human glomerulus.

Results: The cases demonstrated severe failure to thrive and in addition to commonly described features profound proteinuria and albuminuria, together with hypoalbuminaemia, suggesting glomerular involvement of this syndrome. Western blotting of conditionally immortalised human glomerular cells, and exvivo immunofluorescent analysis of the human glomerulus revealed that VPS33B and VIPAR were highly expressed in glomerular endothelium, and podocytes, but not in the mesangium.

Conclusions: ARC syndrome affects the glomerulus as well as the proximal tubule in the kidney. Our molecular studies suggest that both cell types that constitute the glomerular filtration barrier are affected in this condition; providing an explanation for the albuminuria that we have observed in our cases.

P483

ERK5 involvement in the regulation of human podocyte phenotype and survival

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Introduction: Podocytes are highly specialised cells necessary for normal kidney function, however in diabetic conditions injury occurs leading to an impaired ability to operate due to compromised phenotype and/or cell death. ERK5 is an atypical MAPK involved in pathways modulating cell survival, proliferation and phenotype. Previously we have demonstrated the expression and activation of ERK5 in human podocytes, the role of which remains largely unknown in these cells under conditions associated with diabetic nephropathy.

Methods: Conditionally immortalised human podocytes were stimulated with EGF (10ng/ml), TGF-β1 (2.5ng/ml) and D-glucose (30mM). Inhibition of ERK5 activation was conducted with the chemical inhibitor BIX02188 (10μM) directed to the upstream MEK5. Intracellular signalling proteins were investigated by western blotting; phenotype was explored with markers of podocytes, epithelia and mesenchymal cells by immunofluorescence; apoptosis was studied by western blot detection of cleaved caspase-3 and annexin V-FITC flow cytometry.

Results: EGF increased nuclear staining of the epithelial marker P-cadherin by immunofluorescence that coincided with increased proliferation determined by an MTS assay; the proliferation was prevented by BIX02188 whilst P-cadherin was unaltered. Conversely, TGF-β1 decreased P-cadherin and increased the myofibroblast marker α-SMA which was prevented by BIX02188. BIX02188 alone reduced cytoplasmic staining of the podocyte marker synaptopodin. TGF-β1 increased apoptosis determined by flow cytometry as did BIX02188 alone and with TGF-β1 co-treatment. High D-glucose incubation increased apoptosis and BIX02188 co-incubation enhanced the apoptosis observed with BIX02188 alone.

Conclusion: Inhibition of ERK5 activation prevented EGF-induced proliferation as well as TGF-β1-induced epithelial-to-mesenchymal transition. Under hyperglycaemic conditions MEK5 inhibition increased apoptosis. ERK5 activity is required for podocyte survival and maintenance of a carefully balanced phenotype.

P484

Global analysis of glucocorticoid action in podocytes

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Background: Children presenting with nephrotic syndrome typically receive a course of glucocorticoid therapy without undergoing renal biopsy. Glucocorticoid action is mediated by activated glucocorticoid receptors binding to various genomic loci to regulate the expression of target genes. Although accumulating evidence suggests that the target cell of glucocorticoid therapy is the podocyte, the clinically-relevant and specific mechanisms of action have not been determined.

Objectives: To undertake a global analysis of glucocorticoid-regulated genes in human podocytes and generate hypotheses for glucocorticoid mechanisms of action.

Methods: Wild type human podocytes (Saleem MA et al.) underwent 5 hour exposure to either glucocorticoid-containing culture medium or standard culture medium. The Affymetrix U133 Plus 2.0 Array was used to produce whole genome expression data, and by comparing results from the untreated and treated cells, a list of glucocorticoid-regulated genes was produced. The gene list underwent enrichment analysis for gene ontology terms, and selected pathways underwent further experimental validation.

Results: 54,614 genes were identified in total. Following statistical analysis, 606 glucocorticoid-regulated podocyte genes were identified. Of these 606 genes, 411 were upregulated and 195 were downregulated following glucocorticoid exposure. Enriched gene ontology terms included: regulation of apoptosis, cell signalling and cell motility. Preliminary data show glucocorticoid exposure affects podocyte motility and morphology *in vitro*.

Conclusions: Microarrays provide a powerful tool for determining glucocorticoid-mediated changes in podocyte gene expression. These data can now be used for generating hypotheses for clinically-relevant mechanisms of glucocorticoid actions on podocytes in nephrotic syndrome. Initial results show glucocorticoid effects suggested by the microarray data do occur *in vitro*.

P485

OCRL1 interacts with CD2AP and is expressed in human podocytes

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Introduction: Mutation of the inositol polyphosphate 5-phosphatase, OCRL1, causes the X-linked disorder oculocerebrorenal syndrome of Lowe (Lowe syndrome), characterised by eye, brain and kidney defects. The renal phenotype comprises a proximal tubulopathy characterised by low molecular weight proteinuria; additionally, a subset of patients have been found to have glomerulosclerosis on renal biopsy. We therefore hypothesised that OCRL1 plays an important role in podocyte function, possibly in the maintenance of the slit-diaphragm, which is a crucial component of the glomerular filtration barrier. As a first step to investigate this hypothesis we investigated OCRL1 expression and its molecular interactions in human podocytes.

Methods: Using wild-type human podocytes [1], we performed immunoblotting, immunoprecipitation, protein pull-down experiments and immunocytochemistry to characterise expression, interaction and localisation of OCRL1. In addition we reviewed a renal biopsy from a patient with Lowe syndrome and renal dysfunction.

Results: We found that OCRL1 is expressed in human podocytes and went on to demonstrate an interaction with CD2AP, which likely occurs indirectly via IPIP27A, a key regulator of endocytic traffic. Within podocytes, both OCRL1 and CD2AP co-localise with components of the early endocytic pathway, providing evidence that OCRL1 may function, in a protein complex with CD2AP and IPIP27A, to regulate these pathways within the podocyte *in vitro.* In addition, we found evidence of glomerular pathology in a patient with Lowe syndrome.

Discussion: Our findings suggest that OCRL1 may have a role in endocytic trafficking in podocytes in addition to renal tubular cells and future studies will focus on defining this functional role. In parallel, further investigation of patients with Lowe syndrome will help to determine whether they are at risk of developing glomerular dysfunction.

1. Saleem, M.A., et al., *A conditionally immortalized human podocyte cell line demonstrating nephrin and podocin expression.* JASN, 2002. **13**(3): p. 630-8.

P486

Insulin directly stimulates VEGF-A production in the glomerular podocyte

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Podocytes are critically important for maintaining integrity of the glomerular filtration barrier and preventing albuminuria. Recently it has become clear that to achieve this they need to be insulin sensitive, and produce an optimal amount of vascular endothelial growth factor-A (VEGF-A). In other tissues insulin has been shown to regulate VEGF-A release but this has not been previously examined in the podocyte.

Using an *in-vitro* and *in-vivo* approach we now show that insulin regulates VEGF-A in the podocyte in mouse and man. Insulin directly increases transcription and translation of VEGF-A in conditionally immortalized wild type human podocytes. Furthermore, when podocytes are rendered insulin resistant *in vitro* (using stable short hairpin RNA knockdown of the insulin receptor) or *in vivo* (using transgenic podocyte specific insulin receptor knockout mice) podocyte VEGF-A production is impaired. Importantly, *in vivo* this occurs prior to the development of any podocyte damage due to podocyte insulin resistance.

VEGF-A has been widely reported to be elevated early in diabetic nephropathy and then becomes depressed as pathology develops. We propose that alterations in podocyte insulin signaling could account for these changes.

P487

Albuminuria: too few glomeruli and too much testosterone

David Long[1], Maria Kolatsi-Joannou[1], Karen Price[1], Cecile Dessapt-Baradez[2], Jennifer Huang[1], Eugenia Papakrivopoulou[1], Ron Korstanje[3], Luigi Gnudi[2], Adrian Woolf[4]

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Introduction: Normally, the glomerular filtration barrier excludes circulating albumin from entering the urine. Major barrier disruptions cause massive protein leakage whilst more moderate albumin excretion above the normal range may also be clinically important and precede nephropathy. We hypothesised that studying mouse strains with naturally-occurring variations in albuminuria would identify potential mechanisms which lead to protein leakage.

Methods: We utilised two in-bred strains of mice; one resistant to renal disease (C57) and the other susceptible (FVB). We examined albuminuria in both sexes of each strain and glomerular gene expression using microarray. The effect of sex on albuminuria was evaluated by administration of testosterone to female mice.

Results: Albuminuria was increased in female B6<male B6<female FVB/N<male FVB/N mice, whereas numbers of glomeruli/kidney were the exact opposite. We identified a common set of 39 genes, significantly differentially-expressed in each of the following four comparisons: male *versus* female B6; male *versus* female FVB/N; male FVB/N *versus* male B6; and female FVB/N *versus* female B6 mice. We focused on genes from our microarray found within albuminuria quantitative tract loci in mice. Protein levels of CYP4A12A, a cytochrome P450 and ACY3 (aspartocyclase 3) were markedly greatest in the glomeruli of FVB/N mice. CYP4A12A was localised in glomeruli; with some of the signal in podocytes and was detected in cultured podocytes. ACY3 was predominantly immunolocalised in parietal glomerular epithelia, with faint signals in glomerular tufts. Testosterone administration increased albuminuria and glomerular mRNA levels of *Acy3* and *Cyp4a12a* in B6 female mice, but not FVB/N. *Acy3* and *Cyp4a12a* were also upregulated following exposure of cultured podocytes to exogenous testosterone.

Discussion: We have demonstrated that low numbers of glomeruli and testosterone are potential mechanisms leading to albuminuria in mice. Several unsuspected genes have been identified which correlate with albuminuria which may represent novel biomarkers and therapeutic targets for early renal disease.

P488

Investigation of the human glomerular Insulin like growth factor binding protein (IGFBP) axis reveals an important function for IGFBP1 on the podocyte

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Podocytes are key cells in maintaining the integrity of the filtration barrier in the glomerulus of the kidney and preventing albuminuria. It is now clear that these cells are both insulin and insulin-like factor (IGF) sensitive. IGFs are controlled at a cellular level by insulin-like growth factor binding proteins (IGFBPs), which are able bind to these hormones and regulate their bioavailability. However, IGFBPs can also have direct cellular effects independent of binding to IGFs.

Studying conditionally immortalised forms of the three human glomerular cell types (podocytes, mesangial cells and glomerular endothelial cells) we have found that these cells differentially secrete IGFBP1-4 locally into the glomerulus.

Focusing on the podocyte we have discovered that IGFBP release from this cell can be rapidly modified by IGF-I and II, that IGFBP1-4 can signal independently of the major IGF receptor (IGF-IR) to the podocyte via the PI3K and MAPK pathways and that functionally, IGFBP1 is particularly important in controlling a number of essential cellular properties of the podocyte including survival, adhesion and motility.

Collectively this work demonstrates that there is local production of IGFBP1-4 in the human glomerulus and that IGFBP1 is particularly important in controlling a number of critical features in the podocyte. We propose that this axis is important in maintaining integrity and health of the glomerulus.

P489

Secreted frizzle - related protein 2 (sFRP2) in podocyte differentiation and injury

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Secreted frizzled related proteins (sFRPs) are a family of proteins that bind and interact with Wnt ligands and thus modulate Wnt signaling. Most of the functions of sFRPs have been attributed to their ability to antagonize Wnt signaling although recently other functions have been identified including regulation of neuronal branching, axon guidance and angiogenesis. sFRP2 has been shown to play an important role in the repair process of heart tissue post myocardial infarction. In the kidney, sFRPs are highly expressed during development with sFRP2 specifically expressed in early nephron structures. Based on the above observations, we hypothesised that sFRP2 regulates podocyte branching during development and its expression is altered following injury. Using a well characterised immortalised mouse podocyte cell line, we have previously shown that differentiated podocytes form processes similar to those seen *in vivo*. We studied expression of sFRP2 in proliferative and differentiated cells (n=4 in each condition) and found that sFRP2 transcripts were significantly up-regulated by 2.4-fold ($p<0.05$) in differentiated podocytes. Addition of recombinant sFRP2 led to longer processes (53± 4.6 vs 76 ± 9.1, arbitrary units, $p<0.05$); more processes/cell (8± 0.96vs11 ± 1.01, $p<0.05$) and more cells with processes with one or more branching points (35± 17%vs73± 12%, $p<0.05$). These effects were not mediated by RhoA activation. To examine the role of sFRP2 in glomerular injury we exposed podocytes to Adriamycin and observed a 7-fold increase in sFRP2 gene expression ($p<0.05$). We also examined sFRP2 expression in human kidney biopsy samples from the European renal cDNA bank consortium. In this study, total RNA is isolated from microdissected glomeruli and qRT-PCR is performed using Affymetrix gene chip technology. Transcripts for sFRP2 were up-regulated 8- fold in patients with focal and segmental glomerulosclerosis compared to controls (living donor transplant biopsies). This data suggests that sFRP2 regulates podocyte differentiation by promoting process formation and may be important in glomerular disease although its exact role remains to be elucidated.

Poster session

Wednesday 13th March

18:15 - 19:25

Registry and epidemiology 1

P490

Demographics and outcomes study in patients with autosomal dominant polycystic kidney disease (ADPKD) and end stage renal failure (ERF): a UK renal registry analysis on behalf of the ADPKD study group

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Introduction: Despite ADPKD being the most common genetic cause of ERF, uncertainty remains over aspects of optimisation of routine clinical care.

Aim: To describe ADPKD specific demographics, clinical characteristics and renal replacement treatment patterns in a population with ERF.

Methods: An incident adult population commencing RRT between 1/1/2000 and 2/10/2010 was included in this analysis. Simple cross tabulations of baseline demographics, co-morbidity and care related measures were performed. Results are stratified by Primary Renal Disease (PRD).

Results: Between 1/1/2000 and 2/10/2010 47,769 individuals commenced RRT. 3111 (7%) individuals had ADPKD recorded as PRD, 34,595 (72%) individuals had another PRD other than ADPKD or diabetes, and 10,063 (21%) individuals had diabetes recorded as PRD. The median age of starting RRT was lowest in the ADPKD group (55 years (IQR 47-63) compared to 62 years (IQR 50-71) for those with diabetes and 65 (IQR 49-75) years for those with all other causes of PRD . The median age of commencing RRT by PRD group has not changed over the last 10 years. There were less co-morbid conditions in those with ADPKD who were also seen earliest by renal services. Patients with ADPKD were more likely to commence RRT with a renal transplant as first modality (11% in the ADPKD, compared with 5% in the non-ADPKD/non-diabetes group and 4% in the diabetes as PRD group). In those that start with dialysis the median time to transplant was the same irrespective of PRD.

Discussion: Despite early engagement with renal services the median age of starting RRT remains lowest in individuals with ADPKD compared with other PRD's. This could suggest that current management strategies are not effectively influencing the natural history of the disease. An ADPKD-specific national cohort and dataset would be an invaluable resource for research focused on identifying contributing factors to variation in and improvement of outcomes. A national ADPKD-specific study group has been formed to address this issue.

P491

Management of NHS ineligible dialysis requiring patients in the UK - a survey

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Many renal units have reported significant numbers of ineligible foreign asylum / residency seekers with established renal failure presenting for dialysis. There is confusion and variation in the management of these patients who, according to guidelines, are not entitled to full NHS services rather only 'emergency treatment' - but paradoxically no agreed consensus exists that long term dialysis for ERF is an 'emergency treatment'. This results in commissioners declining to reimburse Trusts, which has the potential to destabilise renal units, and treatment may be declined to sick and vulnerable patients. The Home Office is often slow in processing their cases, and these patients end up trailing around emergency rooms, picking up ad hoc dialysis sessions on ITUs and arriving with on renal wards usually in extremis. Such treatment is unethical and paradoxically very much more expensive than regular dialysis. A survey was therefore undertaken amongst UK Renal CDs.

Patients predominantly present to English and (more recently) Scottish units. Management of these patients varies, but most respondents feel they should provide 'standard' treatment, including vascular access and ESAs. Only 14% are fully funded by commissioners. The assertion that these patients pay for their care is a red herring, and most respondents found that the patients have nowhere near the amounts of funds required (95%). Respondents predominantly felt that dialysis should be considered 'emergency treatment' (87%). When NHS ineligibility is established, 43% are repatriated, but often takes some years. In these cases it is estimated that very few (many said less than 10%) will have access to dialysis at home. Respondents overwhelmingly felt that limitations (financial, organisational or clinical) in care had adverse health implications for these patients (96%).

It is suggested that ***emergency treatment*** should comprise ***regular dialysis*** (hd or pd). This seems self evident but would have the effect of clarifying the situation at presentation. Commissioners should establish a central fund, available to Trusts for the treatment of these patients.

P492

Do we transfuse patients with moderate to severe kidney disease appropriately in the NHS?

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Introduction: The National Comparative Audit for blood transfusion was set up to evaluate the quality of blood cell use in hospitals in England, Scotland, Wales and North Ireland with reference to consensus guidelines set by the audit group. The aim of this analysis is to evaluate the use of red cell transfusions amongst patients with moderate and severe kidney disease using MDRD eGFR ranges of 30 – 44 and less than 30 respectively.

Methods: We conducted a prospective and retrospective audit of all medical red cell transfusion in one week of choice during September to November 2011 and in 1 in 3 haematology/oncology cases (age > 18 years, excluding patients transfused in A&E and ICU).Case notes and laboratory information was used to get data. 181 sites (90% of NHS sites) returned data on 9216 cases

Results: 848 (9.3%) and 1040 (11.4%) patients can be classified as having moderate and severe kidney disease respectively. In the data collection, a formal diagnosis of either moderate or severe kidney disease was recorded in 101 / 848 and 460 / 1040 patients. In each group the gender ratio was 1:1. Mean ages were 77 and 72 in moderate and severe renal insufficiency groups. In the moderate kidney disease group – 11.7% had possible iron deficiency, 6.7% had a possible B12 or folate deficiency, 1.4 % possible autoimmune haemolytic anaemia and 5.3% possible renal anaemia (eGFR < 44 and chronic kidney disease as only diagnosis). In the severe kidney disease group – 8.5% had possible iron deficiency, 5.8% had a possible B12 or folate deficiency, 1.2 % possible autoimmune haemolytic anaemia and 28.2% possible renal anaemia.

Discussion: From our initial results, there is a high rate of transfusion in cases with potentially reversible anaemia. However the reason for this is likely multifactorial and is for further analysis in part 2 of the audit with a review of selected cases.

P493

UK study of late referral of children who develop established renal failure: impact on transplantation and survival

Rishi Pruthi[1], Manish Sinha[2], Anna Casula[1], Malcolm Lewis[3], Fiona Braddon[1], Yincent Tse[4], Heather Maxwell[5], Catherine O'Brien[6], Carol Inward[7]

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Background: Early referral of children with chronic kidney disease (CKD) to a paediatric nephrology centre is recommended to minimise clinical complications related to CKD in childhood, and improve pre-emptive transplantation. In the absence of any existing data, this study aims to define late referral rates in the UK paediatric RRT population, and highlight its impact on transplantation and survival.

Methods: Using UK Renal Registry data we analysed all incident patients starting renal replacement therapy (RRT) aged >3months and <16years between 1996 and 2010. Late referral was defined as seeing a paediatric nephrologist less than 3 months from commencing RRT. A chi-squared test was used for group analyses

Results: Of 1554 eligible patients, data completeness of 86.7% allowed analysis of 1347 patients. Overall late referral was seen in 25.5% (n=343) of patients. Late referral was significantly lower in males 20.18% (n=156) than females 32.75% (n=188), P<0.0001, and highest in the 3-months-2 years age group 31.61% (n=49) p=0.0005. Children diagnosed with ERF of unknown aetiology had the highest late referral rate at 78.9% (n=41), p=<0.0001. No significant differences in late referrals were noted amongst different ethnic groups, paediatric centres, or when comparing rates over time. The proportion of children transplanted at 1 year of start of RRT was reduced in the late referral group at 45.1% (n=155) compared to 66.9% (n=672) in the control group, p=<0.0001. No child presenting late underwent pre-emptive transplantation compared to 28.1% (n=282) in the control group, p=<0.0001. Survival analysis adjusted for gender, ethnicity, RRT modality and age at start of RRT did not show any significant difference between groups.

Conclusions: A quarter of all children who develop ERF are referred late to nephrology units, with significantly higher rates in girls and those under 2 years old. These children have lower transplantation rates at 1 year from start of RRT and are unable to benefit from pre-emptive transplantation. There is a need to understand the reasons behind late referral, to help reduce it, and the potential exposure of children to clinical complications that accompany late referral.

P494

National renal biopsy registry - feasibility survey and results

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Aim: A feasibility survey towards setting up a national renal biopsy registry.

Background: Biospy proven renal disease (Glomerulonephritis, GN) is the most common primary renal disease among prevalent RRT (renal replacement therapy) patients and second most common cause in incident end stage renal failure. Additionally biopsy proven glomerulonephritis may recur after kidney transplantation and potentially jeopardize the survival of the graft. Single centre observational studies are often underpowered and prone to selection bias. Understanding the epidemiology of these diseases will hopefully give us an insight into the aetiology of these conditions. Setting up such a registry will help the nephrology community provide a UK wide comparison, biopsy rates by centre, indication for biopsies, baseline treatment data and facilitate large scale studies a reality.

Methods: We carried out a web based survey of UK pathologists via the nephropathology working group. The key questions covered by the survey were regarding coding, pathology systems, export formats and renal IT systems,

Results: We received responses from 20 nephropathologists from 20 centres, 13 transplant centres. These centres they were performing a mean of 215 native kidney biopsies (50-500) and 148 transplant biopsies (5-400). These centres used 5 different versions of snomed coding, with 40% of the centres using snomed v 2 (1979). The 20 centres used 12 different pathology IT systems and 5 different renal electronic patient records. The pathology IT systems could export 8 different formats with the majority of them being able to export to standard office formats and all defined fields of the report. 60 % of centres did not electronically import the renal biopsy report to their renal EPR's. 55 % of the centres had no formal renal-pathology MDM meeting.

Conclusion: The above survey demonstrates a wide variation in number of biopsies, coding and export formats. The first step towards this process is to set up a uniform coding across the UK and explore ways of data linkage.

P495

The majority of CKD patients are unaware of their correct primary renal diagnosis

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Introduction: Renal patients frequently seem unaware of their primary renal diagnosis (PRD). The aim of this study was to examine to what degree patients report their PRD correctly, and factors which may influence this.

Methods: Questionnaires were sent to all patients in CKD stages 3-5 on our renal database PROTON, as part of a study on familial kidney diseases. They were asked to write down the diagnosis of their kidney disease if known. All responses were entered into an access database. Reported patient diagnoses were compared to their coded PRDs (or PRDs listed on letters, where codes not available) and judged to be correct, partly correct, incorrect or unknown. Statistical significance was tested using SPSS.

Results: Of 3,596 questionnaires sent, 2,000 responses (56%) were received and assessed. Of these, 838 patients (42%) reported their diagnosis correctly (32% using correct terminology), 145 (7%) partly correctly, and 1017 (51%) incorrectly or not reported. The underlying PRD was significantly associated with correct reporting: 92% of patients with polycystic kidney disease (PKD) gave a correct diagnosis versus 52% with glomerulonephritis, 48% with diabetic nephropathy, 47% with reflux/pyelonephritis and 16% with hypertensive/ischaemic nephropathy (Chi-square $p<0.001$). Transplant recipients (58% correct diagnoses) did better than dialysis patients (43%) and CKD patients (35%; Chi-square $p=0.03$). Patients with access to Renal Patient View (RPV) gave a correct diagnosis significantly more often (290/489 patients=59% correct diagnoses versus 36% for patients not on RPV, Chi-square $p=0.007$).

Conclusion: The majority of renal patients are unaware of their PRD. Patients with clearly definable familial disease such as PKD are more likely to know their PRD; as are transplant recipients and those with access to RPV. To improve patients' awareness, we need to communicate their PRD more explicitly, perhaps in writing. RPV can be a helpful tool in this process and should be promoted more strongly.

P496

Stroke thrombolysis in end-stage renal disease: a national opinion survey

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Background: Systemic thrombolysis for acute ischaemic stroke is standard of care in the UK with defined pathways to expedite treatment. In the absence of trial data on the safety and efficacy of this treatment that is offered to patients with end-stage renal disease [ESRD] we aimed to capture the perspective of UK nephrologists and highlight healthcare policy & research objectives.

Methods: Consultant nephrologists in the UK were invited to participate in an internet-based questionnaire by e-mail invitations. Respondents were asked about their experience, their wish for involvement in thrombolysis decisions, safety concerns in haemodialysis [HD] and peritoneal dialysis [PD] patients rated from 1-10 [10=highest risk], views on stroke rehabilitation in HD & PD, opinions on antiplatelet and warfarin use for stroke prevention in atrial fibrillation [AF].

Results: 122/433 [28%] clinicians responded [69% with >15 yrs consultant experience]. 75% wanted involvement in thrombolysis decisions although just 10% gave input in practice. 64% expressed a high degree of concern [≥7/10] regarding intracranial bleeding risk in HD. Overall risks of intra- & extra-cranial bleeding were rated lower in PD vs. HD [$p<0.001$]. 85% felt the HD schedule impacted negatively on rehabilitation whereas 63% felt this was the case in PD [$p=0.001$]. Over 75% would start/augment antiplatelet therapy after stroke. This was not influenced by modality although more clinicians would use warfarin for stroke prevention in PD patients with AF than in HD patients [79% vs. 66%, $p=0.04$]. 71% wished to participate in national collaborative studies of stroke in ESRD.

Conclusions: The majority of UK nephrologists want involvement in thrombolysis decisions for their ESRD patients. We validate concerns about bleeding risk with thrombolysis and pertinently identify a stark need to improve access to stroke rehabilitation in the UK especially in HD patients. Finally this survey provides a clear mandate for wider, national research into stroke in ESRD.

P497

Observational study on factors affecting the length of stay of patients on a renal ward in a busy tertiary centre in North West of England

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Introduction: Salford Renal Network West sector, serves a population of 1.3 million with 120 peritoneal patients, 308 haemodialysis patients and 350 transplant patients. In July 2011, Salford Royal Foundation Trust renal centre bed capacity was reduced by 12 beds. It is hoped that by reviewing and improving admission and discharge processes, trust can improve the patient experience by reducing the number of days spent in hospital, and save bed days thus increasing capacity and saving money – quoted from NHS institute for innovation and improvement. Co – morbidity burden of a patient can be measured by Charles co morbidity index score (CIS) and we have used this measure in this study.

Objective: To assess the pattern of length of stay in a large tertiary referral centre in North West of England and look for any associated factors which may predict prolonged admission.

Method: All renal admission to either a renal ward or renal high dependency unit bed between 30th January 2012 to 29th February 2012. Information on patient demographics, co – morbidities, renal status, admission diagnosis, co diagnosis, inpatient events directly related to length of stay and discharge plans and outcomes were obtained from the trust electronic patient record system. A CIS was calculated for each patient. The data was analysed with by SPSS comparing means with independent sample t test and analysing co morbidities and co – morbidity index with Pearson correlation test

Results and discussion: There were 66 separate renal admission episodes in this time period. Of statistical significance, mean length of stay was shorter in the following groups - males, haemodialysis and transplant patients compared to other modalities and conservative care patients. There were statistically significant positive correlations between length of stay and CIS and the following co morbid states 1.diabetes with end organ complications, 2.malignancies with metastases, 3.lymphoma and 4.previous myocardial infarction. Through this data collection, we hope to formulate plans to aid and improve our length of stay targets.

Poster session

Friday 15th March

11:30 - 12:30

Registry and epidemiology 2

P498

Seasonal variation in histologically-defined renal diseases

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Introduction: Previous studies have suggested seasonal patterns in glomerular and rheumatological diseases. However it is also possible that non-biological factors related to clinical practice influence the timing of renal biopsy and the apparent seasonal incidence of renal disease.

Methods: The date, indication and histological diagnosis of all native renal biopsies performed in the Greater Glasgow, Clyde, Forth Valley Renal Service serving a population of 1.5 million, from Jan 2000 - Dec 2010 were extracted from the electronic patient record. Incidences of all biopsies and emergency biopsies, pre-defined prospectively recorded indications and pre-defined disease groups in each of the four seasons were analysed per million population (pmp) per year with each season standardised to 91 days. 4 X 2 chi square test was carried out to confirm whether seasonal variation was statistically significant.

Results: There were a total of 1811 native renal biopsies during the period of 2000-2010 giving an overall incidence of native renal biopsy of 110 pmp/year ranging from 28.35 pmp/year in spring and summer to 26.03 pmp/year in winter; p=0.41.There was no seasonal variation in biopsy practice for either elective (p = 0.77) or emergency biopsies (p = 0.31). There was a statistically significant nadir in incidence of acute interstitial nephritis (AIN) in winter (1.1pmp/year in winter, 2.33 in spring, 1.74 in summer, 2.18 in autumn; p = 0.04).There was a trend to increased diagnosis of IgA nephropathy in summer (4.49 pmp/year) and spring (4.25 pmp/year) compared with winter (3.3 pmp/year) and autumn (3.09 pmp/year) (p= 0.09).There was no significant seasonal variation in the diagnosis of Pauci-immune crescentic GN and the other thirteen glomerular and interstitial disease categories studied.

Conclusion: In a large defined population overcoming many of the limitations of previous studies, we detected no significant seasonal variation in biopsy practice or the incidence of most of the common histologically-defined renal diseases. The nadir of AIN in winter warrants further study.

P499

The development of: - personal health information logs: P.H.I.L

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Introduction: It is not a new concept that patients have asked for, or have even demanded that their care providers not only take time to listen to them, explain things to them fully, in a way which they understand; they demand that they themselves can interpret and understand the given information. This demand has expanded into the need not only for openness and honesty in all things relating to their health, medications, diagnostic tests, procedures and events relating to them but the information given must be of high quality and jargon free.

Method: In beginning the journey, I began to look at how a product could be used in the adult setting to enhance compliance with transplant medication regimes. The Personal Health Information Log (P.H.I.L) was the acronym chosen and the thought is that the name "PHIL" will stick with the patients and become a familiar asset. The design is based around the look of a "filofax". The "Filofax" has pages for diary, maps, addresses, personal information etc, with no relation to health or medication. It was then that my idea of developing a product that could be carried by the patient to clinics, into hospital, on holiday; the uses where numerous. This would be ideal for many patients in an age where most information is delivered or obtained electronically and not all patients have access to the internet or a "Smart phone" and traditionally people still like to have something in writing. The information is for the new transplant recipients and provides information on the new medication the patients will be taking, along with other important post transplant information.

Conclusion: As health care providers we often decide what and when patients should be told something about their health; however patients with long term chronic conditions tend to know more about their health than the person looking after them. In further developing P.H.I.L other ideas will be introduced and expanded on and as it is the patients' own property they themselves can add items appropriate to them. This is not only information for the patient it is information about the patient.

P500

Diabetic kidney disease in the UK: prevalence and associations in the national diabetes audit

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Introduction: Diabetic kidney disease (DKD) is the most common cause of established renal failure in the UK. We aimed to investigate the prevalence of DKD and its association with other clinical and demographic variables.

Method: National Diabetes Audit data were available for the 2007-08 cycle. Type 1 and 2 diabetes patients with a valid serum creatinine and urinary albumin:creatinine ratio record were included. Estimated glomerular filtration rates were calculated using the CKD-EPI equation. DKD was defined as an eGFR <60ml/min/1.73m^2, albuminuria or both. Patients were stratified by eGFR and albuminuria status. Logistic regression was used to assess the associations between DKD and other variables including year of birth, year of diagnosis, ethnicity, Strategic Health Authority (SHA), clinical measurements (e.g. systolic blood pressure) and other laboratory results.

Results: In a total population of 868,616 patients analysed, 22,073 type 1 diabetes patients and 338,385 type 2 diabetes patients had DKD. The majority of patients had CKD stage 1-3 (95.6%). After adjustment, increases in body mass index and HbA1c were associated with an increased odds of DKD (e.g. in type 1 patients each 1% increase in HbA1c was associated with a 20% increased odds of DKD). Type 1 and 2 patients of Asian ethnicity were more likely to have DKD than those of white ethnicity (odds ratio 1.74 and 1.32 respectively). Current smokers were more likely to have DKD than non-smokers (OR 1.19 and 1.26 in type 1 and 2 patients respectively). Significant regional variations were also present e.g. in type 1 patients odds ratios for the presence of DKD varied from 0.74 in South West SHA to 1.25 in South Central SHA when compared to London.

Conclusions: This study has highlighted a large proportion of the diabetes population who are at higher risk of premature mortality, primarily from cardiovascular disease, or progressive kidney disease. It has also identified regions and patient groups who may benefit from targeted interventions to improve outcomes.

P501

Comparing double robust regression in large observational studies with randomised controlled trials in nephrology

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Background: Double robust regression (DRR) is a novel statistical technique that combines multivariate outcome regression with propensity score weighting. This allows simultaneous consideration of confounding effects on both patient outcome and treatment assignment. Though proven to work in theoretical datasets, DRR has not been validated in a real-life setting. Here we apply DRR to two large observational studies in CKD and compare results against landmark RCT.

Methods: Patients from the Chronic Renal Insufficiency Standards Implementation Study and Salford Renovascular Database were selected based upon inclusion / exclusion criteria from three key trials (ASTRAL, TREAT and SHARP). Univariate regression analysis was used to identify associations between baseline covariates and treatment assignment / patient outcome. Variables with significant associations were included in the DRR estimator, and a range of primary and secondary study end-points considered. DRR results were contrasted against Cox proportional hazards analysis in the same population.

Results: The DRR estimator generated results more consistent with published trial data than Cox regression. Data are presented below.

	Randomised trial			**DRR of observational data**		
	HR	**Treat-ment**	**Control**	**HR**	**Treat-ment**	**Control**
	ASTRAL (n=73/435)					
Reciprocal sCr	N/A	-0.07	-0.13	N/A	0.03	-0.13
ESKD	0.97	8%	8%	1.7	8.5%	6.6%
	TREAT(n=71/230)					
Death/RRT	1.06	32.4%	30.5%	1.2	29.3%	26.2%
Death	1.05	20.5%	19.5%	0.7	19.2%	24.5%
	SHARP (n=224/182)					
MACE	0.83	11.3%	13.4%	0.36	11.0%	13.9%

sCr – serum creatinine (l/µmol/year). Numbers for each trial within observational data are presented as treatment / control

Conclusion: In large observational data sets, the DRR estimator appears to produce comparable results to large scale RCT. This novel technique could be applied to study rare diseases or end-points and guide future RCT design.

P502

Renal Association patient safety project: 5 years on

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Introduction: The Renal Association (RA) Patient Safety project commenced in June 2007, initially in collaboration with the National Patient Safety Agency (NPSA)

Methods: 101 incidents, risks, and reports and 4 surveys have been circulated by the project lead to renal unit clinical directors and lead nurses by email over 65 months. Solutions have been circulated. The source or author of the alerts have been Renal Units/Project lead (n=50), MHRA (n=30), NPSA (n=15), DH/Health Protection Agency (n=5), Association of Renal Technologists (n=3), others (n=2).

Results: Causes of alerts were equipment failure, mostly dialysis machines or disposables (n=57), technique failure or use error (n=36), medication (n=6), infection (n=6). The contribution of nurses and technologists has progressively increased. 17 national reports and guidelines have been circulated, both renal and generic safety guidelines. 4 surveys have been undertaken: Venous needle dislodgement, Risks for renal patients (n=2), and Water plants and sterilisation protocols. Notable outcomes have been production of guidelines for preventing venous needle dislodgement, evaluation of a blood loss detector, and the creation of national guidelines for Water Standards (as a result of incidents of haemolysis from sterilisation of water supplies). It remains uncertain to what extent these circulated incidents and solutions are discussed in clinical governance meetings.

Discussion: Failure of dialysis equipment and use error remain the major risks to patient safety. Rapid sharing of and response to incidents has been achieved and with no additional funding. As the NPSA has now been disbanded, analysis of the National Reporting and Learning System (NRLS) database needs to be maintained. Equipment failure and variation of manufacturing standards emphasises the importance of links with the MHRA. Technique failure and use error indicates the importance of training and competency assessment.

Future objectives: Collaborating with the BRS will further promote multi-professional involvement. Key patient risks will be targeted and sharing of best practice will be encouraged. A link with UK Renal Registry data will be invaluable.

P503

Second year results of quality improvement programme in renal replacement therapies using modified breakthrough series collaborative methodology

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Introduction: A large gap remains between what is best practice and what is actually delivered despite synthesis of guidelines and national standards. This is amply demonstrated by the widely varying achievement of recommended standards published in the UK Renal Registry. Quality improvement (QI) is a way to close this implementation gap. However, there is little evidence of using specific QI methodology in the area of renal replacement therapies. We report our second year clinical and financial outcomes for an ambitious improvement programme in renal replacement therapies within our renal network.

Purpose: We aimed to continue to uplift local performance in clinical care to within the top 10% of renal units in the UK Renal Registry by working within current technologies using a QI programme.

Design: We used a modified Institute for Healthcare Improvement Breakthrough Series Collaborative methodology, in which 5 teams were given a different clinical indicators and aims to work on for one year. The teams will also work to sustain improvement that has been made during the first year. We evaluated the effectiveness of our work by comparing it to pre-intervention period and by analysing the cost savings made during the work.

Findings: The 5 teams have met their aims and made remarkable improvement.

Area	Aim	Pre-intervention result	Result after 1 year	Percentage improvement
Bolton Dialysis	90% haemodialysis patients will achieve urea reduction rate (URR) >65%	68.9% of patients	91.1% of patients	24% p=0.002
Community Dialysis	Halve Community team peritoneal dialysis peritonitis rate to 55 infections per year	105 episodes (1 infection every 13 patient months)	62 episodes (1 infection every 23 patient months)	41% P=0.001
Salford Dialysis	Reduce catheter related bacteraemia rate to 1 episode per 120 days	1.27 per 1000 catheter days	0.49 per 1000 catheter days	48% p=0.01
Wigan Dialysis	98% of Wigan haemodialysis patients will be cardiovascular bundle compliant by the end of May 2012	56% of patients	100% of patients	79% P=0.001
Dietician team	80% of Salford, Wigan, Bolton, Rochdale & community dialysis patients achieve phosphate below 1.8	68.1% of patients	80.8% of patients	17% p=0.001

Preliminary financial analysis revealed that the improvement work in the second year has made an aggregate project saving of £ 527, 674. Furthermore, the teams have also sustained improvement made in the first year.

Conclusion: The participating teams have shown remarkable rapid improvement as the result of a quality improvement collaborative that simply would not have occurred in normal clinical care. This collaborative is beginning to deliver greatly improved patient care to within the maximum currently achievable with existing technology. In the process, we have demonstrated improvement in significant cost savings for the NHS. These outcomes will likely be of interest to patients and their families, clinicians, clinical leaders and policy makers in the UK and beyond.

P504

An outbreak of influenza on the dialysis unit

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Background: Royal College of Physicians and Renal Association guidance for renal units in the event of an influenza pandemic lack a published renal-specific evidence base. Our in-centre haemodialysis population of 113 patients suffered in March 2012 an outbreak of an acute respiratory infection consistent with Influenza.

Aims: To investigate our outbreak and contribute to an evidence base of the impact of influenza on a dialysis unit.

Methods: Bacterial cultures of sputum & blood, viral swab PCR & viral serology, questionnaire, and review of case notes and human resources data.

Results: Of 87 respondents, 43 (49%) suffered an acute respiratory illness consistent with influenza. 11 patients required admission, 1 died. In all tested patients, viral PCRs were confirmatory, or serology supportive, of infection with Influenza A H3N2. This echoed national & European experience of relatively late influenza activity, higher rates of institutional outbreaks despite low incidence in the community, and high attack rates despite reasonable but incomplete levels of vaccination. Bacterial, respiratory and cardiac complications were common in admitted patients. We managed all patients without neuraminidase inhibitors. There was a striking difference in attack rate between in-centre and home dialysis patients, consistent with an in-centre outbreak. There was a statistically significant difference in attack rate between patients dialysing on different days, consistent with an effect of between-day segregation. Staff members were also affected by the illness, with increased short-term staff sickness placing a strain on services.

Conclusions and discussion: We present evidence that dialysis units, both patients and staff, should be considered to be vulnerable to outbreaks of influenza, a potentially fatal respiratory infectious disease. Practical, unit-specific plans should be made to detect and limit the harms of outbreaks of respiratory infection in dialysis patients.

Poster session

Friday 15th March

11:30 - 12:30

Nephrology - basic science 1

P505

Knowledge-based discovery of *in vitro* anti-fibrotic activities

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Introduction and aims: Fibrosis, also known as scarring, sclerosis or cirrhosis, is a pathological condition characterised by excessive extracellular matrix deposition and distortion of normal tissue architecture, often leading to chronic organ failure. Few drugs, if any, effectively target fibrosis, making the condition a leading cause of mortality. This report summarises our experience in the discovery of *in vitro* anti-fibrotic activities from herbal entities used in traditional Chinese medicine (TCM).

Materials and methods: An innovative model of fibrosis induced by transforming growth factor 1 in NRK-49F normal rat kidney fibroblasts was used to quantify anti-fibrotic activities (Am J Physiol Renal Physiol 2007;293:F631-40). Selection of 21 herbal compounds, 12 individual herbs and 27 herbal formulae was guided by the literature (Nephrol Dial Transplant. 2009; 24:3033-41). An additional 26 herbs and one fungus were selected according to TCM theories and as advised by two senior TCM practitioners (www.intechopen.com/books/recent-advances-in-theories-and-practice-of-chinese-medicine/knowledge-based-discovery-of-anti-fibrotic-and-pro-fibrotic-activities-from-chinese-materia-medica).

Results: Among the herbal entities chosen according to the literature, five compounds (Quercetin, Baicalin, Baicalein, Salvianolic acid B and Emodin), ethanolic extracts of three herbs (Danshen, Huangqin and Dahuang) and decoctions of 16 formulae (Fuzhenghuayu, Chailingtang, Baweidihuangwan, Yinchenhaotang, Mahuangtang, Guiyuanfang, Xiaochaihutang, Qingganhuoxuetang, Buzhongyiqitang, Bushenrougantang, Yiqihuoxuetang, Yigankang, Guzhangpian, Kangxianbaogantang, Hujinkeli and Xuelongchongji) showed reproducible anti-fibrotic activities. Of the remaining herbs and fungus tested, methanolic extracts of Lingzhi, Shiliuhua, Baibeiyegen, Jixieteng, Moyao, Liedang, Meiguiqie and Gusuibu showed reproducible anti-fibrotic activities.

Conclusions: We conclude that (i) our *in vitro* model of fibrosis is suitable for detecting anti-fibrotic activities not only of pure herbal compounds but also of complex herbal extracts; (ii) medicinal materials used in TCM are a rich resource for discovery and re-discovery of anti-fibrotic activities; (iii) the identified herbal compounds, individual herbs and herbal formulations deserve further studies so that safe, effective and affordable TCM anti-fibrotic drugs could be developed to meet the ever-increasing clinical needs.

P506

MicroRNA regulation of the cell cycle in aristolochic acid nephropathy

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Problem: Aristolochic acid nephropathy (AAN) is characterised by rapidly progressive tubulointerstitial nephritis culminating in end stage renal failure. A recent study causally links epithelial cell G_2/M cell cycle arrest to fibrosis following acute ischaemic, aristolochic acid (AA), and obstructive injuries (Yang L et al. Nat Med 2010; 16(5) 535). We have previously characterised microRNA expression in response to AA, including the induction of cell cycle associated microRNAs, miR-192, -194, -450a, and -542-3p.

Purpose: To investigate the mechanism of microRNA regulation of cell cycle arrest in AAN.

Design: An *in vitro* study in proximal tubular epithelial cells in a model of AAN, using stable-expression cell lines, TaqMan RT-qPCR, flow cytometry, Western blots, and immunofluorescence.

Findings: AA induced profound G_2/M arrest in proximal tubular cells via p53-mediated downstream inactivation of the maturation promoting complex CDK1/Cyclin-B1. This was associated with the formation of RNA granules, termed processing-bodies, indicative of translational repression. The enforced expression of miR-192 recapitulated the G_2/M arrest and translational repression. The mechanism of G_2/M arrest was identified as miR-192 mediated repression of the E3 ubiquitin ligase MDM2, a negative regulator of p53. The subsequent increase in p53 transcriptionally induced $p21^{cip1}$ and the growth arrest and DNA damage 45 (GADD45) proteins, which phosphorylate, inactivate and disassociate the maturation promoting complex CDK1/Cyclin-B1.

Conclusion: These data define a mechanism by which microRNAs control cell cycle in proximal tubular epithelial cells. This is of mechanistic importance in the recently described pro-fibrotic G_2/M arrest seen following a range of acute renal injuries.

P507

Development of therapeutic antibodies specifically targeting transglutaminase type 2 for the treatment of kidney fibrosis

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Background and aim: Transglutaminase type 2 (TG2 catalyses the formation of an ε-(γ-glutamyl)-lysine iso-peptide bond between adjacent peptides or proteins including those of the extracellular matrix (ECM). TG2 is tightly associated with the progression of renal scarring and fibrosis, where increased extracellular TG2 activity leads to accelerated ECM deposition and reduced clearance. Several small molecule pan TG inhibitors have been developed which are highly effective in preventing experimental kidney fibrosis. However, as they all inhibit other TG family members, numerous side effects prevent clinical application. To address this, we have developed a high affinity TG2 specific inhibitory antibody.

Methods: A recombinant protein spanning amino- acids 143 -473 of the human TG2 catalytic core was used to immunise mice. Splenocytes were fused to Sp2/0-Ag-14 myeloma cells. Initial hybridoma supernatants were screened for TG2 specificity by ELISA (TG1, 2, 3, 6, 7 and Factor XIIIa) and for inhibition of TG2 activity using the ^{3}H-putrescine incorporation assay. Positive hybridoma were subsequently cloned and IgG isolated. Epitopes were mapped by phage display using a random fragment human TG2 library.

Results: 960 hybridoma were screened, leading to the identification of seventy-five hybridoma supernatants showing specific reactivity to TG2 by ELISA. Ten of these inhibited TG2 activity, with an IC_{50} range against 100ng rhTG2 of 8 to 160nM. Epitope mapping of the inhibitory antibodies binding site on hTG2 identified 3 distinct inhibitory epitopes at amino acids 304 to 327, 351-364 and 450 to 468. The 3 lead antibodies (AB1, DC1, BB7) all targeting the same 304 to 327 epitope in the catalytic canal.

Conclusion: Immunising mice with naked TG2 core domain enables the generation of a unique set of TG2 specific inhibitory monoclonal antibodies, that couldn't be isolated by immunisation with native TG2. These antibodies are potentially suitable for human application in treating kidney fibrosis and are currently being humanised for clinical studies.

P508

A comparative assessment of transglutaminase 2 inhibitory antibodies targeting two different epitopes in an HK2 cell system

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Introduction: The fibrogenic enzyme transglutaminase-2 (TG2) is critical to the development of renal fibrosis in chronic kidney disease (CKD). The amelioration of renal fibrosis through inhibition of TG2 activity may, therefore, represent a novel therapeutic strategy in the management of CKD patients. Until recently, therapeutic exploitation of TG2 inhibition has not been clinically viable due to a lack of TG2 specific agents. Recently we have developed novel monoclonal antibodies (mAbs) to specifically inhibit TG2 activity. While these work well against rhTG2, their effectiveness against cell presented and ECM incorporated TG2 is unknown. We describe here initial results from application of these agents in cell culture systems.

Methods: 13 inhibitory anti-TG2 mAbs previously generated and isolated were tested in a cell culture system incorporating HK2 human proximal tubular epithelial cells. mAb induced changes in TG2 extracellular activity was measured using the incorporation of biotin cadaverine into fibronectin by 4×10^{-4} HK2 cells over 1 hour.

Results: Of thirteen mAbs tested at a set dose of IgG, three clones, DC1, BB7 and DD6, were superior inhibiting TG2 activity by 54%, 49% and 22% relative to control. These all targeted around the epitope at amino acids 313-325. In more detailed inhibition curve studies, the 2 most effective clones DC1 and BB7 inhibited 50% of extracellular TG2 activity in HK2 cells at 18 µg/ml and 29.6 µg/ml concentrations respectively.

Conclusions: These studies have identified candidate mAbs with potent TG2 inhibitory activity against native cell presented TG2, identifying a lead epitope. On-going studies will characterise ECM protein changes caused by antibody-mediated inhibition of TG2 in *in vitro* fibrosis models. Ultimately, this approach will yield data to ensure appropriate selection of an antibody (or antibodies) for extrapolation into long term *in vivo* studies.

P509

Phagocytic properties of macrophages from young and aged mice

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Introduction: Macrophages play an active role in renal regeneration. In acute kidney injury, aging is associated with worse injury, diminished reparative capacity and poorer outcomes. Recent studies of repair following spinal cord injury in aged and young mice indicate that young macrophages (Mϕ) are more phagocytically competent that aged Mϕ and are key to setting the scene for effective regeneration (Ruckh et al Cell Stem Cell 2012). In this study we determined whether bone-marrow-derived Mϕ (BMDM) from aged mice exhibited defective phagocytosis of apoptotic cells (AC). Efficient AC phagocytosis requires both multiple receptors on the Mϕ cell surface and various serum opsonins (e.g. C1q).

Methods: BMDMs were prepared from mice aged 3, 12 or 18 months and phenotyped by CD11b and F4/80 co-expression. BMDMs were incubated with CMgreen labelled ACs (80% annexin V +ve) for 30, 60 or 180 minutes before washing and flow cytometric quantification of phagocytosis (expressed as % phagocytosis). Fluorescent beads were used as a control particle and enabled the additional calculation of the phagocytic index i.e. the proportion of Mϕ ingesting 1, 2, 3, 4 or 5 or more beads.

Results: BMDMs from young and aged mice exhibited comparable CD11b/F4/80 co-expression (>95%). The proportion of BMDMs ingesting ACs/beads increased with time. However, ACs were ingested more avidly than beads at both 30 mins (40% vs 25%) and 1 hr (80% vs 60%). AC ingestion was saturated by 1 hr whereas bead ingestion continued to increase up to 3 hrs. The bead phagocytic index of BMDMs from young and aged mice was remarkably comparable at all time points. These were consistent findings across multiple experiments.

Conclusion: These data suggest that (i) BMDMs preferentially recognise and ingest ACs (a particle of real biological significance) to inert beads and, (ii) the proposed phagocytic deficiency of Mϕ from aged mice is not evident in BMDMs *in vitro*. It may be that the 'aged environment' may modulate Mϕ phagocytosis and the effect of aged mouse serum upon Mϕ phagocytosis is currently being tested.

P510

Use of laser capture micro dissection to determine MicroRNA expression patterns in individual nephron segments

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Background: MicroRNAs (miRs) are post-transcriptional regulators of gene expression that play fundamental roles in cellular processes in both health and disease. As miRs are known to exhibit organ and tissue specificity their expression may differ considerably along the nephron. Thus miR expression in whole biopsy tissue may mask significant changes in particular nephron segments

Methods: Using laser capture micro dissection (LCM) we were able to isolate and extract RNA from glomeruli, proximal convoluted tubules (PCT), distal convoluted tubules (DCT) and medulla from CD10 antibody stained (highlighting glomeruli and PCT) FFPE renal biopsy tissue in a control group of 6 pts (4 pts with thin basement membrane disease, 2 pts with histologically normal biopsies). We then performed a pooled Taqman Low Density Array (TLDA) to determine miR expression in a) isolated glomerular samples and b) whole biopsy samples from this control group. qPCR was then used to determine the expression patterns of selected miRs in individual nephron segments.

Results: Using the array data we identified the top 20 miRs that were most highly expressed in glomeruli and whole biopsy samples. As expected there were significant differences in the expression patterns of numerous miRs in glomerular samples as compared to whole biopsy. We then chose selected miRs of interest and examined their expression profiles across the nephron. We found that the miR expression in cortex samples closely mirrored that found in whole biopsy samples, with the predominant signal coming from the PCTs. Expression patterns within the DCT, medulla and glomeruli were significantly different to that obtained in the whole biopsy samples.

Discussion: MiR expression in the cortex (largely composed of PCTs) is the predominant contributor to whole biopsy miR expression. Changes in miR expression in other nephron segments, notably glomeruli, will be missed if such a whole biopsy approach is used. This has important implications for the study of glomerular diseases.

Poster session

Friday 15th March

11:30 - 12:30

Shared care and shared decision making 1

P511

Implementing kidney care planning (KCP) – a single centre experience

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Introduction: By the end of 2011, all patients in our unit were undergoing pre-dialysis counselling with a specialist nurse but formal structure and suitable documentation were still lacking. We successfully secured funding from NHS Kidney Care to develop and extend the Kidney Care Planning (KCP) process to our peritoneal dialysis (PD) population.

Methods: NHS Kidney Care provided funding for a Lead KCP Nurse for six months. All 57 PD patients were invited to participate. Patient information and documentation for KCP was developed, with assistance from the multidisciplinary (MDT) KCP Group and patient representatives. Patients were asked to complete an anonymous patient satisfaction survey at the end of the six month period.

Results: 23/57 (40%) patients engaged with the KCP process. At six months, around half (11/23) were still using the KCP. Of the 12/23 that were not, it was no longer applicable in 9/12 (deceased or transplanted), the remaining 3/12 had transferred to haemodialysis (HD). All patients approved of the idea of KCP. However, they all felt that their needs were already being met and were unsure that the extra documentation was necessary. Only 3 patients said they would definitely continue to use the KCP, the rest remained unsure.

Discussion: This has been useful to develop our KCP documentation and understand the place of KCP. Significant investment of nursing and MDT time is necessary for adequate patient support. NHS Kidney Care have agreed funding for a further six months to extend the project to our HD population. Although uptake of formal KCP was lower than expected, we feel this is testament to the active empowerment and support already provided by the PD Specialist Nurses.

P512

Patient literacy, activation and knowledge amongst those attending a general nephrology clinic

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Background: Literacy, patient activation and education have all been shown to have a positive correlation with health outcomes. We set out to assess these in patients attending a general nephrology clinic, with a view to establishing a baseline prior to the introduction of a new educational programme.

Methods: Written questionnaires were offered to general nephrology outpatients over a two month period. In addition to demographic variables, the questionnaires contained validated measures of literacy and patient activation (PAM-13). Knowledge was assessed using a modified Kidney Knowledge Score.

Results: 89 questionnaires were completed. The mean age of participants was 57 years (range 18-90), with a gender and ethnicity split representative of our nephrology clinic population. 72% responders had attended the clinic at least five times, with 21% attending for either the first or second time. Only five participants were identified as having low literacy levels. There was an equal spread over each of the four stages of activation amongst respondents. No significant relationships between literacy, activation score and demographic variables were demonstrated. However, activation scores were significantly higher in those attending the clinic for the first of second time in comparison to more frequent attendees ($p=0.01$). Patients scored an average of 61% in the knowledge questionnaire. We found that 69% patients correctly identified an appropriate target blood pressure and only 54% of patients knew to avoid ibuprofen. Knowledge scores were independent of demographic variables, attendance and activation. However, those with low literacy scores had significantly lower knowledge scores ($p=0.006$).

Discussion: The questionnaire sampled higher literacy scores than we were expecting for our population. Nevertheless, the knowledge scores suggest that an educational programme may be beneficial even amongst this group. The finding of poor knowledge amongst those with low literacy is well established and ways to reach these patients also need to be considered. How the educational intervention will impact on activation, knowledge and outcomes has yet to be established.

P513

How long do I have to live- eGFR and albumin values are significant predictors of mortality in patients who opt for conservative care

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Renal disease is increasingly detected in the western world, especially with an increasingly ageing population. As well as being older, many of these patients are frail and have other comorbidities such as diabetes or cardiovascular disease and renal symptom burden. Our renal unit offers a dedicated integrated programme of advanced kidney care counselling including advice on conservative care. However, for patients who opt for conservative care, the question most commonly asked– 'how long do I have to live' remains an uncertainty and challenge to answer.

We aimed to analyse the mortality outcomes of patients who had opted for conservative care in our unit and satellite centres, with a focus on time till death and factors which may aid the physician in predicting time to death.

Our data encompassed the period between July 2007 - April 2011. 142 patients had died within this time frame. Mean age of death was 82.4 (6.0), range 61- 85 years. Discussions relating to CKD planning were initiated a mean 12.9 (10.6) months before death. A final decision confirming conservative care as CKD modality was made 10.3 (9.8) months before death. 20% of patients died at home, 13% in a nursing home or hospice.

19% died from end stage renal disease, the rest died primarily from other causes (cardiovascular events, sepsis, carcinoma, old age). eGFR was a significant predictor of death. When the eGFR was 15ml/min, patients had a median 25 months to live, when 12ml/min- 23 months to live, when 10ml/min – 19 months to live, when 8ml/min- 6 months to live, when 5ml/min- 3 months to live. A low albumin was a significant predictor of death even at 1 year before death. Haemoglobin values were not a significant value of outcome.

In this single centre study, eGFR and albumin values were significant predictors of time to death in patients who opted for or changed their mind to receive conservative care. These 2 values are readily available and may aid clinical staff when counselling patients.

P514

Impact of end stage kidney disease on education and employment in young adults: a mixed methods study

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Introduction: Young adult kidney patients are at an important stage of development when achievement in education influences long term employment opportunities. ESKD may adversely influence progress in education and employment.

Method: Education and career achievements in young adults with ESKD were recorded quantitatively using a self-report questionnaire (n=57): in a mixed methods study design: 14/57 participants were selected for indepth semi-structured interviews.

Results: 57 young adults with CKD 5 or ESRD with recruited from a population of 112(57%). 27(47.4%) had transitioned from paediatric to adult care and 30((52.6%) presented first to adult care. Median age 25(19-30) yrs: 7% (n=4) pre-dialysis;14% (n = 8) on dialysis, 79% (n=45) kidney transplant recipients. 49% left school at age 16; 14/57 (24.6%) were still studying and 43/57 (75.4%) had completed education. 34/57 (59.7%) were in employment (23 full-time, 11 part-time). 19/57 (33.3%) were unemployed and 4 were full time students. 27/45 (60%) of those transplanted were employed;. 21/27 full-time (77.8%), whilst of 8 dialysis patients, 5/8 were employed, but only 1/8 full-time (12.5%). Overall unemployment rate, of those not in full time education, was 33.3% compared to 22% in 18-24 year olds in the general population in the UK. A higher proportion left school early aged 16 or less 49% compared with 20% of the general population, and a smaller proportion obtained a degree 15.8% versus 25% of the general population. In interviews themes impacting adversely on education and employment included low energy levels, time missed due to ESRD, loss of self-esteem, lack of understanding of educators and employers, feelings of loneliness and isolation , depression and recreational drug use.

Conclusions: Impact of ESKD on young adults at a critical stage of personal development is profound, and misunderstood by educators and employers. Barriers limiting achievement apply to young adults under both paediatric and adult health care. There is a need for health care providers to recognise this and increase investment in dedicated support for young adults with ESKD through initiatives such as young adult clinics and appointment of youth workers.

P515

Right information, right decision - what do patients think?

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Background: Patient choice is a key factor in making the decision about renal replacement therapy (RRT). However, achieving this can be difficult and the important question is whether the patient feels the right decision was made.

Method: The aim was to determine patients' perceptions of the choice of initial RRT based on their contentment with that choice some months later. An anonymous questionnaire was developed and distributed to all patients who had a pre emptive transplant or started dialysis for the first time in 2011 within the East Midlands Renal Network (361 patients). Questions related to whether patients believed they had received enough information, were given a choice of treatment and that the right decision was made.

Results: 156 completed questionnaires were returned, giving a response rate of 43 %. Responses were received from all main and satellite units across the region; 56% were known to the renal team for more than a year prior to starting treatment. Analysis showed that 84% felt that they had been given enough information prior to starting RRT, with the help of unit based seminars and specialist nurses, and 72% were given a choice. 92% felt that the right decision was made and 82% would not have done anything differently. Just fewer than 10% had started RRT as an emergency and a number of these felt that their only option was to have haemodialysis at that time. 53% said that a doctor was the most influential person in the decision, though a significant number (28%) felt that they had made the decision themselves, and this was more likely to have happened if they had been known to the renal team for more than 12 months prior to starting RRT. Although the majority were content with the decision, some said they would have liked more information.

Conclusion: Despite its limitations, our survey will help clinical teams to identify ways to improve the patient experience and build on existing strengths. With the right support at the right time patients can start RRT feeling that they have had enough information and that the right decision has been made.

P516

Dialysis withdrawal and impact of advanced care planning. A single centre experience

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Introduction: Discontinuation of dialysis is a common cause of death in end-stage renal disease, especially with an aging dialysis population. Little data exists regarding predictors and length of survival in maintenance dialysis patients following dialysis withdrawal. Advanced care planning (ACP) was introduced in September 2010 in our trust to involve patients in the decision-making process as they approach end-of-life.

Objectives: Our main aim was to investigate duration of survival after cessation of maintenance dialysis and if there were any possible clinical correlates. We also looked at the impact of advanced care planning on dialysis withdrawal.

Method: We performed a retrospective analysis on data collected from the Electronic Patient Record of all patients who died after dialysis withdrawal from dialysis in our unit between April 2009 and November 2012. 262 dialysis patients died during this period of which 43(16.4%) died after dialysis withdrawal.

Results: In our cohort of 43 patients, the mean age was 72 $\pm$ 10. Majority (84%) were on haemodialysis and the rest were on peritoneal dialysis. 72% of patients were on maintenance dialysis for at least 2 years. In 69% the decision to stop haemodialysis was made during their hospital admission by the medical team. Mean days of survival after dialysis withdrawal was 8$\pm$ 5 days. Survival in peritoneal dialysis patients was 10 $\pm$ 7 days, whereas in haemodialysis patients it was 8 $\pm$ 5 days. A high CRP was linked to a shorter survival after withdrawal of dialysis. 34(79%) had Advanced Care Planning. 82% of patients who had ACP died in their place of preference compared to 65% of patients without ACP, although not statistically significant (p=0.438).

Conclusions: Survival post-withdrawal of dialysis had no significant clinical correlates. ACP although still in its early days, seems to improve outcomes in patients who are approaching end of life. Further longitudinal studies on larger populations need to be performed to provide more information on the impact of ACP.

P517

The use of a structured framework to identify risk in a shared care model of renal transplantation

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[1]Southmead Hospital, Bristol, UK, [2]Royal Devon & Exeter Hospital, Exeter, UK

One in ten patients admitted to hospital suffers harm as a result of their care. Renal transplant patients typically have complex medical needs and are therefore a high risk group. In our unit, renal patients undergoing surgery including transplantation are managed in a shared care environment. They remain the responsibility of the nephrologist with input from the visiting surgical team. This system requires the effective sharing of all relevant information. Any failure in this process may compromise patient safety.

We used the Health Foundation Safer Clinical Systems methodology to identify risks within the patient pathway. A high level process map of the patient pathway was developed. Risks within the pathway were diagnosed using Failure Modes & Effect Analysis, Hierarchical Task Analysis and Performance Influencing Factors. The risks were ranked and the highest risk tasks at each step of the pathway identified.

The highest risk tasks at each pathway step are; 1. Timely medical assessment by a senior doctor 2. Communicating the decision on operative timing 3. Preparing the patient for the operation 4. Completing operation documentation 5. Meeting the requirements for safe discharge 6. Communication between different teams. Failure of communication was the main contributor to the high risk scoring for these tasks.

Inadequate handover of information contributes the highest risk in a shared care model of renal transplantation. Analysis of the failure modes, performance influencing factors and current control measures will guide interventions to address the identified risks. This methodology utilises a proactive approach to patient safety rather than simply reacting to adverse events. This framework may be applied to other patient pathways identifying potential risk with the aims of improving system reliability and patient safety.

P518

Does multi-disciplinary pre-dialysis care affect outcome: survival, cardiac events and inpatient admissions after starting dialysis

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Background: Multidisciplinary care (MDC) is known to improve the management of chronic disease. Our initial study in 2010 compared outcomes at the start of dialysis and beyond between a cohort of MDC patients (n=171) and a cohort of patients seen in a nephrologist only clinic (=194). Groups were well-matched demographically, and initial study showed patients attending a multidisciplinary pre-dialysis clinic were better prepared for dialysis, with initial survival advantage. This follow-up study looked at long-term survival, number of cardiac events and number of hospital admissions between the same groups.

Aims: Look at differences in mortality, survival time, number of hospital admissions and cardiac events between the 2 groups.

Methods: Retrospective case-control study of clinic letters, discharge summaries, radiology reports, pathology results and renal database.

Results: Average follow-up time of nephrolist only group was 11.1years, and MDC group was 7.53 years. Analysis using Kaplan-Meier survival plot showed a continued survival advantage in the MDC group compared to the nephrology clinic group, (p-value = 0.019 by Gahan-Breslow Wilcoxon analysis). The number of cardiac events was significantly fewer in the MDC group at 0.28 cardiac events per patient per year versus 0.86 in the nephrologist only group (p-value = 0.03). The number of inpatient admissions was also significantly fewer in the MDC group, with an average of 2.58 admissions per patient per year versus 4.62 in the nephrologist clinic group (p-value = 0.0011). The MDC group had a slightly higher chance of having a functioning transplant at time of analysis 28/171 (16.4%) versus the nephrologist only group 27/193 (14.0%).

Discussion: Results show patients having multi-disciplinary pre-dialysis care have significant long-term survival advantage over patients who have pre-dialysis care by nephrologists alone. Survival advantage is greatest in the initial years, as suggested by the Gahan-Breslow Wilcoxon analysis. Patients have significantly fewer cardiac events and inpatient hospital admissions after starting dialysis.

P519

What determines whether end-stage kidney disease patients commence on their chosen treatment modality?

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Introduction: Despite the use of pre-dialysis programmes, there is often a discrepancy between initial pre-dialysis choice and actual treatment modality commenced. We aimed to examine the factors that determine whether end-stage kidney disease (ESKD) patients commence treatment on their chosen modality.

Methods: This is a follow-up study of a previously published questionnaire study in 118 pre-dialysis patients. The questionnaire consisted of 20 items that patients were asked to rate based on their importance in influencing their modality decision. We followed up the study participants for 43 months to determine whether they indeed commenced treatment on their initial chosen modality.

Results: 49% of patients reached ESKD. 94.3% (n=35) and 53.8% (n=13) of patients that chose haemodialysis (HD) and peritoneal dialysis (PD) respectively, commenced on their initial chosen modality. The remaining patients that chose PD started on HD. This was not due to PD technique failure. 90.0% (n=10) of patients that selected conservative management (CM) retained their choice. There was no association between age, gender or ethnicity and retention of choice. For HD choice, scoring the 'distance to travel to hospital' item highly was associated with commencement on HD (p=0.024). Among patients who had chosen PD, those who valued 'modality fitting with lifestyle' highly (p=0.008) or were more functionally able (p=0.015) were more likely to commence on PD. Interestingly the 'modality fitting with lifestyle' factor was also found to be a crucial determinant of PD choice versus HD in our original study. There was a trend for patients with low educational attainment and patients who scored the item 'importance of family in helping with decision' highly, to commence on HD instead of their initial choice of PD, although the results did not reach statistical significance (p=0.092, p=0.060).

Conclusion: Patients who initially chose PD but did not perceive the lifestyle benefits of PD as important, or were less functionally able, were more likely to commence on HD. These findings are important in informing the design of more effective pre-dialysis programmes to increase the uptake of self-care modalities.

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